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Note

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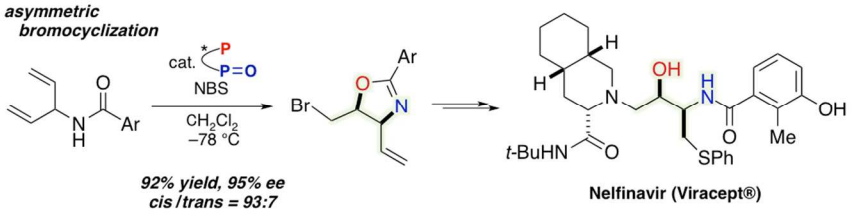
Supporting Information Placeholder



ABSTRACT: We describe a concise enantioselective synthesis of the HIV-protease inhibitor nelfinavir (**1**) via a new route, in which the key step is construction of the central optically active 1,2-amino alcohol framework via asymmetric bromocyclization of bisallylic amide with *N*-bromosuccinimide in the presence of a catalytic amount of (*S*)-BINAP or (*S*)-BINAP monoxide. The remaining alkene and bromo functionalities were used to install the requisite thioether and chiral perhydroisoquinoline units, respectively.

Infection with human immunodeficiency virus (HIV) is the cause of acquired immune deficiency syndrome (AIDS),[1] and AIDS patients are at risk of opportunistic infections, cancer, and dysfunction of various organ systems, if not appropriately treated. Many antiretroviral drugs have been developed, targeting various stages of the HIV life cycle. At present, nucleoside/non-nucleoside reverse-transcriptase inhibitors, HIV-protease inhibitors, integrase strand-transfer inhibitors, and C-C chemokine receptor type 5 (CCR5) inhibitors are in clinical use for the treatment of HIV infection. Current guidelines recommend the use of combination antiretroviral therapies, and these enable HIV-infected patients to live essentially normal lives. However, there are nearly 36.7 million patients in the world, and their number is still increasing. In 2016, 1 million people died from AIDS-related diseases, while about 1.8 million people were newly infected. Thus, HIV/AIDS is still a very important issue, and there is a continuing need to reduce the cost of synthesizing anti-HIV agents, especially for the treatment of patients in less developed countries, where this is a particular concern.

Nelfinavir (**1**; Figure 1), the active ingredient in Viracept, is one of the most widely prescribed HIV-protease inhibitors owing to its efficacy, safety, and favorable pharmacokinetics.[2] In addition, recent studies have revealed that **1** inhibits the growth of a wide variety of tumor cells and triggers apoptosis.[3–4] These findings have stimulated research on **1** as a potential anti-cancer agent, and several clinical trials of **1** in combination with other well-established chemotherapeutic agents or radiation therapy are underway. In this context, a variety of synthetic approaches to **1** have been investigated,[5,6] including syntheses through optical resolution, chiral pool methodology, and asymmetric catalysis. These earlier approaches mainly focused on the synthesis of the optically active central four-carbon framework **2**, in which each carbon is connected to heteroatom functionalities.[7] Among them, Inaba and co-workers have developed a highly efficient synthesis of **1**, in which chiral titanium catalyst was utilized for asymmetric aminolysis of *meso*-epoxides with racemic amine.[6b,7a]

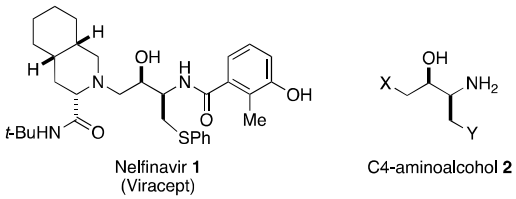
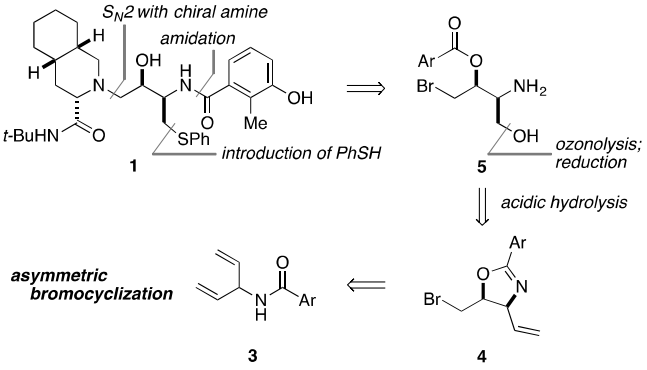


Figure 1. Structure of nelfinavir.

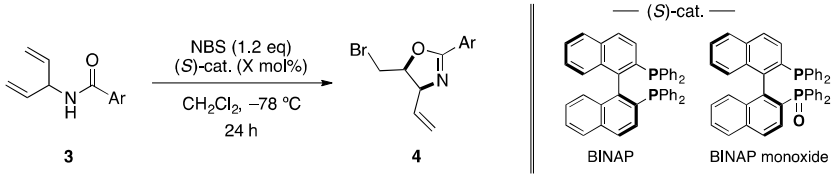
Catalytic asymmetric halo-functionalization of alkenes has attracted great interest over the last decade.[8] The enantioenriched heterocyclic products are of great utility as key intermediates in syntheses of natural products and medicinal agents. In our continuing research program on asymmetric halogenation reactions,[9] we have recently developed a desymmetrization of bisallylic amides **3** by enantioselective bromocyclization with BINAP monoxide as a catalyst (Scheme 1).[10] In this bromocyclization reaction, the catalytic bromophosphonium (P^+Br) species was first generated

by the reaction of the catalyst with *N*-bromosuccinimide (NBS). This P^+Br substructure is considered to function as a Lewis acid, which interacts with the pendant amide nucleophile to define its position, thus affording enantiomerically enriched oxazolines **4** with vicinal chiral carbon stereocenters. Since hydroxyethylamine substructures are well known as bioisosteres of amide bonds in the development of inhibitors against aspartyl protease such as HIV protease and γ-secretase, the compound **4** would be a useful platform in synthesizing this class of peptidemimetics and other bioactive compounds. Considering the *cis*-orientation of the oxazoline ring and facile derivatization to the advanced intermediate **5** with suitable functional groups for further manipulation, we anticipated that the oxazoline **4** would be an appropriate intermediate for an efficient synthesis of **1**. As a suitable demonstration of the utility of our asymmetric bromocyclization, we embarked on the synthesis of **1** according to the retrosynthesis in Scheme 1. Herein, we report a concise enantioselective synthesis of **1** using our catalytic asymmetric bromocyclization of bisallylic amides as a key step.



Scheme 1. Retrosynthesis of 1.

Table 1. Optimization of desymmetrization of bisallylic amides.[a]

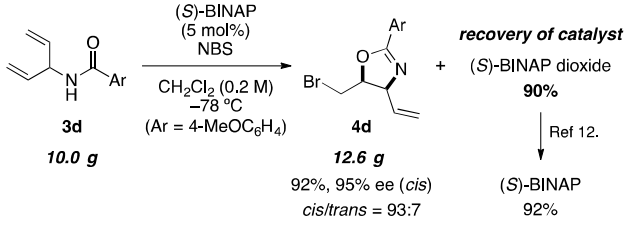


entry	(*S*)-cat.	X (mol%)	**3**	Ar	**4**	conc. (M)	yield[b] (%)	*cis*/*trans*[c]	ee[d] (%)
1	BINAP monoxide	10	**3a**	3-MeO-2-MeC_6H_3	**4a**	0.05	79[e]	82:18	37
2	BINAP monoxide	10	**3b**	Ph	**4b**	0.05	91[e]	93:7	92
3	BINAP monoxide	10	**3c**	4-BrC_6H_4	**4c**	0.05	87[e]	93:7	93
4	BINAP monoxide	10	**3d**	4-MeOC_6H_4	**4d**	0.05	88[e]	94:6	95
5	BINAP	10	**3d**	4-MeOC_6H_4	**4d**	0.05	89	93:7	94
6	BINAP	5	**3d**	4-MeOC_6H_4	**4d**	0.05	92	93:7	91
7	BINAP	5	**3d**	4-MeOC_6H_4	**4d**	0.1	99	93:7	92
8	BINAP	5	**3d**	4-MeOC_6H_4	**4d**	0.2	95	93:7	95
9	BINAP	5	**3d**	4-MeOC_6H_4	**4d**	0.5	91	93:7	94
10	BINAP	3	**3d**	4-MeOC_6H_4	**4d**	0.5	91	93:7	91

[a]CH_2Cl_2: fixed at 2.0 mL, **3**: varied from 0.10 mmol to 1.0 mmol as appropriate. [b]NMR yield of the *cis*-product. [c]Determined by ^1H NMR spectroscopic analysis of the crude mixture. [d]Enantiomeric excess (ee) of *cis*-**4** was determined by HPLC analysis. [e]Isolated yield of the *cis*-product.

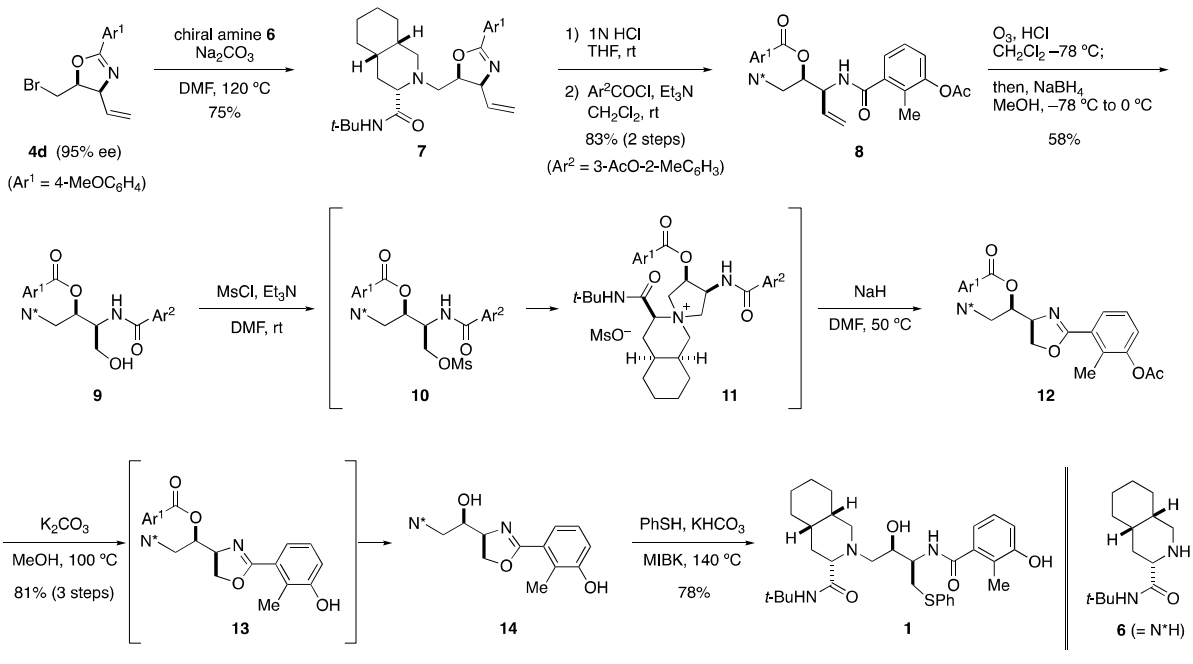
Initially, we set out to identify suitable reaction conditions for the key asymmetric bromocyclization of **3**. Considering the chemical structure of the benzamide unit, the use of 3-methoxy-2-methylbenzamide **3a** would streamline the synthesis of **1** by eliminating an additional amidation process. Unfortunately, however, the reaction with 10 mol% of (*S*)-BINAP monoxide (P/P=O cat.) in CH_2Cl_2 gave the oxazoline product **4a** with unsatisfactory enantioselectivity (Table 1, entry 1).[11] Therefore, we needed to install the requisite amide moiety at a later stage. Among the other bisallylic amides screened (entries 2–4), 4-methoxybenzamide **3d** afforded **4d** with the highest enantioselectivity (95% ee) (entry 4). Commercially available simple BINAP (P/P cat.) serves as a catalyst precursor to afford **4d** in comparable yield and stereoselectivity, which would be advantageous for practical application (entry 5). The enantioselectivity of **4d** was slightly reduced when the catalyst amount was decreased to 5 mol% (entry 6). Interestingly, however, this reaction exhibited improved enantioselectivity at higher concentration. Thus, **4d** was obtained with comparable stereoselectivity (94% ee, 93:7 diastereomeric ratio) in tenfold 0.5 M CH_2Cl_2 solution (entry 9). At this higher concentration, high yield and acceptable stereoselectivity were achieved even with 3 mol% of the BINAP catalyst (entry 10). However, the reaction mixture tended to coagulate during the reaction pro-

cess when the reaction was carried out at 0.3–0.5 M, probably due to the poor solubility of the oxazoline product. Considering that homogeneous reaction is generally desirable from the viewpoint of reproducibility, we selected the conditions shown in entry 8 for a gram-scale reaction. Thus, the asymmetric bromocyclization with 10.0 g of bisallylic amide **3d** proceeded without difficulty, affording **4d** in 92% yield with 95% ee (dr = 93:7) (Scheme 2). After aqueous work-up, the catalyst was fully oxidized to BINAP dioxide (P=O/P=O cat.), which was readily isolated in 90% yield during the purification of **4d**. This recovered dioxide was subsequently reduced to BINAP in 92% yield according to the reported procedure,[12] allowing for efficient recycling of the costly BINAP catalyst.

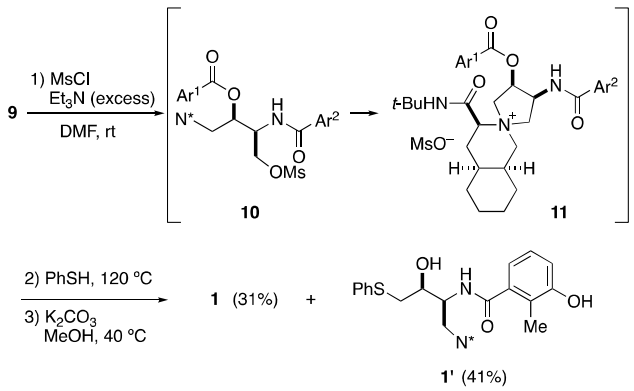


Scheme 2. Gram-scale reaction of 3d.

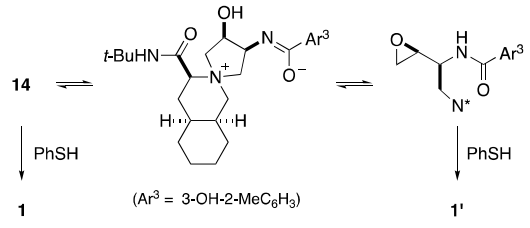
Synthesis of **1** from the oxazoline product **4d** is illustrated in Scheme 3. Compound **4d** was treated with L-phenylalanine-derived chiral amine **6** in DMF to give enantiomerically pure **7** in 75% yield.[13] The oxazoline ring was efficiently hydrolyzed by treatment with 1 N HCl to give the corresponding benzoate intermediate, and the resulting primary amino group was coupled with 3-acetoxy-2-methylbenzoyl chloride to afford amide **8** as the sole product.[14] In contrast, when **4c** was subjected to hydrolysis, the *p*-bromobenzoyl group migrated partially to the resulting primary amine during the purification, affording a mixture of the corresponding ester and amide. Ozonolysis of the terminal alkene of **8** under typical conditions gave a complex mixture, probably due to undesired decomposition induced by oxidation of the tertiary amine structure. Therefore, the reaction was carried out in the presence of a slight excess of acid additive to protect the amine.[15] The ozonolysis proceeded cleanly, and reductive work-up with sodium borohydride directly delivered alcohol **9** in 58% yield. The stage was set for the incorporation of the thiolate group. As shown in Scheme 4, a straightforward, three-step approach to nelfinavir (**1**) from **9** was unsuccessful, being accompanied by formation of the regioisomer **1'**, the amine and sulfur functionalities of which were transposed from their original positions. This undesired production of **1'** could be explained by assuming the following reaction process. During the course of mesylation of **9**, the transient mesylate **10** might undergo an intramolecular S_N2 reaction with the tertiary amine to form quaternary ammonium salt **11**. Ring-opening of the pyrrolidinium intermediate **11** with PhSH seemed poorly regioselective, and thus the subsequent methanolysis of the two ester groups afforded **1** in only 31% yield along with **1'** in 41% yield. Inaba and coworkers observed a similar transposition reaction in the conversion of the oxazoline **14** to **1**, which was considered to occur through the formation of the corresponding quaternary ammonium salt (Scheme 5).[6b] After extensive investigations, they found that the formation of the positional isomer **1'** could be minimized by using the combination of $KHCO_3$ as a base and methyl isobutyl ketone (MIBK) as a solvent. Since all of our attempts at the ring opening of **11** under various reaction conditions were unsuccessful, we planned to lead **9** to Inaba's precursor **14**. To our delight, upon treatment with NaH in DMF at 50 °C, **11** was transformed smoothly to the more stable oxazoline **12**. The transformation from **9** proceeded in one pot. After removal of DMF under reduced pressure, treatment with MeOH under basic conditions afforded the desired intermediate **14** in 81% yield over three steps. This methanolysis first gave the benzoyl-protected intermediary **13**. We also attempted oxazoline opening of the isolated **13** with thiolate ion under various conditions, but the reaction did not proceed well. Finally, **14** was reacted with PhSH under Inaba's conditions,[6b] furnishing nelfinavir (**1**) in 78% yield.



Scheme 3. Synthesis of nelfinavir 1.



Scheme 4. Unsuccessful attempt at the introduction of PhSH.



Scheme 5. An epoxide intermediary through a transient cyclic quaternary ammonium salt to 1'.

In summary, we have developed a concise synthetic route to the HIV-protease inhibitor nelfinavir. Asymmetric bromocyclization of bisallylic amide with a catalytic amount of BINAP was performed on a 10-gram scale without difficulty, and the requisite chiral 1,2-amino alcohol framework was obtained efficiently. Further application of our bromocyclization to asymmetric synthesis of other bioactive compounds is underway in our laboratory.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, materials were purchased from commercial suppliers and were used without purification. THF, toluene and CH_2Cl_2 were purified by passing through a solvent purification system (Glass Contour). (*S*)-BINAP was purchased from Kanto Chemical Co. Ltd and used as received. NBS was purified by recrystallization from water according to a general method. Bisallylic amides were recrystallized from *n*-hexane and CH_2Cl_2. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless steel needle. All workup and purification procedures were carried out with reagent-grade solvents under ambient air. Flash column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm) purchased from Kanto Chemical Co. Ltd.

Infrared (IR) spectra were recorded on a S.T. Japan Inc. DuraSamplIR II infrared spectrophotometer. NMR spectra were recorded on JEOL ECA500 NMR spectrometers. Proton chemical shifts are reported as δ in units of parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ppm, DMSO-d_6: δ 2.50 ppm). For ^{13}C NMR, chemical shifts are reported in the scale relative to the NMR solvent ($CDCl_3$: 77.0 ppm, DMSO-d_6: 39.5 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. High-resolution mass spectra (TOF(+)) were measured on Bruker Deltonics micrOTOF. Optical rotation was measured using a 1 mL cell with a 1.0 dm path length on a JASCO polarimeter P-2200. HPLC analysis was conducted on a Shimadzu HPLC system with chiral-stationary-phase columns (ϕ 0.46 cm × 25 cm). Compounds **4b**, **4c**, **4d**, **14**, and **1** are known compounds (CAS registry numbers 2149042-27-1, 2149042-29-3, 2149042-31-7, 188936-07-4 and 159989-64-7, respectively).

(4*S*,5*S*)-5-(Bromomethyl)-2-(3-methoxy-2-methylphenyl)-4-vinyl-4,5-dihydrooxazole (4a). **4a** was synthesized according to the procedure reported in Ref 10. IR ($CHCl_3$) ν 1647, 1584, 1464, 1261 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.00–5.91 (m, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 5.36 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.98–4.92 (m, 2H), 3.84 (s, 3H), 3.50–3.45 (m, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.2, 158.0, 132.5, 128.0, 127.9, 126.1, 122.0, 119.4, 112.6, 81.0, 70.7, 55.8, 30.3, 13.2; HRMS (ESI) calcd. for $C_{14}H_{17}BrNO_2$ *m/z* 310.0437 $[M+H]^+$, found 310.0451; $[\alpha]_D^{22}$ −9.2 (*c* 1.2 $CHCl_3$, 37% ee); CHIRALPAK AD-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 5/95, flow rate 1.0 mL/min, column temp. 40 °C, detection at 254 nm, t_R = 6.4 min (major), 9.5 min (minor).

(4*S*,5*S*)-5-(Bromomethyl)-2-phenyl-4-vinyl-4,5-dihydrooxazole (4b). **4b** was synthesized according to the procedure reported in Ref 10. Colorless oil; IR ($CHCl_3$): ν 1653, 1608, 1583, 1435, 1298 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.02-7.98 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.44-7.41 (m, 2H), 5.93 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.46 (d, *J* = 17.2 Hz, 1H), 5.36 (d, *J* = 10.3 Hz, 1H), 5.00 (dt, *J* = 9.8, 6.9 Hz, 1H), 4.91 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.49 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 163.5, 132.5, 131.7, 128.4, 128.4, 127.1, 119.7, 81.6, 70.4, 30.3; CHIRALPAK AD-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 5/95, flow rate 0.8 mL/min, column temp. 40 ºC, detection at 254 nm, t_R = 6.1 min (major), 7.1 min (minor). These spectral data for **4b** were consistent with those reported in Ref 10.

(4S,5S)-5-(Bromomethyl)-2-(4-bromophenyl)-4-vinyl-4,5-dihydrooxazole (4c). **4c** was synthesized according to the procedure reported in Ref 10. Colorless oil; IR ($CHCl_3$): ν 1724, 1651, 1593, 1485, 1265 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 5.91 (ddd, *J* = 17.0, 10.5, 7.5 Hz, 1H), 5.45 (d, *J* = 17.0 Hz, 1H), 5.36 (d, *J* = 10.5 Hz, 1H), 4.99 (dt, *J* = 9.5, 6.5 Hz, 1H), 4.91 (dd, *J* = 9.5, 7.5 Hz, 1H), 3.48 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 162.7, 132.2, 131.7 129.9, 126.5, 126.1, 119.8, 81.9, 70.5, 30.1; CHIRALPAK AD-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 5/95, flow rate 1.0 mL/min, column temp. 40 ºC, detection at 254 nm, t_R = 7.4 min (major), 11.0 min (minor). These spectral data for **4c** were consistent with those reported in Ref 10.

(4*S*,5*S*)-5-(Bromomethyl)-2-(4-methoxyphenyl)-4-vinyl-4,5-dihydrooxazole (4d, large-scale) To a 500 mL flask equipped with a magnetic stirring bar and a three-way glass stopcock were added (*S*)-BINAP (1.43 g, 2.30 mmol), **3d** (10.0 g, 46.0 mmol) and dry CH_2Cl_2 (230 mL). The flask was immersed in a cooling bath at −78 °C. To the solution was added NBS (9.83 g, 55.2 mmol), and the mixture was stirred at −78 °C for 24 h at the same temperature. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ aq. in one portion. The mixture was allowed to warm gradually to room temperature. The separated aqueous layer was extracted with CH_2Cl_2 three times and the combined organic layers were washed with brine, and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and a small aliquot of the resulting residue was submitted to ^1H NMR analysis to determine the diastereomeric ratio (93:7). The crude product was purified by flash column chromatography (*n*-hexane/EtOAc = 3/1–1/1) to give **4d** (12.6 g, 92%) as a yellowish amorphous solid and BINAP dioxide (1.36 g, 90%). as a colorless solid. **4d** is a known compound (Ref 10). Colorless oil; IR ($CHCl_3$): ν 1649, 1637, 1610, 1512, 1257 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.92 (d, *J* = 9.2 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 2H), 5.90 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.3 Hz, 1H), 4.96 (dt, *J* = 9.8, 6.3 Hz, 1H), 4.86 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.84 (s, 3H), 3.47 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 163.3, 162.4, 132.7, 130.2, 119.5, 119.5 113.7, 81.5, 70.3, 55.4, 30.4; HRMS (ESI) Anal. calcd. for $C_{13}H_{15}BrNO_2$ *m/z*

296.0286 $[M+H]^+$, found 296.0287; $[\alpha]_D^{26}$ −16.1 (*c* 1.1, $CHCl_3$, 95% ee); CHIRALPAK AD-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 5/95, flow rate 1.0 mL/min, column temp. 40 ºC, detection at 254 nm, t_R = 11.4 min (major), 17.1 min (minor). These spectral data for **4d** were consistent with those reported in Ref 10.

(3*S*,4a*S*,8a*S*)-*N*-(*tert*-Butyl)-2-(((4*S*,5*R*)-2-(4-methoxyphenyl)-4-vinyl-4,5-dihydrooxazol-5-yl)methyl)decahydroisoquinoline-3-carboxamide (7) A mixture of **4d** (12.6 g, 42.7 mmol), L-Phe-derived amine **6** (12.2 g, 51.3 mmol) and Na_2CO_3 (6.8 g, 64.1 mmol) in DMF (150 mL) was stirred for 30 h at 120 ºC. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography (*n*-hexane/EtOAc = 1/1–1/3) to give **7** (14.6 g, 75%) as a colorless solid: Mp: 153-154 ºC; IR (ATR) ν 1670, 1645, 1611, 1510, 1452, 1256 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.40 (brs, 1H), 5.70 (ddd, *J* = 17.5, 10.0, 8.0 Hz, 1H), 5.32 (d, *J* = 17.5 Hz, 1H), 5.21 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.79–4.71 (m, 2H), 3.84 (s, 3H), 3.21 (d, *J* = 11.5, 3.0 Hz, 1H), 2.78 (dd, *J* = 14.5, 2.0 Hz, 1H), 2.66 (dd, *J* = 10.5, 3.0 Hz, 1H), 2.38–2.29 (m, 2H), 1.86–1.73 (m, 4H), 1.70–1.67 (m, 1H), 1.61–1.57 (m, 1H), 1.55–1.20 (m, 6H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.7, 163.8, 162.2, 134.0, 130.0, 120.0, 118.8, 113.7, 83.5, 71.3, 69.7, 58.7, 57.1, 55.4, 50.3, 35.7, 32.9, 30.7, 30.4, 28.8, 26.2, 26.0, 20.6; HRMS (ESI) calcd. for $C_{27}H_{40}N_3O_3$ *m*/*z* 454.3070 $[M+H]^+$, found 454.3078; $[\alpha]_D^{22}$ −110.8 (*c* 0.29, $CHCl_3$).

(2*R*,3*S*)-3-(3-Acetoxy-2-methylbenzamido)-1-((3*S*,4a*S*,8a*S*)-3-(*tert*-butylcarbamoyl)octahydroisoquinolin-2(1*H*)-yl)pent-4-en-2-yl 4-methoxybenzoate (8) To a solution of **7** (14.6 g, 32.2 mmol) in THF (320 mL) was added 1 N HCl aq. solution (150 mL) at room temperature. The mixture was stirred for 3.5 h at the same temperature, and then saturated $NaHCO_3$ aq. solution and water were added to neutralize it. The separated organic layer was dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2 (300 mL), and then 3-acetoxy-2-methyl-benzoyl chloride (8.2 mL, 48.3 mmol) and Et_3N (9.0 mL, 64.7 mmol) were added at 0 ºC. Stirring was continued for 30 min at room temperature, then the reaction mixture was quenched with saturated aq. NH_4Cl solution. The separated aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with brine, and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (*n*-hexane/EtOAc = 3/1–1/1) to give **8** (17.2 g, 83%) as a pale yellowish solid: Mp: 193–195 ºC; IR (ATR) ν 1767, 1709, 1659, 1643, 1605, 1510, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.67–6.65 (m, 1H), 6.26 (brs, 1H), 6.08 (ddd, *J* = 17.0, 11.0, 7.0 Hz, 1H), 5.51–5.49 (m, 1H), 5.34 (d, *J* = 17.0 Hz, 1H), 5.25 (d, *J* = 11.0 Hz, 1H), 5.06 (dd, *J* = 7.5, 7.0 Hz, 1H), 3.83 (s, 3H), 2.90 (dd, *J* = 11.5, 2.5 Hz, 1H), 2.75 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.57 (dd, *J* = 11.0, 3.0 Hz, 1H), 2.38 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.29 (s, 3H), 2.22–2.18 (m, 1H), 2.21 (s, 3H), 1.84 (q, 13.0 Hz, 1H), 1.70–1.55 (m, 4H), 1.52–1.43 (m, 3H), 1.31–1.21 (m, 2H), 1.27 (s, 9H), 1.11–1.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.8, 169.1, 168.5, 165.9, 163.6, 149.7, 138.6, 133.5, 131.8, 128.5, 126.6, 124.6, 123.5, 122.2, 118.0, 113.7, 74.5, 70.8, 59.5, 56.7, 55.4, 53.5, 51.0, 35.7, 33.3, 30.8, 30.7, 28.6, 26.1, 25.4, 20.8, 20.5, 12.9; HRMS (ESI) calcd. for $C_{37}H_{50}N_3O_7$ *m*/*z* 648.3643 $[M+H]^+$, found 648.3659; $[\alpha]_D^{22}$ −59.2 (*c* 0.64, $CHCl_3$).

(2*R*,3*S*)-3-(3-Acetoxy-2-methylbenzamido)-1-((3*S*,4a*S*,8a*S*)-3-(*tert*-butylcarbamoyl)octahydroisoquinolin-2(1*H*)-yl)-4-hydroxybutan-2-yl 4-methoxybenzoate (9) A solution of **8** (1.0 g, 1.54 mmol) and 4 N HCl (in EtOAc, 540 μL, 2.15 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C. A mixture of O_3/O_2 was then bubbled through the solution for 20 min. Stirring was continued for 15 min at the same temperature, then the solution was purged with Ar, and $NaBH_4$ (233 mg, 6.16 mmol) in MeOH (10 mL) was added dropwise. The mixture was stirred for 10 min at −78 ºC and for 3 h at 0 ºC, and then the reaction was quenched with saturated $NaHCO_3$ aq. solution. The resulting mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ aq. and brine, and then dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (*n*-hexane/EtOAc = 2/1–1/2) to give **9** (581 mg, 58%) as a colorless solid: Mp: 205–208 ºC (decomp.); IR (ATR) ν 3380, 1759, 1709, 1643, 1605, 1549, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.54 (brs, 1H), 5.42–5.38 (m, 1H), 4.89–4.77 (m, 1H), 3.88–3.83 (m, 2H), 3.85 (s, 3H), 3.16 (d, *J* = 10.5 Hz, 1H), 2.80 (dd, *J* = 12.5, 10.0 Hz, 1H), 2.52–2.49 (m, 1H), 2.33–2.27 (m, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 2.05–1.98 (m, 1H), 1.90–1.83 (m, 1H), 1.79–1.66 (m, 3H), 1.57–1.51 (m, 3H), 1.45–1.20 (m, 5H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 169.1, 168.9, 165.8, 163.6, 149.7, 138.7, 132.0, 128.5, 126.5, 125.0, 123.4, 122.2, 113.7, 73.0, 70.7, 62.1, 59.8, 55.4, 55.2, 52.5, 51.4, 35.7, 33.9, 30.9, 30.9, 28.5, 26.3, 25.3, 20.8, 20.5, 12.9; HRMS (ESI) calcd. for $C_{36}H_{50}N_3O_8$ *m*/*z* 652.3592 $[M+H]^+$, found 652.3602; $[\alpha]_D^{22}$ +29.1 (*c* 0.39, $CHCl_3$).

(3*S*,4a*S*,8a*S*)-*N*-(*tert*-Butyl)-2-((*R*)-2-hydroxy-2-((*S*)-2-(3-hydroxy-2-methylphenyl)-4,5-dihydrooxazol-4-yl)ethyl)decahydroisoquinoline-3-carboxamide (14) To a solution of **9** (1.20 g, 1.84 mmol) and Et_3N (380 μL, 2.73 mmol) in DMF (8.0 mL) was added dropwise MsCl (160 μL, 2.02 mmol), and the reaction mixture was stirred for 20 min at room temperature. NaH (60% dispersion in mineral oil, 184 mg, 4.60 mmol) was added and the resulting mixture was further stirred at 50 ºC for 3 h. After removal of DMF under reduced pressure, the resultant residue and K_2CO_3 (254 mg, 14.7 mol) were suspended in MeOH (10.0 mL) in a PYREX® screw cap culture tube. The reaction vessel was sealed with a PTFE-lined cap and heated at 100 °C in an oil bath for 2 h. Volatiles were removed, water (80 mL) was added, and the resultant precipitate was collected by filtration. The crude **14** was suspended in ether to remove the mineral oil derived from NaH and the co-product, methyl *p*-anisate. The resultant precipitate was collected by filtration and dried under reduced pressure to give pure **14** (685 mg, 81%) as a colorless solid: Mp: 233-235 ºC (decomp.); IR (ATR) ν 3250, 1643, 1605, 1557, 1362, 1279; ^1H NMR (DMSO-d_6) δ 9.58 (brs, 1H), 7.40 (s, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 4.77 (brs, 1H), 4.47–4.45 (m, 1H), 4.28–4.25 (m, 1H), 4.14–4.12 (m, 1H), 3.75 (brs, 1H), 2.90 (d, *J* = 11.5 Hz, 1H), 2.57 (d, *J* = 11.5 Hz, 1H), 2.35 (dd, *J* = 11.0, 9.5 Hz, 1H), 2.28 (s, 3H), 2.11 (d, *J* = 11.0 Hz, 1H), 2.05 (d, *J* = 12.0 Hz, 1H), 1.91–1.81 (m, 2H), 1.73–1.65 (m, 2H), 1.58–1.46 (m, 3H), 1.36–1.14 (m, 5H), 1.24 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 172.6, 163.4, 155.6, 129.2, 125.7, 124.3, 120.1, 116.4, 69.5, 69.2, 69.0, 66.8, 64.9, 59.3, 58.5, 49.9, 35.7, 33.1, 30.6, 30.0, 28.4, 25.9, 25.3, 20.1, 15.2, 13.3; $[\alpha]_D^{22}$ −58.4 (*c* 0.49, DMF). These spectral data for **14** were consistent with those reported in Ref 6b.

Nelfinavir (1) Compound **14** (125 mg, 0.27 mmol), PhSH (55 μL, 0.54 mmol) and dried $KHCO_3$ (54 mg, 0.54 mmol) were suspended in methylisobutylketone (1.2 mL) in a PYREX® screw cap culture tube. The reaction vessel was sealed with a PTFE-lined cap and heated at 140 °C in an oil bath for 5 h. Volatiles were removed, water and EtOAc were added to the resultant mixture, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography (*n*-hexane/EtOAc = 3/2–1/1) to give **1** (121 mg, 78%) as a white solid: Mp >300 ºC; IR (ATR) ν 1622, 1527, 1454, 1287; ^1H NMR (DMSO-d_6) δ 9.36 (s, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.48 (s, 1H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.81–6.77 (m, 2H), 4.81 (d, *J* = 5.2 Hz, 1H), 4.35–4.30 (m, lH), 3.94–3.91 (m, 1H), 3.56 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.14 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.95 (d, *J* = 9.7 Hz, 1H), 2.53–2.49 (m, 2H), 2.12 (s, 3H), 2.02–1.98 (m, 2H), 1.91 (q, *J* = 11.5 Hz, 1H), 1.70–1.67 (m, 2H), 1.55–1.50 (m, 2H), 1.49–1.46 (m, 2H), 1.37–1.20 (m, 5H), 1.14 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 173.0, 169.2, 155.4, 139.4, 136.9, 128.7, 127.7, 125.7, 124.9, 121.5, 117.8, 115.1, 68.9, 68.5, 58.4, 57.9, 50.8, 50.0, 35.6, 33.4, 31.4, 30.6, 30.0, 28.3, 25.9, 25.1, 20.3, 12.7; $[\alpha]_D^{22}$ −141.4 (*c* 0.38, DMF). These spectral data for **1** were consistent with those reported in Ref 6b.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of synthesized compounds, HPLC chart for **4a** through **4d**, and characterization of intermediates en route to **1**. This Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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