http://dx.doi.org/10.5012/bkcs.2012.33.7.2213

From L-Ascorbic Acid to Protease Inhibitors: Practical Synthesis of Key Chiral Epoxide Intermediates for Aspartyl Proteases

Sun Ki Chang, Soon Mog So,[†] Sang Min Lee,[†] Min Kyu Kim,[‡] Kyoung Mee Seol,[‡] Sung Min Kim,[‡] Jae sung Kang,[‡] Dong Joon Choo,[*] Jae Yeol Lee,[*] and B. Moon Kim[†,*]

Research Institute for Basic Sciences and Department of Chemistry, College of Sciences, Kyung Hee University, Seoul 130-701, Korea. [*]E-mail: djchoo@khu.ac.kr (D. J. C.); ljy@khu.ac.kr (J. Y. L.)
[†]Department of Chemistry, Seoul National University, College of Natural Sciences, Seoul 151-747, Korea
[*]E-mail: kimbm@snu.ac.kr
[‡]ST Pharm Co., Ltd. Shihwa Industrial Complex 1Na- 802, Gyeonggi-do 429-912, Korea
Received December 8, 2011, Accepted March 30, 2012

Efficient synthetic routes were developed to prepare a sizable amount (4-15 grams) of the chiral epoxides **4-6** as versatile intermediates for the synthesis of aspartyl protease inhibitors of therapeutic interest such as HIV protease and β-secretase. Oxidative cleavage of the C(2)-C(3) double bond of L-ascorbic acid followed by functional group manipulation led to the preparation of the epoxide **10**, which was opened with an azide to yield a common aziridine intermediate **12**. Through opening of the aziridine ring of **12** with either a carbon or a sulfur nucleophile, chiral epoxide precursors **4-6** could be prepared for various HIV protease inhibitors. Except for the final low melting epoxides **5** and **6**, all intermediates were obtained as crystalline solids, thus the synthetic pathway can be easily applied to a large-scale synthesis of the chiral epoxides.

Key Words : L-Ascorbic acid, Protease inhibitors, Aziridine opening, HIV protease, Epoxide

Introduction

Inhibitors of human immunodeficiency virus protease (HIV PR) have been developed as one of the effective chemotherapeutic agents for the treatment of AIDS.[1,2] The HIV PR inhibitors often exhibit complex structural features equipped with multiple stereogenic centers. Thus development of an efficient and practical synthetic route toward these inhibitors presents a challenge to synthetic organic chemists. The installation of the stereogenic, transition state hydroxyl-bearing carbon requires either efficient asymmetric synthesis or employment of an enantiomerically pure starting material from chiral pools. Herein we report an efficient, versatile and practical synthetic pathway leading to the stereospecific synthesis of the HIV protease inhibitor backbone structures containing both isomers of the chiral hydroxyl group starting from L-ascorbic acid (vitamin C), an abundant starting material. L-Ascorbic acid has often been utilized as a useful chiral source for the synthesis of enantiomerically pure products.[3]

Three different HIV PR inhibitors,[4] *i.e.* saquinavir (**1**),[5] amprenavir (**2**),[6] and nelfinavir (**3**),[7] all belong to the hydroxyethylamine (HEA) class of inhibitors[8] and can be prepared from common epoxide intermediates **4** or **5**.[9] These epoxides can also be utilized as synthetic intermediates for the inhibitors against other aspartyl protease inhibitors such

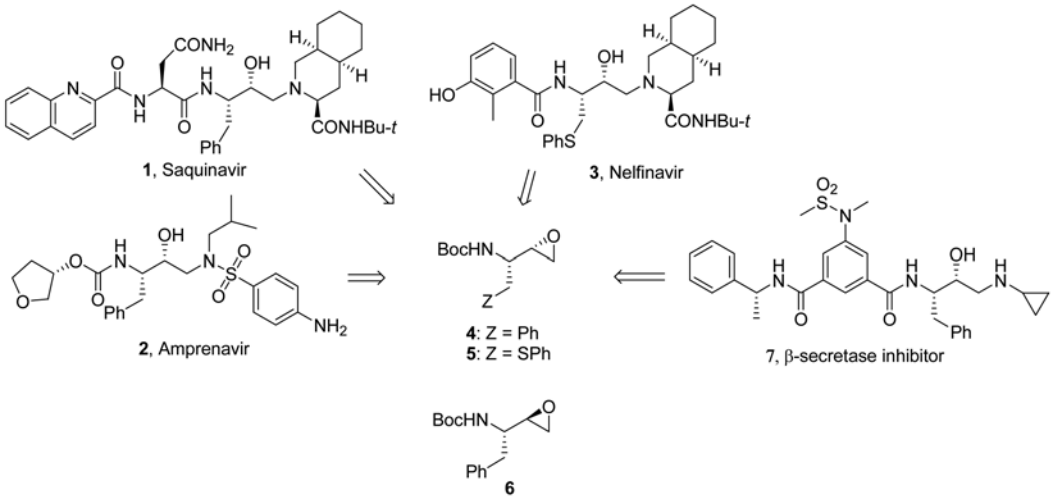
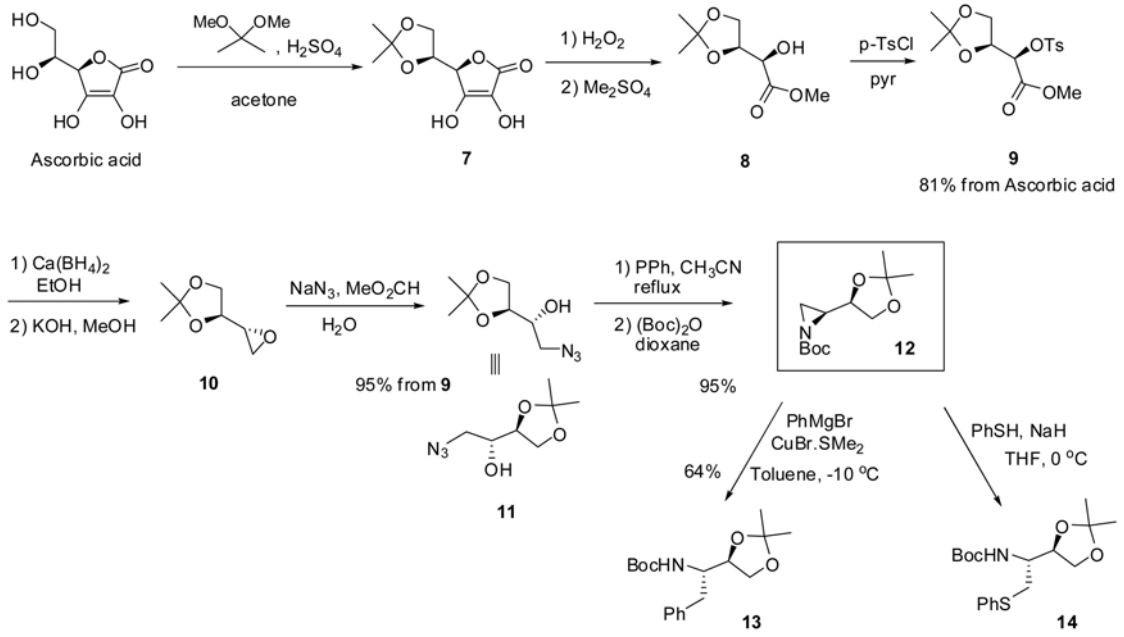


Figure 1. Common epoxide intermediates for aspartyl protease inhibitors.

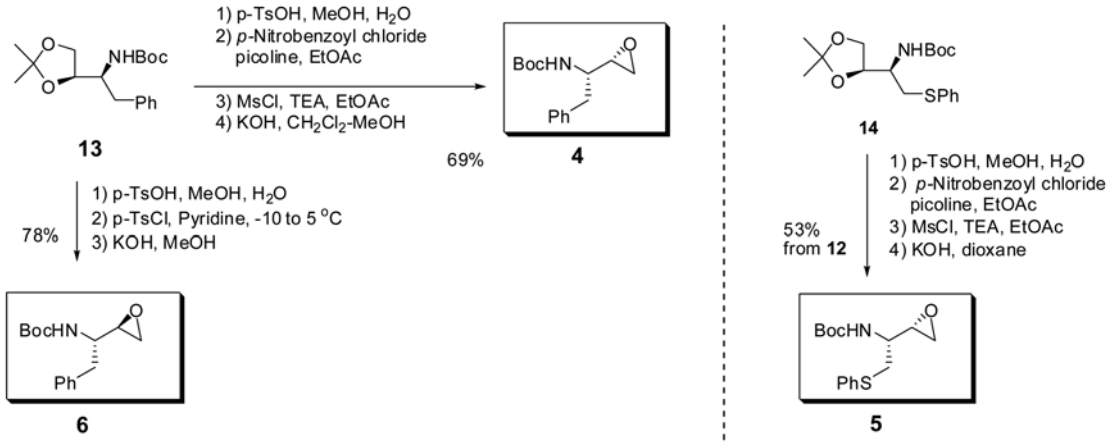


Scheme 1. Preparation of epoxide precursors **13** and **14**.

as β-secretase (BACE).[10] Therefore much effort has been concentrated on the efficient synthesis of chiral epoxides **4-6**. We have previously reported on the new synthetic methodology based upon chiral aziridine intermediate, which provided an access to a common intermediate for both **4** and **5**.[9m] Herein we report on a new synthetic route for the epoxide intermediates **4-6** starting from L-ascorbic acid, an extremely abundant and cheap starting material.

Results and Discussion

Several reports exist on the oxidative cleavage of the C(2)-C(3) double bond of L-ascorbic acid (**1**) to a four-carbon unit threonic acid derivative such as compound **8**.[11] The preparation of compound **8** was performed using a procedure slightly modified from the report of Wei *et al.*[11a] Protection of L-ascorbic acid using 2,2-dimethoxypropane in presence of a catalytic amount of concentrated sulfuric acid in acetone followed by oxidation using H_2O_2 in aqueous $NaHCO_3$ solution and subsequent methyl ester formation using dimethyl sulfate provided α-hydroxy ester **8**. The hydroxl group of compound **8** was tosylated using *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine to give compound **9** as a crystal (mp 51-52 °C) in overall 81% yield from L-ascorbic acid. Conversion of compound **9** to epoxide **10** was achieved through reduction of the ester using *in situ* generated $Ca(BH_4)_2$ in ethanol followed by treatment of the resulting alcohol with methanolic KOH. Opening of the epoxide **10** with sodium azide in presence of methyl formate provided the azido alcohol **11** in excellent yield (95%) over two steps.[12] Reduction of the azide moiety of **11** using PPh_3 led to the formation of an aziridine, which was *in situ* protected through treatment with $(Boc)_2O$. Overall Boc-aziridine **12** was obtained in 95% total yield over two steps. As we have previously reported,[9m] this aziridine derivative can be opened with a variety of nucleophiles and for the purpose of



Scheme 2

obtaining inhibitors against aspartyl proteases such as HIV and β-secretase, it was opened with phenylmagnesium cuprate or thiophenoxide to provide **13** or **14** in 64% and quantitative yields, respectively. [9m,13]

Final conversion of the protected diols **13** and **14** to epoxides **4-6** have been carried out as depicted in Scheme 2. For the inversion of the secondary alcohol stereochemistry, the diol obtained from deprotection of **13** was treated with *p*-nitrobenzoyl chloride in presence of 2-picoline to selectively form the primary alcohol ester. The formation of 88% of mono(*p*-nitrobenzoyl)- and 12% di(*p*-nitrobenzoyl) esters was observed through HPLC analysis (UV, 259 nm). After the selective monobenzoylation, the remaining secondary alcohol was methanesulfonylated using methanesulfonyl chloride in presence of triethylamine in ethyl acetate. Liberation of the primary alcohol through saponification of the *p*-nitrobenzoate then led to epoxide **4** with inversion of the stereochemistry at the secondary alcohol site. The epoxide **4** was obtained as a white solid after recrystallization from isopropyl alcohol and water (mp 122-123 °C) in 69% overall yield from compound **13**.

Likewise, the preparation of the epoxide **5** was accomplished through the same sequence as used for **4**, yielding **5** as a white solid (mp 63-64 °C) in 53% overall yield from compound **12** after silica gel column chromatography. For the preparation of epoxide **6** with the retention of the secondary alcohol stereochemistry, the diol acetonide **13** was first deprotected with *p*-TsOH in aqueous methanol and the product alcohol was recrystallized in hexane to yield 90% of the alcohol. This alcohol was treated with *p*-TsCl in pyridine at −10 °C to selectively tosylate the primary alcohol (94% mono- and 6% ditosylation from HPLC analysis using UV detection at 259 nm) and treatment of the resulting primary alcohol tosylate with methanolic KOH led to the desired epoxide **6**. Since epoxide **6** was a low-melting solid (mp 48-49 °C), it was purified on a silica gel chromatographic column to give the desired epoxide **6** in 78% yield from the alcohol.

In summary, efficient synthetic routes were developed to prepare a sizable amount (4-15 grams) of the chiral epoxides **4-6**, which can be served as versatile intermediates for the synthesis of aspartyl protease inhibitors of therapeutic interest such as HIV protease and β-secretase. Through opening of the intermediate aziridine ring with either carbon or sulfur nucleophiles, they could be used for the synthesis of advanced intermediates for either saquinavir and amprenavir, or nelfinavir in the case of HIV PRI. The whole sequence is easily scalable since most of the compounds were obtained as crystals and the column chromatography was required only for the final low melting epoxides **5** and **6**. Medicinal chemistry research on aspartic proteases such as HIV PR and BACE can be facilitated through employing the key chiral epoxide intermediates.

Experimental

General. The NMR-spectra were measured with Bruker DPX-300 (300 MHz) spectrometers. Chemical shifts were measured as part per million (δ values) from tetramethylsilane as an internal standard at probe temperature in $CDCl_3$. Infrared spectra were obtained on a Bruker IR-IFs 45 and peaks were assigned in cm^{-1}. Low- and high-resolution mass spectra were recorded on a JMS AX 505WA spectrometer using FAB method. Ratios of mono- *vs.* di-esterification were determined using Hewlett Packard 1100 series HPLC with normal phase columns. Reactions requiring anhydrous conditions were carried out in flame-dried glassware under positive pressure of dry N_2 using standard syringe technique. TLC's were taken using silica gel 60F254 coated on aluminum sheet (E. Merck, Art. 5554). Column chromatography was performed on silica gel (Merck. 7734 or 9385 Kiesel gel 60)). All materials were obtained from commercial supplier and used without further purification.

Methyl-2-*O*-(*p*-toluenesulfonyl)-3,4-*O*-isopropylidene-L-threonate (9). To a solution of L-ascorbic acid (50.0 g, 284 mmol) and 2,2-dimethoxypropane (38.4 mL, 312 mmol) in dry acetone (200 mL) was slowly added concentrated H_2SO_4 (0.300 mL, 5.62 mmol) and the mixture was stirred for 5 h at 0 °C. To the reaction mixture was slowly added $NaHCO_3$ (71.5 g, 851 mmol) and H_2O (200 mL). Acetone was removed using rotary evaporator under reduced pressure and to the residue was slowly added 35% H_2O_2 (55.0 mL, 566 mmol) using a dropping funnel at rt. After stirring the mixture for 3 h, Na_2SO_3 (7.15 g, 56.7 mmol) was added and the mixture was stirred for 30 min. Then, $NaHCO_3$ (96.4 g, 1.14 mol) and dimethyl sulfate (112.8 mL, 1.19 mol) were added and the mixture was stirred for 5 h at 50 °C. The reaction mixture was filtered and the aqueous layer was extracted with CH_2Cl_2 (200 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give a colorless oil. To the residue in CH_2Cl_2 (58 mL) were slowly added pyridine (58 mL) and *p*-TsCl (53.3 g, 280 mmol) at 5 °C. After stirring for 3 h, the mixture was diluted with CH_2Cl_2 (200 mL) and washed with water (150 mL), 1 N HCl (150 mL), and water (150 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give a white solid (78.6 g, 81% yield): mp 51-52 °C; $[\alpha]_D^{22}$ +32.8 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3148, 2992, 2943, 1921, 1762, 1598, 1373, 1274, 1217, 1113, 1059, 956, 857, 734, 665; ^{1}H NMR (300 MHz, $CDCl_3$) 1.29 (s, 6 H), 2.44 (s, 3 H), 3.69 (s, 3 H), 3.96 (dd, *J* = 5.2, 9.0 Hz, 1 H), 4.04 (dd, *J* = 6.7, 9.0 Hz, 1 H), 4.48-4.42 (m, 2 H), 4.84 (d, *J* = 4.8 Hz, 1 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 7.83 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 21.5, 25.0, 25.8, 52.7, 65.0, 74.6, 76.58, 110.5, 128.1, 129.7, 132.9, 145.2, 166.8; HRMS (FAB) *m/z* calcd 345.1008 for $C_{15}H_{21}O_7S$ $[M + H]^+$, found 345.0999.

(2*R*,3*S*)-1-Azido-2-hydroxy-3,4-isopropylidenebutane-2,3,4-triol (11). To a solution of compound **9** (78.6 g, 228 mmol) in EtOH (400 mL) was slowly added $NaBH_4$ (8.62 g, 228 mmol) followed by $CaCl_2$ (12.6 g, 114 mmol) as a solution in EtOH (82 mL) at −5 °C. After the mixture was stirred for 3 h at 5 °C, the reaction temperature was brought

down to −5 °C and water (300 mL) was added. The reaction mixture was acidified to pH 6.5 by addition of acetic acid and it was extracted with CH_2Cl_2 (600 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (410 mL) and to it was added 85% technical grade KOH (18 g, 273 mmol). After stirring for 3 h at 10 °C, to the mixture was added methyl formate (14.0 mL, 228 mmol) and stirring continued for 30 min. To the mixture were added water (40 mL) and NaN_3 (36.9 g, 568 mmol) and stirring was continued for 6 h at 60 °C. Solvent was concentrated and the residue was partitioned between water (300 mL) and CH_2Cl_2 (300 mL). The aqueous layer was extracted with CH_2Cl_2 (300 mL × 2) and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give a pale yellow oil (40.6 g, 95%): $[\alpha]_D^{20}$ +6.9 (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}) 3439, 2989, 2933, 2096, 1648, 1448, 1370, 1260, 1154, 1067, 848, 793; ^{1}H NMR (300 MHz, $CDCl_3$) 1.34 (s, 3 H), 1.41 (s, 3 H), 2.72 (br, 1 H), 3.39 (dd, *J* = 6.6, 12.6 Hz, 1 H), 3.52 (dd, *J* = 3.2, 12.6 Hz, 1 H), 3.73-3.75 (m, 1 H), 3.92-4.09 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.3, 26.5, 53.9, 66.2, 71.4, 76.1, 109.5.

(2*R*,3*S*)-1,2-*O*-Isopropylidene-3,4-(*t*-butoxycarbonyl)-iminobutane-1,2-diol (12). To a solution of compound **11** (40.6 g, 217 mmol) in acetonitrile (800 mL) was added PPh_3 (56.9 g, 217 mmol) and the resulting mixture was stirred for 4 h at 40 °C. The reaction mixture was refluxed for 12 h, cooled to rt, and concentrated under reduced pressure. The residue was dissolved in water (200 mL) and 1,4-dioxane (200 mL), followed by the addition of $NaHCO_3$ (36.4 g, 433 mmol) and $(Boc)_2O$ (47.4 g, 217 mmol). After stirring for 1 h at 0 °C, the mixture was concentrated and diluted with *n*-hexane (250 mL). The organic layer was washed with water (250 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give a colorless oil (50.0 g, 95%): $[\alpha]_D^{20}$ −64.8 (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}) 3616, 3073, 2983, 2936, 1721, 1460, 1373, 1159, 1062, 997, 930, 850, 798, 511; ^{1}H NMR (300 MHz, $CDCl_3$) 1.35 (s, 3 H), 1.44 (s, 3 H), 1.46 (s, 9 H), 2.13 (d, *J* = 3.7 Hz, 1 H), 2.27 (d, *J* = 6.3 Hz, 1 H), 2.51-2.55 (m, 1 H), 3.81-3.87 (m, 1 H), 3.80-3.87 (m, 1 H), 4.03-4.09 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.4, 26.5, 27.7, 28.4, 38.1, 66.3, 75.0, 81.2, 109.6, 161.9; HRMS (CI) *m/z* calcd 244.1548 for $C_{12}H_{22}NO_4$ $[M + H]^+$, found 244.1547.

(2*R*,3*S*)-1,2-*O*-Isopropylidene-3-(*t*-butoxycarbonyl)-amino-4-phenybutane-1,2-diol (13). To a solution of compound **12** (50.5 g, 205 mmol) in toluene (308 mL) were slowly added $CuBr{\cdot}SMe_2$ (2.10 g, 10.2 mmol) and PhMgCl (154 mL, 2 M in THF) at −10 °C under nitrogen. After stirring for 1 h at −10 °C, the mixture was quenched with 10% aq NH_4Cl solution (330 mL) and the mixture was extracted with toluene (300 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give a white solid (42.2 g, 64%): mp 88-89 °C; $[\alpha]_D^{22}$ −39.1 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3373, 2977, 2888, 1685, 1523, 1453, 1370, 1323, 1254, 1218, 1163, 1075, 847, 755; ^{1}H NMR (300 MHz, $CDCl_3$) 1.34 (s, 3H), 1.42 (s, 9H), 1.48 (s, 3H), 2.81-2.97 (m, 1H), 3.65-3.70 (m, 1H), 3.84-3.94 (m, 1H), 4.08-4.13 (m, 1H), 4.81 (d, 1H), 7.20-7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.9, 26.3, 28.3, 39.5, 52.0, 66.2, 75.1, 79.4, 108.9, 126.4, 128.4, 129.4, 138.0, 155.4; HRMS (FAB) *m/z* calcd 322.2019 for $C_{18}H_{28}NO_4$ $[M + H]^+$, found 322.2020.

(2*S*,3*S*)-3-(*t*-Butoxycarbonyl)amino-1,2-epoxy-4-phenyl-butane (4). To a solution of compound **13** (26.2 g, 81.5 mmol) in H_2O (20 mL) and MeOH (180 mL) was added *p*-TsOH·H_2O (0.77 g, 4.07 mmol) and the mixture was stirred for 6 h at 50 °C. Then the reaction mixture was neutralized with K_2CO_3 (1.13 g, 8.15 mmol) and concentrated under reduced pressure. To the residue were added CH_2Cl_2 (110 mL) and 5% aq H_3PO_4 solution (50 mL). The organic layer was separated, washed with 5% aq H_3PO_4 solution (50 mL), 5% aq $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. *n*-Hexane (230 mL) was added to the residue and the mixture heated to 50 °C. After cooling to room temperature, a white precipitate (20.6 g, 90% yield) was formed and collected through filtration. To a solution of the solid (20.0 g, 71.1 mmol) in ethyl acetate (130 mL) were slowly added 2-picoline (9.20 mL, 92.4 mmol) and *p*-nitrobenzoyl chloride (15.8 g, 85.3 mmol) at 0 °C. After stirring for 12 h at 5 °C, MsCl (6.60 mL, 85.3 mmol) and triethylamine (23.8 mL, 170.6 mmol) were slowly added to the mixture. Stirring was continued for 2 h and the mixture was washed with 1 N aq HCl solution (100 mL), 5% aq $NaHCO_3$ solution (100 mL) and water (100 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. To the residue in CH_2Cl_2 (100 mL) was added dropwise a solution of KOH (85%, 5.20 g, 78.2 mmol) in methanol (19.8 mL) at 0 °C. After stirring for 2 h at rt, water (100 mL) was added to the mixture and the organic layer was washed with H_2O (100 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The desired product was recrystallized from *i*-propyl alcohol and water to give a white solid (13.0 g, 69% yield): mp 122-123 °C; $[\alpha]_D^{22}$ +6.7 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3377, 3055, 2982, 2934, 1682, 1519, 1454, 1360, 1248, 1168, 1027, 926, 848, 745, 603; ^{1}H NMR (300 MHz, $CDCl_3$) 1.40 (s, 9H), 2.75-3.02 (m, 5H), 3.68-3.73 (m, 1H), 4.49 (br, 1H), 7.23-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.3, 37.6, 46.8, 52.7, 53.2, 79.6, 126.4, 128.5, 129.4, 136.7, 155.2; HRMS (FAB) *m/z* calcd 264.1600 for $C_{15}H_{22}NO_3$ $[M + H]^+$, found 264.1606.

(2*R*,3*S*)-3-(*t*-Butoxycarbonyl)amino-1,2-epoxy-4-phenyl-butane (6). To a solution of compound **13** (26.2 g, 81.5 mmol) in H_2O (20 mL) and MeOH (180 mL) was added *p*-TsOH·H_2O (0.77 g, 4.07 mmol) and the mixture was stirred for 6 h at 50 °C. Then the reaction mixture was neutralized with K_2CO_3 (1.13 g, 8.15 mmol) and concentrated under reduced pressure. To the residue were added CH_2Cl_2 (110 mL) and 5% H_3PO_4 (50 mL). The organic layer was separated, washed with 5% H_3PO_4 (50 mL), 5% $NaHCO_3$ (50 mL), dried over anhydrous $MgSO_4$, filtered and the

filtrate was concentrated under reduced pressure. *n*-Hexane (230 mL) was added and the mixture heated to 50 °C. After cooling to room temperature, a white precipitate was formed and collected through filtration (20.6 g, 90%). To a solution of the residue (20.0 g, 71.1 mmol) in pyridine (40 mL) was added dropwise a solution of *p*-TsCl (15.2g, 78.2 mmol) in pyridine (15 mL) at −5 °C . After stirring at −10 °C for 24 h, the mixture was treated with dropwise addition of H_2O (40 mL) over 30 min, maintaining the internal temperature between 5 and −10 °C . After stirring at this temperature for 15 min, CH_2Cl_2 (100 mL) was added. The organic layer was separated, and to it was added dropwise 85% KOH (5.60 g, 85.3 mmol) in methanol (19.7 mL) at 0 °C and the resulting mixture was stirred for 1 h at that temperature. The mixture was washed with H_2O (40 mL × 2), dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified on column chromatography to give compound **6** as a white solid (14.6 g, 78%): mp 48-49 °C; $[\alpha]_D^{21}$ +4.1 (*c* 2.0, $CHCl_3$); IR (KBr, cm^{-1}) 3389, 2934, 1943, 1697, 1516, 1394, 1157, 1023, 974, 848, 745, 603; ^{1}H NMR (300 MHz, $CDCl_3$) 1.41 (s, 9H), 2.60-2.62 (m, 1H), 2.69-2.72 (m, 1H), 2.89-3.04 (m, 3H), 4.14 (br, 1H), 4.50 (br, 1H), 7.22-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.2, 39.7, 44.4, 50.5, 52.5, 79.4, 126.5, 128.4, 129.3, 137.3, 155.3; HRMS (FAB) *m/z* calcd 264.1600 for $C_{15}H_{22}NO_3$ $[M + H]^+$, found 264.1599.

(2*S*,3*R*)-(1-Oxiranyl-2-phenylsulfanylethyl)carbamic acid tert-butyl ester (5). To a suspension of NaH (4.16 g, 173 mmol) in THF (200 mL) was slowly added PhSH (17.8 mL, 173 mmol) at 0 °C under nitrogen. After stirring at rt for 30 min, compound **12** (38.3 g, 157 mmol) as a solution in THF (180 mL) was added to the mixture and the resulting mixture was stirred for 2 h at rt. The reaction mixture was concentrated under reduced pressure and partitioned between water (300 mL) and CH_2Cl_2 (300 mL). The aqueous layer was extracted with CH_2Cl_2 (300 mL × 2) and the combined organic layer was concentrated under reduced pressure. To the residue dissolved in MeOH (315 mL) and water (45 mL) was added *p*-TsOH·H_2O (1.50 g, 7.85 mmol). The mixture was stirred at 50 °C for 12 h and neutralized with K_2CO_3 (2.18 g, 15.8 mmol). Water (250 mL) was added to the mixture and the resulting mxiture was extracted with EtOAc (250 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. *n*-Hexane (50 mL) was added and the mixture heated to 50 °C. After cooling to room temperature, a white precipitate (35.6 g, 114 mmol) was formed and collected through filtration. To a solution of solid (8.00 g, 25.5 mmol) in ethyl acetate (64 mL) were slowly added 2-picoline (3.3 mL, 33.2 mmol) and *p*-nitrobenzoyl chloride (5.7 g, 30.6 mmol) at 0 °C. The mixture was stirred for 7 h at 5 °C and to it were slowly added MsCl (2.4 mL, 30.6 mmol) and TEA (8.5 mL, 61.3 mmol). After stirring for 2 h, the mixture was washed successively with 1 N aq HCl solution (48 mL), 5% aq $NaHCO_3$ solution (48 mL) and water (48 mL). Charcoal was added, and the mixture was refluxed for 1 h, filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (115 mL) and 85% KOH (3.71g, 56.2 mmol) as a solution in 28 mL of H_2O. After stirring for 2 h at rt, water was added to the mixture (180 mL) and the mixture was extracted with toluene (180 mL). The organic layer was washed with water (180 mL) and 5% aq $NaHCO_3$ solution (180 mL). It was concentrated and the residue was purified on column chromatography to give compound **5** as a white solid (4.0 g, 53.1%): mp 63-64 °C; $[\alpha]_D^{22}$ –24.8 (*c* 0.9, $CHCl_3$); IR (KBr, cm^{-1}) 3388, 2982, 1714, 1501, 1370, 1327, 1239, 1166, 1019, 927, 864, 749; ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (s, 9H), 2.76-2.79 (m, 2H), 2.97-3.01 (m, 1H), 3.18-3.26 (m, 2H), 3.63 (br, 1H), 4.92 (br, 1H), 7.21-7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.7, 36.7, 47.2, 52.3, 53.2, 80.3, 127.1, 129.5, 130.3, 135.9, 155.6; HRMS (FAB) *m/z* calcd 295.1243 for $C_{15}H_{21}NO_3S$ $[M]^+$, found 295.1252.

Acknowledgments. We thank the ST Pharm Co., Ltd. for generous financial support. BMK thanks support from the National Research Foundation of Korea (NRF), the Ministry of Education, Science and Technology (2009-0073645).

References

1. Flexner, C. *New Eng. J. Med.* **1998**, *338*, 1281-1292.
2. For reviews on the development of HIV PR inhibitors, see: (a) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305. (b) Meek, T. D. *J. Enz. Inhib* **1992**, *5*, 65. (c) Wlodwer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, 543. (d) Martin, J. A. *Antiviral Research* **1992**, *17*, 265. (e) Tomasselli, A. G.; Heinrikson, R. L. *Biochim. Biophys. Acta* **2000**, 189.
3. (a) Czarnocki, Z.; Mieczkowski, J. B.; Ziólkowski, M. *Tetrahedron: Asymm.* **1996**, *7*, 2711. (b) Le Merrer, Y.; Gravier-Pelletier, C.; Gerrouache, M.; Jean-Claude Depezay, J. *Tetrahedron Lett.* **1998**, *39*, 385. (c) Thopate, S. R.; Kulkarni, M. G.; Puranik, V. G. *Angew. Chem. Int. Ed*. **2000**, *39*, 4573. (d) Bond, S.; Perlmutter, P. *Tetrahedron* **2002**, *58*, 1779. (e) Wróblewski, A. E.; Gowacka, I. E. *Tetrahedron: Asymm.* **2002**, *13*, 989. (f) Paquette, L. A.; Chang, J.; Liu, Z. *J. Org. Chem.* **2004**, *69*, 6441. (g) Ishikawa, T.; Ishii, H.; Shimizu, K.; Nakao, H.; Jin Urano, J.; Kudo, T.; Saito, S. *J. Org. Chem.* **2004**, *69*, 8133.
4. For papers on the synthesis and clinical trials of HIV PR inhibitors, see: (a) Dorsey, D. D.; Levi, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Azel, M. G.; Ostovic, D.; Anderson, P. S.; Hu, J. R. *J. Med. Chem*. **1994**, *34*, 3443. (b) Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavanoda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Kong, X.-P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H.; Robin, T.; Srewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W. *Proc. Natl. Acad. Sci.: U.S.A*. **1995**, *92*, 2484. (c) Sham, H. L.; Kempf, D. J.; Molla, A.; Marsh, K. C.; Kumar, G. N.; Chen, C. M.; Kati, W.; Stewart, K.; Lal, R.; Hsu, A.; Betebenner, D.; Korneyeva, M.; Vasavanonda, S.; McDonald, E.; Saldivar, A.; Wideburg, N.; Chen, X.; Niu, P.; Park, C.; Jayanti, V.; Grabowski, B.; Granneman, G. R.; Sun, E.; Japour, A. J.; Norbeck, D. W. *Antimicrob. Agents Chemother*. **1998**, *42*, 3218. (d) Thaisrivongs, S.; Skulnick, H. I.; Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Johnson, P. D.; Aristo, P. A.; Judge, T. M.; Gammill, R. B.; Morris, J. K.; Romaines, K. A.; Chrusciel, R. A.; Hinshaw, R. R.; Chong, K.-T.; Tarpley, W. G.; Poppe, S. M.; Slade, D. E.; Lynn, J. C.; Hog, M.-M.; Tomich, P. K.; Seest, E. P.; Dolak, L. A.; Howe,

W. J.; Howard, G. M.; Schwende, F. J.; Toth, L. N.; Padbury, G. E.; Wilson, G. J.; Shiou, L.; Zipp, G. L.; Wilkinson, K. F.; Rush, B. D.; Ruwart, M. J.; Koeplinger, K. A.; Zhao, Z.; Cole, S.; Zaya, R. M.; Kakuk, T. J.; Janakiraman, M. N.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 4349. (e) Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. Kynostatin. *Chem. Pharm. Bull*. **1992**, *40*, 2251. (f) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; DeLucca, G. V.; Eyerma, C. J.; Chang, C.-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P. N.; McHugh, R. J.; Han, Q.; Li, R.; Markwalder, J. A.; Seitz, S. P.; Sharpe, T. R.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winsloe, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. *J. Med. Chem*. **1996**, *39*, 3514. (g) Bold, G.; Fassler, A.; Capraro, H.-G.; Cozens, R.; Klimkait Lazdins, J.; Mestan, J.; Poncioni, B.; Rosel, J.; Stover, D.; Tintelnot-Blomley, M.; Acemoglu, F.; Beck, W.; Boss, E.; Eschbach, M.; Hurlimann, T.; Masso, E.; Roussel, S.; Ucci-Stoll, K.; Wyss, D.; Lang, M. *J. Med. Chem*. **1998**, *41*, 3387.

5. Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galphin, S. A.; Handa, B. K.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358.
6. Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 1181.
7. Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.
8. For the definition and various structures of HIV PR transition state isosteres, see reference 2.
9. (a) Ghosh, A. K.; McKee, S. P.; Lee, H. Y.; Thompson, W. J. *Chem. Commun.* **1993**, 273. (b) Parkes, K. E. B.; Bushnell, D. J.; Cracjeff, P. H.; Dunsdon, S. J. Freeman, A. C.; Gunn, M. P.; Popkins, R. A.; Lambert, R. W.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656. (c) Gurjar, M. K.; Devi, N. R. *Tetrahedron: Asymm.* **1994**, *5*, 755. (d) Beaulieu, P. L.; Wernic, D. *J. Org. Chem*. **1996**, *61*, 3635. (e) Shibata, N.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 619. (f) Beaulieu, P. L.; Lavallée, P.; Abraham, A.; Anderson, P. C.; Boucher, C.; Bousquet, Y.; Duceppe, J. S.; Gillard, J.; Gorys, V.; Grand-Maître, C.; Grenier, L.; Guindon, Y.; Guse, I.; Plamondon, L.; Soucy, F.; Valois, S.; Wernic, D.; Yoakim, C. *J. Org. Chem.* **1997**, *62*, 3440. (g) Rieger, D. L. *J. Org. Chem.* **1997**, *62*, 8546. (h) Ghosh, A. K.; Fidanz, S. *J. Org. Chem.* **1998**, *63*, 6146. (i) Corey, E. J.; Zhang, F. Y. *Angew. Chem. Int. Ed*. **1999**, *38*, 1931. (j) Inaba, T.; Yamada, Y.; Abe, H.; Sagawa, S.; Cho, H. *J. Org. Chem.* **2000**, *65*, 1623. (k) Zook, S. E.; Busse, J. K.; Borer, B. C. *Tetrahdron Lett.* **2000**, *41*, 7017. (l) Tamamura, H.; Hori, T.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 577. (m) Kim, B. M.; Bae, S. J.; So, S. M.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. S. *Org. Lett*. **2001**, *3*, 2349.
10. (a) John, V.; Tung, J.; Fang, L.; Mamo, S. S. WO 00/077030, 2000. (b) Hom, R.; Mamo, S.; Tung, J.; Gailunas, A.; John, V.; Fang, L. WO 01/070672, 2001. (c) Fang, L. Y.; Hom, R.; John, V.; Maillaird, M. WO 02/002505, 2002. (d) Fang, L. Y.; John, V. WO 02/002506, 2002. (e) Maillaird, M.; Hom, R.; Gailunas, A.; Jagodzinska, B.; Fang, L.Y.; John, V.; Freskos, J. N.; Pulley, S. R.; Beck, J. P.; TenBrink, R. E. WO 02/002512, 2002. (f) Beck, J. P.; Gailunas, A.; Hom, R.; Jagodzinska, B.; John, V.; Maillaird, M. WO 02/002520, 2002. (g) Schostarez, H.; Chrusciel, R. A.; Centko, R. S. WO 02/094768, 2002. (h) Freskos, J. N.; Aquino, J.; Brown, D. L.; Fang, L.; Fobian, Y. M.; Gailunas, A.; Guinn, A.; John, V.; Romero, A. G.; Tucker, J.; Tung, J.; Walker, D. WO 02/098849, 2002. (i) Pulley, S. R.; Beck, J. P.; TenBrink, R. E.; Jacobs, J. S. WO 02/100399, 2002. (j) Schostarez, H. J.; Chrusciel, R. A. WO 02/100818, 2002. (k) Maillaird, M.; Tucker, J. A. WO 02/100820, 2002. (l) Pulley, S. R.; Beck, J. P.; TenBrink, R. E. WO 02/100856, 2002. (m) John, V.; Hom, R.; Tucker, J. WO 03/002122, 2003. (n) Schostarez, H. J.; Chrusciel, R. A. WO 03/006013, 2003. (o) Schostarez, H. J.; Chrusciel, R. A. WO 03/006021, 2003. (p) Gailunas, A.; Hom, R.; John, V.; Maillard, M.; Chrusciel, R. A.; Fisher, J.; Jacobs, J.; Freskos, J. N.; Brown, D. L.; Fobian, Y. M. WO 03/006423, 2003. (q) Schostarez, J. H.; Chrusciel, R. A. WO 03/006453, 2003. (r) Gailunas, A.; Tucker, J. A.; John, V. WO 03/027068, 2003. (s) Fisher, J. F.; Jacobs, J. S.; Sherer, B. A. WO 03/029169, 2003. (t) Tang, J. N.; Koelsch, G.; Ghosh, A. K. WO 02/53594, 2002. (u) Tang, J. J. N.; Hong, L.; Ghosh, A. K. WO 01/00665, 2001.
11. (a) Wei, C. C.; de Bernardo, S.; Tengi, J. P.; Borgese, J.; Weigele, M. *J. Org. Chem*. **1985**, *50*, 3462. (b) Merrer, Y. L.; Pelletier, C. G.; Dumas, J.; Depezay, J. C. *Tetrahedron Lett*. **1990**, *31*, 1003. (c) Kim, K. S.; Cho, I. H.; Ahn, Y. H.; Park, J. I. *J. Chem. Soc. Perkin Trans*. *1* **1995**, 1783. (d) Andre, C.; Bolte, J.; Demuynck, C. *Tetrahedron: Asymm*. **1998**, *9*, 1359.
12. (a) Saito, S.; Yamashita, S.; Nishikawa, T.; Yokoyama, Y. *Tetrahedron Lett*. **1989**, *30*, 4153. (b) Saito, S.; Nishikawa, T.; Yokoyama, Y.; Moriwake, T. *Tetrahedron Lett*. **1990**, *31*, 221.
13. (a) Kang, S. H.; Ryu, D. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2959. (b) Remuzon, P.; Dussy, C.; Jacquet, J. P.; Roty, P.; Bouzard, D. *Tetrahedron: Asymm*. **1996**, *7*, 1181. (c) Kang, S. H.; Ryu, D. H. *Bull. Korean Chem. Soc*. **1996**, *17*, 219. (d) Kang, S. H.; Choi, H. W. *Bull. Korean Chem. Soc*. **1996**, *17*, 219. (e) Inaba, T.; Yamada, Y.; Abe, H.; Sagawa, S.; Cho, H. *J. Org. Chem*. **2000**, *65*, 1623.