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Diastereoselective synthesis of (3r, 3as, 6ar)-hexahydrofuro [2, 3-*b*] furan-3-Yl (2r, 3r)-4-(4-amino-*N*-isobutylphenylsulfo- namido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (diastereomer of darunavir)

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ABSTRACT

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl(2S,3S)-4-(4-amino-N-isobutylphenylsulfonamido) -3-hydroxy-1-phenylbutan-2-ylcarbamate ***4*** *was synthesised from 4-amino-N-((2S,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzenesulfo- namide* ***3*** *via N-protected amino alcohol intermeidate* ***2*** *while (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yloxy)carbonyloxy)-1-phenylbutan-2-yl carbamate* ***6*** *was prepared from (3R, 3aS, 6aR)-hexahydrofuro [2, 3-b] furan-3-yl 4-nitrophenyl carbonate* ***3a****. The desired drug* ***4*** *was obtained with 99 % diastereoselectivity. The spectroscopic analyses performed by NMR, LCMS, UV–Vis, SOR and FT-IR.*

Key words: (R, S) – Epoxide, diastereo selectivity, enantioselctivity, bis-THF phenyl carbonate, protease inhibitors.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a chronic, lifethreatening condition caused by the human immunodeficiency virus (HIV). By damaging or destroying the cells of the immune system, HIV interferes with the body's ability to fight effectively against viruses, bacteria and fungi that cause the disease. The introduction of highly active antiretroviral therapy (HAART) in 1996, in combination with HIV-1 protease inhibitors and reverse transcriptase inhibitors has dramatically changed the management of HIV/AIDS [1]. HIV protease inhibitors are important components of the current drug regimens to treat HIV infection. Protease inhibitors interrupt HIV replication at a later stage in its life cycle by interfering with an enzyme known as HIV protease [2]. The introduction of innovative therapeutic treatments and regimens often changes the impact of disease. HIV-1 protease inhibitors are the most potent anti-AIDS drugs reported to

date and are essential components of highly active antiretroviral therapy (HAART) [3,4,5]. Anti-AIDS chemotherapy based on HIV-1 protease and reverse-transcriptase inhibitors has been remarkably successful in decreasing the mortality rates in HIV-infected patients. HIV PR inhibitors such as darunavir [6], saquinavir [7], amprenavir [8], nelfinavir [9], indinavir [10] and atazanavir [11] all belong to the HEA class of inhibitors [12], and there are many reports on the synthesis of this class of inhibitors [13]. HIV-1 protease plays a critical role in the virus life cycle by processing the viral Gag and Gag-Pol polyproteins into structural and functional proteins essential for viral maturation.

These therapies have significantly improved the course of HIV management and halted the progression of AIDS. However, the majority of protease inhibitors contains substantial peptide-like features and as a result possesses the traditional problems of peptide-based drugs. However, under the selective pressure of drug therapy, the emergence of many viable multidrug resistant (MDR) protease variants is posing a great challenge to the efficacy of currently available protease inhibitors [14, 15].

Due to the emergence of drug resistance, scientists have made significant efforts to develop exceedingly potent inhibitors with excellent resistance profiles. The advent of HAART has significantly reduced morbidity and mortality and has improved the quality of life for HIV-infected patients, particularly in developed nations [16]. Despite this important breakthrough, current and future management of HIV/AIDS is being challenged by the rapid emergence of multi-drug-resistant HIV-1 strains and drug-related side effects [17]. Consequently, developments of novel and effective treatment regimens are critically important.

Our goal was to achieve an efficient synthesis of the diastereomer **4** in high diastereomeric purity through diastereoselective synthesis by employing solvent free conditions as shown in Scheme 1, step 1, two stereocenters chirality needs to be controlled. The nitro group was reduced to amino group in step 2 without reducing other reducible groups, further deprotectin of amino moiety is also a sensitive reaction. The final step (Scheme 1) was performed in non-nucleophilic mild base solvent was used to get the optically pure diastereomer **4**. In Scheme 2, the synthesis of **6** was accomplished by reacting with excess of (3R, 3aS, 6aR)-hexahydrofuro [2, 3-b] furan-3-yl 4-nitrophenyl carbonate **3a**. Herein, we report our efforts on this synthetic strategy and ultimately achieved a relatively short synthesis with high diastereo- and enantioselectivities for **4** and **6**.

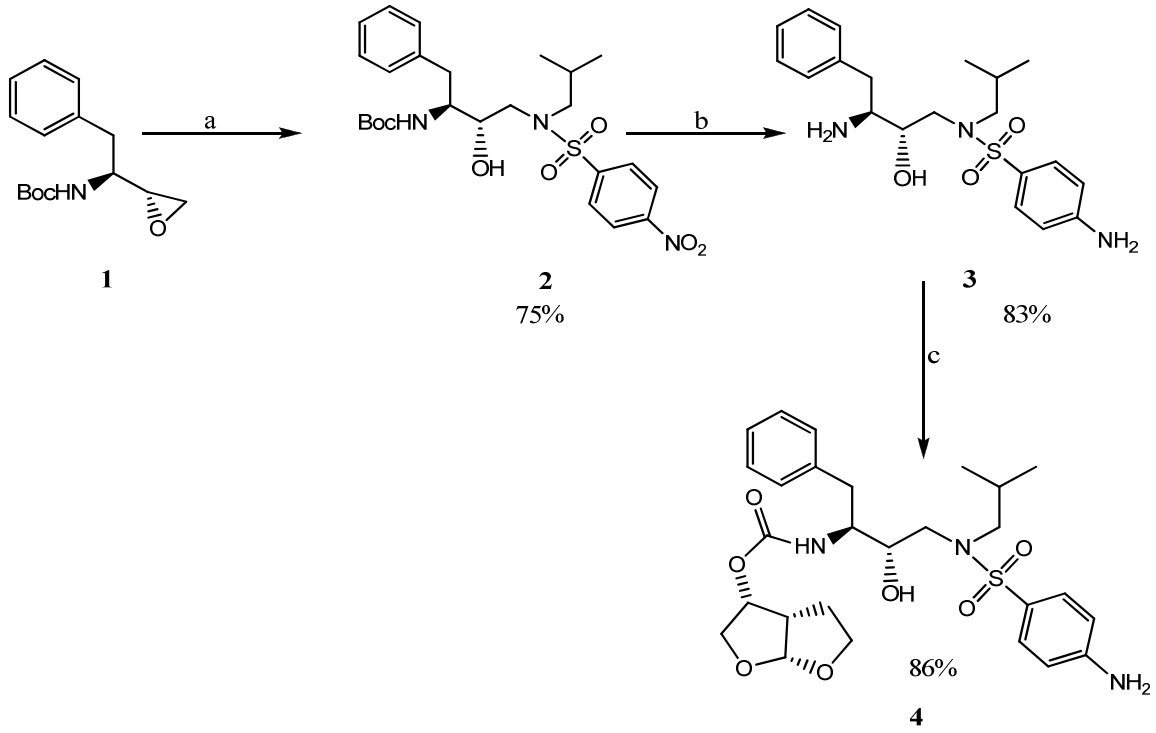
RESULTS AND DISCUSSION

For the past several years, we have been interested in designing a simple and an efficient asymmetric synthesis for various bioactive target compounds, which remains a challenging area, despite impressive progress in organic synthesis. To this end, we have extensively used inexpensive and easily accessible (R, S)-epoxide **1** as a versatile chiral template. A diastereoselective approach, combining these methodologies may often provide easy access to the target compounds, as is illustrated in this paper for the syntheses of the title compound **4**.

As shown in Scheme 1, ring opening of (R, S)-epoxide is an important method for obtaining 1, 3-amino alcohol. It is a highly diastereoselective ring opening reaction. This is accomplished by using isobutyl amine under solvent free conditions. Typically the products are obtained with varying levels of cleavage products due to the forcing conditions required. To develop a scalable

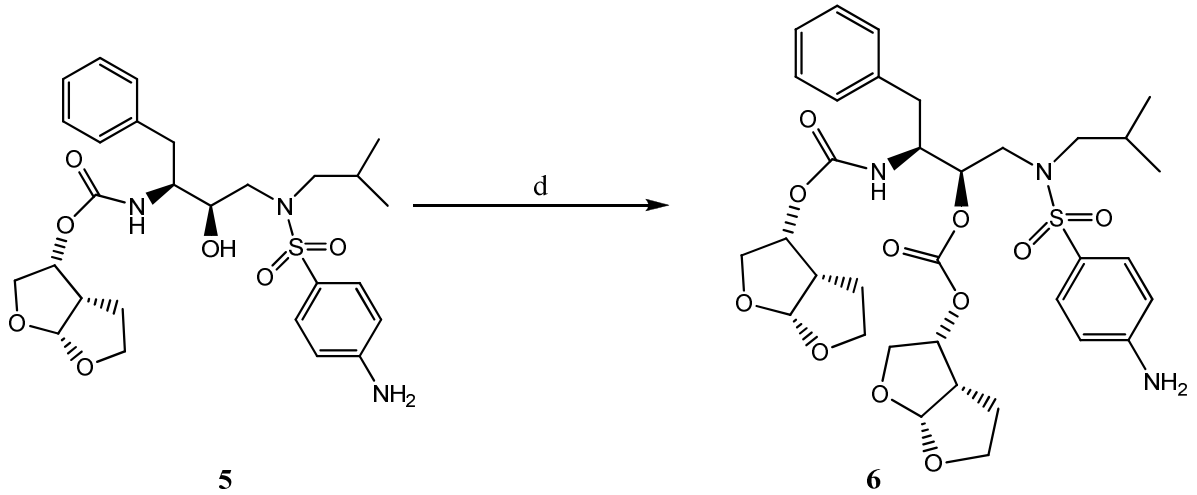
synthesis of the HIV protease inhibitor, optically active darunavir diastereomer **4** [18, 19], a practical method of obtaining the diamino alcohol **3** [19, 22] was required. Previously, some groups have reported on the preparation of **2** [19, 20, 21] by a sequential reduction of the nitro group using a 10 % palladium carbon, followed by treatment with concentrated hydrochloric acid to deprotect the aliphatic amino group. In this paper, we report on the optimization of conditions to obtain improved diastereoselectivity for the reduction of the readily available amino alcohol **3**. [19, 22]

As shown in Scheme 2, enantiomerically pure darunavir **5** an active pharmaceutical ingredient (API) was taken and treated with optically active, enantiomerically pure (3R, 3aS, 6aR)-hexahydrofuro [2, 3-b] furan-3-yl 4-nitrophenyl carbonate in presence of triethylamine (TEA) and N-methyl 2-pyrrolidone without any change in chirality of the substrate to obtain the optically active enantiomerically pure (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (2S,3R) -4-(4-amino-N-isobutylphenylsulfonamido)-3-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yloxy) carbonyloxy)-1-phenylbutan-2-ylcarbamate **6**.[6]



(a). Isobutyl amine, p-nitro benzene sulfonylchloride, TEA, MDC, reflux, 75% (b). 10 % Pd/C, tri ethanol amine, conc. HCl, reflux, 83% (c). N-methyl pyrrolidone, (3R, 3aS, 6aR)-hexahydrofuro [2, 3-b]furan-3-yl 4-nitrophenyl carbonate, rt, 8 h, 86%.

Scheme 1



5 **6**

(d). N-methyl-2-pyrrolidone, (3R, 3aS, 6aR)-hexahydrofuro [2,3-b]furan-3-yl 4-nitrophenyl carbonate **3a,** TEA, 45 °C, 72 h, 70 %

Scheme 2

MATERIALS AND METHODS

General

General information: Chemicals were procured from Sigma-Aldrich, Merck and Lancaster, and used as such without further purification. Melting points (m.p.) were determined using a calibrated thermometer by Buchi Melting Point apparatus B-545. They expressed in degrees centigrade (°C) and are uncorrected. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence lamp. Silica gel (particle size 100-200 mesh) was used for chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. ^{1}H NMR spectra were reported using Me_4Si (δ 0.0 ppm) as internal standard. ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm) and DMSO-d_6 (δ 48.5 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and are reported in wave numbers (cm^{-1}). Optical rotations (in degrees, °) were recorded in methanol on a Perkin-Elmer Model 241 polarimeter at the sodium D line. LC mass spectra were recorded on a Jeol SX 102 DA / 600 Mass spectrometer.

Synthesis of tert-butyl (2S, 3S)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfona- mido)-1-phenylbutan-2-ylcarbamate ***(2)*** [19, 20, 21].

To a stirred solution of *tert*-butyl (S)-1-((R)-oxiran-2-yl)-2-phenylethylcarbamate (**1**) (5 g, 0.0190 mol), isobutyl amine (15 g, 0.2050 mol) was added at 30 °C, the resulting mixture was refluxed for 3 h, reaction progress was monitored by TLC (hexane: ethyl acetate, 7:3), excess isobutyl amine was completely removed under reduced pressure at 65 °C, white colored solid was obtained. It was taken into methylene dichloride (50 mL), triethylamine (2.5 g, 0.0247 mol) was added, the resulting mixture was heated to reflux, p-nitro benzenesulfonyl chloride (4.4 g, 0.0198 mol) in methylene dichloride (25 mL) was added to the reaction mixture at 40 °C during 1 h, resulting reaction mixture was stirred for 2 h. Reaction progress was monitored by TLC (hexane: ethyl acetate, 7:3), then the reaction mixture was cooled to room temperature, washed with DM water, the organic layer was concentrated in vacuo, finally recrystallised from

isopropyl alcohol to obtain white colored solid (**2**) (7.5 g, 75 %): mp 175-180 ºC; R_f 0.42; (hexanes: ethyl acetate, 7:3 v/v):

IR (KBr). 3376, 2966, 2931, 1675, 1609, 1543, 1524, 1530, 1351, 1249, 1158, 1087, 1023, 985, 853, 793, 740, 608, 557 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6**)** δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.14-7.29 (m, 5H), 6.56 (d, *J* = 8.8 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 1H), 3.62 (s, 2H), 3.57 (s, 1H), 3.07-3.32 (m, 3H), 2.91-2.96 (m, 1H), 2.72-2.77 (m, 1H), 1.87-1.90 (m, 1H), 1.25 (s, 9H), 0.83 (d, *J* = 7.2 Hz, 6H) ppm. $[\alpha]_D^{25}$ = -25.9° (*c* = 1 in $CHCl_3$). LCMS (m/z): 522 $[M+H]^+$.

Synthesis of 4-amino-N-((2S,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-benzene sulfonamide ***(3)*** [19, 22].

Catalytic amount of triethanol amine was added to tert (2S, 3S)-3-hydroxy-4-(N-isobutyl-4-nitro-phenylsulfo namido)-1-phenylbutan-2-ylcarbamate **(2) (**6.5 g, 0.0124 mol) and 10 % palladium on charcoal was suspended in methanol and kept in an autoclave, rendered inert and evacuated. At an inside temperature of 45 °C, about three equivalents of hydrogen were added at over 6 kg/cm^3 pressure during 1 h, then catalyst was removed by filtration. Concentrated HCl (4.1 mL) was added to the filtrate at room temperature and heated to reflux for 2 h. After complete conversion, reaction mixture P^H was adjusted to 9.5 with 20 % NaOH solution, most of the methanol was removed by distillation to get the crude product finally recrystallised from a mixture of isopropyl alcohol and DM water. The process yielded 4 g (83 %) of an off-white powder **3**. mp 168-170 ºC; R_f 0.5; (methylenedichloride: methanol, 9:1 v/v): IR (KBr). 3493, 3394, 3205, 2929, 1691, 1603, 1521, 1448, 1367, 1325, 1251, 1173, 1018, 978, 849, 753, 700, 618 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6**)** δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.16-7.29 (m, 5H), 6.61 (d, *J* = 8.4 Hz, 2H), 5.95 (s, 2H), 4.62 (d, *J* = 5.2 Hz, 1H), 3.49 (br s, 1H), 3.31-3.38 (m, 1H), 2.69-2.91 (m, 5H), 2.91 (s, 1H), 2.33-2.36 (t,1H), 1.91-1.95 (t, 1H), 1.22 (br s, 2H), 0.79- 0.83 (m, 6H) ppm. $[\alpha]_D^{25}$ = +8.2° (*c* = 1 in $CHCl_3$). LCMS (m/z): 392 $[M+H]^+$.

Synthesis of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3S)-4-(4-amino-N-isobuty- phenylsulfon amido)-3-hydroxy-1-phenylbutan-2-ylcarbamate ***(4)*** [18,19].

(3R, 3aS, 6aR)-Hexahydrofuro [2,3-b]furan-3-yl 4-nitrophenyl carbonate **(3a)** (2.26 g, .0076 mol) in N-methyl-2-pyrrolidone (6 mL) was added to a solution of 4-amino-N-((2S,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl benzenesulfonamide **(3)** (3 g, 0.0076 mol) and N-methyl-2-pyrrolidone (9 mL) at 0°C during 1 h, the resulting mixture was heated to room temperature and stirred for 8 h. After completion of the reaction, monitored by HPLC, quenched into mixture of DM water (15 mL) and ethyl acetate (30 mL). Aqueous layer was extracted with ethyl acetate, both organic layers were mixed and washed with 10 % Na_2CO_3 solution (2x15 mL) followed by 10 % NaCl solution (15 mL), organic layer was dried over Na_2SO_4 and concentrated in vacuo to get the off-white colored residue with 95 % HPLC purity. It was purified by column chromatography by eluting with 5% methanol in methylene dichloride, concentrated in a rotary evaporator to get off-white crystals of **4** (3.6 g, 86 %) with 99% HPLC purity. mp 83-85 ºC; IR (KBr): 3454, 3372, 3063, 3029, 2961, 2931, 2873, 1708, 1632, 1597, 1504, 1456, 1368, 1317, 1259, 1148, 1090, 1020, 832, 777, 748, 702, 672 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6**)** δ 7.36 (d, *J* = 8.7 Hz, 2H), 7.13-7.26 (m, 2H), 7.13-7.26 (m, 2H), 7.13-7.26 (m, 1H), 7.09 (d, *J*= 9.0 Hz, 1H), 6.59 (d, *J* = 8.7 Hz, 2H), 5.95 (br s, 2H), 5.53 (d, *J* = 10.2 Hz, 1H), 4.87-4.93 (m, 1H) 4.87-4.93 (m, 1H), 3.85-3.90 (dd, *J* = 9.3 and 6.0 Hz, 1H) 3.56-3.79 (m, 1H),

3.56-3.79 (m, 1H), 3.56-3.79 (m, 1H), 3.56-3.79 (m, 1H), 3.19-3.23 (m, 1H), 2.56-2.89 (m, 2H), 2.56-2.89 (m, 2H), 2.56-2.89 (m, 1H), 2.55-2.89 (m, 1H), 1.83-1.87 (m, 1H), 1.46-1.53 (m, 2H), 0.80 (d, *J* = 6.6 Hz, 6H), 0.76 (d, *J* = 6.6 Hz, 6H) ppm. ^{13}C NMR: 155.2, 152.6, 139.2, 129.0, 128.8, 127.9, 125.8, 124.0, 112.6, 108.7, 72.3, 70.5, 70.4, 68.8, 56.6, 55.8, 51.6, 44.9, 35.8, 26.2, 25.5, 19.9, 19.96. $[\alpha]_D^{25}$ = -30.38° (*c* = 1 in $CHCl_3$). LC-MSD: 570 $[M+Na]^+$, 548 $[M+H]^+$, 435, 391, 320, 241.

The diastereomeric excess (%*de*) was determined to be 99% by HPLC using Intersil ODS 3V 250*4.6 5 µm column (30% ethanol/ hexane + 1 mL diethyl amine, 1 mL/min, 265 nm): t_R (minor, 22.84 min), t_R (major, 22.89 min).

*Synthesis of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3R)-4-(4-amino-N-isobutyl- phenylsulfon amido)-3-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yloxy) carbonyloxy)-1-phenylbutan-2-ylcarbamate **(6)*** [19].

(3R, 3aS, 6aR)-Hexahydrofuro [2,3-b]furan-3-yl 4-nitrophenyl carbonate **3a** (7.54 g, 0.0255 mol) in N-methyl 2-pyrrolidone was added to a solution of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3R)-4-(4-amino-N-isobutylphenyl sulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (**5**) (5 g, 0.0091mol) in N-methyl-2-pyrrolidone (25 mL) at 0°C during 1 h in presence of triethylamine(1.83 g, 0.0183 mol). The resulting mixture was raised to 45 °C and stirred for 72 h. The reaction progress was monitored by HPLC, quenched into mixture of DM water (25 mL) and ethyl acetate (50 mL), further, aqueous layer was extracted with ethyl acetate (25 mL), both organic layers were mixed and washed with 10 % Na_2CO_3 solution (2x25 mL) followed by 10 % NaCl solution (25 mL). Organic layer was dried over Na_2SO_4, and concentrated in vacuo to get the yellow colored residue with 65 % HPLC purity. It was purified by column chromatography by eluting with 5% methanol in methylene dichloride, concentrated in a rotary evaporator to get yellow coloured product (**6**) (4.5 g, 70%) with 97% HPLC purity. mp 73-75 ºC; IR (KBr): 3457, 3371, 2962, 2875, 1745, 1707, 1631, 1597, 1515, 1504, 1456, 1388, 1369, 1318, 1257, 1151, 1091, 1037,834, 772, 703,670 cm^{-1}. UV-Vis: 268, 208 nm. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (d, *J* = 9.3 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.15-7.28 (m, 2H), 7.15-7.28 (m, 2H), 7.15-7.28 (m, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 6.03 (br s,2H), 5.61 (d, *J* = 5.1 Hz, 1H), 5.11 (d, *J* = 5.1 Hz, 1H), 5.03-5.10 (m, 1H), 4.92-4.96 (m, 1H), 4.81-4.88 (m, 1H), 3.94-4.04 (m, 1H), 3.94-4.04 (m, 1H), 3.81-3.89 (m, 1H), 3.81-3.89 (m, 1H), 3.65-3.74 (m, 1H), 3.65-3.74 (m, 1H), 3.65-3.74 (m, 1H), 3.54-3.63(m, 1H), 3.54-3.63(m, 1H), 3.34-3.39 (m, 1H), 3.00-3.11 (m, 1H), 2.74-2.89 (m, 1H), 2.74-2.89 (m, 1H), 2.54-2.64 (m, 1H), 2.54-2.64 (m, 1H), 1.94-2.01 (m, 1H), 1.75-1.85 (m, 1H), 1.75-1.85 (m, 1H), 1.34-1.42 (m, 1H), 1.14-1.20 ss (m, 1H), 0.79 (d, *J* = 6.6 Hz, 6H) ppm. ^{13}C NMR : 155.3, 153.5, 152.9, 138.0, 129.1, 129.0, 128.0, 126.1, 122.5, 112.7, 108.7, 108.7, 79.6, 76.3, 70.2, 69.9, 68.7, 68.7, 57.5, 53.3, 49.2, 45.0, 44.4, 35.1, 26.3, 25.5, 25.4. $[\alpha]_D^{25}$ = -3.38° (*c* = 1 in $CHCl_3$).LC-MSD: 721 $[M+NH_4]^+$, 704 $[M+H]^+$, 547, 418, 392, 241, 216.

The enantiomeric excess (% *ee*) was determined to be 99% by HPLC using Intersil ODS 3V 250*4.6 5 µm column (30% ethanol/ hexane + 1 mL diethyl amine, 1 mL/min, 265 nm): t_R (minor, 29.03 min), t_R (major, 30.49 min).

CONCULSION

A highly diastereo- (99:1) and enantioselective (99:1) synthesis of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3S)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate **4** and (3R, 3aS, 6aR)-hexahydrofuro[2, 3-b]furan-3-yl (2R, 3R)-4-(4-amino-N-isobutylphenyl- sulfonamido)-3-(((3R, 3aS, 6aR)- hexahydrofuro[2, 3-b]furan-3-yloxy) carbonyloxy)-1-phenylbutan-2-ylcarbamate **6** were accomplished. Compound **6** is an important protease inhibitor (PI). To our knowledge, this represents the first reported example of substoichiometric catalysis to obtain both excellent diastereo- and enantioselectivities in the synthesis of this class of important compounds (PIs).

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REFERENCES

[1] KA. Sepk-owitz, *N. Engl. J. Med.*, **2001,** 344, 1764.
[2] (a) A. K Ghosh, B. D Chapsal, I. T.Weber, H. Mistaya, *Acc. Chem. Res.*, **2008,** 41, 78. (b) A. K Ghosh, P. R Sridhar, N Kumaragurubaran, Y Koh, I. T.Weber, H. Mitsuya, *Chem. Med.Chem.*, **2006,** 1, 939.
[3] J. A. Bartlett, R. DeMasi, J. Quinn, C. Moxham, F. Rousseau, *AIDS.*, **2001,** 15, 1369.
[4] R. M. Gulick, J. W. Mellors, D. Havlir, J. J. Eron, A. Meibohm, J. H. Condra,
F. T. Valentine D. McMahon, C. Gonzalez, L. Jonas, E. A.Emini, J. A. Chodakewitz, R. Isaacs, D. Richman, *Ann. Intern. Med.*, **2000,** 133, 35.
[5] F. J. Palella, K. M. Delaney, A. C. Moorman, M. O. Loveless, J. Fuhrer,G. A. Satten, D. J. Aschman, S. D. Holmberg, *N. Engl. J. Med.*, **1998,** 338, 853.
[6] D. L. Surleraux, A. Tahri, W. G. Verschueren, G. M. Pillede, H. A. Kock, T. H. Jonckers, A. Peeters, S. De Meyer, H. Azijn, R. Pauwels, M. P. de Bethune, N. M King, M. Prabu-Jeyabalan, C. A. Schiffer, P. B. Wigerinck, *J. Med. Chem.*, **2005,** 48, 1813.
[7] D. J. Kempf K. C.Marsh, J. F. Denissen, E. McDonald, S. Vasavanonda,C. A. Flentge, B. E. Green, L. Fino, C. H. Park, X. P. Kong, N. E. Wideburg, A. Saldivar, L. Ruiz, W. M. Kati, H. L. Sham, T. Robins, K. D.Stewart, A. Hsu,J. J. Plattner, J. M. Leonard D. W. Norbeck, Proc. *Natl. Acad. Sci.*, U.S.A. **1995,** 92, 2484.
[8] S. R. Brett, A. R Keith, Q.G. Yi-fei Gong, A.S. David , S.B. Wade, J. T. Brian, A.D. Carol, F. Djang, J. Richard, *Antimicrob. Agents Chemother.*, **2000,** 44, 2093.
[9] H. L.Sham, D. J. Kempf, A. Molla, K. C. Marsh, G. N. Kumar, C. M. Chen, W. Kati, K. Stewart, R. Lal, A. Hsu, D. Betebenner, M. Korneyeva, S. Vasavanonda, E. McDonald, A. Saldivar, N. Wideburg, X. Chen, P. Niu,C. Park, V. Jayanti, B. Grabowski, G. R. Granneman, E. Sun, A. J. Japour,J. M. Leonard, J. J. Plattner, D. W. Norbeck, *Antimicrob. Agents Chemother.*, **1998,** 42, 3218.
[10] S. W. Kaldor, V. J. Kalish, J. F. Davies, B. V. Shetty, J. E. Fritz, K. Appelt, J. A. Burgess, K. M. Campanale, N. Y. Chirgadze, D. K. Clawson,B. A. Dressman, S. D. Hatch, D. A. Khalil, M. B. Kosa, P. P. Lubbehusen,M. A. Muesing, A. K. Patick, S. H. Reich, K. S. Su, J. H. Tatlock, *J. Med. Chem.*, **1997,** 40, 3979.

[11] Y. Koh, H. Nakata, K. Maeda, H. Ogata, G. Bilcer, T. Devasamudram, J. F.Kincaid, P. Boross, Y. F. Wang, Y. Tie, P. Volarath, L. Gaddis,R. W. Harrison, I. T.Weber, A. K. Ghosh, H. Mitsuya, *Antimicrob. Agents Chemother.,* **2003,** 47, 3123.
[12] M. K. Gurjar, N. R. Devi, *Tetrahedron: Asymmetry.,* **1994,** 5, 755.
[13] (a) P. L. Beaulieu, D. Wernic, *J. Org. Chem.,* **1996,** 61, 3635. (b) N. Shibata, T. Katoh, S. Terashima, *Tetrahedron Lett.,* **1997,** 38, 619. (c) P. L. Beaulieu, P. Lavalle´e, A. Abraham, P. C. Anderson, C. Boucher, Y. Bousquet, J.S. Duceppe, J. Gillard,V. Gorys, C. Grand-Maıˆtre, L. Grenier, Y. Guindon, I. Guse, L. Plamondon, F. Soucy, S.Valois, D. Wernic, C. Yoakim, *J. Org. Chem.,* **1997,** 62, 3440. (d) D. L. Rieger, *J. Org. Chem.,* **1997,** 62, 8546. (e) A.K.Ghosh, S. Fidanze, *J. Org. Chem.,* **1998,** 63, 6146. (f) S. E. Zook, J. K. Busse, B. C. Borer, *Tetrahdron Lett.,* **2000,** 41, 7017.
[14] J. H. Condra, W. A. O. M. Schleif, Blahy, L. J. Gabryelski, D. J. Graham, J. C.Quintero, A. Rhodes, H. L. Robbins, E. Roth, M. Shivaprakash, *Nature* (London) **1995,** 374, 569.
[15] F. Clavel, A. J. Hance, *N. Engl. J. Med.,* **2004,** 350, 1023.
[16] F.J. Palella, K.M.Delaney, A.C. Moorman, M.O. Loveless, J. Fuhrer, G.A. Satten, D.J. Aschman, S.D.Homberg, *N. Engl. J. Med.,* **1998**, 338, 853.
[17] D.Boden, M. Markowitz, *Antimicrob Agents Chemother.,* **1998,** 42, 2775.
[18] K.G. Arun, L. Sofiya, N. Marcus, *J. Org. Chem.,* **2004,** 69, 7822.
[19] Goyvaerts, Nicolas Martha, PCT/EP2004/053692, WO 2005/063770 A1.
[20] A. R. Haight, T. L. Stuk, M. S. Allen, L. Bhagavatula, M. Fitzgerald,S. M. Hannick, F. A. J. Kerdesky, J. A. Menzia, S. I. Parekh, T. A. Robbins, D. Scarpetti, J. H. J. Tien, *Org. Process Res. DeV.,* **1999,** 3, 94.
[21] J. S. Ng, C. A. Przybyla, S. Zhang, *PCT Int. Appl.,* **1996,** WO 9622275.
[22] M. Nakano, Y. Sato, *J. Org. Chem.,* **1987,** 52, 1844.