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The Chemical Development of LB71350

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Abstract:

An efficient synthesis of the HIV-1 protease inhibitor LB71350 (1) is described. High diastereoselective epoxidation of the *cis*-allylic carbamate fragment of (5*S*)-[*N*-(benzyloxycarbonyl)-amino]-*N*-[2-methyl-(1*R*)-[(phenyl)carbonyl]-propyl]-6-phenylhex-(*Z*)-enamide (16) and one-pot preparation of *N*-[(1-methyl-ethoxy)carbonyl]-3-(methylsulfonyl)-L-valine (4) are the key features of the synthesis.

Introduction

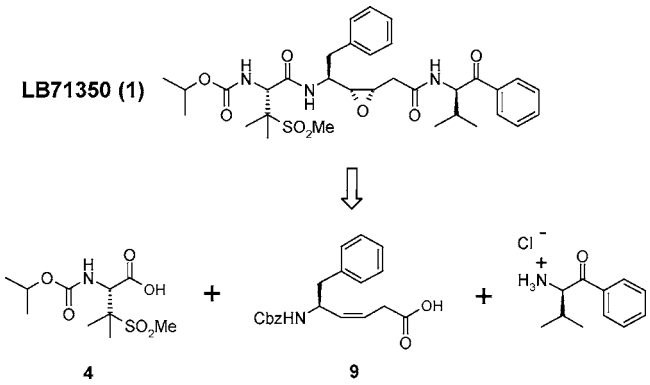
The human immunodeficiency virus encodes a protease that is responsible for processing the *gag* and *gag-pol* polyproteins into individual proteins required for viral maturation.[1] Thus, the genetic inactivation of the protease leads to noninfectious and immature viral particles with severely reduced reverse transcriptase activity.[2] Therefore, the inhibition of this critical enzyme is considered as a promising target for the potential drug to treat AIDS.

Through mechanistic and structural studies, we have previously reported that compounds containing the isostere PheΨ[(*R*,*S*)-*cis*-epoxide]Gly[3] irreversibly inactivate the HIV protease with high selectivity. Among them, **LB71350** (**1**)[4] is the most conspicuous in terms of both an excellent oral bioavailability and a potent activity.

Results and Discussions

Retrosynthetic cleavage of the amide bonds in **LB71350** provides three fragments **4**, **9**, and phenylvalinone hydrochloride[5] (Scheme 1). The compound **5**, dicyclohexylamine salt of **4**, was prepared at the early stage of the development through the following operations: (i) S-alkylation and carbamation of L-penicillamine (**2**) followed by extractive workup and concentration, (ii) oxidation of the sulfide group in **3,** with Oxone in methanol/water cosolvent, and subsequent extractive workup and filtration, and (iii) final salt formation with dicyclohexylamine and filtration. Two problems were observed in the large-scale operation. Since both **3** and **4** are quite polar compounds, partial loss of the product

Scheme 1



4 **9**

was inevitable during the workup. At the stage of oxidation of the sulfide, removal of salts from the reaction mixture required a large amount of water to dissolve all the inorganic salts, and Celite-assisted filtration of the concentrated organic layer was required for the removal of a small amount of residual salts. To circumvent these problems, various oxidizing agents were screened with the aim of executing the preparation of **4** from L-penicillamine (**2**) in one-pot fashion.

Clorox mediated oxidation[6] of the crude reaction mixture containing **3** did not go to completion even with excess reagent and under refluxing conditions. A successful outcome was obtained from a hydrogen peroxide/[7]transition metal catalyst system. Methyltrioxorhenium-catalyzed[8] reaction of the acidified two-phase mixture of **3** proceeded with a clean conversion with a relatively high 3 mol % catalyst loading. More efficient catalysis was observed with tungstic acid,[9] which converted the crude acidified two-phase reaction mixture of **3** to **4** with only 0.1 mol % catalyst loading. Vanadium sulfate[10] gave results comparable to those with tungstic acid. The preparation of **4** was executed in one-pot manner, starting with L-penicillamine (**2**) (Scheme 2). For easy handling and purification of **4**, it was transformed into **5** after a reaction with dicyclohexylamine.

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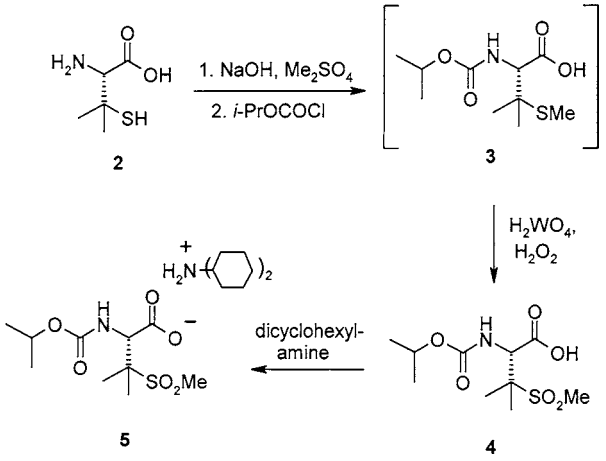
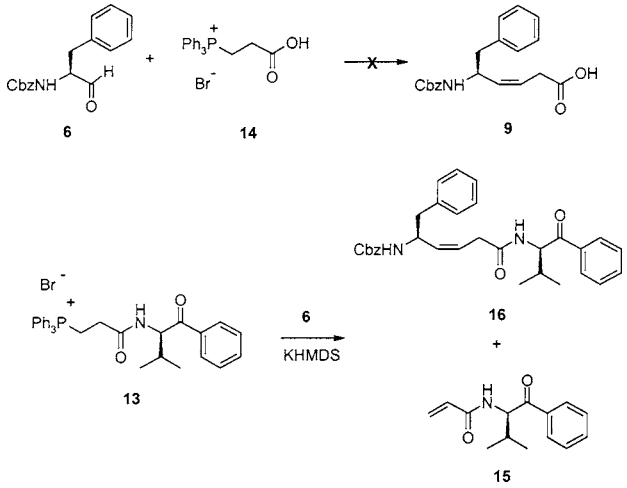
Scheme 2



Scheme 3



For the synthesis of **9**, Wittig reaction of the phosphonium salt **14**[11] with *N*-Cbz-phenylalaninal (**6**)[12] was initially tested but resulted in complete failure under the known reaction conditions. The only observed products in the reaction are from the β-elimination of **14** to yield acrylic acid and triphenylphosphine.

Reaction of the more elaborated phosphonium salt **13**[13] with **6** in the presence of 1.0 equiv of potassium hexamethyldisilazide (KHMDS) afforded the desired product in only 28% yield along with the elimination product, phenylvalinone acrylate (**15**) (Scheme 3). Attempted optimization efforts turned out to be futile under various reaction conditions.

The synthesis[14] of **9** was optimized through Wittig reaction of the ortho ester phosphonium salt (**7**)[15] with *N*-Cbz-phenylalaninal (**6**) (Scheme 4). Reaction of **6** with the phosphonium salt **7** in the presence of 1.2 equiv of KHMDS and subsequent deprotection of the ortho ester group with 0.5 N aqueous HCl solution gave **9** of 83% ee with high 24:1 *Z*:*E* selectivity. To dissolve the compound **9** into the aqueous phase, the reaction mixture was made basic after the hydrolysis of **8**. Subsequent wash with methylene chloride removed triphenylphosphine oxide. Reacidification of the separated aqueous layer and extraction with methylene chloride and concentration afforded crude **9** which is free of triphenylphosphine oxide but contaminated with 3-(diphenylphosphoryl)propionic acid (**11**).[16] Careful examination revealed that this side product was formed at the Wittig reaction stage where the phosphine oxide ortho ester **10** was formed[17] and converted to **11** upon acid hydrolysis. It was found that the amount of **11** largely depends on the concentration of water. Thus, **11** was formed in 4.3% with THF with water content of $\leq$0.02% and increased to 13.5% with THF of water content $\leq$0.08%. Due to this impurity, short silica gel filtration of crude **9** was inevitable.

Coupling of **9** and phenylvalinone hydrochloride was initially attempted with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate[18] (BOP), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate[19] (HATU), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) to afford **16** in 70−75% yield. Due to high cost of these coupling reagents, alternatives were investigated. Activation of **9** with methanesulfonyl chloride and *i*-butylchloroformate provided **16** in 60 and 72% yields, respectively. Employment of dicyclohexylcarbodiimide (DCC) and diisopropylcarbodiimide (DIC) improved the yields to 77−78%. Inclusion of *N*-hydroxylbenzotriazole (HOBT) increased the yields to 83% for DCC and 94% for DIC (Scheme 4). Finally, DIC/HOBT was chosen as the coupling reagents and the separated organic layer of **16** after the workup procedure was used for the epoxidation step.

Epoxidation of **16** with *m*-CPBA afforded the desired **17**α and its β-epoxide **17**β in the ratio of 3:1. Since it was commented by Roush[20] that the stereoselectivity of (*Z*)-allylic

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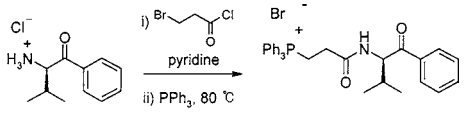
(13) Phosphonium salt **13** was prepared in the sequence of reactions: (i) coupling of phenylvalinone hydrochloride with 3-bromopropionyl chloride to give *N*-[(1*R*)-1-benzoyl-2-methylpropyl]-3-bromopropanamide (**12**), (ii) reaction of **12** with triphenylphosphine and solidification in diethyl ether to afford **13**. Spectroscopic data of **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.94 (m, 2H), 7.63−7.47 (m, 3H), 6.52 (br, d, NH, J = 8.2 Hz), 5.64 (1H, dd, J = 8.8, 4.2 Hz), 3.71−3.60 (m, 2H), 2.90−2.83 (m, 2H), 2.22−2.19 (m, 1H), 1.04 (d, 3H, J = 6.8 Hz), 0.78 (d, 3H, J = 6.8 Hz). Spectroscopic data of **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, 1H, J = 4.1 Hz) 7.95 (d, 2H, J = 7.4 Hz), 7.85−7.65 (m, 15H), 7.55−7.42 (m, 2H), 5.08 (dd, 1H, J = 6.9, 5.5 Hz), 3.84−3.74 (m, 2H), 3.14−3.11 (m, 2H), 2.30 (m, 1H), 0.98 (d, 6H, J = 6.0 Hz).



(14) Lee, C. S.; Choy, N.; Son, Y. C.; Park, C.; Choi, H.; Moon, K. Y.; Jung, W. H.; Kim, S. C.; Yoon, H. *Bull. Korean Chem. Soc*. **1996**, *17*, 294.

(15) Corey, E. J.; Raju, N. *Tetrahedron Lett*. **1983**, *24*, 5571.

(16) Spectroscopic data of **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br, 1H), 7.72−7.68 (m, 4H), 7.54−7.44 (m, 6H), 2.71−2.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1 (J_{cp} = 13.4 Hz), 132.4, 131.6, 130.9 (J_{cp} = 9.5 Hz), 129.0 (J_{cp} = 11.5 Hz), 26.7, 24.7 (J_{cp} = 73.4 Hz).

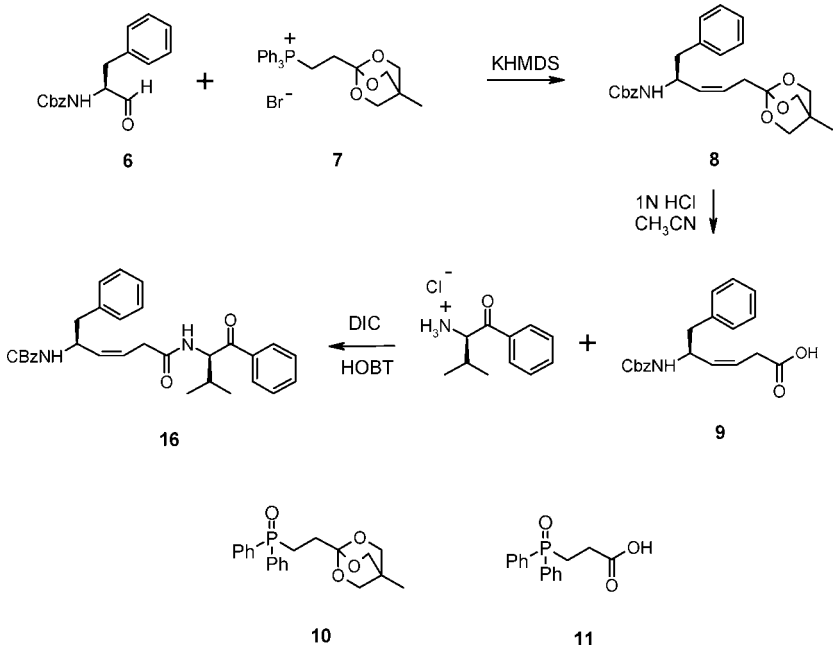
(17) In general, triphenylphosphonium salt is transformed to diphenylphosphine oxide under reflux in strongly basic aqueous conditions, see: Buss, A. D.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2307.

(18) Castro, B.; Dormoy, J. R. *Tetrahedron Lett*. **1973**, 3243.

(19) Carpino, L. A. *J. Am. Chem. Soc*. **1993**, *115*, 4397.

(20) The observed selectivity is quite close to Roush's result on (*Z*)-allylic carbamate. Please refer to: Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem*. **1987**, *52*, 5127.

Scheme 4



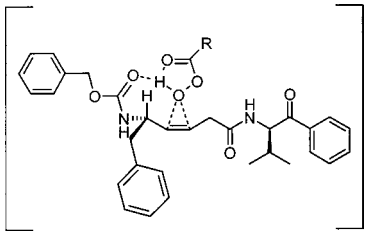


Figure 1. **Proposed transition state of the epoxidation of 16.**

carbamate is highly sensitive to carbamate functionality and epoxidation reagents, other oxidizing agents including $MeReO_3$ and H_2O_2,[21] DCC and H_2O_2,[22] and Im_2SO_2 and H_2O_2,[23] were screened, but disappointingly only moderate diastereoselectivity was observed, ranging from 2.5 to 1.4:1 with α-epoxide as the major product. The rationale for the moderate stereoselectivity of *m*-CPBA epoxidation is proposed from synergistic combination of allylic 1,3-strain[24] and the directing effect[25] of the carbamate group of **16**. In other words, allylic strain makes the conformation of the single bond between the allylic chiral center and the double bond rigid enough to experience the directing influence of the carbamate group as illustrated in Figure 1. If the degree of the interaction of the epoxidation reagent and the carbamate group be increased, the stereoselectivity would also increase. In that context, we were pleased to find two relevant references[26] that describe the dependency of directed epoxidation diastereoselectivity on the electrophilicity of peracids. Encouraged by these reports, we have investigated the influence of peracids on the selectivity of the epoxidation of **16**. Epoxidation of **16** with permaleic acid in methylene chloride enhanced the diastereoselectivity to 10:1, and the most electrophilic trifluoroperacetic acid[27] prepared in situ from trifluoroacetic anhydride (TFAA) and urea−hydrogen peroxide (UHP) improved diastereoselectivity amazingly to greater than 150:1 (Table 1).

Table 1. **Influence of epoxidation reagents on the stereoselectivity**

entry	peracid	selectivity (**17**α: **17**β)
1	DCC/H_2O_2	1.4:1
2	Im_2SO_2/H_2O_2	2.4:1
3	$MeReO_3/H_2O_2$	2.0:1
4	*m*-CPBA	3:1
5	permaleic acid	10:1
6	trifluoroperacetic acid	>150:1

The residual HOBT left in the crude **16** has dramatic influence on the stereoselectivity. Controlled experiments with various levels of externally added HOBT clearly demonstrated its influence on the diastereoselectivity (Table 2). To ensure high diastereoselectivity, basic washing of the crude reaction mixture of **16** was included in the workup stage to control the level of HOBT to below 3%. The origin of the influence of the residual HOBT is not clear, but we speculate that the residual HOBT is transformed to a more polar HOBT *N*-oxide[28] in the course of epoxidation, which could attenuate the directing effect of the carbamate group. All of these results support the hydrogen-bonding-mediated directed effect of the carbamate group.

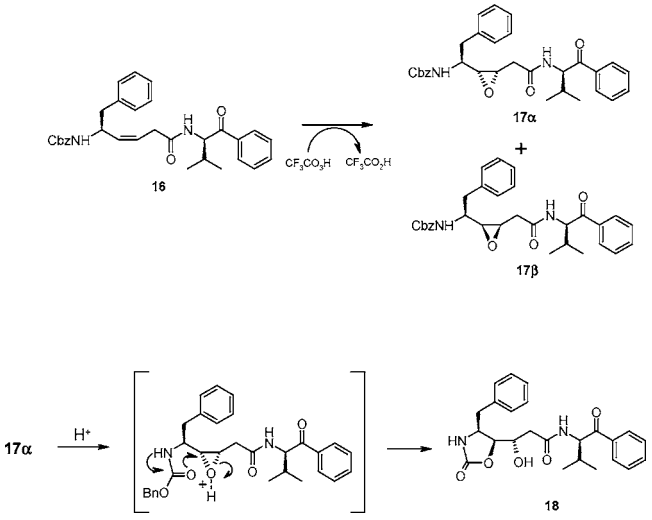
(21) Boehlow, T. R.; Spilling, C. D. *Tetrahedron Lett*. **1996**, *37*, 2717.
(22) (a) Murray, R. W.; Iyanar, K. *J. Org. Chem.* **1998**, *63*, 1730. (b) Majetich, G.; Hicks, R. *Synlett* **1996**, 949.
(23) Schultz, M.; Kluge, R.; Liebsch, S.; Lessig, J.; Halik, M.; Gadissa, F. *Tetrahedron* **1996**, *52*, 13151.
(24) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(25) For an excellent review on the directing effect of various groups in epoxidation, see: Dryuk, V. G.; Kartsev, V. G. *Russ. Chem. Rev.* **1999**, *68*, 183.
(26) (a) Jensen, A. J.; Luthman, K. *Tetrahedron Lett*. **1998**, *39*, 3213, (b) Fehr, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2407.
(27) Permaleic acid and trifluoroperacetic acid were prepared in situ by the addition of maleic anhydride or trifluoroacetic anhydride (TFAA), respectively to urea−hydrogen peroxide (UHP). The safety concern on the use of these reagents was discussed in detail in the reference. See: Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.
(28) Aurich, H. G.; Weiss, W. *Chem. Ber*. **1973**, *106*, 2408.

Table 2. **Effect of the level of residual HOBT on the stereoselectivity**

entry	residual HOBT (HPLC area %)[a]	selectivity (**17**α: **17**β)
1	2.4	>150:1
2	6.2	9.9:1
3	13.8	8.2:1
4	15.3	7.8:1

[a] Area % was normalized for **16** and HOBT.

Scheme 5



Although the diastereoselectivity with trifluoroperacetic acid was increased to a great extent, a new impurity was formed. The structure of the impurity was later identified as the oxazolidinone **18**, which was formed through trifluoroacetic acid-catalyzed ring opening of the epoxide moiety with the internal carbamate group[29] (Scheme 5). On the basis of this hypothesis, the effects of an acid quencher, such as sodium phosphate dibasic, and reaction temperature on the formation of **18** were investigated, and the results are summarized in Table 3. In the absence of the acid quencher, the reaction went to completion with 1.5 equiv of TFAA and 2.0 equiv of UHP to form **18** in 12 and 8% at 25 and 0 °C, respectively (entries 1 and 2). Inclusion of sodium phosphate dibasic required extra equiv of TFAA and UHP for the completion of the reaction, and at least 4 equiv of sodium phosphate dibasic was necessary for a significant reduction of **18** (entries 3−5). The formation of **18** was suppressed to about 1% under optimized conditions (entry 6). Fortunately, crystallization of the crude **17**α removed all the impurities derived from (*R*)-isomer of **9** and *trans*-**9** to provide pure **17**α in 60% overall yield over two steps from **9**.

Deprotection of the Cbz group of **17**α was initially performed under atmospheric pressure of hydrogen in the presence of palladium−charcoal catalyst in methanol. At this step, overreduction of the phenyl ketone group to the hydroxyl group to form **19-OH** was the major side reaction

Table 3. **Effect of the acid quencher and the temperature on the formation of 18**

	equiv				HPLC (area %)[a]		
entry	TFAA	UHP	Na_2HPO_4	temp (°C)	**16**	**18**	**17**α
1	1.5	2.0	none	25	0.0	12.6	87.4
2	1.5	2.0	none	0	0.0	8.1	91.9
3	1.5	2.0	1.75	25	4.0	9.8	86.2
4	1.5	2.0	3.0	25	36.7	5.2	58.1
5	2.0	4.5	4.25	0	0.0	4.4	95.6
6	2.0	4.5	4.25	−5	0.0	1.2	98.8

[a] Area % was normalized for **16**, **18**, and **17**α.

(Scheme 6). However, exchanging the solvent system to a less polar 4:1 mixture of methanol and THF eradicated the overreduction problem. Coupling of **5** and **19** was achieved through mixed anhydride activation of **5**. Thus, the formation of the mixed anhydride of **5** with *i*-butyl chloroformate in the presence of 0.5 equiv of *N*-methylmorpholine and subsequent reaction with **19** afforded **LB71350** (**1**) in 60% yield in two steps. It was found that the use of 0.5 equiv of a base is essential for the good yield. Careful ^{1}H NMR analysis of the reaction[30] revealed that in the absence of the base, the formation of the mixed anhydride with *i*-butyl chloroformate progressed to only 50% and more than 0.5 equiv of the base slowly decomposed the anhydride intermediate.

In summary we have developed an efficient and scalable synthetic route towards **LB71350** (**1**). Noteworthy is the high diastereoselective epoxidation of **16** with trifluoroperacetic acid and the one-pot preparation of **4**, employing tungstic acid and hydrogen peroxide.

Experimental Section

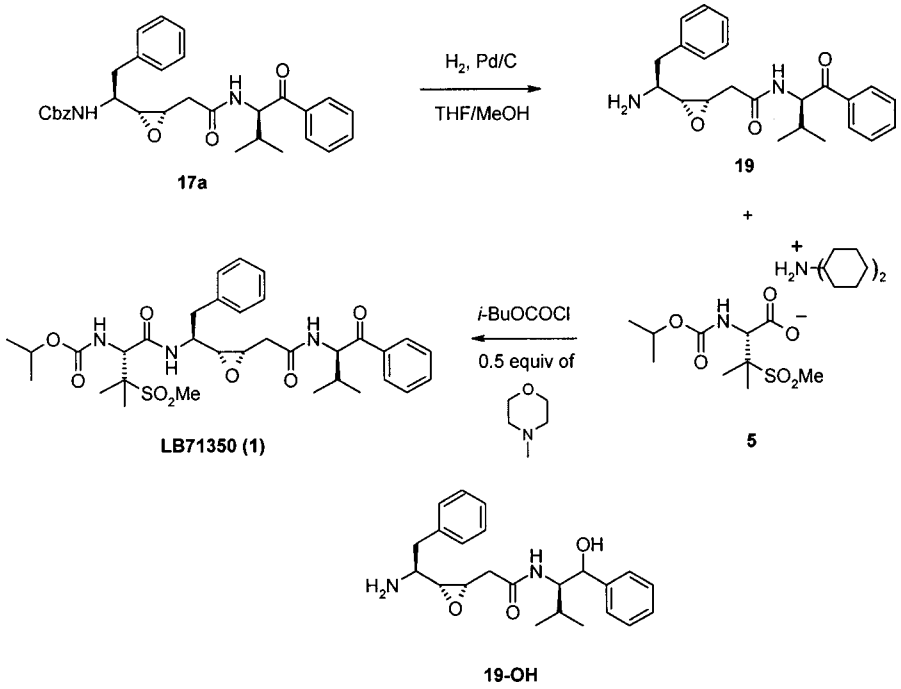
Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were obtained on a Bruker 400 MHz and a JEOL 500 MHz spectrometer. HPLC analyses were carried out on a Hewlett-Packard 1100 system and a Waters 490E detector and 616 pump system. Mass spectra were collected using a Finnegan LCQ mass spectrometer system and a JEOL JMX-700 mass spectrometer.

***N*-[(1-Methylethoxy)carbonyl]-3-(methylsulfonyl)-L-valine Dicyclohexylamine Salt (5).** To a mechanically stirred solution of sodium hydroxide (88 g, 2.2 mol) in 1.2 L of water was added L-penicillamine (100 g, 0.67 mol) at 5 °C. To the solution was added dimethyl sulfate (83 mL, 0.88 mol), maintaining the reaction temperature below 10 °C. After addition, the mixture was warmed to room temperature, and stirred for 1 h. The mixture was cooled to 0 °C, and a solution of isopropyl chloroformate (656 mL, 1 M solution in toluene, 0.66 mol) was added dropwise over 90 min below 5 °C. After addition the mixture was warmed to room temperature and stirring was continued for 15 h. Concentrated HCl (160 mL) and tungstic acid (0.17 g, 0.68 mmol) were

(29) Casado-Bellver, F. J.; Gonzalez-Rosende, M. E.; Asensio, A.; Jorda-Gregori, J. M.; Alvarez-Sorolla, A.; Sepulveda-Arques, J. Orena, M.; Galeazzi, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1650.

(30) The methylene protons of *i*-butyl chloroformate and the corresponding protons of the formed mixed anhydride of **5** were distinguishable in the ^{1}H NMR at 4.03 and 4.05 ppm in $CDCl_3$, respectively.

Scheme 6



added, and 30% of hydrogen peroxide (160 mL, 1.67 mol) was added dropwise. After heating the reaction mixture at 60−70 °C for 1 h, the mixture was cooled to 5 °C, and solid Na_2SO_3 (85 g, 0.67 mol) was added portionwise below 10 °C. The mixture was warmed to room temperature, and ethyl acetate (1.0 L) was added. After stirring for 15 min, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (1.5 L). The separated organic layer was combined, washed with 3 N HCl solution (200 mL), and concentrated. The residue was diluted with *tert*-butylmethyl ether (MTBE, 1.2 L), and dicyclohexylamine (127 mL, 0.64 mol) was added dropwise over 2 h. After keeping overnight, the formed solid was filtered, washed with MTBE (about 1 L), and dried with nitrogen purge to provide 212 g (68.4%) of **5**. Spectroscopic data of **5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (bs, 2H), 5.63 (d, J = 8.7 Hz, 1H), 4.85 (m, 1H), 4.37 (d, J = 9.6 Hz, 1H), 2.97 (m, 2H), 2.94 (s, 3H), 1.97 (d, J = 10.6 Hz, 4H), 1.78(d, J = 13.0 Hz, 4H), 1.64−1.12 (m, 12H), 1.53 (s, 3H), 1.48 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 155.7, 67.9, 63.9, 59.9, 52.2, 36.3, 28.6, 28.5, 24.8, 24.4, 21.8, 21.7, 19.7, 18.4; Mass *m*/*z* 463 (M^+ + 1); HRMS calcd for $C_{22}H_{43}N_2O_6S$ (M + 1) 463.2842, found 463.2838.

(*S*)-(1-Formyl-2-phenylethyl)-carbamic Acid, Phenylmethyl Ester (6). Methylene chloride (53.72 kg) and oxalyl chloride (6.23 kg, 49.08 mol) was charged to a 250-L reactor. To the solution was added over 2 h a solution of dimethyl sulfoxide (5.48 kg, 70.14 mol) in methylene chloride (10.94 kg) at −15 to −20 °C. After the completion of addition, the mixture was stirred for 30 min at −20 °C, and Cbz-L-phenylalaninol (10.0 kg, 35.05 mol) was added over 10 min, maintaining reaction temperature below −20 °C. After 1 h, diisopropylethylamine (13.66 kg, 105.12 mol) was added over 30 min, and stirring was continued for 2 h at −15 to −20 °C. A solution of 5% $KHSO_4$ (62 kg) was added, and the mixture was stirred for 30 min. The organic layer was separated and washed with brine (62.6 kg). The collected organic layer was concentrated under vacuum at 20 °C until the reaction volume was reduced to about half. Hexane (65.15 kg) was added, and about two-thirds volume of the mixture was removed by vacuum evaporation. Additional hexane (29.98 kg) was added. The formed solid was filtered, washed with hexane (22 kg), and dried with nitrogen purge to give 9.5 kg (95.5%) of product as a white solid. Chiral HPLC analysis showed 98.4% ee.[31]

(5*S*)-[*N*-(Benzyloxycarbonyl)-amino]-6-phenyl-(3*Z*)-hexenoic Acid (9). To the reactor (250 L) was charged [2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)ethyl]triphenylphosphonium bromide (**7**, 17.98 kg, 36 mol) and THF (94 kg). To the mixture was added over 10 min a solution of KHMDS (18% in THF, 36.57kg, 33 mol) at 0 °C. After 2 h, phenylalaninal (**6**, 8.50 kg, 30 mol) was added portionwise, maintaining the reaction temperature at 0−5 °C, and stirring was continued for 1 h. $NaHCO_3$ solution (3%, 84 kg) was added, and most of organic solvent was removed under vacuum (100−200 mbar). Methylene chloride (118.6 kg) was added, and the mixture was stirred for 30 min. The organic layer was separated and concentrated in vacuo, and the residue was used without further purification for the next step.

To the residue was added acetonitrile (81.5 kg) and 0.5 N HCl solution (90.08 kg) in sequence at room temperature. The mixture was heated at reflux for 15 h.[32] The mixture

(31) The optical purity of **6** was determined from the analysis of Cbz-L-phenylalaninol obtained from the reduction of **6** by $NaBH_4$ in methanol. Cbz-L-phenylalaninol and Cbz-D-phenylalaninol showed retention time 11.5 and 13.7 min, respectively, under the analysis conditions: Chiralpack (4.5 mm i.d. × 250 mm, Daicel, Japan), 210 nm, 1.0 mL/min, hexane/2-propanol = 90/10.

(32) In-process analysis showed that the reaction was completed in 6 h.

was cooled to 20 °C, and methylene chloride (109 kg) was added. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (61.7 kg). The collected organic layer was extracted with 1 N NaOH solution (89.7 kg). The separated aqueous layer was washed two times with methylene chloride (91 kg × 2). To the separated aqueous layer was added dropwise a solution of 6 N HCl (18.98 kg), and the mixture was extracted two times with methylene chloride (90 and 50.2 kg, respectively). The combined organic layers were passed through silica gel (12.3 kg) and eluted with methylene chloride (40 L). The eluent was concentrated in vacuo until the mixture volume reached about 50 L. The residue was diluted with carbon tetrachloride[33] (53.02 kg) and hexane (59 kg). Concentration of the mixture was continued until about 50 L of distillate was collected. Hexane (20 L) was added, and the mixture was stirred for 30 min. The formed solid was filtered, washed with hexane (20 L), and dried under nitrogen purge to afford 6.66 kg (65.3%) of product **9** of 83% ee. HPLC analysis (Chiralcel OJ, 210 nm, 1.0 mL/min, hexane/ethanol/trifluoroacetic acid = 50/50/1 (v/v), **9** at 6.0 min, (*R*)-isomer of **9** at 9.7 min, and *trans*-**9** at 13.9 min) showed 88.0% of **9**, 8% of (*R*)-isomer of **9** and 4% of *trans*-**9**. Spectroscopic data of **9**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 7.36−7.17 (m, 10H), 5.54−5.50 (m, 1H), 5.48−5.41 (m, 1H), 4.96 (dd, J = 16.4, 12.8 Hz, 2H), 4.39 (ddd, J = 14.4, 7.2, 7.2 Hz, 1H), 2.99 (dd, J = 17.6, 6.4 Hz, 1H), 2.80 (m, 2H), 2.64 (dd, J = 13.2, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 155.2, 138.1, 137.1, 132.5, 129.2, 128.2, 128.0, 127.6, 127.5, 126.0, 122.9, 65.0, 49.9, 40.4, 32.3; mp 90−91 °C.

(5*S*)-[*N*-(Benzyloxycarbonyl)-amino]-(3*S*,4*R*)-epoxy-*N*-[2-methyl-(1*R*)-[(phenyl)carbonyl]-propyl]-6-phenylhexanamide (17α). To a stirred solution of **9** (100 g, 0.295 mol, 1.0 equiv) in CH_2Cl_2 (1000 mL) was added HOBT (43.8 g, 0.32 mol, 1.1 equiv) at room temperature. The mixture was cooled to 5−10 °C. DIC (50.8 mL, 0.32 mol, 1.1 equiv) was added dropwise, maintaining the reaction temperature below 15 °C. After addition, the reaction mixture was allowed to warm to room temperature and stirred for an additional 30 min. The mixture was cooled to 5−10 °C. *N*-methylmorpholine (48.6 mL, 0.442 mol, 1.5 equiv) and phenylvalinone hydrochloride (66.1 g, 0.31 mol, 1.05 equiv) were added to the mixture, maintaining the reaction temperature below 15 °C. After 5 h, 1 N NaOH solution (750 mL) was added to the mixture, and the formed solid was filtered. The filter cake was washed with CH_2Cl_2 (200 mL). The organic layer was separated from the filtrate and washed with 0.5 N NaOH solution (750 mL) and 0.5 N HCl solution (750 mL) in sequence. To the separated organic layer were added UHP (124.7 g, 1.33 mol, 4.5 equiv) and Na_2HPO_4 (177.8 g, 1.252 mol, 4.25 equiv). The mixture was cooled to −5 °C, and TFAA (83.2 mL, 0.59 mol, 2.0 equiv) was added over 30 min, maintaining the reaction temperature below −5 °C. After 1 h at −5 °C, 0.5 N NaOH (1000 mL) solution was added to the mixture. The organic layer was separated and washed with 10% Na_2SO_3 (1000 mL) solution and H_2O (1000 mL). The separated organic layer was concentrated (950 mL of CH_2Cl_2 was distilled), and MTBE (1000 mL) was added to the residue. After stirring for 5 h, the formed solid was filtered and washed with MTBE (100 mL). The filter cake was dried with nitrogen purge to give 90.2 g (60% yield) of **17**α as a white solid. Spectroscopic data of **17**α: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 7.8 Hz, 2H), 7.59 (t, J = 7.4, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.36−7.19 (m, 10H), 6.60 (s, 1H), 5.55 (dd, J = 4.6, 4.2 Hz, 1H), 5.12 (s, 2H), 5.02 (br. 1H), 3.79 (m, 1H), 3.30 (m, 1H), 3.08 (m, 1H), 3.02 (dd, J = 7.8, 4.1 Hz, 1H), 2.88 (dd, J = 13.3, 7.8 Hz, 1H), 2.30 (dd, J = 14.7, 7.8 Hz, 1H), 2.17 (m, 1H), 2.02 (dd, J = 15.6, 4.2 Hz, 1H), 0.98 (d, J = 6.4 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 169.5, 155.9, 136.5, 135.4, 133.8, 129.6, 128.9, 128.8, 128.7, 128.6, 128.2, 127.1, 67.0, 58.2, 58.0, 54.3, 51.6, 39.5, 35.4, 31.7, 20.1, 16.9; HRMS calcd for $C_{31}H_{35}N_2O_5$ (M + 1) 515.2546, found 515.2536.

Spectroscopic data of **17**β: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.4 Hz, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.35−7.20 (m, 10H), 6.98 (br, 1H), 5.60 (dd, J = 9.2, 4.6 Hz, 1H), 5.03 (dd, J = 19.7, 12.4 Hz, 2H), 4.79 (d, J = 8.7 Hz, 1H), 3.72 (m, 1H), 3.40 (dd, J = 9.7, 6.0 Hz, 1H), 3.09 (dd, J = 14.2, 4.1 Hz, 1H), 2.92 (dd, J = 10.7, 7.1 Hz, 2H), 2.87 (dd, J = 9.7, 4.2 Hz, 1H), 2.67 (m, 1H), 2.21 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 169.9, 156.0, 136.3, 136.0, 135.5, 133.7, 129.6, 128.8, 128.7, 128.6, 128.2, 127.1, 67.2, 58.3, 58.1, 55.7, 49.8, 38.5, 36.0, 31.6, 20.1, 17.0.

Spectroscopic data of **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.4 Hz, 2H), 7.61 (m, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.33−7.17 (m, 5H), 6.78 (d, J = 8.7 Hz, 1H), 5.58 (dd, J = 8.7, 4.1 Hz, 1H), 5.30 (s, 1H), 4.27 (dd, J = 5.1, 3.2 Hz, 1H), 4.13 (m, 1H), 3.99 (d, J = 9.2 Hz, 1H), 2.91 (dd, J = 13.3, 5.1 Hz, 1H), 2.83 (dd, J = 13.3, 8.2 Hz, 1H), 2.67 (dd, J = 15.1, 9.6 Hz, 1H), 2.45 (dd, J = 15.6, 3.2 Hz, 1H), 2.19 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 171.3, 136.0, 135.3, 133.9, 129.1(×2), 129.0, 128.7, 127.4, 83.0, 68.6, 58.3, 54.9, 42.0, 38.3, 31.7, 20.1, 16.7; MS (CI) m/z 425 (M^+ + 1).

(3*S*,4*R*)-Epoxy-(5*S*)-[[*N*-[(1-methylethoxy)carbonyl]-3-(methyl-sulfonyl)-L-valinyl]-amino]-*N*-[2-methyl-(1*R*)-[(phenyl)-carbonyl]propyl]-6-phenylhexanamide (LB71350). To a stirred solution of **17**α (3.20 kg, 6.22 mol) in methanol (10.28 kg) and THF (2.96 kg) was added Pd/C (228 g, Degussa E101NE/W, 10% Pd, 58 wt %) at room temperature. The mixture was blanketed with hydrogen using hydrogen control box (pressure 0.1−0.15 kgf/cm^2), and stirring was continued for 15 h. The catalyst was filtered through Celite, and the filter cake was washed with THF (10 L). After the filtrate was concentrated, acetonitrile (3.68 kg) was added to the residue, and the mixture was concentrated again in vacuo. HPLC analysis of the residue showed 74.3% of **19**, 1.5% of **19-OH**, and 1.2% of **17**α.

To a stirred solution of **5** (2.74 kg, 5.92mol) in methylene chloride (23 kg) were added dropwise *N*-methylmorpholine

(33) Carbon tetrachloride is harmful to liver, kidney, and central nervous system. Exposure to 1000−2000 ppm for 30−60 min can be fatal to humans.

(2.95 mol) and *i*-butylchloroformate (0.82 kg, 5.92 mol), maintaining the reaction temperature below −20 °C. After 30 min, methylene chloride solution of **19** (7.7 kg of methylene chloride was used for the dilution of crude **19**) was added dropwise. After addition, the mixture was warmed to 0 °C, and stirring was continued for 2 h. The reaction mixture was washed with 0.5 M H_2SO_4 solution (10 L), 0.1 N NaOH solution (5 L), and water (10 L) in sequence. The separated organic layer was concentrated and diluted with MTBE (20 L). After keeping overnight, the formed solid was filtered and washed with MTBE to provide 2.4 kg (60% overall) of **LB71350** (**1**). Spectroscopic data of **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.7, 1.4 Hz, 2H), 7.58 (m, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.30 (t, J = 6.9 Hz, 2H), 7.25−7.20 (m, 5H), 6.94 (m, 1H), 6.69 (d, J = 8.7 Hz, 1H), 5.86 (br s, 1H), 5.55 (dd, J = 8.8, 4.6 Hz, 1H), 4.93 (heptet, J = 6.4 Hz, 1H), 4.57 (d, J = 8.7 Hz, 1H), 4.10 (m, 1H), 3.31 (m, 1H), 3.06 (dd, J = 7.9, 4.2 Hz, 1H), 3.01 (m, 1H), 2.92 (s, 3H), 2.31 (dd, J = 16.1, 8.3 Hz, 1H), 2.17 (m, 1H), 2.07 (dd, J = 15.1, 3.7 Hz, 1H),1.65 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.24 (dd, J = 6.4, 1.9 Hz, 6H), 0.97 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 169.9, 168.6, 136.7, 135.7, 134.1, 129.8, 129.2, 129.1, 129.0, 127.5, 69.9, 64.9, 58.4, 58.2, 58.0, 54.7, 50.2, 39.4, 37.7, 35.5, 32.0, 22.4, 22.4, 20.5, 20.4, 19.7, 17.2; $[\alpha]_D = -25.5°$ at 589 nm (c = 1% in MeOH); HRMS calcd for $C_{33}H_{46}N_3O_8S$ (M + 1) 644.3006, found 644.3023.

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