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Development of a Kilogram-Scale Synthesis of *cis*-LC15-0133 Tartrate, a Potent Dipeptidyl Peptidase IV Inhibitor

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Abstract:

(4*S*)-*N*-Boc-4-fluoro-L-proline methyl ester (4) was prepared from the following sequence of reactions: esterification of *trans*-4-hydroxy-L-proline (2), Boc protection, and fluorination by DAST. Reaction of 4 with lithiated oxadiazole provided oxadiazolyl ketone 7. Deprotection of the Boc group of 7 and subsequent coupling with bromoacetyl bromide gave bromide 9. Coupling reaction of 9 with excess oxazolidine 16 provided coupled product 17. Unexpectedly, the stereogenic center of 17 was completely epimerized to a virtually 1:1 mixture of *cis*- and *trans*-17 at this stage. After the deprotection of the *N,O*-methylene acetal group of 17 using aqueous ammonium chloride, *crystallization induced dynamic resolution (CIDR)* of *cis*- and *trans*-mixture of LC15-0133 (1) in the course of tartrate salt formation provided *cis*-LC15-0133 (1a) tartrate salt in 83% yield (>98% de).

Introduction

Type 2 diabetes (formerly noninsulin-dependent diabetes) is a severe and increasingly prevalent disease.[1] Diabetics may suffer debilitating cardiovascular, eye, kidney, and nerve damage, which are the result of glucose toxicity caused by their hyperglycemia. A progressive reduction in insulin sensitivity and insulin secretion are features of the disease, which eventually result in failure of the pancreatic islet cells and dependence on exogenous insulin. The hormone glucagon-like peptide 1 (GLP-1) is a potent stimulator of endogenous insulin release. GLP-1 has beneficial effects on islet β-cell function and insulin sensitivity without induction of hypoglycemia.[2] Unfortunately, GLP-1 is rapidly degraded in vivo. Therefore, inhibition of GLP-1 degradation by dipeptidyl peptidase IV (DPP-IV) has emerged as a promising approach for the treatment of type 2 diabetes[3] and has been aggressively pursued by numerous laboratories. We are also involved in the discovery of potent DPP-IV inhibitors, among which LC15-0133 (**1**) was chosen as a development candidate on the basis of its potent activity

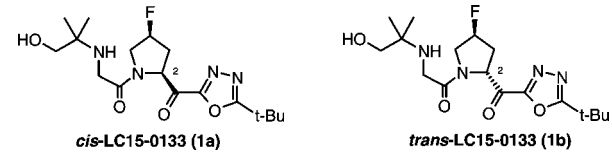
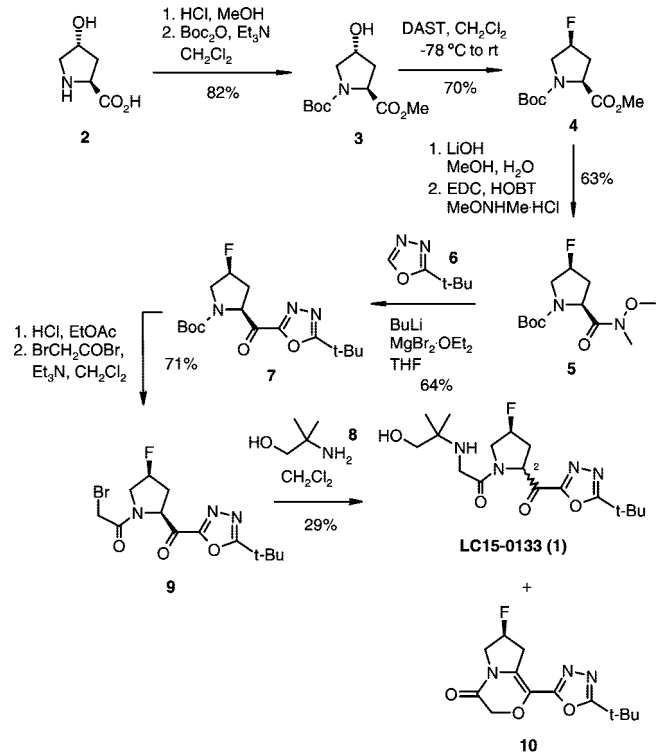


Figure 1

Scheme 1. **Medicinal chemistry route**



(Figure 1).[4] Herein, we report an efficient and scalable synthesis toward *cis*-LC15-0133 (**1a**) tartrate salt.

Result and Discussions

The medicinal chemistry route towards LC15-0133 (**1**) as illustrated in Scheme 1 needs a couple of improvements for a large-scale preparation, i.e. (1) increase of the moderate yields of Weinreb amide formation and the preparation of oxadiazolyl ketone **7** and (2) minimization of the side product **10** in the

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(1) *Fact Sheet No. 138*; World Health Organization: Geneva, 2002.
(2) Knudsen, L. B. *J. Med. Chem.* **2004**, *47*, 4128–4134.
(3) (a) Mest, H.-J.; Mentlein, R. *Diabetologia* **2005**, *48*, 616–620. (b) Weber, A. E. *J. Med. Chem.* **2004**, *47*, 4135–4141. (c) Drucker, D. J. *Expert Opin. Invest. Drugs* **2003**, *12*, 87–100. (d) Augustyns, K.; Van der Veken, P.; Senten, K.; Haemers, A. *Expert Opin. Ther. Pat.* **2003**, *13*, 499–510.
(4) (a) Lee, C.-S.; Koo, K. D.; Koh, J. S.; Kim, S.; Kim, D.-M.; Kim, M.-J.; Kim, B. C.; Yoon, S. K.; Kim, S.; Yim, H. J.; Hur, G.-C.; Lee, S. H.; Han, H. O.; Kim, K.-H.; Kim, G. T.; Kwon, O. H.; Kwon, T.-S.; Lee, H. B.; Chung, H. K.; Kim, M.; Lim, D.; Kim, Y. C.; Kim, S. PCT Int. Appl. WO2005037828, 2005. (b) Koo, K. D.; Kim, M. J.; Kim, S.; Kim, K.-H.; Kong, S. Y.; Hur, G.-C.; Yim, H. J.; Kim, G. T.; Han, H. O.; Kwon, O. H.; Kwon, T. S.; Koh, J. S.; Lee, C.-S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4167.

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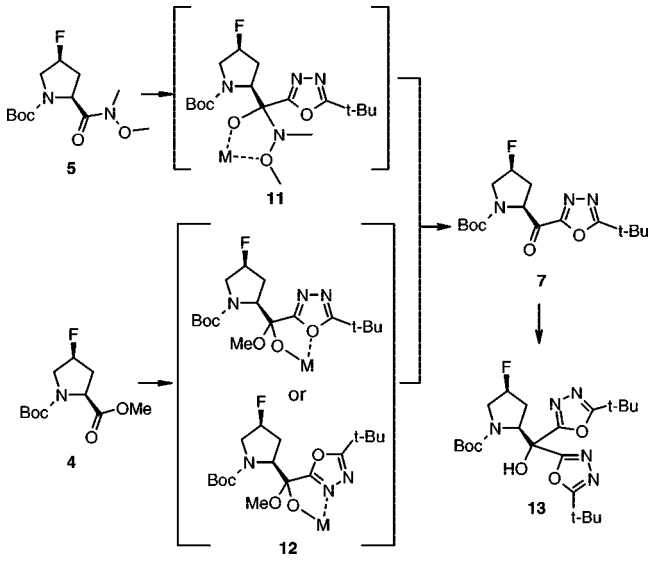
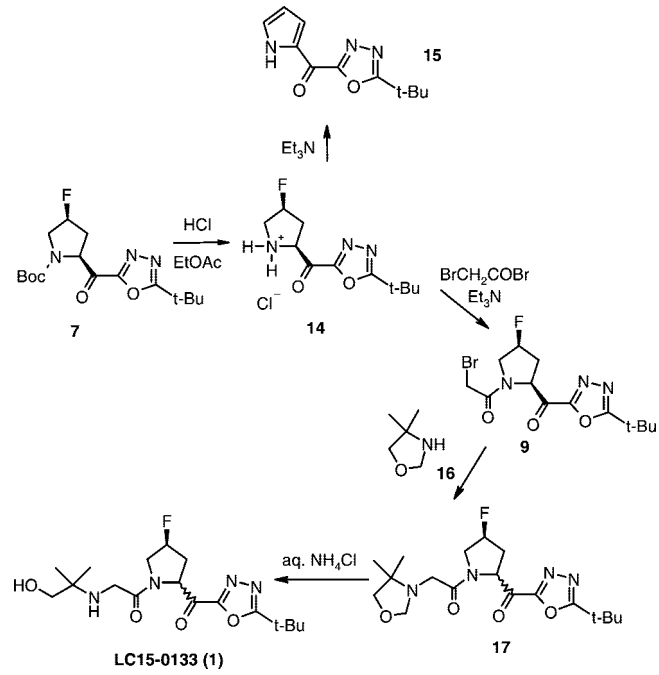
Scheme 2. **Direct conversion of 4 to 7**



Scheme 3. **Synthesis of LC15-0133 (1)**



coupling of **8** with **9**. In addition to those, unambiguous determination of the chemical identity of **1** became a critical issue in the later stage of chemical development because, contrary to the belief that **1** would be a single diastereomer, it turned out to be a mixture of *cis*- (**1a**) and *trans*-isomer (**1b**) reflecting significant epimerization of the C-2 stereogenic center in the course of the synthesis. Therefore, preparation of the desired *cis*-LC15-0133 (**1a**) was urgently required for further development.

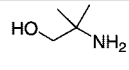
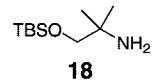
trans-4-Hydroxy-L-proline (**2**) was converted to its methyl ester under Fisher esterification conditions, which reacted with Boc_2O in the presence of triethylamine at ambient temperature to provide the *N*-Boc proline ester **3** as a white solid in good yield (82%). Fluorination under Middleton's protocol[5] using (diethylamino)sulfur trifluoride (DAST, 1.1−1.2 equiv at −78 °C) provided fluoride **4** in 70% yield. Quick optimization revealed that the reaction could also be executed at 0 °C and the use of excess of DAST (1.9 equiv) could increase the yield to 85% along with ∼5% of elimination byproduct. In the medicinal chemical approach, the introduction of the oxadiazolyl moiety[6] to **4** was accomplished via a sequence of reactions: (1) hydrolysis of the ester group of **4**, (2) Weinreb amide formation, and (3) addition of lithiated oxadiazole **6** in the presence of $MgBr_2 \cdot OEt_2$. Since the overall yield of these steps was ∼30−40%, it became imperative to increase the yield for a large-scale preparation. To this end, we considered the direct use of the ester functionality of **4** for the introduction of the oxadiazolyl group on assumption that the heteroatoms of the oxadiazole fragment would play a similar role as those of the Weinreb amide **11** in the stabilization of tetrahedral intermediate **12** via chelation (Scheme 2). Initial attempts for this assumption turned out to be disappointing: Grignard-type oxadiazole anion[7] generated from lithiated oxadiazole in the presence of $MgBr_2 \cdot OEt_2$ led to more side product **13** with incomplete conversion. In contrast, use of lithiated anion itself afforded desired ketone **7** in moderate yield of 50−60% along with starting material and the *tert*-alcohol **13** when the reaction temperature was raised up to 0 °C. After considerable experimentation, we found that the optimal reaction temperature should be within the range of −45 to −30 °C for the minimal formation of the side product **13**, thus increasing the yield to 70%. As temperature was raised above −20 °C, the chelated complex rapidly collapsed to give ketone **7**, which was immediately reacted with excess lithiated oxadiazole (2.2 equiv) to lead to significant formation of the tertiary alcohol **13**. After an extractive workup, crude ketone **7** was readily solidified by triturating with *n*-hexane in 67% yield contaminated with less than 5% of **13** by ^1H NMR analysis.

Boc deprotection of **7** was carried out under typical reaction conditions using anhydrous HCl to give the amine salt **14** in excellent yield (Scheme 3). At the stage of bromoacetylation of **14**, the addition sequence of two reagents, bromoacetyl bromide and triethylamine is very critical: attempted neutralization of **14** by triethylamine instantly formed pyrrole **15** as a major side product, whereas dropwise addition of triethylamine to a stirred mixture of bromoacetyl bromide and **14** in CH_2Cl_2 at 0 °C afforded desired bromide **9** without any formation of the byproduct **15** in good yield (85% in two steps overall).

According to the medicinal chemical route, the coupling of bromide **9** with 2-amino-2-methyl-1-propanol (**8**) in CH_2Cl_2 provided a substantial amount of the intramolecular cyclized byproduct **10** (Table 1, entry 2). To minimize this side reaction, the influence of solvents and nucleophiles such as **16**, **8**, and **18** were tested, and the results are outlined in Table 1. In general, the coupling reaction using **8** as a nucleophile in various solvents (entries 1−5) proceeded rapidly to give the desired adduct **1** and a substantial amount of **10** with complete conversion within 1.0 h. Among the tested solvents, CH_2Cl_2 and EtOAc (entries 2 and 3) were marginally better than the rest. Change of the

(5) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(6) Ohmoto, K.; Yamamoto, T.; Horiuchi, T.; Kojima, T.; Hachiya, K.; Hashimoto, S.; Kawamura, M.; Nakai, H.; Toda, M. *Synlett* **2001**, 299.
(7) Ohmoto, K.; Yamamoto, T.; Okuma, M.; Horiuchi, T.; Imanishi, H.; Odagaki, Y.; Kawabata, K.; Sekioka, T.; Hirota, Y.; Matsuoka, S.; Nakai, H.; Toda, M. *J. Med. Chem.* **2001**, *44*, 1268.

Table 1. **Effect of solvent polarity and nucleophiles on the coupling reaction**

entry	solvent	amine	yield (%)[a] coupling product	yield (%)[a] **10**
1	toluene	 **8**	23	77
2	CH_2Cl_2	**8**	39	61
3	EtOAc	**8**	54	46
4	DMF	**8**	33	67
5	CH_3OH	**8**	0	100
6	CH_2Cl_2	 **18**	74	26
7	EtOAc	**18**	74	26
8[b]	CH_2Cl_2	**16**	52	3.0
9[c]	$ClCH_2CH_2Cl$	**16**	79	3.5

[a] Yield was based on area % of HPLC. [b] 3.0 equiv of oxazolidine was used, and 35% of starting bromide remained. [c] 6.0 equiv of oxazolidine was used.

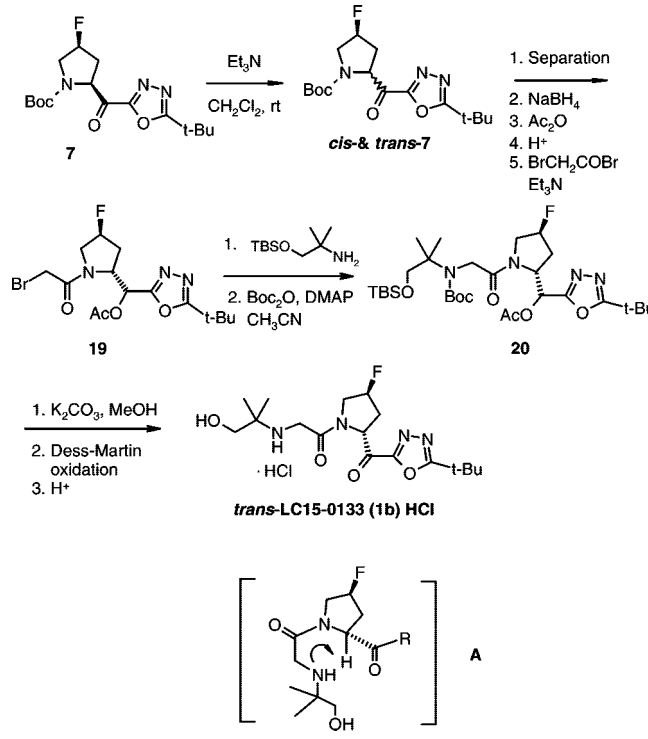
nucleophile to TBS-protected aminoalcohol **18** led to significant reduction of the side product **10** (entries 6 and 7) with concomitant slow-down of the reaction rate. Use of the oxazolidine **16**[8] showed retarded reaction rate as well, compared to that of **8** and **18**: the starting bromide **8** was not completely consumed in 24 h even with 3 equiv of **16** (entry 8). However, although the reaction rate was retarded significantly, the side product **10** was also dramatically reduced to 3.0% (entries 8 and 9). Therefore, we chose **16** as the optimal nucleophilic partner, and after extensive experimentations, optimal conditions were determined to use 6.0 equiv of oxazolidine **16** in dichloroethane at ambient temperature in which 80% of coupling product **17** was obtained along with only 3.5% of **10** (entry 9).

Next, the deprotection of *N,O*-methylene acetal moiety of **17** was accomplished according to Falorni's protocol (3 N HCl in EtOAc) to give LC15-0133 (**1**)·HCl salt in good yield in a laboratory scale.[9] However, on a large laboratory scale (~200 g), the deprotection reaction resulted in a number of byproducts, which might be attributed to the incomplete removal of excess HCl in the crude concentrate. Therefore, we examined several deprotection conditions suitable for a pilot scale. Serendipitously, aqueous NH_4Cl was found to cleave effectively the *N,O*-methylene acetal moiety of **17** at room temperature, and this protocol was successfully applied to the preparation of LC15-0133 (**1**) in a pilot scale.

(8) Aqueous 4,4-dimethyloxazolidine (**16**, 75 wt %) is commercially available from Aldrich. Oxazolidine **16** was extracted twice with CH_2Cl_2 or dichloroethane (1.0 L and 500 mL, based on 1.0 L of 75% aqueous oxazolidine) and used after concentration.

(9) Falorni, M.; Conti, S.; Giacomelli, G.; Cossu, S.; Soccolini, F. *Tetrahedron: Asymmetry* **1995**, *6*, 287.

Scheme 4. **Synthesis of *trans*-LC15-0133 (1b)·HCl salt**



At this stage, we carefully analyzed LC15-0133 (**1**) by HPLC and unfortunately found that it was a virtually 1:1 mixture of *cis*- and *trans*-diastereomers. Quick retrospective investigation on the cause of this outcome was undertaken, and we found that the epimerization at the carbonyl group-bearing stereogenic center occurred in the coupling reaction of bromide **9** with **16**. To prove unequivocally the analytical HPLC and TLC results,[10] independent syntheses of *cis*-LC15-0133 (**1a**) and *trans*-isomer **1b** were carried out as in Scheme 4. Epimerization of *cis*-ketone **7** in the presence of 2.0 equiv of triethylamine over 12 h gave an almost 1:1 diastereomeric mixture of **7**, the diastereomers of which were readily separated by column chromatography. To avoid epimerization in the coupling with amine **18**, the ketone group of *trans*-**7** was reduced and the formed hydroxyl group was protected as acetate, which was transformed to **19** via deprotection of the Boc group and coupling with bromoacetyl bromide. Subsequent coupling of **19** with **18** proceeded smoothly to afford the coupled product, the amine group of which was reacted with Boc_2O in the presence of DMAP to give **20**. Deprotection of the acetyl group of **20** followed by Dess−Martin oxidation gave *N*-Boc-, *O*-TBS-protected *trans*-LC15-0133 (**1b**). Simultaneous deprotection of the Boc and the TBS groups under acidic conditions gave *trans*-LC15-0133 (**1b**)·HCl salt. In the same manner, *cis*-LC15-0133 (**1a**)·HCl salt was prepared. Through comparison with respective ^1H NMR spectra (Figure 2) and HPLC analysis of *cis*- and *trans*-isomers, the story behind the epimerization was unambiguously cleared: after the stage of the coupling reaction, all the intermediates underwent rapid epimerization under neutral and

(10) Careful analysis of TLC showed two spots. However, upon isolating them by preparative TLC, each isolated material turned out to be the same mixture before purification. HPLC analysis was performed with C1 column with CH_3CN/H_2O = 3:97 containing 0.1% TFA as an eluent at 254 nm; retention times of *trans*- and *cis*-**1** were 10.9 and 17.8 min, respectively.

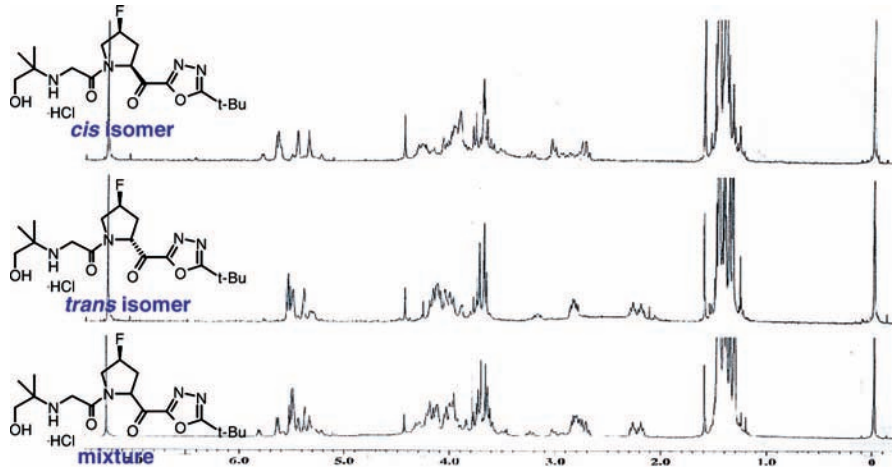
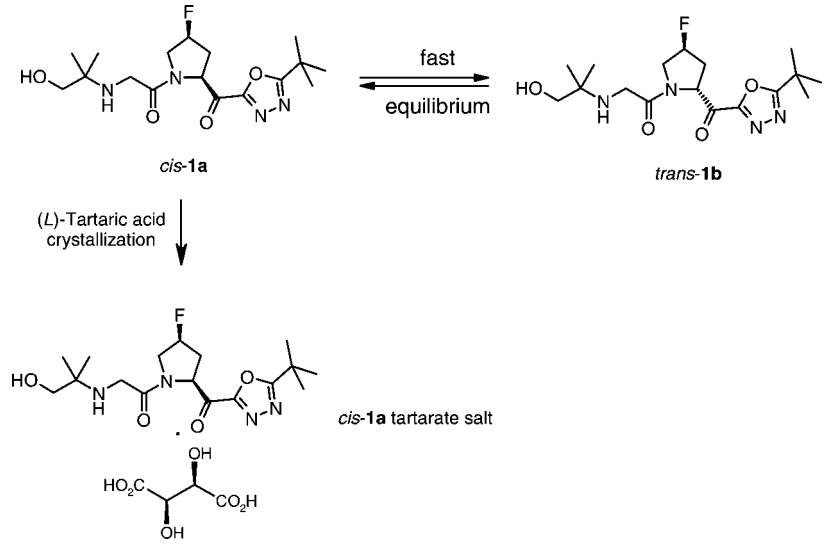


Figure 2. **Comparison of ^{1}H NMR spectra of *cis*-1a·HCl, *trans*-1b·HCl, and a diastereomeric mixture of 1·HCl.**

Scheme 5. **Preparation of *cis*-LC15-0133 (1a) tartrate via CIDR**



basic conditions. We speculate that the instant epimerization might be facilitated significantly by proximity effect of the internal amine as a base (see the transition structure A in Scheme 4). Thus, HPLC analysis of them should be carried out with an acidic eluent containing 0.1% TFA.

From the study on the X-ray crystallographic analysis of the complex of DPP-IV and LC15-0133 (**1**), we knew that only the *cis* form **1a** is active. Moreover, to ensure consistent quality control and provide clear description of the chemical identity of the final API, we were required to develop a process to prepare *cis*-LC15-0133 (**1a**) which is viable for a large-scale operation. To this end, selective crystallization conditions for the preparation of *cis*-LC15-0133 (**1a**) out of the *cis*- and *trans*-mixture of **1** via salt formation with a variety of acids was investigated. Among many acids tested, crystallization of **1** using tartaric acid in acetonitrile provided highly crystalline tartrate salt. To our surprise, the resulting crystal was found to be the *cis*-isomer **1a** exclusively in better than 98% de, which reflected that in the course of crystallization of the *cis*- and *trans*-mixture **1** with tartaric acid, *cis*-**1a** tartrate salt was selectively crystallized out with concomitant dynamic equilibration of the *cis*- and *trans*-isomers. This *crystallization-induced dynamic resolution (CIDR)*[11] methodology was successfully applied for the preparation of ~0.5 kg of *cis*-LC15-0133 (**1a**) tartrate salt in 83% yield from **1** with better than 98% de (Scheme 5).

In conclusion, we have established an efficient and scalable synthetic route toward a potent DPP-IV inhibitor, *cis*-LC15-0133 (**1a**). In the course of the study, we established direct additions of lithiated oxadiazole to methyl ester **4** to render the preparation of **7** more efficient, and judicious selection of oxazolidine **16** as an equivalent of 2-amino-2-methyl-1-propanol (**8**) led to minimal formation of the side product **10** at the coupling reaction with bromide **9**. Serendipitous discovery of CIDR of a diastereomeric mixture of LC15-0133 (**1**) in the course of tartaric acid salt formation led to the isolation of *cis*-LC15-0133 (**1a**) tartrate salt as an exclusive product. This finding implies that, when working with a stereochemically labile compound, it would be a very useful strategy to consider CIDR as a possible solution, particularly at the final stage of the synthesis. Using the mentioned improvements, the kilogram-scale synthesis of *cis*-**1a** tartrate salt was efficiently implemented without any chromatographic purification in a total of 10 steps.

(11) For an excellent review, see: Anderson, N. G. *Org. Process Res. Dev.* **2006**, *10*, 683.

Experimental Section

***N*-Boc-*trans*-4-hydroxy-L-proline Methyl Ester (3).** To a stirred slurry of *trans*-4-hydroxy-L-proline (**2**, 2.3 kg, 17.5 mol) in methanol (9.4 kg) was added portionwise thionyl chloride (2 kg, 0.96 equiv) using a feeding pump over 1 h at 5 °C. During the addition, the reaction temperature was slowly warmed to 34 °C. After the completion of the addition, the resulting slurry was heated to 60 °C and stirred for 24 h to give a clear light-brown solution. The mixture was evaporated under reduced pressure to give methyl ester as a light-brown solid containing a small amount of methanol, which was used in the next step without further purification. Boc_2O (4.3 kg, 1.12 equiv) was added portionwise to a stirred suspension of crude methyl ester in dichloromethane (25 kg). To the mixture was added slowly a solution of triethylamine (5.0 L, 2.04 equiv) in CH_2Cl_2 (10 kg). When most of staring material was consumed by TLC analysis (approximately 3.5 h), the reaction mixture was quenched with 1 *N* HCl solution (11 kg). The organic layer was separated and evaporated under reduced pressure to give a brown viscous liquid. *n*-Hexane (6.0 L) was added to the concentrate, and the resulting slurry was vigorously stirred at ambient temperature. Filtration of the formed solid and drying with N_2 purge gave alcohol **3** as an off-white solid (3.5 kg, 14.3 mol, 81.5%). ^{1}H NMR (a mixture of rotamers, 400 MHz, $CDCl_3$) δ 1.38 (s, 3.6 H), 1.44 (s, 5.4H), 1.75 (br s, 1H,), 2.08 (m, 1H), 2.30 (m, 1H), 3.46 (br d, J = 11.8 Hz, 0.4 H), 3.56 (br d, J = 11.8 Hz, 0.6 H), 3.65 (dd, J = 4.4, 11.8 Hz, 1H), 3.74 (s, 3H), 4.40 (t, J = 8.0 Hz, 0.6 H), 4.44 (t, J = 8.0 Hz, 0.4 H), 4.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 28.7, 38.6, 39.3, 52.4, 52.5, 54.9, 55.0, 57.9, 58.3, 69.3, 70.0, 80.6, 80.7, 154.4, 155.0, 173.9, 174.1.

(4*S*)-*N*-Boc-*cis*-4-fluoro-L-proline Methyl Ester (4). Diethylaminosulfur trifluoride (DAST) (4.5 kg, 1.9 equiv) was added dropwise using a feeding pump to a stirred solution of **3** (3.5 kg, 14.2 mol) in dichloromethane (50 kg) at −2 °C. During the addition, a slight exotherm was observed that resulted in a temperature increase to 7.8 °C. After completion of the addition, the mixture was slowly warmed to ambient temperature and stirred for 14 h. To the mixture was added over 5 h saturated aqueous $NaHCO_3$ solution at 0 °C. The organic layer was separated and the aqueous layer was extracted again with 8.0 kg of dichloromethane. The combined organic layer was concentrated under reduced pressure to give the crude brown oil **4** (3.29 kg), which was directly used for the next step without further purification. ^{1}H NMR (a mixture of rotamers, 400 MHz, $CDCl_3$) δ 1.44 (s, 5H), 1.49 (s, 4H), 2.25−2.55 (m, 2H), 3.56−3.93 (m, 2H), 3.75 (s, 3H), 4.43 (d, J = 9.2 Hz, 0.5H), 4.55 (d, J = 9.2 Hz, 0.5H), 5.20 (br d, J = 52.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 27.9, 36.1 (d, $^2J_{CF}$ = 21.5 Hz), 36.9 (d, $^2J_{CF}$ = 21.5 Hz), 51.6, 51.7, 52.4 (d, $^2J_{CF}$ = 23.9 Hz), 52.6 (d, $^2J_{CF}$ = 23.9 Hz), 56.8, 57.2, 79.6, 79.7, 90.8 (d, $^1J_{CF}$ = 176.5 Hz), 91.9 (d, $^1J_{CF}$ = 176.5 Hz), 153.2, 153.5, 171.4, 171.8.

2-*tert*-Butyl-1,3,4-oxadiazole (6). To a stirred solution of 5.02 kg of pivalic acid (49.13 mol) in 5.0 L of toluene and 8.0 L of *n*-butanol was added NH_2NH_2 monohydrate (80% purity, 51% of hydrazine, 1.15 equiv). During the addition, the reaction temperature rose from 18 to 32 °C. After completion of the addition, the mixture was heated to 90 °C, and Ti(O-*i*-Pr)$_4$ (140 g, 1 mol%) was added slowly. After 1.5 h at the same temperature, the reaction mixture was heated to 115 °C for 4 h with azeotropic distillation using a Dean−Stark separator (∼2.5 L of distilled water was collected). After cooling to 56 °C, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give a waxy solid. Trituration of the residue with *n*-hexane (5 L) and filtration afforded 2,2-dimethylpropanohydrazide (4.32 kg, 75%) as a white solid. ^{1}H NMR of (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 3.92 (br s, 2H), 7.29 (br s, 1H).

Catalytic amount of *p*-toluenesulfonic acid monohydrate (140 g, 2 mol%) was added to a stirred mixture of 2,2-dimethylpropanohydrazide (4.30 kg, 37 mol) and trimethyl orthoformate (5.0 L, 1.23 equiv) at ambient temperature (16 °C). The reaction mixture was heated to 70 °C. After 2 h, the temperature was raised to 106 °C to remove methanol via a Dean−Stark separator. The resulting brown solution was distilled under reduced pressure (55−60 mmHg) to give a *tert*-butyl-1,3,4-oxadiazole[12] (**6**, 3.70 kg, 28.5 mol, 75%) as a colorless liquid.^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 8.32 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 32.4, 152.9, 173.3.

***tert*-Butyl-(2*S*,4*S*)-2-[(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)carbonyl]-4-fluoropyrrolidine-1-carboxylate (7).** To a stirred solution of oxadiazole (**6**, 1.9 kg, 15 mol) in THF (20 L) was added slowly 6.0 L of *n*-BuLi (2.5 M in hexane) under positive N_2 pressure over 4 h, maintaining the reaction temperature below −60 °C (After ∼2.0 h, the reaction mixture changed to an off-white slurry due to the formation of lithiated oxadiazole). After completion of the addition, the reaction mixture was stirred for 40 min and cooled to −70 °C. A solution of methyl ester **4** (1.75 kg, 7.0 mol) in THF (2.0 L) was added over 1.5 h to a stirred slurry of lithiated oxadiazole, maintaining the reaction temperature below −60 °C. After the completion of the addition, the reaction temperature was warmed slowly to −30 °C over 2 h. After completion of the reaction was confirmed by ^{1}H NMR analysis, the reaction mixture was quenched by an aqueous NH_4Cl solution (3 kg of NH_4Cl and 15 kg of H_2O). The organic layer was separated and concentrated under reduced pressure to give a brown-colored oil, which was vigorously triturated with *n*-hexane (3.0 L) to give ketone **7** (1.6 kg, 4.68 mol, 67%) as a white solid, including less than 5% of tertiary alcohol **13** on the basis of NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 4.5H), 1.47 (s, 4.5H), 1.49 (s, 9H), 2.57−2.74 (m, 2 H), 3.74 (m, 1H), 3.93 (m, 1H), 5.32−5.42 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 28.3, 29.6, 32.7, 32.8, 36.4 (d, $^2J_{CF}$ = 21.5 Hz), 37.3 (d, $^2J_{CF}$ = 21.5 Hz), 53.1 (d, $^2J_{CF}$ = 23.9 Hz), 53.4 (d, $^2J_{CF}$ = 23.9 Hz), 61.9, 62.0, 80.7, 91.9 (d, $^1J_{CF}$ = 176.5 Hz), 92.2 (d, $^1J_{CF}$ = 176.5 Hz), 153.2, 153.9, 169.7, 175.4, 175.6, 183.6, 184.0. Spectroscopic data of **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.43 (s, 9H), 1.51 (s, 9H), 2.61−2.79 (m, 2H), 3.53 (dd, J = 13.2, 23.6 Hz, 1H), 3.73 (ddd, J = 4.9, 13.2, 30.6 Hz, 1H), 5.01 (dm, J = 54.4 Hz, 1H), 5.16 (dd, J = 3.2, 9.6 Hz, 1H), 7.81 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 28.2, 32.3, 32.4, 35.3 (d, $^2J_{CF}$ = 22.9 Hz), 54.6 (d, $^2J_{CF}$ = 25.0 Hz), 62.7, 74.3, 82.8, 90.5 ($^1J_{CF}$ = 177.7 Hz), 158.4, 162.9, 164.4, 173.9, 174.4.

(12) Please refer to ref 7.

[(2*S*,4*S*)-1-(Bromoacetyl)-4-fluoropyrrolidin-2-yl](5-*tert*-butyl-1,3,4-oxatriazol-2-yl)methanone (9). To a stirred solution of ketone **7** (2.28 kg, 8.26 mol) in ethyl acetate (20 L) was added a solution of saturated HCl in ethyl acetate (20 L) at ambient temperature, and the resulting mixture was stirred for ~1.5 h. The color of the reaction mixture slowly changed to dark purple. Concentration of the mixture afforded amine salt **14** (2.18 kg, > 95%) as a dark purple-colored solid, which was used in next step without purification.^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.82−3.16 (m, 2H), 3.82−4.05 (m, 2H), 5.40 (dm, J = 52.8 Hz, 1H), 5.70 (d, J = 9.6 Hz, 1H), 9.20 (br s, 1H), 11.10 (br s, 1H).

To a mixture of amine salt **7** (1.0 kg, 3.6 mol) and bromoacetyl bromide (0.35 L, 1.1 equiv based on ketone **7**) in dichloromethane (15 L) was added slowly triethylamine (10.6 L, 2.1 equiv) at 0 °C. After completion of the addition, the reaction temperature was warmed to 20 °C over 40 min. The mixture was washed with 0.5 *N* HCl solution (20 L) and saturated aqueous $NaHCO_3$ solution (20 L) in sequence. The organic layer was concentrated to give bromide **9** (1.15 kg, 88%) as a light purple-colored solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 7H), 1.50 (s, 2H), 2.60−2.86 (m, 2H), 3.56 (d, J = 11.0 Hz, 0.2H), 3.76 (d, J = 11.0 Hz, 0.2H), 3.85 (d, J = 11.0 Hz, 0.8H), 3.93 (d, J = 11.0 Hz, 0.8H), 3.85−4.14 (m, 2H), 5.27 (dm, J = 52.0 Hz, 0.2H), 5.38 (dm, J = 52.0 Hz, 0.8H), 5.59 (d, J = 10.4 Hz, 0.2H), 5.61 (d, J = 10.4 Hz, 0.8H). Spectroscopic data of pyrrole **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 6.42 (m, 1H), 7.21 (m, 1H), 7.70 (br s, 1H), 10.0 (br s, 1H).

LC15-0133 (1). A mixture of bromide **9** (1.15 kg, 3.17 mol) and oxazolidine **16** (4.5 kg, 4.8 equiv based on **9**) in dichloromethane (10 L) was stirred at ambient temperature (25 °C). After 14 h, TLC showed that approximately 5−10% of starting bromide **9** was not consumed. Additional oxazolidine **16** (1.8 kg, 1.9 equiv) was added, and the mixture was stirred for 4 h. To the reaction mixture was added CH_2Cl_2 (10 kg) and H_2O (15 kg). The organic layer was separated, and the separated aqueous layer was re-extracted with 6.0 kg of CH_2Cl_2. The combined organic layer was concentrated under reduced pressure to provide a *cis*- and *trans*-diastereomeric mixture **17** as brown-colored viscous oil. ^{1}H NMR (*cis*- and *trans*-mixture, 500 MHz, $CDCl_3$) δ 1.00 (s, 2H), 1.01 (s, 2H), 1.07 (s, 2H), 2.24 (dddd, J = 3.7, 10.4, 14.4, 39.7 Hz, 0.7H), 2.56−2.79 (m, 1.3H), 3.05 (d, J = 11.7 Hz, 0.8H), 3.13 (d, J = 11.7 Hz, 0.8H), 3.22−3.43 (m, 2.1H), 3.53 (d, J = 16.0 Hz, 0.3H), 3.79−4.02 (m, 2H), 5.36 (dm, J = 52.0 Hz, 0.3H), 5.41 (dm, J = 52.0 Hz, 0.7H), 5.42 (dd, J = 8.0, 9.8 Hz, 0.7H), 5.61 (dd, J = 1.5, 10.0 Hz, 0.3H).

To s stirred solution of **17** in cosolvents of 4.22 kg of CH_2Cl_2, 20.8 kg of methanol, and 3.20 kg of H_2O was added 640 g of NH_4Cl (12.0 mol) at ambient temperature (21 °C). After stirring for 2.5 h, the reaction mixture was diluted with 20 kg of H_2O and 30 kg of CH_2Cl_2. The pH of the heterogeneous mixture was adjusted to 8.0 with triethylamine (220 g), and the organic layer was separated. The separated aqueous layer was re-extracted with 15 kg of CH_2Cl_2, and the combined organic layer was concentrated under reduced pressure to give crude LC15-0133 (**1**) as a waxy light brown-colored solid. Diethyl ether (6.0 L) was added, and the resulting slurry was vigorously stirred for 1.0 h. Filtration and drying with N_2 purge overnight provided LC15-0133 (**1**) (680 g, 58% from **9**) as an off-white solid. ^{1}H NMR (*cis*- and *trans*-diastereomeric mixture, 500 MHz, $CDCl_3$) δ 1.00 (s, 2H), 1.01 (s, 2H), 1.07 (s, 2H), 1.45 (s, 9H), 2.24 (dddd, J = 3.7, 10.4, 14.4, 39.7 Hz, 0.7H), 2.56−2.79 (m, 1.3H), 3.05 (d, J = 11.7 Hz, 0.8H), 3.13 (d, J = 11.7 Hz, 0.8H), 3.22−3.43 (m, 2.1H), 3.53 (d, J = 16.0 Hz, 0.3H), 3.79−4.02 (m, 2H), 5.36 (dm, J = 52.0 Hz, 0.3H), 5.41 (dm, J = 52.0 Hz, 0.7H), 5.42 (dd, J = 8.0, 9.8 Hz, 0.7H), 5.61 (dd, J = 1.5, 10.0 Hz, 0.3H). ^{13}C NMR (125 MHz, CD_3OD with 0.1% TFA) δ 19.4, 19.6, 27.0, 32.6, 35.1 (d, $^2J_{CF}$ = 20.3 Hz), 42.2, 52.8 (d, $^2J_{CF}$ = 25.0 Hz), 60.3, 62.6, 65.3, 92.4 ($^1J_{CF}$ = 180.0 Hz), 160.0, 164.6, 175.7, 181.9; MS(ESI) *m*/*z* 371 (M + H).

***cis*-LC15-0133 (1a) Tartrate Salt.** To a solution of LC15-0133 (**1**) (410 g, 1.1 mol) in methanol (2.0 L) was added L-(+)-tartaric acid (167 g, 1.0 equiv) at ambient temperature (18 °C). After the mixture became a homogeneous brown-colored solution, methanol was removed under reduced pressure to give a waxy solid. To the residue was added 3.0 L of CH_3CN. On dissolving the solid, crystals began to form. After 1.0 h, the resulting solid was filtered and dried with N_2 purge overnight to provide *cis*-LC15-0133 (**1a**) tartrate salt (475 g, 83%, 98% de) as an off-white solid.^{1}H NMR (400 MHz, CD_3OD with 0.1% TFA) δ 1.27 (s, 0.65H), 1.28 (s, 0.65H), 1.34 (s, 4.7H), 1.46 (s, 7H), 1.47 (s, 2H), 2.65−2.88 (m, 2H), 3.52−3.68 (m, 2H), 3.81−4.08 (m, 3.2H), 4.15 (d, J = 16.5 Hz, 0.8H), 4.52 (s, 2H), 5.31 (dm, J = 52.0 Hz, 0.2H), 5.39 (dm, J = 52.0 Hz, 0.8H), 5.53 (d, J = 9.8 Hz, 0.6H), 5.58 (m, 0.8H). ^{13}C NMR (125 MHz, CD_3OD with 0.1% TFA) δ 19.4, 19.6, 27.0, 32.6, 35.1 (d, $^2J_{CF}$ = 21.5 Hz), 42.2, 52.8 (d, $^2J_{CF}$ = 25.0 Hz), 60.4, 62.6, 65.3, 72.1, 92.4 ($^1J_{CF}$ = 180.0 Hz), 159.9, 164.7, 173.5, 175.8, 182.0; MS(ESI) *m*/*z* 371 (M + H).

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