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# Practical Synthesis of a Peptide Deformylase (PDF) Inhibitor

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**Abstract:**

**A practical chromatography-free synthesis of an *N*-formylated hydroxylamine peptide deformylase inhibitor LCD320 is described. A diastereoselective Michael reaction of (4*S*)-3-[2-(cyclobutylmethyl)-1-oxo-2-propenyl]-4-(phenylmethyl)-2-oxazolidinone with *O*-benzyl hydroxylamine was used to establish the key stereogenic center. We found that traces of residual $Li^+$ from a previous step had a great impact on the diastereoselectivity of this reaction. A very efficient amidation coupling reaction of proline derivative (2*S*,4*R*)-4-fluoro-1,2-pyrrolidinedicarboxylic acid 1,1-dimethylethyl ester with weakly nucleophilic 3-pyridazinamine using methanesulfonyl chloride in the presence of 1-methylimidazole in DMF was also developed that proceeded without racemization.**

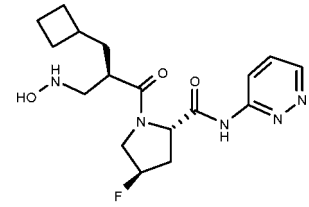
## Introduction

LCD320 (**1**) belongs to a novel class of antimicrobial agents known as peptide deformylase (PDF) inhibitors.[1] It is a follow-up compound to LBM415.[2,3] Peptide deformylase is a highly conserved bacterial enzyme that plays a key physiological role in bacterial cell growth and sustained viability. PDF modulates a step in prokaryotic protein synthesis not generally found in the cytosolic protein synthesis of eukaryotes of mammalians, thus providing a new target for the development of a novel class of antibacterial agents with an entirely new mechanism of action. Respiratory tract infections (RTIs) comprise the single largest market for all antibacterials (>$15 billion annually). The major pathogen that causes RTIs, *Streptococcus pneumoniae*, is now becoming resistant to many existing therapies on the market. The need for a new class of antibacterials that are active against resistant strains and have no cross-resistance with currently used agents is the number one priority in antibacterial research.

Large quantities of LCD320 (**1**) were needed for toxicology and clinical studies, which required a practical synthesis that was suitable for scale-up.

## Results and Discussion

On the basis of our experiences with the $\beta$-lactam route[2] to LBM415, we decided to use the same strategy for LCD320.



**1**

We first synthesized $\beta$-lactam intermediate **12** and investigated the ring-opening reaction with proline derivative **13** (vide infra). Compound **4**, which was made by the alkylation of diethyl malonate with bromomethyl cyclobutane (vide infra), was decarboxylated in a minimal amount of 1-methyl-2-pyrrolidinone (NMP) or DMF at 110 °C for 2 h to afford compound **5** in quantitative yield (Scheme 1). Other solvents such as toluene and ethanol did not give any decarboxylated product **5**. Acid **5** was treated with trimethylacetyl chloride and triethylamine to form the corresponding mixed anhydride, which reacted with (*S*)-(−)-4-benzyl-2-oxazolidinone in the presence of LiCl[4] to afford the desired product **6** in 90% yield. Asymmetric hydroxymethylation of **6** was accomplished using *s*-trioxane and $TiCl_4$ in the presence of *N,N*-diisopropylethylamine in dichloromethane to afford **7** in 85% yield as a single diastereomer. Quite interestingly, racemization of the newly generated stereogenic center occurred if the reaction mixture was not quenched promptly. To obtain high diastereoselectivity, the reaction had to be quenched at ∼95% conversion. Hydrolysis of **7** using $LiOH/H_2O_2$ afforded chiral acid **8** in 94% yield. Acid **8** was coupled with *O*-benzylhydroxylamine hydrochloride (**9**) in aqueous sodium hydroxide solution in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) to give amide **10** in 77% yield, which upon treatment with methanesulfonyl chloride in the presence of pyridine afforded mesylate **11** in 79% yield. $\beta$-Lactam **12** was produced in 90% yield by treatment of **11** with aqueous potassium carbonate in isopropyl acetate in the presence of 10 mol % of tetrabutylammonium bromide. With the desired $\beta$-lactam **12** in hand, we investigated the ring-opening reaction with **13**. Unfortunately, a mixture of the desired product **14** and bicyclic product **15** were formed in ∼1:9 ratio under a variety of conditions when the conversion of **12** was >95%. We also identified that byproduct **15** was produced via the intermediacy of desired compound **14**, since the ratio increased with reaction time. Although not anticipated when we first selected this approach, now it became obvious that the pyridazin-3-ylamino group was such a good leaving group that cyclization of **14** to produce **15**

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(1) (a) For a discussion of PDF inhibitors, see: Huntington, K. M.; Yi, T.; Wei, Y.; Pei, D. *Biochemistry* **2000**, *39*, 4543 and references therein. (b) Pratt, L. M.; Beckett, R. P.; Davies, S. J.; Launchbury, S. B.; Miller, A.; Spavold, Z. M.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2585.

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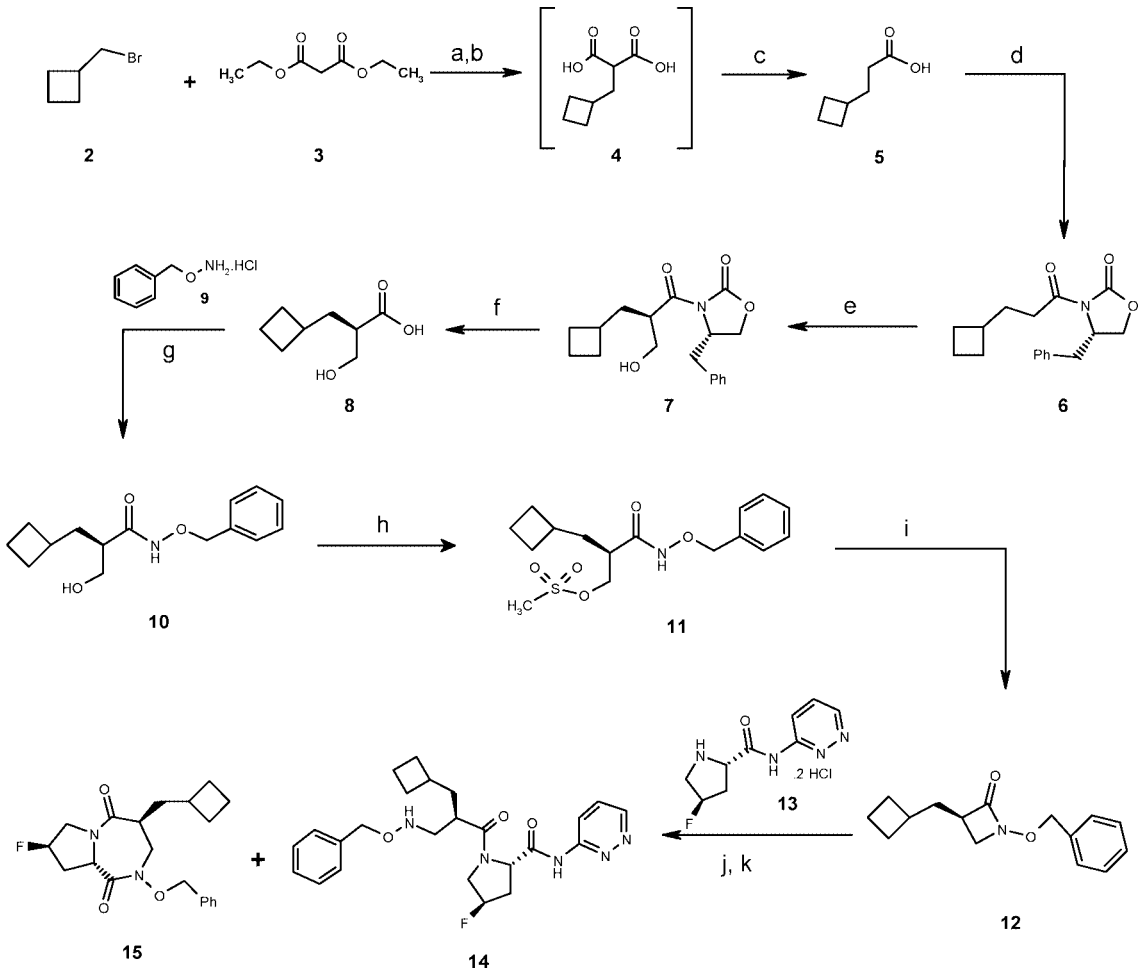
***Scheme 1***[a]




[a] Reagents and conditions: (a) NaOMe, NaOH; (b) HCl, 69%; (c) NMP, 110 °C, quantitative; (d) pivalyl chloride, LiCl, (*S*)-(−)-4-benzyl-2-oxazolidinone, THF, −15 °C, 90%; (e) s-trioxane, $TiCl_4$, *N,N*-diisopropylethylamine, $CH_2Cl_2$, 0 °C, 85%; (f) LiOH monohydrate, $H_2O_2$, THF, 0 °C, 94%; (g) **9**, NaOH, EDCI, $H_2O$, 77%; (h) $CH_3SO_2Cl$, DMF, pyridine, 79%; (i) *i*PrOAc, $K_2CO_3$, $H_2O$, $Bu_4NBr$, 90%; (j) **13**, NaOH, rt; (k) 2-ethylhexanoic acid, THF.

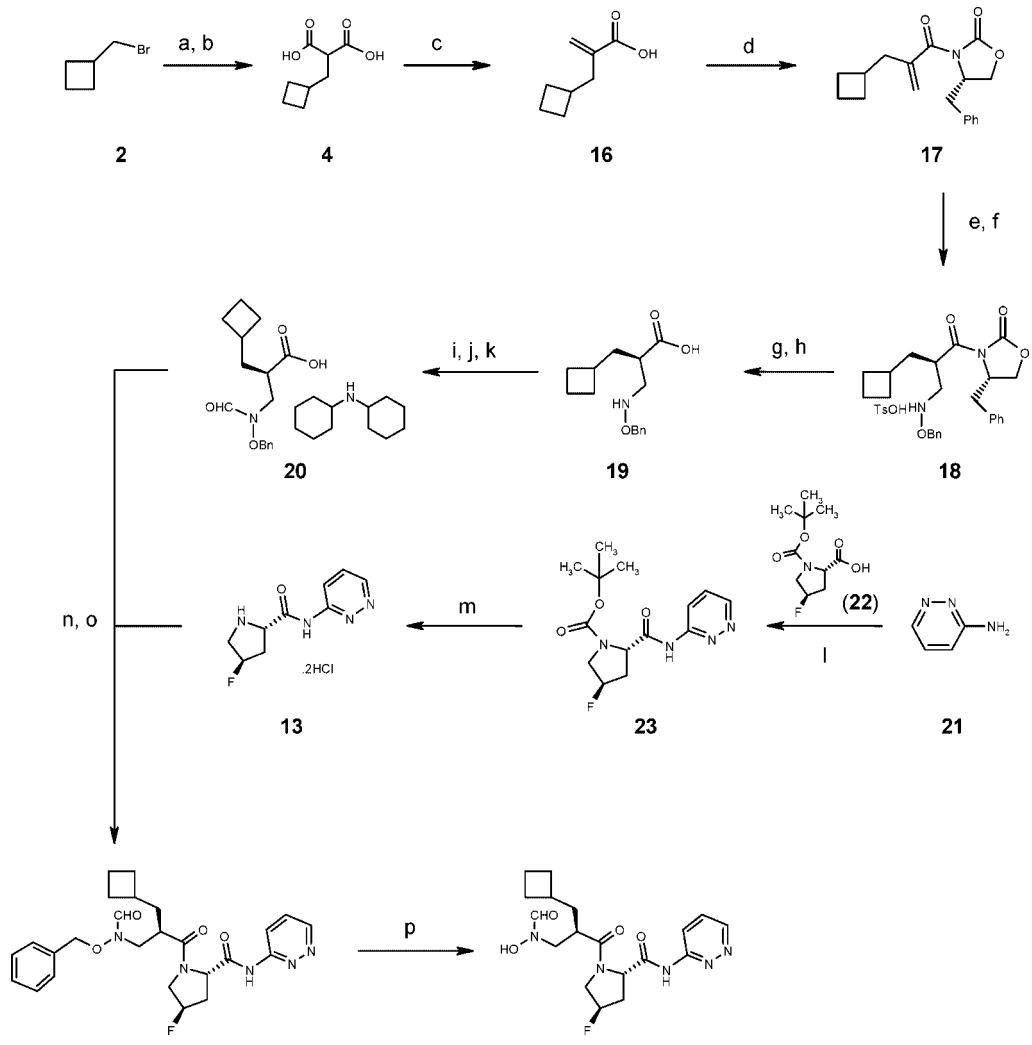
seemed to be inevitable. Therefore, another approach had to be developed.

We decided to use the Michael addition route[3] that was originally used for LBM415. This alternative synthesis started with a simple alkylation reaction of diethyl malonate with bromomethyl cyclobutane (**2**; Scheme 2). For molecules that lack chromophores, it is generally challenging to develop a simple and reliable HPLC method for in-process controls. By monitoring the reaction at 220 nm using HPLC, we were able to determine the end-point of this reaction reliably. The product **4** was isolated as a solution in isopropyl acetate and was carried directly to the next step. This avoided purification by silica gel chromatography. The yield of **4** was 69% as determined by concentrating a known amount of the solution to dryness and subsequent $^1$H NMR analysis of the residue. Since conversion of **4** to **16** had to be run in ethanol, a solvent exchange from isopropyl acetate to ethanol was performed prior to the reaction. Then the ethanol solution of **4** was added to a mixture of piperidine (1.1 equiv) and aqueous formaldehyde solution (4.5 equiv), and the mixture was heated at reflux until the reaction was complete (∼2.5 h). Ethanol was removed, and the product **16** was extracted into isopropyl acetate. Acid **16** was not isolated, and the isopropyl acetate solution was used directly in the next step. Thus, purification of **16** by silica gel chromatography was not necessary. The yield of **16** was 78% as determined by concentrating a known amount of the solution to dryness. The HPLC purity of **16** was 95.6%.

The coupling of **16** with (*S*)-(−)-4-benzyl-2-oxazolidinone was achieved using an improved literature procedure.[4] Thus, **16** (1 equiv) was mixed with trimethylacetyl chloride (0.95 equiv) in the presence of triethylamine (2.5 equiv) in tetrahydrofuran at −15 °C to form the corresponding mixed anhydride, and then (*S*)-(−)-4-benzyl-2-oxazolidinone (0.9 equiv) and anhydrous lithium chloride (1 equiv) were added sequentially. The reason for using <1 equiv of trimethylacetyl chloride was because unreacted **16** could be easily removed upon aqueous workup. The reaction mixture was warmed to 20–25 °C and stirred for 16 h. Product **17** was isolated by using aqueous workup and crystallization from *tert*-butyl methyl ether/heptanes in 82% yield with >99% purity.

The key stereogenic center was created by a diastereoselective Michael reaction of *O*-benzyl-hydroxylamine with **17**.[3] The reaction was rather slow in THF at 45 °C, requiring 67 h to complete. Higher reaction temperature resulted in decreased diastereoselectivity. To reduce the reaction time, we executed the reaction under fairly concentrated conditions by adding the fluffy solid **17** to a solution of 2 equiv of *O*-benzyl hydroxylamine in a minimal amount of toluene, heating the slurry to

***Scheme 2***[a]

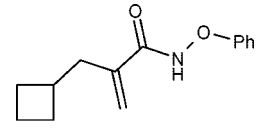



[a] Reagents and conditions: (a) diethyl malonate (**3**), NaOMe, NaOH; (b) HCl, 69%; (c) piperidine, HCHO, 78%; (d) pivalyl chloride, LiCl, (*S*)-(-)-4-benzyl-2-oxazolidinone, THF, −15 °C, 82.2%; (e) $BnONH_2$ hydrochloride (**9**), toluene, $NaHCO_3$, rt (f) TsOH monohydrate, EtOAc, rt, 60%; (g) NaOH, EtOAc, rt; (h) LiOH monohydrate, $H_2O_2$, THF, 0 °C, 74%; (i) $Ac_2O$, $HCO_2H$, 0 °C; (j) EtOAc, −10 °C (k) toluene/heptanes, dicyclohexylamine, rt, 79%; (l) **22**, 1-methylimidazole, $CH_3SO_2Cl$, DMF, −10 °C, 77.4%; (m) *conc.* HCl, $CH_3CN$, rt, 96.5%; (n) toluene, citric acid, rt; (o) 1-methylimidazole, $CH_3SO_2Cl$, DMF, −12 °C; (p) 10% Pd/C, $HCO_2NH_4$, EtOH, 60 °C, 60.1%.

48 °C for 3 h to obtain a clear solution and then distilling part of the toluene to further accelerate the Michael addition reaction. The reaction was usually complete in 40 h. The reaction mixture was then diluted with ethyl acetate and reacted with *p*-toluenesulfonic acid monohydrate to form the salts. The *O*-benzyl-hydroxylamine tosylate salt was insoluble in ethyl acetate and was filtered off. The mother liquor that contained **18** was concentrated, and *tert*-butyl methyl ether was added as an antisolvent to precipitate the desired salt **18**. Although the diastereoselectivity in the reaction mixture was ∼3–4:1, the undesired diastereomer remained in the mother liquor, allowing the isolation of the desired product **18** as a solid in 60–64% yield containing only <1% of the undesired diastereomer.

Surprisingly, a use-test with intermediate **17** obtained from scale-up in the pilot plant gave dramatically lower diastereoselectivity (from 3:1 to 2:3), leading to lower yield of **18**. A major byproduct **25** was isolated in substantial amounts.

Because **17** obtained on large scale was not different by HPLC and NMR compared with small-scale laboratory samples,



**25**

we postulated that the change in diastereoselectivity was probably due to water or some very minor impurities in compound **17**, considering that we had been using the same batch of *O*-benzylhydroxylamine. We first ruled out the possibility of water affecting the reaction by analyzing the water content in **17**, and it did not contain any water. We suspected that LiCl, which was used as a reagent in the preparation of **17**, might not have been efficiently removed during workup and later on acted as a Lewis acid in the Michael addition step, therefore affecting the diastereoselectivity of the reaction. To test this hypothesis, we intentionally added 0.5 equiv of LiCl into the reaction mixture using **17**, prepared in the laboratory, that had already given good diastereoselectivity. Indeed, the

**Table 1**

| entry | $Li^+$ (ppm) | yield of **18** (%) | by-product **25** (%) | **18**:diastereomer |
|---|---|---|---|---|
| 1 | 1 | 60.1 | 4.6 | 3.1:1 |
| 2 | 1 | 64.1 | <1 | 3.7:1 |
| 3 | 1 | 62.0 | 1.5 | 3.1:1 |
| 4 | 16 | 60.0 | 6.4 | 2.7:1 |
| 5 | 64 | 22.5 | 14.4 | 1.1:1 |
| 6 | 76 | not determined | 20.5 | 1:1.5 |

diastereomeric ratio of the products decreased to 1:1.5, and byproduct **25** was also formed in a large amount. Both the reversal of the diastereoselectivity and the formation of byproduct **25** can be rationalized by the chelating effect of $Li^+$ to the carbonyls of the imide, which will favor the formation of the wrong diastereomer and also make the external carbonyl group more electrophilic.

These results prompted us to analyze the lithium content of all batches of intermediate **17** that had been used in the Michael additions, and the results on the effect of lithium content on diastereoselectivity and byproduct **25** formation are summarized in Table 1.

It was clear that the $Li^+$ content adversely affected the diastereoselectivity and the yield. With this knowledge, we modified the workup conditions during the purification of **17** by performing three aqueous washes versus only one wash used before, affording **17** with only 1 ppm of $Li^+$. As expected, the reaction using this batch of **17** worked very well and afforded the desired product **18** with good diastereoselectivity (3–4:1) and yield (60–64%).

The chiral auxiliary was removed under standard conditions.[5] Thus, **18** (1 equiv) was treated with sodium carbonate solution (1.5 equiv) in ethyl acetate at 20–25 °C to generate the free base, which was dissolved in THF after removal of ethyl acetate by distillation. Then water and hydrogen peroxide (2.16 equiv) were added to the THF solution at 0 ± 3 °C, followed by addition of LiOH (1.2 equiv) solution. The hydrolysis was complete within 2 h. The excess hydrogen peroxide was quenched with sodium sulfite, and the chiral auxiliary was removed by two extractions with ethyl acetate. After adjusting the pH to 5 ± 0.5, amino acid **19** was extracted into ethyl acetate. It is important not to overacidify to pH < 2, otherwise $SO_2$ will be generated, giving a bad odor. The yield of **19** was 74% based on concentration of a known amount of the ethyl acetate solution of **19** to dryness. Compound **19** was not stable and polymerized easily upon storage. It was isolated in ethyl acetate solution and was used directly in the next step as soon as possible.

Addition of FAM (formyl acetyl mixed-anhydride, made by reacting 2 equiv of acetic anhydride with 8 equiv of formic acid) to the above solution of **19** afforded the *N*-formylated product. We had thought that the residual water in the **19** solution might destroy some of the formylation agent FAM, but this was proved to be of no concern since the formylation reaction at −15 °C was very fast and FAM was used in excess. Because the *N*-formylated product was an oil, we decided to isolate it as a salt. Concerned that there might be some racemization during the previous step, we initially opted to use (*R*)-α-methylbenzylamine for the salt formation. This decision was based on our knowledge that the (*R*)-α-methylbenzylamine salt of the undesired enantiomer was an oil, while the desired enantiomer gave a crystalline solid. We did obtain the (*R*)-α-methylbenzylamine salt in 85% yield on a small scale, but it was critical to remove most of the acetic acid azeotropically with toluene before (*R*)-α-methylbenzylamine was added. Otherwise, the salt would not crystallize, and the product would revert back to **19** (∼10% in 16 h) slowly. The formation of **19** was probably due to the deformylation of the product by (*R*)-α-methylbenzylamine. We have proved later that dicyclohexylamine worked equally well to afford compound **20** with comparable yield and excellent ee (>99%). What was more important, there was no deformylation when dicyclohexylamine was used. Again, it was also necessary to remove acetic acid to a defined level in this case.

Prolinamide intermediate **13** was synthesized by a coupling reaction of pyridazin-3-ylamine (**21**) and (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (**22**) to afford intermediate **23**, followed by the deprotection of the Boc group in **23** with hydrochloric acid. The coupling reaction was very difficult due to the very low nucleophilicity of **21**. The prior method for the coupling reaction involved the use of Ghosez reagent[6] ((1-chloro-2-methylpropenyl)dimethylamine) in dichloromethane to produce compound **23** in only 32% after purification by silica gel chromatography. Not only was Ghosez reagent not available on a large scale, the use of dichloromethane was undesirable because of environmental constraints. Because (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (**22**) was extremely expensive and very difficult to obtain in large amounts, it became necessary to improve the yield of this amidation coupling reaction. Many conditions using different coupling reagents were investigated. $Ph_2POCl$ and CDMT gave low conversion, whereas EDCI/HOBt afforded the desired product in only 42% yield. It was reported[7] in the literature that *N*-protected proline derivatives could be coupled with amines via the intermediacy of the mixed anhydride formed with MsCl in the presence of *N*-methylimidazole. The coupling reaction was conducted in dichloromethane at 40 °C, leading to epimerization of the C-2 center of the *N*-protected proline derivative. When we used these conditions with **21** and **22**, we obtained **23** in 65% yield, but a significant amount of the diastereomer of **23** was also observed, apparently as a result of the epimerization of the C-2 stereogenic center of **23**. To minimize the epimerization, we investigated the reaction in DMF at lower temperature and found that the epimerization of the C-2 center was minimized to 1–2% at 0 °C and nearly none at −10 °C. Equally important, the yield of **23** was improved to 77%, and the product was isolated as a crystalline compound by simple addition of NaCl solution into the reaction mixture.

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(7) Ueki, H.; Ellis, T. K.; Martin, C. H.; Boettiger, T. U.; Bolene, S. B.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7104.

The Boc group was easily removed with concentrated HCl (4.5 equiv) at 25 °C in acetonitrile to afford **13** in 96.5% yield.

The coupling reaction of acid **20** and amine **13** was initially done in acetonitrile using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)[8] as the coupling reagent. The product was extracted into isopropyl acetate after removal of acetonitrile and addition of water. The isopropyl acetate solution was washed with water, 20% citric acid solution, and sodium bicarbonate solution repeatedly to remove the polar byproduct generated from HATU. On a small scale, after these washes, the crude product **24** was pure enough for the next step, and compound **1** could be obtained in ~60% yield by crystallization after hydrogenolysis of **24** using standard transfer-hydrogenation conditions. Unfortunately, when the coupling reaction was scaled up, we encountered difficulty in crystallizing the drug substance using the crude **24** obtained with the HATU procedure. It was desirable to develop a new procedure without having to use HATU because it was expensive and generated polar byproducts that were hard to remove. Since we already had success with methanesulfonyl chloride in the coupling of **21** and **22**, we decided to use our new amidation reaction conditions for the coupling of **20** and **13**. Indeed, the coupling reaction of **20** and **13** worked very well under the same conditions, and the yield of **24** was 82.4%. Because (2*S*,4*R*)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (**22**) was very expensive and hard to obtain, amine **13** became more precious compared to acid **20** at this point. To maximize the yield of **24** per 1 g of **13**, we decided to perform the coupling reaction with a slight excess of **20** (1.05 equiv). As expected, we obtained **24** in 85.2% yield based on **13**, which was 8% more than what would have been obtained using the original stoichiometry. Compound **24** was isolated as a solution in isopropyl acetate and was used directly in the next step after being concentrated to a defined volume.

The debenzylation of **24** involved heating **24** (1 equiv), ammonium formate (1.05 equiv), and 10% Pd/C (50% wet) at 60 °C for 30 min. After screening a number of solvents and solvent combinations, we found that the drug substance could be crystallized from isopropyl acetate/ethanol (~15:1, v/v). When HATU was used as the coupling agent to produce **24**, the polar byproducts formed in the HATU coupling reaction were partially carried over to this step. These polar byproducts, albeit present in very small amounts, slowed down the crystallization of **1**. The crystallization usually took 7 days, and the yield of the drug substance was low (25–45%) and unpredictable. A significant amount of the drug substance stayed in the mother liquor. By using our new coupling procedure involving methanesulfonyl chloride, these polar byproducts from HATU no longer existed. Hydrogenolysis of **24** was conducted under the same conditions, and the ethanol solution of crude **1** was treated with activated charcoal (Pica P1400) for 4 h at 35 °C to remove Pd to <2 ppm. The activated charcoal was filtered, and the mother liquor was concentrated to a defined volume. Addition of isopropyl acetate followed by seeding with pure **1** initiated the crystallization of the product. To ensure consistent recovery of **1** in the crystallization, we also defined an in process control that involved monitoring the decrease of the concentration of **1** in solution by HPLC. This way, **1** was consistently obtained in ~60% yield and with >99% purity. It was interesting to note that when the hydrogenation reaction was done using $H_2$/$Pd(OH)_2$, the reaction was clean but the drug substance failed to crystallize even upon seeding. The exact reason is not known.

All steps were successfully scaled up in the pilot plant to deliver >3.0 kg of LCD320 (**1**).

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

## Conclusions

A practical chromatography-free synthesis of the *N*-formylated hydroxylamine peptide deformylase inhibitor **1** was achieved by using a diastereoselective Michael reaction of **17** with *O*-benzylhydroxylamine to establish the key stereogenic center. We found that traces of $Li^+$ had great impact on the diastereoselectivity of this reaction. The very expensive and not readily available Ghosez reagent used in the coupling reaction of **21** with **22** was replaced by a cheap and readily available reagent methanesulfonyl chloride in the presence of 1-methylimidazole. Dichloromethane was replaced with DMF, and lowering the reaction temperature eliminated epimerization of C-2 in **22**. The coupling reaction using these new conditions was much cleaner, and intermediate **23** was isolated as a solid. In the coupling reaction **20** + **13** → **24**, HATU was replaced with methanesulfonyl chloride as well, and the crude **24** could be carried to the next step without purification. Intermediate **24** was hydrogenated with 10% Pd/C and ammonium formate to afford **1**, which was crystallized from isopropyl acetate/ethanol, thus avoiding purification by silica gel chromatography.

## Experimental Section

Materials were obtained from commercial suppliers and were used without purification. Melting points were obtained on Thomas-Hoover capillary melting-point apparatus. NMR data were obtained on a Bruker instrument operating at 500 MHz for $^1$H and 126 MHz for $^{13}$C. High resolution mass spectra were recorded on a Micromass LCT mass spectrometer with an Agilent 1100 LC system, or with a Micromass GCT mass spectrometer with field ionization direct probe. All reaction temperatures given refer to internal temperatures.

**(4*S*)-3-[2-(Cyclobutylmethyl)-1-oxo-2-propenyl]-4-(phenylmethyl)-2-oxazolidinone (17).** An inerted 800-L reactor was charged with diethyl malonate (**3**, 30.4 kg, 189.77 mol) and ethanol (111 kg). Then 30% w/w sodium methoxide in methanol (34.2 kg, 189.77 mol) was added (exothermic) via an addition funnel over 10 min while maintaining the internal temperature at 20–30 °C. The reaction mixture was heated to 70 ± 3 °C over a period of 40 min and was stirred at this temperature for an additional 1 h. The reaction mixture was cooled to 65 ± 3 °C, and bromomethyl cyclobutane (**2**, 23.6 kg, 157.95 mol) was added over 20 min while maintaining the internal temperature at 62–73 °C. The yellow solution was heated to 70 ± 3 °C (reflux) and stirred at this temperature for 6 h. A solution of sodium hydroxide (19.0 kg, 475.0 mol) in deionized water (318 kg) was added over a period of 30 min while maintaining the internal temperature at 65–75 °C. The reaction mixture was heated to an internal temperature of 80 ± 3 °C over 10 min and stirred for an additional 3 h. It was

cooled to 25–30 °C over a period of 30 min and concentrated under reduced pressure (130–200 mbar) to ~350 L batch volume. Isopropyl acetate (103 kg) was added. The mixture was stirred for 5 min, and the bottom aqueous layer was separated. The aqueous layer was cooled to 0 ± 3 °C over 20 min, and concentrated hydrochloric acid (50.4 kg) was added over a period of 20 min to adjust the pH to 2 ± 0.5 while maintaining the internal temperature at 0–20 °C. Isopropyl acetate (61 kg) was added to the batch, and the mixture was stirred for 10 min while warming to 20 ± 5 °C. The upper organic layer was separated and washed with 10% (w/v) aqueous sodium chloride solution (15 kg) to afford ~90 kg of compound **4** solution in isopropyl acetate (containing 18.8 kg of **4**). The solvent was removed under reduced pressure (130–200 mbar) to a batch volume of approximately 27 L, and ethanol (200 proof, 55 kg) was added. The solution was distilled under reduced pressure (110–150 mbar) to a batch volume of approximately 32 L, and the residue was cooled to 25 ± 5 °C over 20 min. Ethanol (200 proof, 89 kg) was added followed by 37% aqueous formaldehyde solution (44.2 kg, 546.92 mol). The mixture was stirred at 20 ± 5 °C, and piperidine (11.2 kg, 130.84 mol) was added over 30 min while maintaining the internal temperature at 20–35 °C to obtain a slurry. The slurry was heated to 80 ± 3 °C (reflux, $CO_2$ evolution) over 50 min and stirred at this temperature for an additional 2.5 h. The reaction mixture was a solution at this point. The reaction mixture was cooled to 20 ± 3 °C over 40 min. The solvent was distilled under reduced pressure (90–120 mbar) to a batch volume of ~34 L. Isopropyl acetate (74 kg) was added, and the batch was distilled under reduced pressure (130–200 mbar) to ~34 L in volume. The distillation residue was diluted with isopropyl acetate (48 kg) and cooled to 20 ± 3 °C over 15 min. Then 2 N HCl (56 kg) was added over a period of 30 min while maintaining the temperature at 20–35 °C to adjust the pH to <3. The mixture was stirred for 5 min, and the upper organic layer was separated. The organic layer was washed with 2 N HCl (39 kg) and water (19 kg) to afford 85 kg of the **16** solution in isopropyl acetate (containing 11.8 kg of **16**), which was used in the next step. The solution was distilled under reduced pressure (20–120 mbar) to a batch volume of ~24 L, and dry and peroxide-free tetrahydrofuran (147 kg) was added. Triethylamine (21.3 kg, 209.8 mol) was added dropwise over 10 min while maintaining the internal temperature at 20–25 °C. The mixture was cooled to −15 ± 3 °C, and trimethylacetyl chloride (9.6 kg, 80.15 mol) was added over 20 min while maintaining an internal temperature of −15 ± 3 °C to get a suspension. The suspension was stirred for 1 h at −15 ± 3 °C. (*S*)-(−)-4-Benzyl-2-oxazolidinone (13.4 kg, 75.79 mol) was added portion-wise over 10 min, followed by anhydrous lithium chloride (3.57 kg, 84.2 mol). The internal temperature of the reaction mixture rose from −18 to −13 °C in 10 min. The reaction mixture was heated to 20 ± 5 °C over 1 h and stirred at this temperature for an additional 2 h. *tert*-Butyl methyl ether (59 kg) and deionized water (80 kg) were added. The mixture was stirred vigorously for 10 min, and the upper organic layer was separated. The organic layer was washed with deionized water (3 × 45 kg) and concentrated under reduced pressure (200–270 mbar) to ~110 L. To the batch were added heptanes (185 kg) to obtain a suspension. The batch was distilled under reduced pressure (90–150 mbar) to ~220 L and cooled to 20–25 °C. The suspension was stirred at 20 ± 5 °C for 2.5 h. The solid was collected by filtration over a polypropylene filter pad, rinsed with heptanes (2x 16 kg) containing 30 ppm of Octastat, and dried at 50 °C under reduced pressure for 16 h until LOD <1% to afford 18.6 kg (44.2% yield from **2**) of (4*S*)-3-[2-(cyclobutylmethyl)-1-oxo-2-propenyl]-4-(phenylmethyl)-2-oxazolidinone (**17**): mp 90–93 °C. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 1.65–1.79 (m, 2H), 1.80–1.92 (m, 2H), 2.07–2.13 (m, 2H), 2.43–2.53 (m, 3H), 2.80 (dd, $J$ = 13.3, 9.6 Hz, 1H), 3.38 (dd, $J$ = 13.3, 3.5 Hz, 1H), 4.17 (dd, $J$ = 8.8, 4.4 Hz, 1H), 4.24 (dd, $J$ = 8.8, 8.2 Hz, 1H), 4.65–4.75 (m, 1H), 5.35 (d, $J$ = 8.2 Hz, 2H), 7.15–7.20 (m, 2H), 7.25–7.30 (m, 1H), 7.30–7.35 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 171.1, 152.8, 142.9, 135.1, 129.4, 129.0, 127.4, 119.2, 66.4, 55.3, 40.0, 37.7, 34.3, 28.2, 18.4. HR-MS calculated for $C_{18}H_{21}NO_3$, 299.1521; found, 300.1610 $[M + H]^+$.

**(4*S*)-3-[(2*R*)-3-Cyclobutyl-1-oxo-2-[[(phenylmethoxy)amino]methyl]propyl]-4-(phenylmethyl)-2-oxazolidinone *p*-Toluene Sulfonic Acid Salt (18).** A 300-L reactor was charged with *O*-benzylhydroxylamine hydrochloride (31.9 kg, 199.9 mol) and toluene (194 kg). The suspension was stirred at 20–25 °C, and a solution of sodium hydroxide (9.6 kg, 240.0 mol) in deionized water (72 kg) was added over 15 min while maintaining the internal temperature at 20–25 °C. The mixture was stirred vigorously for 30 min, and the upper organic layer was separated and washed with deionized water (2 × 46 kg). The organic layer was concentrated under reduced pressure (70–150 mbar) to ~44 L. To the batch was added (4*S*)-3-[2-(cyclobutylmethyl)-1-oxo-2-propenyl]-4-(phenylmethyl)-2-oxazolidinone (**17**, 30.0 kg, 100.0 mol). The suspension was heated to 48 ± 3 °C over 20 min to obtain a solution, which was stirred at this temperature for an additional 3 h. The reaction mixture was concentrated under reduced pressure (40–100 mbar) to a batch volume of ~54 L, and the batch was stirred at an internal temperature of 48 ± 3 °C for an additional 40 h. The reaction mixture was cooled to 20 ± 5 °C and diluted with ethyl acetate (360 kg). Then *p*-toluenesulfonic acid monohydrate (76.0 kg, 399.8 mol) was added. The suspension was stirred at 20–25 °C for 2 h. The batch was filtered over a polypropylene filter pad in a Büchner funnel, and the filter cake was washed with ethyl acetate (108 kg). The combined filtrate was concentrated under reduced pressure (80–150 mbar) to ~180 L. The batch was heated to 43 ± 3 °C over 15 min, and *tert*-butyl methyl ether (414 kg) was added over at least 20 min while maintaining the internal temperature at 40–46 °C. The suspension was cooled over at least 20 min to 20–25 °C and stirred for 2 h. The solid was collected by filtration over a Büchner funnel, rinsed with *tert*-butyl methyl ether saturated with water (3 × 37 kg), and dried at 50 °C under reduced pressure for 16 h until LOD <1% to afford 38.2 kg (60% yield) of (4*S*)-3-[(2*R*)-3-cyclobutyl-1-oxo-2-[[(phenylmethoxy)amino]methyl]propyl]-4-(phenylmethyl)-2-oxazolidinone *p*-toluene sulfonic acid salt (**18**): mp 143–145 °C. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 1.38–1.77 (m, 7H), 1.84–1.96 (m, 2H), 2.17–2.24 (m, 1H), 2.35 (s, 3H), 2.88 (dd, $J$ = 13.5, 2.9 Hz, 1H), 3.55 (dd, $J$ = 13.5, 1.6 Hz, 1H), 3.87 (dd, $J$ = 9.1, 2.5 Hz, 1H), 3.93 (dd, $J$ = 13.9, 9.1

Hz, 1H), 3.99 (t, $J$ = 8.2 Hz, 1H), 4.31–4.35 (m, 1H), 4.44 (dd,$J$ = 13.9, 7.6 Hz, 1H), 5.22 (dd, $J$ = 25.2, 8.6 Hz, 2H), 6.95 (d, $J$ = 7.0 Hz, 2H), 7.19–7.34 (m, 10H), 7.87 (d, $J$ = 8.2 Hz, 2H), 10.88 (br s, 1H), 11.88 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 174.0, 152.9, 141.1, 140.7, 136.0, 132.8, 130.4, 129.6, 129.4, 129.3, 129.2, 129.0, 126.9, 126.2, 66.1, 56.0, 50.5, 38.7, 37.9, 36.3, 33.3, 28.6, 28.2, 21.4, 18.3. HR-MS calculated for $C_{25}H_{30}N_2O_4$, 422.2284; found, 423.2292 $[M + H]^+$.

**(α*R*)-α-[[Formyl(phenylmethoxy)amino]methyl]cyclobutanepropanoic Acid *N*-Cyclohexylcyclohexanamine Salt (1:1) (20).** A 400-L reactor was charged with (4*S*)-3-[(2*R*)-3-cyclobutyl-1-oxo-2-[[(phenylmethoxy)amino]methyl]-propyl]-4-(phenylmethyl)-2-oxazolidinone *p*-toluene sulfonic acid salt (**18**, 38.0 kg, 63.8 mol) and ethyl acetate (120 L). The suspension was stirred at 20–25 °C, and a solution of sodium carbonate (10.1 kg, 94.7 mol) in deionized water (95 kg) was added over 5–10 min. The mixture was stirred vigorously for 10 min, and the upper organic layer was separated. The organic layer was washed with deionized water (2 × 58 kg) and concentrated under reduced pressure (100–170 mbar) to a batch volume of ∼31 L. The batch was diluted with tetrahydrofuran (234 kg) and deionized water (66 kg) to give a clear solution. The solution was cooled to 0 ± 3 °C, and 30% hydrogen peroxide (15.6 kg, 137.9 mol) was added over 5 min while maintaining the internal temperature at 0 ± 3 °C. A solution of lithium hydroxide monohydrate (3.2 kg, 119.8 mol) in deionized water (66 kg) was added over 45 min while maintaining the internal temperature at 0 ± 3 °C. The reaction mixture was stirred at this temperature for 1 h, and a solution of sodium sulfite (22.8 kg, 180.7 mol) in deionized water (266 kg) was added over a period of 30 min while maintaining the internal temperature at 0–10 °C. The reaction mixture was heated to 20–25 °C over 15 min and concentrated under reduced pressure (95–150 mbar) to a batch volume of ∼410 L. Ethyl acetate (270 kg) was added, and layers were separated. The lower aqueous layer was saved. The upper organic layer was extracted with a solution of lithium hydroxide monohydrate (782.2 g, 18.5 mol) in deionized water (16 kg). The combined aqueous layers were extracted with ethyl acetate (270 kg), and the organic layer was discarded. Then 5 N aqueous hydrochloric acid (34.0 kg) was added to the aqueous layer over 30 min at an internal temperature of 5–10 °C to a pH of 5 ± 0.5. The milky mixture was extracted with ethyl acetate (2 × 185.7 kg), and the combined organic layers were washed with deionized water (107 kg). This solution (assay 3.2%, containing ∼12.4 kg (α*R*)-[[(phenylmethoxy)amino]methyl]-cyclobutane-propanoic acid (**19**) in 387 kg of solution) was cooled to −15 °C and used directly in the next operation.

A 22-L, 4-necked round-bottomed flask was charged with acetic anhydride (9.59 kg, 93.7 mol) and was cooled to 0–5 °C. Formic acid (17.33 kg, 376.3 mol) was added over 10 min while maintaining the internal temperature at 5 ± 5 °C. The reaction mixture was stirred at this temperature for an additional 10 min, warmed to 20 ± 5 °C over 10 min, and stirred for an additional 30 min. The resulting mixed anhydride solution was added to the above obtained compound **19** solution over 15 min while maintaining an internal temperature of −10 ± 5 °C. The reaction mixture was stirred at this temperature for an additional 1 h, and deionized water (3.38 kg, 187.7 mol) was added over 5–10 min at −10 ± 5 °C. The mixture was warmed to 20–25 °C over 30 min and concentrated under reduced pressure (40–150 mbar) to a batch volume of ∼45 L. Toluene (132 kg) was added, and the batch was concentrated under reduced pressure (80–120 mbar) to ∼45 L. The above operation was repeated once, and the batch was diluted with toluene (10.7 kg). A solution of dicyclohexylamine (10.2 kg, 56.4 mol) in heptanes (101 kg) was added over 20 min while maintaining the internal temperature at 20–25 °C. The batch was seeded with pure compound **20** (9 g), and the resulting suspension was stirred at 20–25 °C for 16 h. The solid was collected by filtration over a Büchner funnel, washed with heptanes/toluene (3:1 (v/v), 35.4 kg) and heptanes (11.3 kg), and dried under reduced pressure at 25 °C until the combined heptanes and toluene amount was <2% to afford 17.5 kg (58.5% yield) of (α*R*)-α-[[formyl(phenylmethoxy)amino]methyl]cyclobutane-propanoic acid *N*-cyclohexylcyclohexanamine salt (1:1) (**20**): mp 110–112 °C. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 1.11–1.25 (m, 6H), 1.32–1.55 (m, 5H), 1.58–1.84 (m, 11H), 1.92–2.10 (m, 6H), 2.30–2.47 (m, 1H), 2.54–2.65 (m, 1H), 2.85–2.92 (m, 1H), 3.14–3.22 (m, 0.5H, rotomer), 3.61–3.85 (m, 1.5H), 4.78–4.90 (m, 1H), 4.90 (br s, 1H), 7.31–7.50 (m, 5H), 7.96, 8.10 (two singlets, 1:1 rotomers, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 179.4, 178.6, 163.0, 158.4, 135.4, 134.7, 129.5, 129.2, 128.7, 128.4, 128.2, 125.3, 52.64, 51.77, 46.87, 44.66, 38.11, 34.48, 31.89, 29.91, 29.86, 28.72, 28.49, 25.33, 18.53 (mixture of rotomers). HR-MS calculated for $C_{16}H_{21}NO_4$, 291.1471; found, 292.1549 $[M + H]^+$.

**(2*S*,4*R*)-4-fluoro-[(3-pyridazinylamino)carbonyl]-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (23).** A 100-L reactor was thoroughly flushed with nitrogen and charged with (2*S*,4*R*)-4-fluoro-1,2-pyrrolidinedicarboxylic acid 1,1-dimethylethyl ester (**22**, 5.00 kg, 21.4 mol), DMF (23.6 kg) and 1-methylimidazole (3.87 g, 47.2 mol). The solution was cooled to −10 ± 3 °C over 15 min and methanesulfonyl chloride (2.46 g, 21.4 mol) was added over a period of 1 h while maintaining the internal temperature at −10 ± 3 °C (slightly exothermic). The reaction mixture was stirred at an internal temperature of −10 ± 3 °C for 20 min, and a solution of 3-pyridazinamine (**21**, 2.35 kg, 24.7 mol) in DMF (21.7 kg) was added over a period of 1 h while maintaining the internal temperature at −10 ± 3 °C. The reaction mixture was warmed to 20 ± 5 °C over 1 h and stirred for an additional 6 h. The reaction mixture was cooled to 0 ± 5 °C over 20 min, and 20% aqueous sodium chloride solution (105 kg) was added over 40 min while maintaining the internal temperature at 0 ± 8 °C. The suspension was cooled to 0 ± 2 °C over 15 min and stirred at this temperature for an additional 4 h. The solid was collected by filtration over a Büchner funnel, washed with water (∼5 °C, 2 × 12 kg) and isopropyl acetate (∼5 °C, 5.2 kg) and dried under reduced pressure (20 mbar) at 45 °C for 24 h until LOD <1% to give 5.15 kg (77.4% yield) of (2*S*, 4*R*)-4-fluoro-[(3-pyridazinylamino)carbonyl]-1-pyrrolidinecarboxylic acid 1,1-dimethyl ethyl ester (**23**) as a white solid: mp 178–181 °C. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 1.26, 1.40 (two singlets, 9H,

2:1 mixture of rotomers), 2.01–2.21 (m, 1H), 2.50–2.59 (m, 1H), 3.53–3.74 (m, 2H), 4.57–4.63 (m, 1H), 5.23–5.40 (m, 1H), 7.70, 7.73 (two dd, $J$ = 7.6, 3.8 Hz, 1H, 2:1 mixture of rotomers), 8.31, 8.35 (two d, $J$ = 7.6 Hz, 1H, 2:1 mixture of rotomers), 8.98–8.99 (m, 1H), 11.31, 11.39 (two singlets, 1H, 2:1 mixture of rotomers); $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 172.4, 171.8, 162.2, 155.3, 153.4, 152.9, 148.6, 128.6, 128.4, 118.1, 118.0, 93.0, 92.3, 91.8, 91.2, 79.4, 79.2, 58.5, 58.3, 53.6, 53.5, 53.2, 53.1, 37.3, 37.1, 36.6, 36.4, 28.0, 27.8 (mixture of rotomers). HR-MS calculated for $C_{14}H_{19}FN_4O_3$, 310.1441; found, 310.1452 $[M]^+$.

**(2*S*,4*R*)-4-Fluoro-*N*-3-pyridazinyl-2-pyrrolidinecarboxamide Dihydrochloride (13).** A 1-L, 4-necked round-bottomed flask was charged with (2*S*,4*R*)-1-pyrrolidine-carboxylic acid 4-fluoro-[(3-pyridazinylamino)carbonyl]-1,1-dimethylethyl ester (**23**, 5.10 kg, 16.4 mol) and acetonitrile (36 kg). The suspension was stirred under nitrogen at 21 ± 3 °C and concentrated hydrochloric acid (7.39 kg, 74.0 mol) was added over a period of 30 min while maintaining the internal temperature at 21 ± 3 °C. The mixture was stirred at this temperature for an additional 6 h and was cooled to 0 ± 5 °C over 20 min. The resulting suspension was stirred at this temperature for an additional 1 h. The solid was collected by filtration over a Büchner funnel, washed with acetonitrile (2 × 3 kg), and dried under reduced pressure (20 mbar) at 45 °C for 24 h until LOD < 1% to give 4.49 kg (96.5% yield) of (2*S*,4*R*)-4-fluoro-*N*-3-pyridazinyl-2-pyrrolidinecarboxamide dihydrochloride (**13**) as an off-white solid: mp 232–234 °C. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 2.20–2.37 (m, 1H), 2.79–2.88 (m, 1H), 3.50–3.68 (m, 2H), 4.73 (br s, 1H), 5.52 (dt, $J$ = 43.7, 2.9 Hz, 1H), 7.93 (dd, $J$ = 7.6, 4.1 Hz, 1H), 8.40 (d, $J$ = 7.6 Hz, 1H), 9.14 (dd, $J$ = 4.1, 1.3 Hz, 1H), 9.22 (br s, 1H), 11.15 (s, 1H), 12.07 (s, 1H), 12.50 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 167.4, 155.0, 148.3, 129.9, 120.4, 92.5 (d, $J$ = 175.6 Hz), 58.5, 51.6 (d, $J$ = 24.2 Hz), 36.5 (d, $J$ = 20.9 Hz). HR-MS calculated for $C_9H_{11}FN_4O$, 210.0917; found, 210.0927 $[M]^+$.

**1-[(2*R*)-3-Cyclobutyl-2-[(formylhydroxyamino)methyl]-1-oxopropyl]-4-fluoro-*N*-3-pyridazinyl-(2*S*,4*R*)-2-pyrrolidinecarboxamide (1).** A 200-L reactor was charged with α-[(formyl-(phenylmethoxy)amino]-(α*R*)-cyclobutanepropanoic acid dicyclohexylamine salt (**20**, 7.96 g, 17.0 mol) and toluene (55 kg). The suspension was stirred at 20–25 °C, and a solution of citric acid (6.6 kg) in water (60 kg) was added over the period 10 min while maintaining the internal temperature at 20–25 °C. The mixture was stirred vigorously for 20 min, and the upper organic layer was separated. The organic layer was washed with water (2 × 19 kg) and concentrated under reduced pressure (58–50 mbar) at an internal temperature 29–35 °C to a batch volume of ∼9 L. The solution was diluted with *N*,*N*-dimethylformamide (35.3 kg). 1-Methylimidazole (5.0 kg, 60.7 mol) was added. The resulting solution was cooled to −12 ± 3 °C over 15 min, and methanesulfonyl chloride (1.84 g, 16.0 mol) was added over a period of 1 h while maintaining the internal temperature at −12 ± 3 °C. The mixture was stirred at −12 ± 3 °C for 30 min, and (2*S*,4*R*)-4-fluoro-*N*-3-pyridazinyl-2-pyrrolidinecarboxamide dihydrochloride (**13**, 4.31 kg, 15.2 mol) was added over a period of 1 h in 10 equal portions while maintaining the internal temperature at −12 ± 3 °C. The reaction mixture was warmed to 20 ± 5 °C over 1 h and stirred for an additional 6 h. The mixture was cooled to 0 ± 5 °C over 20 min, and 15% aqueous sodium chloride solution (86 kg) was added over 20 min while maintaining the internal temperature at 0 ± 8 °C. Then isopropyl acetate (58 kg) was added to the mixture. The mixture was warmed to 20 ± 5 °C over 20 min and stirred for an additional 30 min. The organic layer was separated. The aqueous layer was extracted with isopropyl acetate (58 kg). The combined organic layer was washed with water (45 kg), saturated sodium bicarbonate solution (46 kg), and water (2 × 45 kg). The organic layer was concentrated under reduced pressure (74–69 mbar) at 25–27 °C to a batch volume of ∼12 L. The batch was diluted with ethyl alcohol (200 proof, 19 kg) to afford ∼35 L of 1-[(2*R*)-3-cyclobutyl-2-[[formyl(phenylmethoxy)amino]-1-oxopropyl]-4-fluoro-*N*-3-pyridazinyl-(2*S*,4*R*)-2-pyrrolidinecarboxamide (**24**) in ethanol/isopropyl acetate. To this solution was added 10% Pd/C (50% wet, 1.07 kg) and ammonium formate (0.86 kg, 13.6 mol). The mixture was heated to 60 ± 5 °C over 0.5 h and stirred for an additional 0.5 h. It was cooled to 20 ± 5 °C over a period 20 min and filtered over a pad of Celite (1.6 kg). The Celite pad was washed with ethanol (200 proof, 2 × 2.5 kg). The filtrate was transferred to a 200-L reactor, and activated charcoal (Pica P1400, 0.67 kg) was added. The mixture was heated to 35 ± 5 °C over 15 min and stirred for an additional 4 h. The mixture was cooled to 20 ± 5 °C over a period 20 min and filtered over a pad of Celite (1.6 kg). The Celite pad was washed with ethanol (200 proof, 2 × 3.8 kg), and the filtrate was concentrated under reduced pressure (80–77 mbar) at 25–27 °C to a batch volume of ∼7.5 L. The batch was heated to 35 ± 3 °C over 15 min, and isopropyl acetate (84 kg) was added over a period of 1 h while maintaining the internal temperature at 35 ± 3 °C. The mixture was seeded with pure **1** (2.4 g) at this temperature. The mixture was cooled to 20 ± 5 °C over a period of 1 h and stirred for an additional 68 h. The solid was collected by filtration over a Büchner funnel, washed with cold isopropyl acetate (∼5 °C, 2 × 3.5 kg), and dried under reduced pressure (20 mbar) at 45 °C for 12 h until LOD < 1% to afford 3.1 kg (60.1% yield) of 1-[(2*R*)-3-cyclobutyl-2-[(formyl-hydroxyamino)methyl]-1-oxopropyl]-4-fluoro-*N*-3-pyridazinyl-(2*S*,4*R*)-2-pyrrolidinecarboxamide (**1**) as a white solid: mp 154–156 °C. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 1.41–2.42 (m, 10H), 2.45–2.95 (m, 2H), 3.25–3.87 (m, 4H), 3.92–4.09 (m, 1H), 4.70–4.75, 4.90–4.92 (m, 1H, mixture of four rotomers), 5.30–5.50 (m, 1H, mixture of four rotomers), 7.65–7.73 (m, 1H, mixture of four rotomers), 7.80, 7.84, 8.15, 8.23 (four singlets, 1H, mixture of four rotomers in 7:1:1:5 ratio), 8.28–8.35 (m, 1H, mixture of four rotomers), 8.98–9.00 (m, 1H, mixture of four rotomers), 9.31, 9.74, 9.75, 10.10 (four singlets, 1H, mixture of four rotomers in 1:7:1:5 ratio), 11.31, 11.52, 11.5 (three singlets, 1H, mixture of four rotomers); $^{13}$C

NMR ($CDCl_3$) $\delta$ (ppm) 171.3, 171.2, 161.7, 157.5, 155.4, 155.3, 148.8, 148.5, 128.5, 118.2, 93.2, 92.0, 91.6, 90.5, 58.7, 58.6, 58.5, 53.6, 53.5, 53.4, 53.3, 51.2, 51.0, 48.2, 47.8, 47.2, 38.8, 38.5, 37.1, 36.6, 35.8, 35.6, 33.4, 27.8, 27.7, 27.6, 27.5, 17.7, 17.8 (mixture of rotomers). HR-MS calculated for $C_{18}H_{24}FN_5O_4$, 393.1812; found, 393.1794 $[M]^+$.


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