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An alternative scalable process for the synthesis of the key intermediate of omarigliptin

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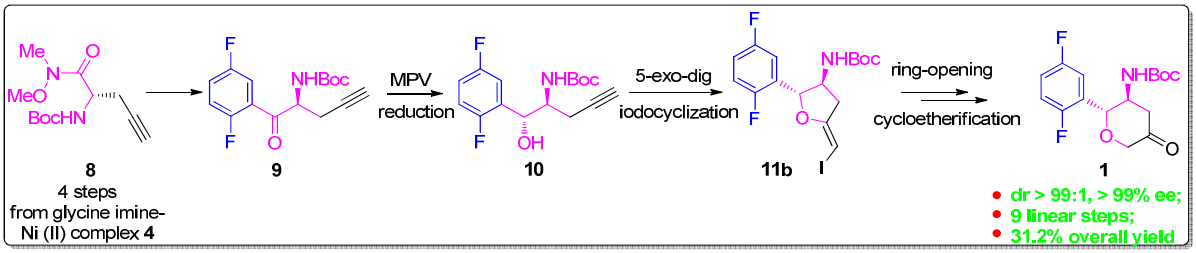


ABSTRACT：

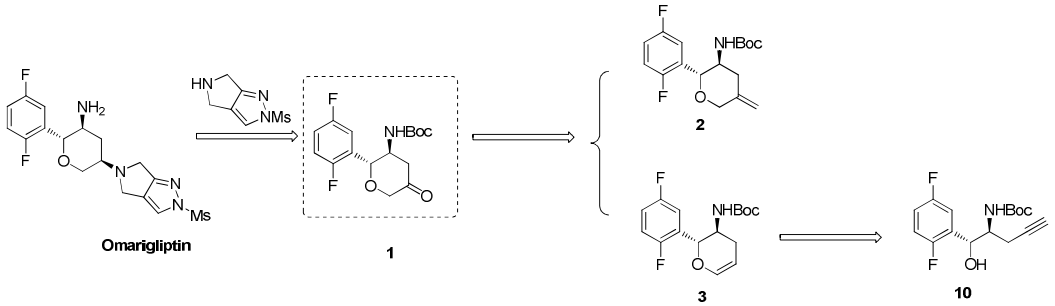
An alternative scalable process for the synthesis of the key intermediate of omarigliptin is described. The asymmetric synthesis relies on the initial diastereoselective alkylation and the subsequent aluminum-catalyzed substrate-controlled Meerwein-Ponndorf-Verley (MPV) reduction. And a highly regioselective 5-exo-dig iodocyclization was followed to afford **11b** which was then subjected to ring-opening, cycloetherification to give the product **1** with >99:1 dr, >99% ee in 31.2% overall yield for nine steps. This synthetic strategy has been successfully applied on multi-kilogram scale production.

KEY WORDS: omarigliptin, key intermediate, MPV reduction, 5-exo-dig iodocyclization, cycloetherification, β-dihydropyranones

Type 2 diabetes mellitus (T2DM), the most common form of diabetes, is a rapidly growing metabolic disorder and considered as a major public health issue all over the world. It accounts for more than 95% of all diabetes cases affecting almost 6% of the overall population.[1] The clinical application of dipeptidyl peptidase-4 (DPP-4) inhibitors has recently proven to be an effective new therapy for the treatment of T2DM. Due to the clinical success of DPP-4 inhibitors, there has been a growing recent interest in this area as exemplified by the newly approved omarigliptin, which is once-a-week rather than once-a-day oral agent compared to existing therapies in DPP-4 inhibitor.[2-6] Thus it is highly desirable to develop an efficient and readily scalable process for the synthesis of omarigliptin.

The retrosynthetic analysis of omarigliptin employed in the previously reported methods[7, 8] shown in Scheme 1 possess a similar synthetic strategy which was logically sound in the use of the key intermediate ketone **1**. These methods differ in the choice of either intermediate **2**[7] or **3**[8] as the precursor to the target molecule **1**.

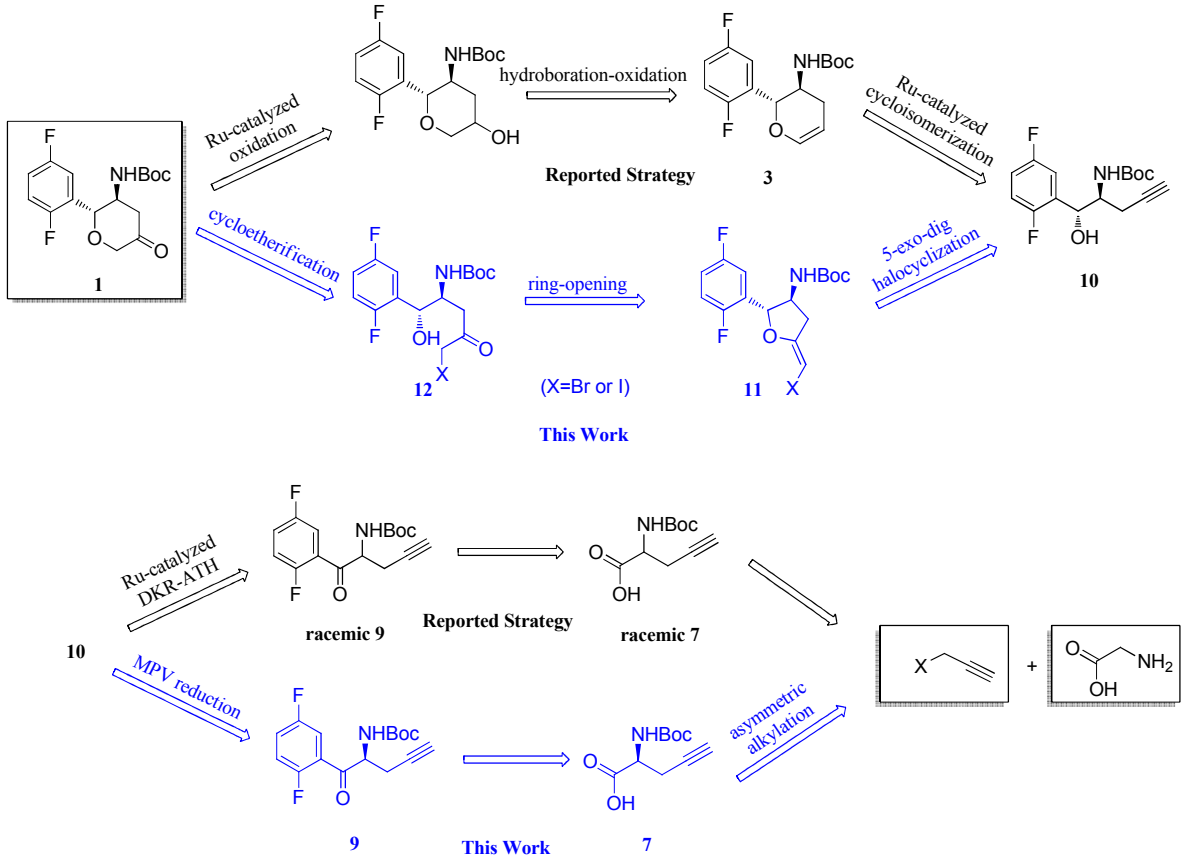
Scheme 1. The reported retrosynthetic analysis of omariglitin.



In recent reports, Xu *et. al.* [8a] developed a Ru-catalyzed cycloisomerization process for the construction of a dihydropyran ring from **10** and subsequent hydroboration-oxidation followed by a Ru-catalyzed oxidation established the ketone group. The two contiguous stereogenic centers in **10** were established by a Ru-catalyzed asymmetric dynamic kinetic resolution (DKR) transfer hydrogenation with the racemic α-amino ketone **9**.

(Reported Strategy, Scheme 2) Although this process has been operated on commercial manufacture,[8b] the drawbacks were obvious due to the use of heavy metals and complex sequential operations. We wish to report herein a convenient and readily scalable approach to the synthesis of **1** based on the retrosynthetic strategy depicted in Scheme 2.

Scheme 2. Retrosynthetic analysis of omariglitin key intermediate 1.

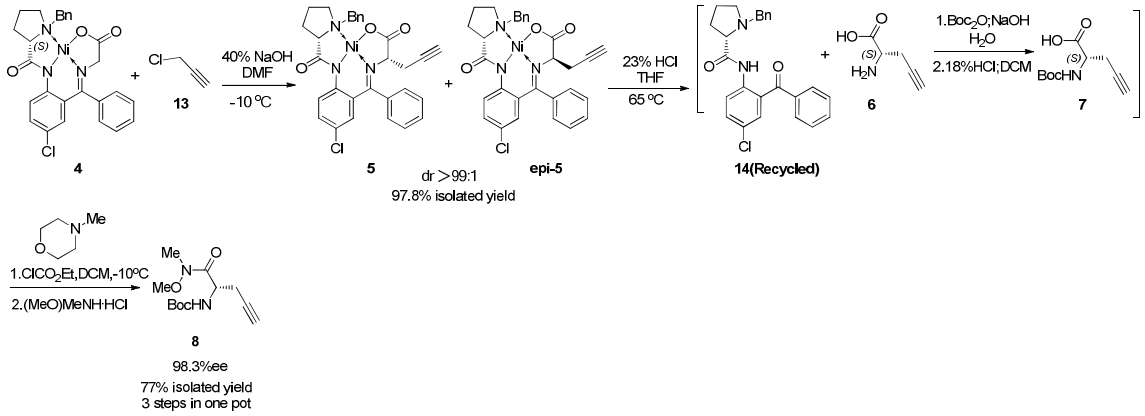


It was envisioned that compound **1** could be generated through a cycloetherification of α-halo-γ'-hydroxy ketone **12**, which might be prepared via a hydrolytic ring-opening reaction of 2-(halomethylene)-tetrahydrofuran **11**. And **11** could in turn be obtained from hydroxy terminal alkyne **10** via a regioselective intramolecular 5-exo-dig halocyclization under appropriate reaction conditions. We further assumed that the second of the two adjacent stereogenic centers in **10** could be established by a

substrate-controlled asymmetric MPV reduction of chiral α-amino ketone **9**, which can be accessed from the Weinreb amide derived from chiral amino acid **7.** And **7** could be assembled from an asymmetric α-alkylation of glycine enolate synthon. This retrosynthetic strategy is envisaged to provide the desired stereoisomer with excellent stereoselectivity as both the diastereoselective MPV reduction and asymmetric α-alkylation of glycine enolate synthons are well documented.

Following this line of retrosynthetic reasoning, we set out to introduce the first stereo center by asymmetric synthesis of the required chiral α-amino acid **7**. Due to their great importance, the synthesis of chiral α-amino acids has been widely studied, and a wide variety of synthetic methods[10] have been developed for their preparation. Among the various synthetic approaches, the application of asymmetric α-alkylation with Ni(II) complex **4** as chiral auxiliary caught our attention, which often proves to be efficient for both the stereoselectivity and applicability for large scale synthesis.[11](Scheme 3)

Scheme 3. Synthesis of Weinreb amide (S)-tert-butyl (1-(methoxy(methyl)amino)-1-oxopent-4-yn-2-yl)carbamate 8.



Thus the synthesis of compound **5** was initially explored, which could be achieved by the asymmetric α-alkylation of Ni(II) complex **4** with **13**.[11b,f] Studies on screening of the reaction conditions revealed that the choice of solvent and temperature seemed to be critical to achieve a reproducible conversion and high

stereoselectivity for this alkylation (see SI Table 1). Under the optimized conditions, the formation of the major byproduct **epi-5** could be efficiently controlled to less than 1.0% when the reaction was performed in the presence of sodium hydroxide (NaOH) in N,N-dimethylformamide (DMF) at -10°C (see SI table 1 entry 4). The isolation and purification of the desired product **5** was extremely simple and efficient. At the end of the reaction, water was added to the reaction mixture and the product **5** crystallized out from the aqueous media containing DMF. On kilo batches, we successfully obtained **5** in 97.8% yield with a purity of 95.8% and **epi-5** was below 1.0% by HPLC.

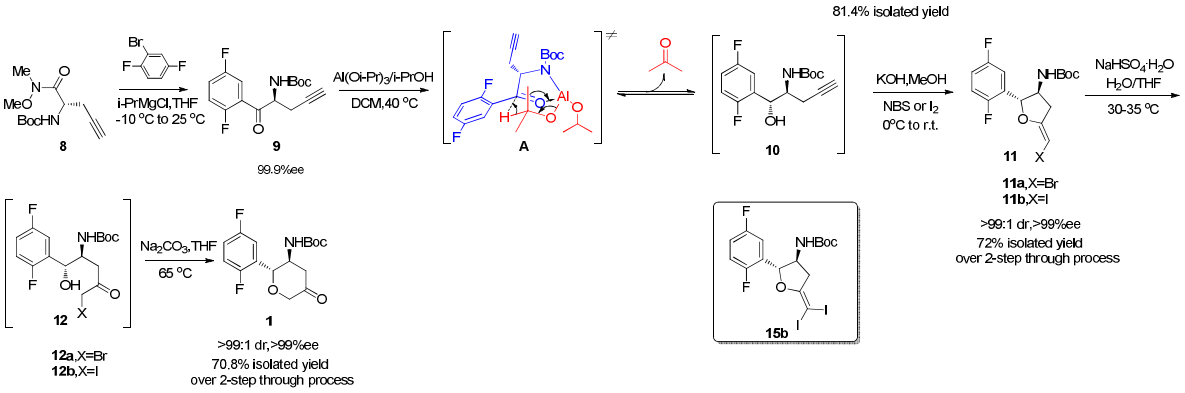
For the following step, it was worth noting that the use of tetrahydrofuran (THF) as the solvent was beneficial for the workup. When the reaction was finished, the reaction system separated to two layers and the lower aqueous phase containing S-propargylglycine **6** was directly subjected to the Boc-protection to obtain **7**, meanwhile the chiral auxiliary **14** could be recycled from the organic layer as its hydrochloric salt with the recovery above 90%.[11d] After acidic workup and extraction with dichloromethane (DCM), the crude **7** was directly used as a DCM solution for the synthesis of **8** without isolation and further purification.

The subsequent treatment of **7** to **8** by a mixed anhydride method was operated in the presence of ethyl chloroformate and N-methylmorpholine in dichloromethane (DCM) below 0°C, which afforded the desired Weinreb amide **8** in 77% yield with above 98% ee over three steps for the one-pot process (see SI Table S2, entry 4). However, the conditions reported in previous literatures[8] using 1,1'-carbonyldiimidazole (CDI) as coupling reagent caused significant racemization (see SI Table S2, entry 1-3).

Transformation of **8** to α-amino ketone **9** was initially attempted using a published procedure[8] (1,4-difluoro-2-bromobenzene with i-PrMgCl in THF) and the reaction gave similar yield. However the ee of **9** was found to vary between batches. For the asymmetric DKR transfer hydrogenation it was not necessary to

control the chiral erasion, but for us it was a challenge that had to be overcome. After a close study, it was found that the temperature during the quenching was a key factor for the control of the ee. When the temperature was kept below 10°C, the ee could be maintained at about 99% (see SI Table S3, entry 1-2), whereas at up to 30°C, the ee decreased drastically (see SI Table S3, entry 4). Quenching at 60°C resulted in even a racemate (see SI Table S3, entry 5). To avoid the racemization, the reaction mixture was quenched by 2 M HCl solution at ≤0 ° C. The ee kept no change when removing THF under vacuum at 40 °C. The residue of was slurried in the mixture of isopropanol and n-heptane to afford enantiomerically pure **9** with 99.9% ee in 81.4% yield. (Scheme 4)

Scheme 4. Synthesis of omariglitin key intermediate 1 from amide 8.

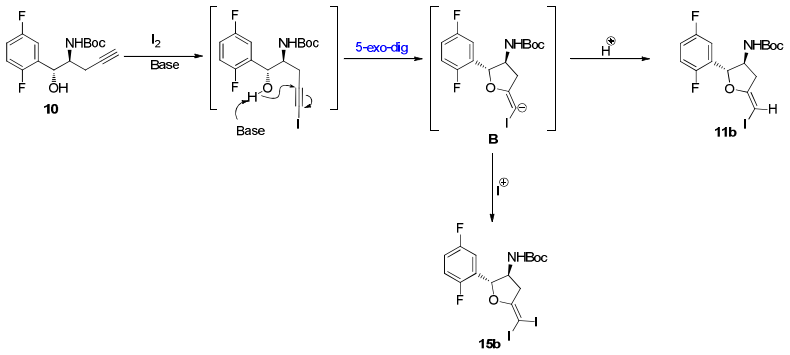


Previously, Yin and co-workers developed a practical reduction of protected α-aminoketones using a highly diastereoselective Meerwein-Ponndorf-Verley (MPV) reaction.[12a] This green process used $Al(Oi\text{-}Pr)_3$ as catalyst and i-PrOH as the hydride source, which was suitable for scale-up.[12b,c,d] Thus **9** was converted to α-aminoalcohol **10** with catalytic amount of $Al(Oi\text{-}Pr)_3$ (0.4eq) and i-PrOH in dichloromethane (DCM) at reflux. This substrate-controlled MPV reduction gave high diastereoselectivity. The reaction might proceed via the rigid six-membered cyclic transition state **A** [12a,e,f] through chelation with the deprotonated carbamate as shown in Scheme 4.

Having accomplished the preparation of **10**, which bears the two desired stereo centers, we turn our focus to its transformation to β-dihydropyranone **1**. As described in Scheme 4, we envisioned that the construction of β-dihydropyranone **1** can be accomplished through a halocyclization-ring-opening—cycloetherification sequence of acetylenic alcohol **10**. To our knowledge, this is the first report to synthesize substituted β-dihydropyranones from terminal hydroxy alkynes by such a synthetic strategy. According to the previous reports[13], the 2-(halomethylene)tetrahydrofuran derivatives could be easily assembled from hydroxy substituted terminal alkynes via intramolecular 5-exo-dig halocyclization in high yields. In our initial studies, the bromocyclization of **10** with NBS was tested as the model reaction. Indeed, 2-(bromomethylene)tetrahydrofuran **11a** could be obtained in good yield(81%, Table S4, entry 1). However, the subsequent cycloetherification of **12a** to **1** was found to be very slow (>48h) and hard to convert totally. It was anticipate that the iodide analog **12b** should be more reactive in its conversion to **1**. In this event the 5-exo-dig iodocyclization of **10** with iodine was thus performed to give enol ether **11b**, and the reaction could be completed within 12h in high yield with excellent diatereoselectivity (see SI, Table S4, entry 2). It was also found that, when methanol was used as the solvent, **11b** directly crystallized out from the reaction system and could be isolated after simple filtration as a single isomer (Z-isomer [13a]) with >99:1 dr, ee>99% in 72% yield over two steps from **9**. The content of bis-iodide **15b** (scheme 4) was less than 5%.

In the proposed mechanism, this iodocyclization reaction might be carried out in stepwise, acetylenic alcohol **10** was first converted to 1-iodoalkyne with iodine under alkaline conditions,[14] followed by a 5-exo-dig cyclization involving a vinylic anion intermediate **B** which could immediately transfer to the desired product **11b** or bis-iodide **15b** in the presence of excess I_2. (Scheme 5) The absolute configuration of compound **11b** is characterized by single crystal X-ray diffraction (see SI Figure S1).

Scheme 5. Proposed Mechanism.



Acidic hydrolysis of **11b** to form the α-iodo-γ'-hydroxy ketone **12b** appeared to be challenging due to the presence of the acid-sensitive Boc protecting group. Surprisingly, such a simple approach was rarely reported so far.[13b] Screening of the acids indicated that sodium bisulfate monohydrate was suitable for this transformation (See SI table S5 entry 1). However, using stronger acids such as BsOH，TsOH，MsOH or performing the reaction at higher temperatures lead to partial cleavage of the Boc protecting group (see SI table S5 entry 2-4,7-8). Whereas the use of HCl gave no product but only the Boc de-protected product (see SI Table S5, entry 5). Under the optimized conditions, the crude **12b** was directly subjected to the cycloetherification without further purification[15]. The cyclization reaction went to completion in THF in the presence of Na_2CO_3 at 65°C. And the crude product **1** was slurried in n-heptane to give the pure product with >99:1 dr and >99% ee in 70.8% overall yield for the last two steps in a one pot process.

Conclusion

In summary, an alternative asymmetric synthesis of the key intermediate of omarigliptin has been developed. This practical synthesis features not only an application of asymmeric alkylation of glycine and substrate-controlled diastereoselective MPV reduction to establish the two contiguous stereogenic centers, but also a highly regioselective 5-exo-dig iodocyclization and the subsequent ring-opening, cycloetherification to

give the product **1** with >99:1 dr, >99% ee in 31.2% overall yield. As the advantage in this process, a heavy metal free transformation of acetylenic alcohol **10** to β-dihydropyranone **1** was developed and has been successfully applied on multi-kilogram scale production. Further optimization to avoid the use of heavy metal in the whole process is underway in our team.

Experimental section

Commercially available materials purchased from Alfa Aesar or Kelong were used as received. If no special indicated, all reagents and solvents were used as commercially available without further purification. NMR spectra were measured on a Bruker Avance 400 spectrometer or 600 spectrometer in the solvents indicated; chemical shifts are reported in units (ppm) by assigning TMS resonance in the ^{1}H spectrum as 0.00 ppm, $CDCl_3$ resonance in the ^{13}C spectrum as 77.0 ppm. Coupling constants are reported in Hz with multiplicities denoted as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. HRMS were performed on Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Analytical HPLC for liquid phase was carried out on a Agilent HPLC workstation, equipped with a Agilent Zorbax Eclipse XBridge^{TM} C18 (4.6 x 250 mm; 5μm) and OJ-H chiral chromatograph. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL solvent).

(S)-2-((E)-((2-((S)-1-benzylpyrrolidine-2-carboxamido)-5-chlorophenyl)(phenyl)methylene)amino)pent-4-ynoic acid nickel complexes (5). S-N- (2- formyl-benzyl-4-chlorophenyl) -1-benzyl-pyrrolidine-2-carboxamide-glycine nickel complexe **4** (2000g, 3.75mol) was added to N, N-dimethylformamide (8 L), then the mixture was cooled to -10^{o}C. Previously prepared 40% sodium hydroxide

(562g, 5.62mol) aqueous solution was added to the reaction mixture in one portion with vigorous stirring. The mixture was stirred at -10 ^{o}C for 0.5 h. Then 3-chloropropyl alkyne **13** (420g, 5.64mol) was added dropwise over 2h at <0 ^{o}C. The mixture was stirred at -10 ^{o}C for at least 2h until the starting material **4** was <3% (determined by HPLC). Water (16L) was added slowly over 5h at <10 ^{o}C. The slurry was stirred at -10 ^{o}C for 2h. Solids were filtered and washed with water until the pH of the filtrate was 7-8. The wet cake was dried under vacuum at 60 ^{o}C to afford 2096g of **5** with 95.8% purity in 97.8% yield. HRMS $[M+H]^+$ for $C_{30}H_{26}ClN_3NiO_3$ calculated 570.1089; found 570.1112.

(S)-tert-butyl-(1-(methoxy(methyl)amino)-1-oxopent-4-yn-2-yl)carbamate (8). A mixture of (S)-2-((E)-((2-((S)-1-benzylpyrrolidine-2-carboxamido)-5-chlorophenyl)(phenyl)methylene)amino)pent-4-yno ic acid nickel complexe **5** (4000 g, 7mol), water (1640 g), and 36% aqueous hydrochloric solution (3000 g) was added into tetrahydrofuran (16 L). The mixture was stirred at 65 ^{o}C for at least 3 h until the starting material **5** was <1% (determined by HPLC). The reaction solution was then cooled to 10 ^{o}C. And ethylenediaminetetraacetic acid disodium salt (3400g, 9.14mol) was added slowly and stirred for 0.5h. The pH was adjusted to 9-10 with 20% sodium hydroxide aqueous solution at <25 ^{o}C. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (8L). The organic layer was discarded. Boc_2O (1.2-1.3eq) was added slowly into the aqueous layer of **6** at ambient temperature. The aqueous layer was then basified with 20% sodium hydroxide aqueous solution to pH 9-10 at ambient temperature every four hours. The mixture was stirred for 30 h at ambient temperature. Then the aqueous phase was washed with dichloromethane (8L). The organic layer was discarded. The aqueous layer was cooled to 10 ^{o}C and acidified with 18% HCl solution to pH 2-3. Then the aqueous layer was extracted with dichloromethane (12L x 2). Water of the combined organic layer was removed azeotropically with dichloromethane until moisture content

was <0.8% and a crude stream of the boc-protected acid **7** was given then. Ethyl chloroformate (759.5g, 7mol) was added into the above solution of **7** at -10 ^{o}C, then 4-methylmorpholine (708g, 7mol) was added dropwise at <0 ^{o}C. After the mixture was stirred at -10 ^{o}C for 0.5 h, N,O-dimethylhydroxylamine hydrochloride (682.7g, 7mol) was added in one portion, then another part of 4-methylmorpholine (708g, 7mol) was added dropwise at <0 ^{o}C. The resulting reaction mixture was stirred at -10 ^{o}C for at least 2h until the rate of **7** was <1% by HPLC and quenched with water (4.8L). The organic phase was separated, and washed sequentially with saturated sodium bicarbonate solution (6.4L) and brine (6.4L). The solvent was removed by distillation under reduced pressure. And the residue was dissolved in isopropyl acetate (10L) and decolorized with activated carbon (640 g), and then the isopropyl acetate was removed in vacuum at 45 ^{o}C. Then the n-heptane (6L) was added to the residue of **8**, and cooled slowly to -5 ^{o}C. The suspension was stirred at -5 ^{o}C for 8 h before filtration. The wet cake was washed with n-heptane (2L) and then dried in vacuum at 30 ^{o}C overnight to afford 1380 g of **8** from **5** with 98.81% purity and 98.3% ee in 77% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (t, J = 36.2 Hz, 1H), 4.79 (s, 1H), 3.75 (s, 3H), 3.19 (d, J = 18.6 Hz, 3H), 2.63 (ddd, J = 39.5, 16.8, 2.8 Hz, 2H), 2.06-1.95 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.73 (s), 155.14 (s), 79.82 (s), 78.90 (s), 71.17 (s), 61.63 (s), 49.05 (s), 32.14 (s), 28.29 (s), 22.62 (s). HRMS $[M+Na]^+$ for $C_{12}H_{20}N_2O_4$ calculated 279.1315; found 279.1327. $[\alpha]_D^{25}$ = -23.22 (c = 1.0 in MeOH); Melting range: 49 ^{o}C-51^{o}C.

(S)-tert-butyl (1-(2,5-difluorophenyl)-1-oxopent-4-yn-2-yl)carbamate (9).

(S)-tert-butyl-(1-(methoxy(methyl)amino)-1-oxopent-4-yn-2-yl) carbamate (**8**) (1000g, 3.9mol), 1-bromo-2,5-difluorobenzene (830g, 4.3mol) were added in tetrahydrofurana (5 L) and cooled to -10 ^{o}C. Then i-PrMgCl solution (2 M in THF, 4875 mL, 9.75mol) was added dropwise into the reaction mixture at <0 ^{o}C.

The reaction mixture was stirred for 1 h at -10 °C and warmed to ambient temperature for another 3 h. Then the reaction mixture was quenched by 2 M HCl solution at <0 °C until the pH was adjusted to 2-3. The separated organic phase was washed with brine (2 x 5 L) and concentrated under vacuum at 40 °C. Then isopropanol (500 mL) and n-heptane (1 L) were added into the residue and heated to 65 °C for 0.5h, then cooled to 30 °C. n-heptane (7 L) was added dropwise into the mixture over 1h. And the slurry was then sitrred at 20 °C for 4 h. Solids were filtered and washed with n-heptane (1 L). The wet cake was dried under vacuum at 40 °C to afford 981.5 g of **9** with 95.8% purity and 99.9% ee in 81.4% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 - 7.50 (m, 1H), 7.29 - 7.24 (m, 1H), 7.21 - 7.06 (m, 1H), 5.70 (d, J = 7.2 Hz, 1H), 5.26 (dd, J = 23.4, 19.6 Hz, 1H), 3.00 - 2.81 (m, 1H), 2.69 (d, J = 17.2 Hz, 1H), 2.03 (d, J = 26.2 Hz, 1H), 1.47 (d, J = 13.4 Hz, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.90 (d, J= 3.8 Hz), 159.62 (s), 157.99 (s), 155.09 (s), 124.42 (d, J= 15.9 Hz), 121.95 (dd, J= 24.6, 9.4 Hz), 118.16 (dd, J= 27.0, 7.9 Hz), 117.33 (dd, J= 25.3, 3.1 Hz), 80.19 (s), 78.17 (s), (s), 71.93 (s), 57.65 (d, J= 8.4 Hz), 28.26 (s), 22.09 (s). HRMS $[M+Na]^+$ for $C_{16}H_{17}F_2NO_3$ calculated 332.1069; found 332.1082. $[\alpha]_D^{25}$ = -20.07 (c = 1.0 in MeOH); Melting range: 108 °C-110 °C.

tert-butyl ((1R,2S)-1-(2,5-difluorophenyl)-1-hydroxypent-4-yn-2-yl)carbamate (10). (S)-tert-butyl (1-(2,5-difluorophenyl)-1-oxopent-4-yn-2-yl)carbamate (**9**) (900g, 2.91mol), aluminum isopropoxide (240g, 1.16mol), and isopropanol (900 mL) were added in dichloromethane (9 L). The solution was warmed to 40 °C and stirred for 12 h. After **9** was <1% (determined by HPLC), the reaction mixture was cooled to 20 °C and the pH was adjusted to 2-3 with 1 M HCl solution. The organic phase was washed with 15% aqueous NaOH solution (4.5 L x 2). The solvent was removed by distillation under reduced pressure at 30 °C to give **10**, which was used for the next step directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (ddd, J = 8.7, 5.5, 3.0 Hz, 1H), 6.95 (pd,

J = 8.9, 4.3 Hz, 2H), 5.13 (d, J = 4.8 Hz, 1H), 4.95 (s, 1H), 4.01 (s, 1H), 2.58 (ddd, J = 17.1, 6.7, 2.6 Hz, 1H), 2.48 - 2.33 (m, 1H), 2.02 (t, J = 2.6 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.07 (d, J= 1.9 Hz), 157.66 (d, J= 2.0 Hz), 156.96 (d, J= 2.2 Hz), 130.07 (s), 116.13 (dd, J= 25.1, 8.4 Hz), 115.50 (dd, J= 24.3, 8.7 Hz), 114.85 (dd, J= 25.1, 4.4 Hz), 80.15 (d, J= 12.7 Hz), 76.74, (s)70.92 (s), 69.13 (s), 53.69 (s), 28.13 (s), 19.98 (s). HRMS $[M+Na]^+$ for $C_{16}H_{19}F_2NO_3$ calculated 334.1225; found 334.1244. $[\alpha]_D^{25}$ = +35.14 (c = 0.47 in MeOH).

tert-butyl ((2R,3S,Z)-2-(2,5-difluorophenyl)-5-(iodomethylene)tetrahydrofuran-3-yl)carbamate (11b). Methanol (540 mL) was added into **10** obtained from the previous step, and then cooled to 0 °C. Potassium hydroxide (660 g, 11.76 mol) dissolved in methanol (2640 mL) was added to the above solution dropwise at <10 °C. This mixture was stirrd at 0 °C for 0.5h. Then iodine (663 g, 2.61 mol) was added in portions to the reaction solution over 0.5 h. The reaction mixture was stirred at 0 °C for another 0.5 h and then warmed to ambient temperature and stirred for 10 h until **10** was <3% by HPLC. After that water (1.8 L) was added dropwise over 1h, and the mixture was cooled to 10 °C and stirred for 4h. Later the mixture was filtered and washed with water (90 mL). The wet cake was slurried with n-heptane (9 L) at 65 °C for 0.5 h and then at 10 °C for another 5 h. The slurry was filtered and washed with n-heptane (900 mL). The wet cake was dried under vacuum at 60 °C to afford 914.5 g of **11b** with dr>99:1, 99.9% ee, 94.5% purity in 72% yield from **9**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 - 6.86 (m, 3H), 5.42 (d, J = 39.0 Hz, 1H), 4.97 (t, J = 17.9 Hz, 1H), 4.85 (s, 1H), 4.35 (s, 1H), 2.94 (dd, J = 16.2, 6.6 Hz, 1H), 2.61 (dd, J = 16.1, 4.0 Hz, 1H), 1.40 (d, J = 27.6 Hz, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.76 (d, J= 2.0 Hz), 159.46 (s), 158.15 (d, J= 2.0 Hz), 154.78 (s), 127.38 (dd, J= 15.9, 7.3 Hz), 116.72 (dd, J= 23.9, 8.5 Hz), 116.35 (dd, J= 24.3, 8.5 Hz), 113.40 (d, J= 27.6 Hz), 82.52 (s),

80.32 (s), 57.21 (s), 41.72 (s), 35.98 (s), 28.26 (s). HRMS $[M+Na]^+$ for $C_{16}H_{18}F_2INO_3$ calculated 460.0192; found 460.0212. $[\alpha]_D^{25}$ = -100.09 (c = 1.0 in MeOH); Melting range: 147 °C-149 °C.

tert-butyl ((1R,2S)-1-(2,5-difluorophenyl)-1-hydroxy-5-iodo-4-oxopentan-2-yl)carbamate (12b). tert-butyl ((2R,3S,Z)-2-(2,5-difluorophenyl)-5-(iodomethylene)tetrahydrofuran-3-yl)carbamate (**11b**) (885.50 g, 2.02 mol) was dissolved in tetrahydrofuran (5.3 L). The sodium bisulfate monohydrate (343.35 g, 2.49 mol) dissolved in water (1.7 L) was added into the reaction mixture above. Then the solution was stirred at 35 °C for 12 h until **11b** was <1% by HPLC. The organic phase was separated and washed with brine, then was concentrated under vacuum at 30 °C to give **12b**. And crude **12b** was used for next step directly. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 - 7.10 (m, 1H), 6.98 (dd, J= 9.0, 4.3 Hz, 1H), 6.95 - 6.92 (m, 1H), 5.44 (d, J= 7.1 Hz, 1H), 5.28 (d, J= 11.0 Hz, 1H), 4.15 (m, 1H), 3.59 (d, J= 10.6 Hz, 1H), 3.54 (d, J= 10.6 Hz, 1H), 2.63 - 2.53 (m, 1H), 2.22 (d, J= 13.0 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8 (dd, J=243, 2 Hz), 155.9 (dd, J=243, 2 Hz), 155.3 (s), 129.59 (dd, J= 15.8, 7.4 Hz), 117.18 (dd, J= 24.3, 8.5 Hz), 116.26 (dd, J= 24.4, 8.6 Hz), 114.0 (d, J=25 Hz), 104.05 (s), 80.98 (s), 80.82 (d, J= 30.8 Hz), 58.88 (s), 42.30 (s), 28.84 (s), 13.21 (s). HRMS $[M+Na]^+$ for $C_{16}H_{20}F_2INO_4$ calculated 478.0297; found 478.0323. $[\alpha]_D^{25}$ = +21.98 (c = 1.32 in MeOH).

tert-butyl ((2R,3S)-2-(2,5-difluorophenyl)-5-oxotetrahydro-2H-pyran-3-yl)carbamate (1). Tetrahydrofuran (7.0 L) and sodium carbonate (260 g, 2.45 mol) was added to **12b** obtained from the previous step. And the reaction mixture was stirred at 65 °C until **12b** was <3% by HPLC. Then the mixture was cooled to 35 °C, and the solvent was removed in vacuum at 35 °C. Isopropyl acetate (4.4 L) and water (3.5 L) were added into the residue. The organic phase was separated and washed with brine (3.5 L x 2). After the solvent

was removed by distillation under reduced pressure at 35 °C, n-heptane (1.3 L) was added into the residue and heated to 50 °C for 0.5 h. Then the slurry was cooled to 20 °C and stirred for 2 h. After that the slurry was filtered and washed with n-heptane (450 mL). The wet cake was then dried under vacuum at 50 °C to afford 469 g of **1** with dr>99:1, >99.9% ee, 94.12% purity in 70.8% yield from **11**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, J = 3.3 Hz, 1H), 7.06 - 6.93 (m, 2H), 4.82 (s, 1H), 4.65 (s, 1H), 4.28 (dd, J = 16.3, 1.6 Hz, 1H), 4.16-4.00 (m, 2H), 3.09-2.99 (m, 1H), 2.72 (s, 1H), 1.30 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.12(s), 159.54 (d, J= 243.1 Hz), 156.78 (d, J= 244.1 Hz), 154.97 (s), 127.82 (dd, J= 16.0, 7.7 Hz), 117.01 (dd, J= 24.3, 8.8 Hz), 115.42 (s), 115.23 (s), 80.70 (s), 75.61 (s), 75.01 (s), 52.91 (s), 45.31 (s), 28.66 (s). HRMS $[M+H\text{-isobutylene}]^+$ for $C_{16}H_{19}F_2NO_4$ calculated 272.0729; found 272.0739. $[\alpha]_D^{25}$ = +4.92 (c = 1.0 in MeOH); Melting range: 158 °C-160 °C.

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds and X-ray structure information for 11b (CIF).

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