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Development of a Practical Synthesis of DPP IV Inhibitor LY2497282†

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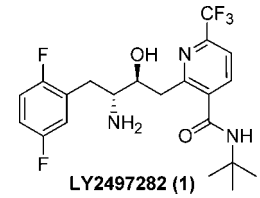
Abstract:

A new synthetic route to LY2497282 (1), a potent and selective DPP IV inhibitor for the potential treatment of diabetes, suitable for the preparation of multikilogram quantities is described. The key step involved a stereoselective addition of the dianion of nicotinamide 8 to *N*-dibenzyl-protected α-amino aldehyde 12, which was derived from *N*-acetyl-protected amino ester 14 without epimerization. The desired Felkin-Anh nonchelation controlled *anti*-amino alcohol 11 was isolated with >99% HPLC area and >99% ee by crystallization. After removing the dibenzyl protecting group under transfer hydrogenation conditions, LY2497282 (1) was finally obtained in 39% overall yield with a six-step longest linear sequence starting from *N*-acetyl-protected amino ester 14.

Introduction

Type 2 diabetes (formerly known as non-insulin-dependent diabetes mellitus) is a severe and increasingly prevalent disease. Inhibition of GLP-1 degradation by dipeptidyl peptidase IV (DPP-IV)[1] has emerged as a promising approach for the treatment of type 2 diabetes and has been aggressively pursued by numerous pharmaceutical companies.[2]

LY2497282 (**1**) was identified at Eli Lilly and Company as a potent and selective DPP IV inhibitor for the treatment of type 2 diabetes.[3] We detail here the development of our synthetic route for the preparation of **1**. The key step involved a stereoselective addition of the dianion of nicotinamide **8** to *N*-dibenzyl protected α-amino aldehyde **12**, which was derived from *N*-acetyl protected amino ester **14** without epimerization. The desired Felkin-Anh nonchelation controlled *anti* amino alcohol **11** was isolated with >99% HPLC area and >99% ee by crystallization. After removing the dibenzyl protecting group under a transfer hydrogenation condition, LY2497282 (**1**) was finally obtained in 39% overall yield with a six-step longest linear sequence starting from *N*-acetyl-protected amino ester **14**.



LY2497282 (1)

Results and Discussion

The original route used presents a very attractive pathway that is based on a key ketone intermediate **9a** (Scheme 1).[3] The synthesis started by coupling commercially available aldehyde **2** and *N*-Boc phosphonate **3** to give enamine intermediate **4**. Asymmetric hydrogenation of enamine **4** afforded *N*-Boc protected amino ester **5** with >99% ee. *N*-Boc protected amino ester **5** was then converted to Weinreb amide **7a**, which was coupled with the dianion of **8** to give ketone intermediate **9a**. Reduction of ketone afforded alcohol **10a**, which was subsequently deprotected to give the amino alcohol LY2497282 (**1**).

The Scheme 1 synthesis of amino alcohol **1** also represented a few issues: (1) the expense of preparing Boc-protected amino ester **5** was high; (2) more than 2 equiv of **8** was needed to subside the deprotonation of NH in **7a** and the extra **8** was difficult to remove; (3) epimerization occurred in the coupling reaction between nicotinamide **8** and Weinreb amide **7a**, which resulted in chiral chromatography at **10a** stage to improve ee; (4) low diastereoselectivity (2:1) was obtained in the reduction of **9a**, and the two resulting diastereomers were difficult to separate.

Despite the issues, we felt that the ketone approach described in Scheme 1 still represented a very attractive and potentially scaleable approach to amino alcohol **1**. Our initial attempt was to improve the route by developing alternative reaction and work up conditions to make it amenable for scale up.

† We dedicate this paper to the memory of Dr. Chris Schmid, a colleague, mentor, and friend, who passed away December 26, 2007.

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(3) Blaszczak, L. C.; Mathes, B. M.; Pulley, S. R.; Robertson, M. A.; Sheehan, S. M.; Shi, Q.; Watson, B. M.; Wiley, M. R. WO 2007/015767 A1, 2007.

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Scheme 1. **Original synthesis of LY2497282 (1)**

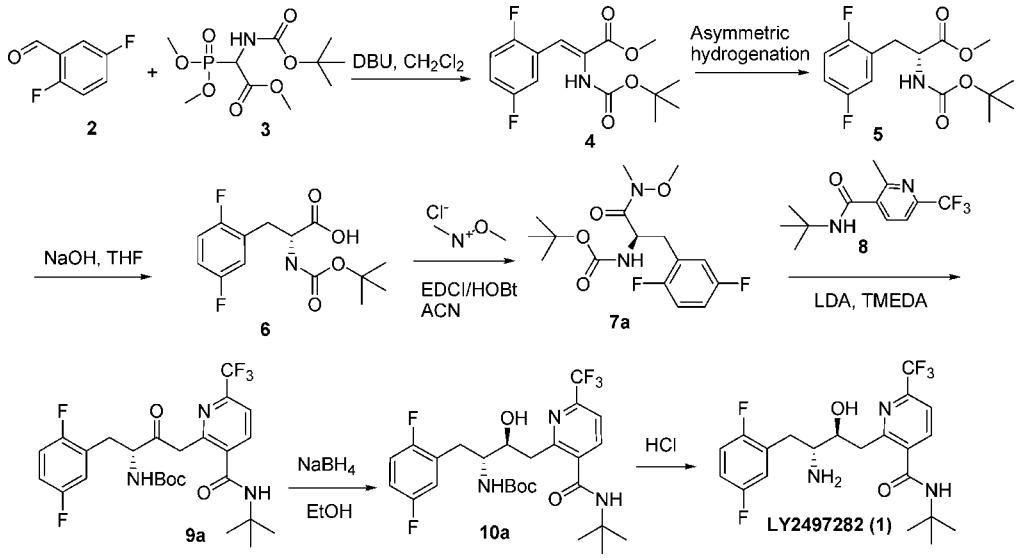
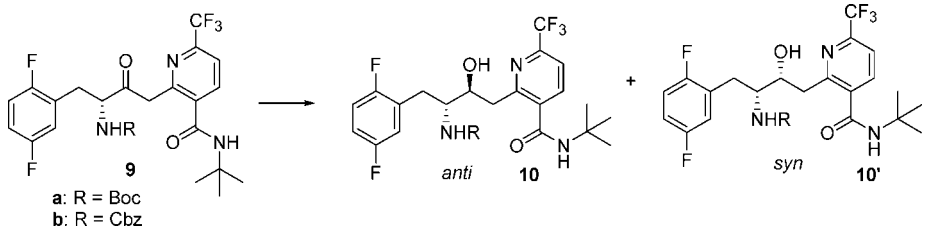


Table 1. **Stereoselective reduction of ketones 9a and 9b**



entry	R	reagent	solvent	*T* (°C)	*anti*:*syn* (**10**:**10′**)	yield (**10**+**10′**) (%)
1	Cbz (**9b**)	$Al(O^iPr)_3$	IPA	50	no reaction	0
2	Boc (**9a**)	$NaBH_4$	EtOH	0	2.5:1	91
3	Boc (**9a**)	$NaB(OCH_3)_3H$	EtOH	0	2.3:1	84
4	Boc (**9a**)	$LiAlH(O^tBu)_3$	THF	−78	1:1	81
5	Boc (**9a**)	$LiAlH(O^tBu)_3$	EtOH	−78	8:1	88
6	Cbz (**9b**)	$LiAlH(O^tBu)_3$	EtOH	−78	15:1	86

The development of synthetic methods for the preparation of *anti*-1,2-amino alcohols through the reduction of *N*-protected amino ketones has received significant attention in recent years.[4] Carbamate groups are ubiquitous protecting groups for amines. Stereocontrol in the reduction of carbamate-protected amino ketones would appear to favor the formation of chelation controlled *anti*-amino alcohols since both the ketone oxygen and the carbamate nitrogen are sterically accessible for coordination to a Lewis acid.[5] To improve the Scheme 1 route, our first objective was to address the poor diastereoselectivity issue observed in the ketone **9a** reduction step. We started our screening studies using racemic ketone starting materials **9a** and **9b**, with *N*-Boc and *N*-Cbz being the protecting groups, respectively (Table 1). The initial attempt was to reduce **9b** with $Al(O^iPr)_3$ in refluxing IPA, the classical Meerwein−Pondorf−Verley reduction condition which had been reported to afford excellent diastereoselectivity in reducing *N*-carbamate protected α-amino ketones.[4c–e] Presumably due to the enone characteristic of ketone starting material **9b**,[6] no reaction was observed under these conditions (Table 1, entry 1). As previously observed, an *anti*/*syn* (**10**:**10′**) ratio of 2.5:1.0 was observed when Boc-protected amino ketone **9a** was reduced with $NaBH_4$ in EtOH at 0 °C (entry 2). A similar ratio of 2.3:1.0 was obtained when $NaB(OCH_3)_3H$ was used as the reducing agent (entry 3). $LiAlH(O^tBu)_3$ in EtOH at −78 °C[5] proved to afford the best diastereoselectivity (entries 5 and 6). Interestingly, Cbz-protected ketone **9a** gave much better selectivity than Boc-protected ketone **9b** (15:1 vs 8:1) when the reduction was carried out with $LiAlH(O^tBu)_3$ in EtOH. Therefore, Cbz-protected ketone **9b** was identified as the best substrate and $LiAlH(O^tBu)_3$ in EtOH at −78 °C was identified as the best condition for the reduction (entry 6).

With acceptable diastereoselectivity results in hand, we next turned our attention to improving the coupling reaction between Weinreb amide **7b** and nicotinamide **8**. We started our

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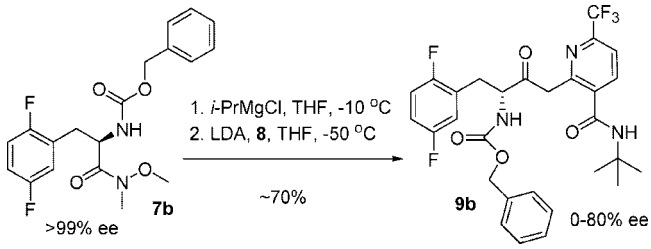
(5) (a) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045. (b) Vabeno, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186.

(6) Ketones **9a** and **9b** were observed as a mixture of ketone and enone forms in NMR.

Scheme 2. **Coupling reaction between Weinreb amide 7b and nicotinamide 8**



investigation with two major development objectives: (1) improve the reaction conditions to avoid low yield and reduce the amount of nicotinamide **8** used and (2) suppress the epimerization occurring during the reaction workup.

Because the deprotonation of the exchangeable amino proton of **7b** was faster than the nucleophilic attack of dianion-**8** at the Weinreb amide, more than 2 equiv of dianion-**8** was needed. When only 1.3 equiv of dianion-**8** was used, almost no product **9b** was observed. To avoid the use of excess of **8**, we therefore adopted a predeprotonation protocol by first deprotonating the amino group of **7b** with 0.95 equiv of *i*-PrMgCl/THF,[7] followed by addition of 1.25 equiv of dianion-**8**.[8] As a result, ketone **9b** was obtained in ~70% yield without the use of excess nicotinamide starting material (Scheme 2).

We next attempted to suppress the epimerization which was reported to occur during the workup of the reaction. It was precedent in the literature that *N*-carbamate protected α-amino ketones could be obtained by coupling *N*-protected α-amino Weinreb amides and metal nucleophiles with retention of stereochemistry.[9] We then examined multiple reaction and workup conditions starting from enantiomerically pure Weinreb amide **7b**. To our disappointment, epimerization was observed under a variety of conditions. The ee of isolated ketone **9b** ranged from 0% to 80%, with lower ee observed when the reaction was performed at larger scale (Scheme 2). We speculated that hydrogen bonding between the ketone oxygen and pyridine nitrogen in **9b** might make the compound more sensitive to epimerization.

Because of the difficulties we encountered in preserving the chiral integrity in the ketone formation step, we decided to investigate alternative approaches for the synthesis of LY2497282 (**1**). An alternative strategy for the preparation of **1** would be nucleophilic addition of dianion-**8** to an appropriately protected α-amino aldehyde.[10] Boc, Cbz and dibenzyl protecting groups[11,12] had been used as the most common protecting groups for related α-amino aldehydes. The stereoselectivity of the addition was strongly dependent on the nature of the substrates and reaction conditions. Since *N*-dibenzyl-protected α-amino aldehydes often led to improved selectivity towards the desired nonchelation-controlled *anti* product, we decided to investigate the aldehyde route using dibenzyl-protected aldehyde **12**. The aldehyde **12** could be derived from *N*-acetyl-protected amino ester **14**, an

(7) A similar predeprotonation protocol has been reported in the synthesis of α-(*N*-Boc-amino)ketones from α-(*N*-Boc-amino)Weinreb amide: Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D *Tetrahedron Lett.* **2002**, *43*, 8223.

(8) The preparation of dianion-**8** was described in the subsequent text in the Scheme 4 approach.

(9) (a) Kaldor, S. W.; Hammond, M.; Dressman, B. A.; Fritz, J. E.; Crowell, T. A.; Hermann, R. A *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1385. (b) Bohnstedt, A. C.; Prasad, J. V. N. V.; Rich, D. H. *Tetrahedron Lett.* **1993**, *34*, 5217. (c) Seki, M.; Matsumoto, K. *Tetrahedron Lett.* **1996**, *37*, 3165.

(10) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(11) Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921.

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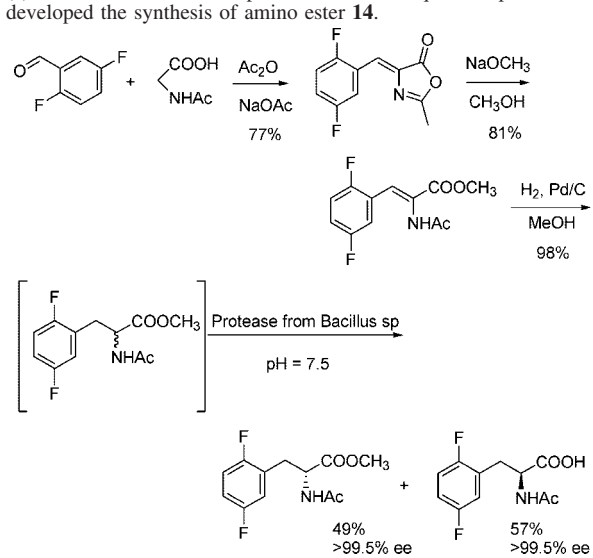
(13) (a) To fund the lab development of the subsequent steps, we also developed the synthesis of amino ester **14**.



The synthesis involved a classical Erlenmeyer condensation of 2,4-difluorobenzyaldehyde with *N*-acetyl glycine, followed by azlactone ring-opening to afford the corresponding dehydroamino ester. Amino ester **14** was further obtained from the dehydramino ester in >99% ee through enzyme resolution or asymmetric hydrogenation approach. For references on the synthesis of amino acids and derivatives, see: Roper, J. M.; Bauer, D. P. *Synthesis* **1983**, 1041. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (c) Boaz, N. W.; Large, S. E.; Ponasik, J. A.; Moore, M. K.; Barnette, T.; Nottingham, W. D. *Org.Process Res. & Dev.* **2005**, *9*, 472. (d) Perdih, A.; Sollner Dolenc, M. *Curr.Org. Chem.* **2007**, *11*, 801. (e) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (f) Humphrey, C. E.; Furegati, M.; Laumen, K.; Vecchia, L. L.; Leutert, T.; Muller-Hartwieg, J. C. D.; Vogtle, M. *Org.Process Res. Dev.* **2007**, *11*, 1069.

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(15) Liu, C.; Ng, J. S.; Behling, J. R.; Yen, C. H.; Campbell, A. L.; Fuzail, K. S.; Yonan, E. E.; Mehrotra, D. V. *Org. Process Res. Dev.* **1997**, *1*, 45.

(16) The ee of the aldehyde **12** was determined at alcohol **13** by reducing an analytical amount of **12** to **13** with $NaBH_4$ in MeOH. See Experimental Section for the ee methods for alcohol **13**.

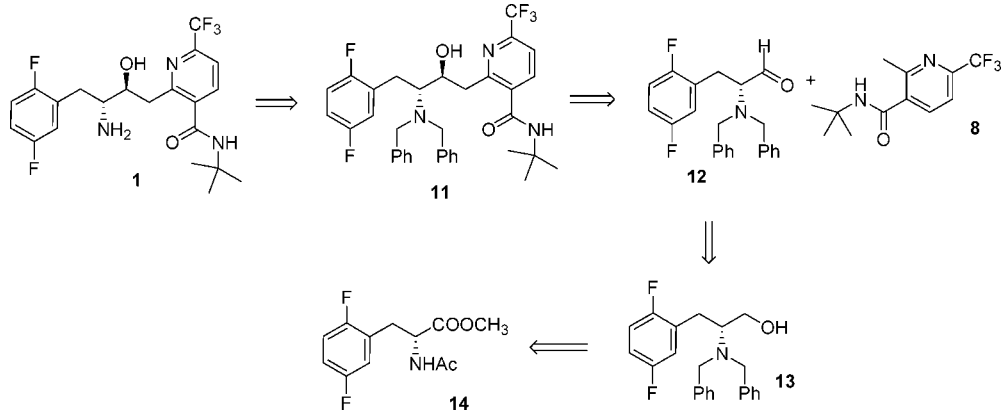
(17) Lower yield was due to the recovery of aldehyde starting material **12**, which may be caused by the aldehyde enolization during the dianion **8** addition. The hypothesis was that the extra diisopropylamine might help suppress the enolization of the aldehyde.

(18) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459. (c) McNeil, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 5655. (d) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212.

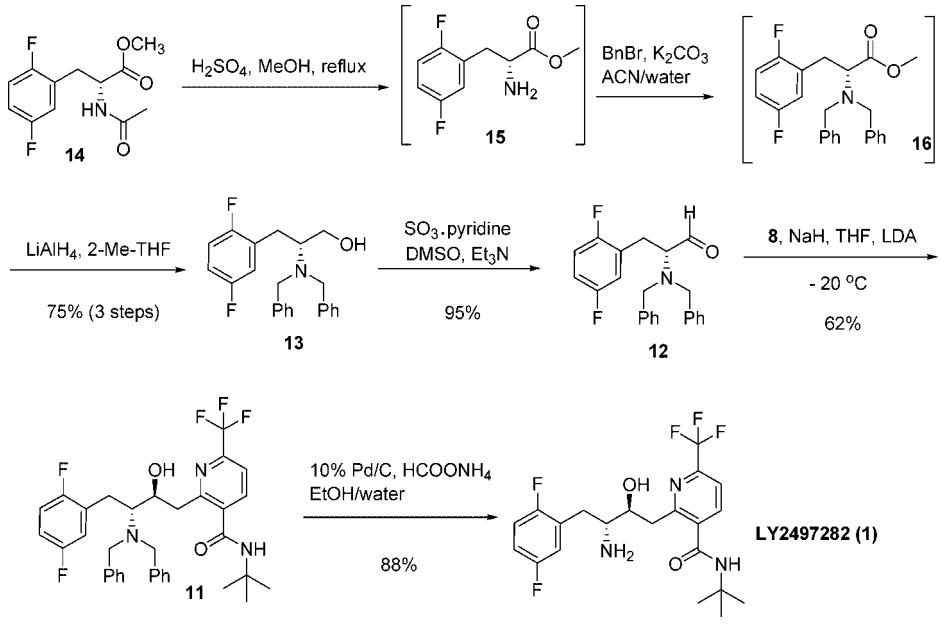
(19) The FTIR instrument is a Mettler-Toledo ReactIR-4000 equippe with a DiComp diamond sensor, a liquid nitrogen cooled MCT detector. Software version ReactIR 3.0 is used.

(20) Ng, J. S.; Przybyla, C. A; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* **1995**, *51*, 6397.

Scheme 3. **Retrosynthetic analysis of LY2497282 (1) using aldehyde approach**



Scheme 4. **Synthesis of LY2497282 (1) from amino ester 14**

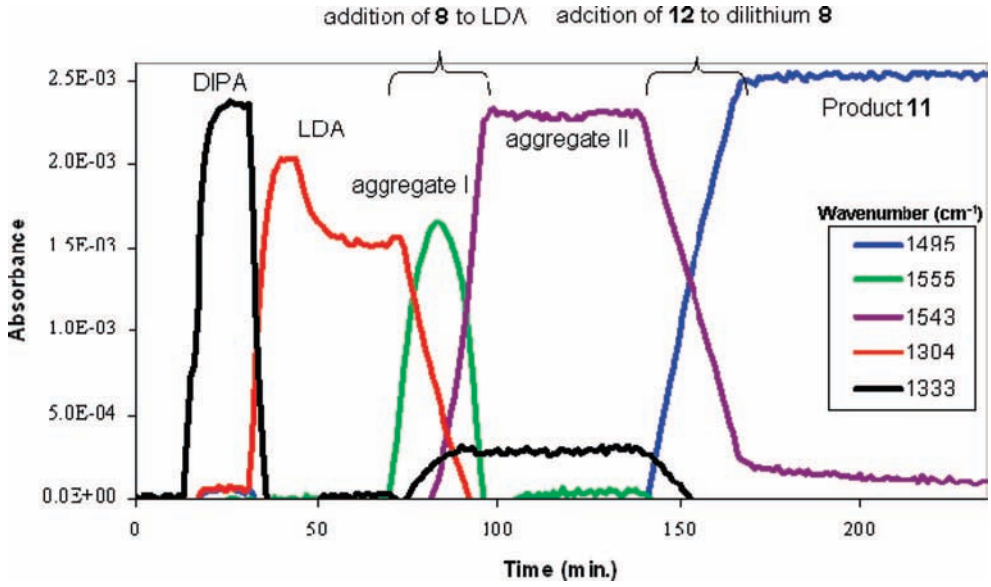


amino ester derivative available through an asymmetric hydrogenation or enzyme resolution approach (Scheme 3).[13]

Since bulk suppliers of nicotinamide **8**[14] and *N*-acetyl-protected amino ester **14** had been identified, they were chosen as the starting materials for our work. The conversion of amino ester **14** to final compound LY2497282 (**1**) was accomplished in six steps, as depicted in Scheme 4. The synthesis started from the deprotection of *N*-acetyl protected amino ester **14**. The acetyl deprotection was first attempted with anhydrous HCl in refluxing MeOH, however a significant amount of ester hydrolysis was observed under the condition. The deprotection was much more effective when **14** was refluxed under concentrated H_2SO_4 in MeOH, affording amine **15** as its H_2SO_4 salt with >97% in situ yield. Since neither the H_2SO_4 salt nor the free base was a crystalline solid, amine **15** was used in the next step without isolation. Thus, upon completion of the reaction, water and MTBE were added to the reaction mixture to promote layer separation. The aqueous layer, with the desired H_2SO_4 salt of **15** in it, was basified with ammonium hydroxide to give free base **15** in MTBE. During the pilot-plant operation, the organic extracts were solvent exchanged to acetonitrile, one of the reaction solvents for the subsequent reaction.

To protect free amine **15** with the dibenzyl protecting group, acetonitrile was first used as the reaction solvent and potassium carbonate as the base. The reaction would not go to completion unless a large excess of benzyl bromide was used. Addition of the phase transfer reagent Bu_4NBr promoted the formation of ~5% of benzyl alcohol as the hydrolysis product of benzyl bromide. To facilitate the solubility of potassium carbonate, water was next used as the cosolvent. Under acetonitrile/water (10:1), the reaction proceeded to completion with 2.1 equiv of benzyl bromide at 78 °C overnight. Upon completion of the reaction, aqueous work up was applied to remove residual potassium carbonate, potassium bromide and potassium bicarbonate. The next step was to reduce ester **16** to alcohol **13** with 1 N $LiAlH_4$in THF. To telescope the steps, 2-methyltetrahydrofuran was chosen as the reaction solvent for the $LiAlH_4$ reduction. Following an aqueous work up at the end of the reaction, alcohol **13** was directly solvent exchanged into heptane, the final crystallizing solvent for **13**. The residual benzyl bromide, a mutagen used in the benzyl protection step, was also completely consumed during the $LiAlH_4$ reduction process. The three-step telescoped procedure afforded alcohol **13** with

Scheme 5. **FTIR absorbance profiles generated during the formation of dilithium-8 and addition of aldehyde 12 to dilithium-8**



>99% ee and 75% yield from methyl ester **14**. The process was carried out at 10 kg scale during the pilot-plant operation.

Following a modification of a literature procedure,[15] alcohol **13** was converted to aldehyde **12** using sulfur trioxide pyridine complex as the oxidation reagent and DMSO as the reaction solvent. The highly volatile dimethyl sulfide byproduct was produced in this reaction. To control the dimethyl sulfide emission, the off gas was scrubbed with 5% NaOCl during scale up. Initially, ethyl acetate was used to extract the product from the aqueous solution. Since the residual ethyl acetate was difficult to remove and would interfere with the next reaction, it was later replaced with MTBE. Removal of residual DMSO through 5% citric acid washes was also more efficient when MTBE was used as the extraction solvent.

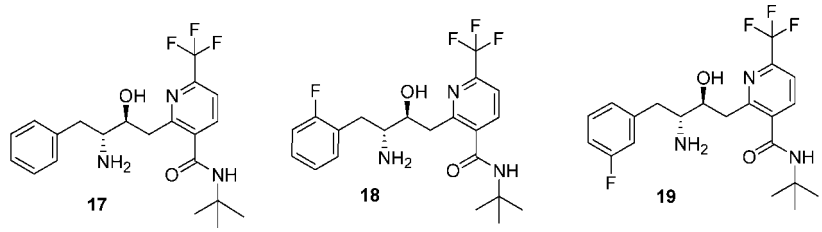
We collected chiral stability data on aldehyde **12**, both as a solid and as a MTBE solution, because we were concerned about our ability to control thermal racemization on scale. Starting with a representative lot of aldehyde **12** with 99.5% ee, the enantiomeric purity was monitored over time under different conditions. The results indicated that little racemization occurred if aldehyde **12** was stored as a solid at room temperature for 24 h. In 20 volumes of MTBE, the enantiomeric excess of **12** would stay at >98% for more than 24 h if the temperature was controlled below 35 °C. During the scale up of aldehyde **12**, the reaction and solvent distillation temperature was controlled below 15 °C. The reaction proceeded smoothly and afforded aldehyde **12** in >95% yield and >99% ee.[16]

The preparation of amino alcohol **11** from aldehyde **12** was the key step of the entire synthetic sequence. The reaction involved two sequential steps. The first step was to deprotonate **8** to form the dianion of **8**. The second step was to couple dianion-**8** with aldehyde **12**. A NaH/LDA combination procedure was first developed to form the dianion of **8**. Thus, the NH proton of **8** was first deprotonated with 1.0 equiv of NaH; subsequently the desired C-H proton was deprotonated with LDA, which was preformed under 1.3 equiv of diisopropylamine and 1.2 equiv of *n*-BuLi in THF. Higher product yield was observed when diisopropylamine was used in slight excess of *n*-BuLi.[17] The dianion-**8** was then reacted with 1.0 equiv of aldehyde **12** at –20 °C to give the two amino alcohols in ~3:1 ratio in favor of the desired Felkin-Anh nonchelation controlled *anti*-amino alcohol **11**. There was no significant difference in the diastereoselectivity if the reaction was carried out at lower temperature. The rejection of wrong diastereomer through heptane/THF crystallization turned out to be extremely efficient. Despite the moderate diastereoselectivity, the desired amino alcohol **11** was isolated in 99.4% HPLC area percentage in 62% yield after one crystallization, with the undesired amino alcohol consistently controlled below 0.1%.

Because of the long-term liability of using NaH, we also developed an alternative procedure by using LDA as the only deprotonating reagent. Thus, addition of a THF solution of nicotinamide **8** to LDA, which was formed in situ by adding 2.2 equiv of *n*-BuLi to 2.4 equiv of diisopropylamine in THF, afforded dilithium-**8** as a red solution. One equivalent of aldehyde was then introduced to the dilithium-**8** solution at −20 °C to give the two diastereomers in 2.6:1.0 ratio. Under this condition, the desired diastereomer was isolated in 56% yield with a impurity profile comparable with that of the one isolated from the NaH/LDA procedure.

Initial results indicated that THF was the best reaction solvent for the LDA-promoted dilithium-coupling reaction. We therefore further investigated the reaction using THF as the solvent. One observation we made during the development was that the reaction was very sensitive to THF concentrations. At −20 °C, no reaction occurred at 0.05 M THF; better aldehyde conversion was observed if the reaction was preformed at 0.4 M rather than 0.2 M. It was well documented that several aggregation states could be present in organolithium dianion reactions and the mixed aggregates might influence reactivity.[18] In an attempt to ensure reproducibility, we decided to monitor the reaction using in situ FTIR[19] to better understand the formation of the dianion and the subsequent aldehyde addition step (Scheme 5). LDA was formed under the standard condition by addition of *n*-BuLi to diisopropylamine in THF at −20 °C. Upon addition of nicotinamide **8** to LDA, the IR absorbance profiles showed the consumption of LDA band (1304 cm^{-1}) and production of a band at 1555 cm^{-1}, which was believed to correspond to

Scheme 6. **Structures of des\-fluorinated impurities**



aggregate I for dilithium-**8**. Upon 50% of nicotinamide **8** addition, the IR profiles showed that the concentration of dilithium-**8** aggregate I reached its maximum. At the same time, dilithium-**8** aggregate II started to grow. The formation of aggregate II was completed at the end of nicotinamide **8** addition, indicating the dianion formation was addition rate controlled. Upon the addition of aldehyde **12** to dilithium-**8**, the IR profiles showed the consumption of the 1543 cm^{-1} band and the production of a product band at 1495 cm^{-1}. Again, the formation of product **11** was completed at the end of aldehyde **12** addition, indicating the coupling reaction was also addition rate controlled. On the basis of the results of these experiments, we were able to shorten the reaction time significantly with no concerns of reproducibility due to an incomplete reaction. The observation of the two dilithium-**8** aggregation states by in situ IR was intriguing. The details on these mixed aggregates and how they influence reactivity will be described in a separate report.

To complete the synthesis of LY2497282 (**1**), the last step was to remove the dibenzyl protecting group of amino alcohol **11**. The deprotection was first attempted under the classical hydrogenation conditions using MeOH or EtOH as the solvent and Pd/C or $Pd(OH)_2$ as the catalyst. The deprotection under these hydrogenation conditions gave highly inconsistent results. For example, for one lot of starting material **11**, the reaction proceeded to completion when it was hydrogenated with 10% water wet Pd/C in EtOH at 60 psi and 65 °C overnight. For another lot of starting material **11**, only 35% conversion was observed when the same lot of catalyst and reaction conditions were applied. When acetic acid was used as the solvent, the reaction proceeded to completion. However, a significant amount of impurity was formed as a result of reduction of the pyridine ring in **11**. Hydrogenation using Pearlman's catalyst (20% palladium hydroxide on carbon) in MeOH[20] also produced inconsistent results. Presumably, the inconsistency was a result of catalyst poisoning caused by residual sulfur carried over from the aldehyde oxidation step. Since the catalyst poisoning was difficult to control, we next turned our attention to transfer hydrogenation conditions for the dibenzyl deprotection. Under the treatment of 10% Pd on carbon, ammonium formate in MeOH and water (10:1) at 65 °C, the reaction consistently proceeded to completion within 2 h to give the target compound LY2497282 (**1**). However, 4% des-fluorinated impurities **17**, **18** and **19** (Scheme 6) were formed under this condition. As expected, the rejection of these impurities were inefficient under a variety of crystallization conditions. To overcome this problem, we further optimized our transfer hydrogenation conditions by replacing MeOH with EtOH as the reaction solvent and reducing the reaction temperature from 65 to 40 °C. The modifications consistently afforded LY2497282 (**1**) in >97% assay yield and controlled the formation of the des-fluorinated impurities below the desired level. Following transfer hydrogenation, the catalyst was removed by filtration and the filtrate went through an aqueous work up to remove the inorganic salts. Final crystallization afforded LY2497282 (**1**) in >99.0% purity and >99.5% ee. In addition, the Pd level was determined to be <1 ppm.

Conclusion

In conclusion, we have developed an efficient and chromatography-free route for the preparation of LY2497282 (**1**), a potent and selective DPP IV inhibitor targeted for the treatment of diabetes. The compound was prepared in 39% overall yield in six steps from *N*-acetyl protected α-amino ester **14**, a chiral intermediate available through an asymmetric hydrogenation or enzyme resolution approach. The second chiral center was established by a stereoselective addition of nucleophile **8** to *N*-dibenzyl protected α-amino aldehyde **12**, which was derived from **14** without epimerization. The reactions described were successfully scaled up from 12 L to pilot-plant scale.

Experimental Section

General. Melting points were obtained using a Thomas-Hoover capillary melting apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded as specified for each experiment with chemical shift recorded as parts per million. Elemental analysis and high-resolution mass spectrometry data was provided by the Physical Chemistry group of Lilly Research Laboratories. Commercially available reagents and solvents were used without further purification. Reaction progress was monitored using an Agilent 1100 series instrument equipped with a UV using the following conditions: Mobile phase: (A) 0.1% TFA in water; (B) 0.1% TFA in CH_3CN. Gradient: $T =$ 0 min 60% A 40% B, $T =$ 20 min 30% A 70% B; flow rate: 1.0 mL/min; column temperature: 30 °C; column: Zorbax SB-C8, 4.6 mm × 250 mm, 5 μm; detector: 254 nm. Chiral assays were performed using an Agilent 1100 series HPLC equipped with a UV.

2-Dibenzylamino-3-(2,5-difluoro-phenyl)-propan-1-ol (13). *N*-acetyl-protected methyl ester **14** (2.0 kg, 7.78 mol) was charged to 16 L of MeOH through a ventilated addition funnel. To the resulting solution was added concentrated sulfuric acid (1.9 kg, 19.4 mol), while maintaining the temperature below 60 °C. The reaction mixture was refluxed at 65 °C for 24 h, and HPLC analysis indicated that <0.5% of methyl ester **14** remained. The reaction mixture was allowed to cool to rt and was then quenched by slow addition of 19.2 L of water followed by 18 L of MTBE. The layers were separated, and the aqueous layer, which contained the salt of **15**, was recharged to the vessel. Eighteen liters of MTBE was added, and the two phases

were allowed to settle. The two phases were separated, and the organic layer was discarded. An additional 18 L of MTBE was added to the aqueous layer, and the pH was adjusted to approximately 9.5 by slow addition of ammonium hydroxide (2.1 kg). The aqueous layer was back extracted with 9 L of MTBE. The organic layers were combined and were assayed to contain 1.6 kg of amine **15** (7.4 mol, 95% yield from **14**).

The organic portion was concentrated by atmospheric distillation to a total volume of 8 L. To the still warm solution, 20 L of acetonitrile was added, and the mixture was concentrated to 8 L. To the still warm solution, 20 L of acetonitrile was added again, and the mixture was concentrated to 18 L. A quantity of 1.8 L of water was added, and the resulting acetonitrile/water solution was charged with potassium carbonate (2.6 kg, 18.5 mol) and benzyl bromide (2.66 kg, 15.5 mol). The mixture was heated to 78 °C and stirred at 78 °C overnight. The reaction mixture was cooled and then quenched with 16 L of water followed by 16 L of EtOAc. The layers were separated, and the organic layer was washed with 16 L of 10% brine solution. The organic layer was assayed to contain 2.8 kg of dibenzyl-protected methyl ester **16** (7.08 mol, 91% yield from **14**).

The organic portion was concentrated by atmospheric distillation to a volume of 10 L. To the still warm solution, 22 L of 2-methyltetrahydrofuran was added, and the mixture was concentrated to 10 L. To the still warm solution, an additional 22 L of 2-methyltetrahydrofuran was added, and the mixture was concentrated to 8 L. The total volume of 2-methyltetrahydrofuran was adjusted to 24 L, and the solution was cooled to –10 °C. Lithium aluminum hydride (4.7 L, 4.7 mol, 1 M THF solution) was added to the above solution over 150 min, while maintaining the pot temperature below 0 °C. The reaction mixture was stirred at 0 °C for 5 h. HPLC analysis indicated that <1% of methyl ester **16** remained. To a separate reactor was added 30 L of water and 2.6 L of hydrochloride acid, and the solution was cooled to 0 °C. The reaction mixture was transferred to the cold hydrochloride solution over 60 min. The reaction mixture was rinsed with 2 L of 2-methyltetrahydrofuran. The layers were separated, and the organic layer was washed with 18 L of 0.1 N HCl solution, followed by 18 L of 10% brine solution. The organic portion was concentrated through atmospheric distillation to a total volume of 10 L. To the still warm solution was added 20 L of heptane. The mixture was concentrated to 8 L. To the still warm solution was again added 20 L of heptane, and the mixture was concentrated to 16 L. The slurry was cooled to rt and stirred at rt for 4 h. The slurry was filtered, and the solid was washed with 8 L of heptane twice. The solid was dried in vacuo at 40 °C to give alcohol **13** as a white solid (2.14 kg, 5.84 mol, 75% yield from **14**). Chiral HPLC analysis indicated that the enantiomeric purity was >99.5%. (ChiralPak AD 250 mm × 4.6 mm, 85% hexanes, 15% EtOH, 0.2% DEA, 1.0 mL/min, 30 °C, 225 nm, t_R = 5.4 min (undesired), 8.5 min (desired)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 7.00–6.96 (m, 1H), 6.91–6.86 (m, 1H), 6.81–6.78 (m, 1H), 3.93 (d, J = 13.2 Hz, 2H), 3.60–3.53 (m, 3H), 3.37 (m, 1H), 3.14 –3.10 (m, 2H), 2.90 (m, 1H), 2.51 (t, J = 10.4 Hz, 1H). ^{13}C (400 MHz, $CDCl_3$) δ 159.7, 158.2, 157.3, 155.8, 138.9, 129.0, 128.6, 127.4, 117.6, 117.4, 116.6, 116.5, 116.3, 114.6, 114.4, 114.3, 60.3, 59.7, 53.2, 25.2. IR (KBr, cm^{-1}) ν 3422, 3079, 3027, 2955, 2938, 2857. MS (EI) *m/z* (rel intensity) 368 (M^+, 100); HRMS (ES^+) exact mass calcd for $C_{23}H_{24}F_2NO$ 368.1820, found 368.1816. Anal. Calcd for $C_{23}H_{23}F_2NO$ C, 75.19, H, 6.31, N, 3.81, found C, 75.11, H, 6.36, N, 4.01.

***N-tert*-Butyl-2-[3-dibenzylamino-4-(2,5-difluoro-phenyl)-2-hydroxy-butyl]-6-trifluoromethyl-nicotinamide (11).** To a 12-L three neck round-bottom flask equipped with an overhead stirrer apparatus, a cooling bath, a thermometer/thermocouple, a nitrogen inlet, and a 2-L addition funnel was charged alcohol **13** (510 g, 1.4 mol), triethylamine (568 g, 5.62 mol), and 100 mL of DMSO. The resulting solution was cooled in an ice/acetone bath to −9 °C. A solution of sulfur trioxide pyridine complex (443 g, 2.73 mol) in 1.96 L of DMSO was added to the reaction mixture at such a rate as to maintain the temperature below 10 °C. The reaction mixture was stirred at 0–10 °C for an additional 30 min. Five liters of water was added over 1 h, and the temperature was again controlled below 10 °C. The cooling bath was removed, and 5 L of MTBE was added. After the layer separation, the aqueous layer was extracted with another 5 L of MTBE. The MTBE layers were combined and washed with 3 × 5 L of aqueous citric acid (5%), followed by 4 L of brine, and dried over 756 g of Na_2SO_4. The solution was filtered and concentrated to give aldehyde **12** (491 g, 1.3 mol, 96% yield) as a yellow semisolid. The crude mixture was used in the next step without further purification.

Method A. To a 2-L round-bottom flask equipped with a condenser, a nitrogen inlet, magnetic stirring, and a thermocouple was charged nicotinamide **8** (42.7 g, 0.164 mmol), followed by 250 mL of THF. NaH (6.56 g, 0.164 mol, 60% dispersion in mineral oil) was added to the nicotinamide solution in portions. The reaction mixture was heated at 65 °C for 1 h, and then it was allowed to cool to rt. To a separate 500-mL round-bottom flask equipped with magnetic stirring, an addition funnel, a nitrogen inlet, and a thermocouple was charged diisopropylamine (21.6 g, 0.213 mol) and 60 mL of THF. The solution was cooled to −30 °C in a dry ice/acetone bath. *n*-BuLi (79.2 mL, 0.198 mol, 2.5 M solution in hexanes) was charged to the addition funnel via syringe and was added to the flask over ~30 min. The addition funnel was rinsed with 10 mL of THF. The sodium-**8** solution above was cooled in a dry ice/acetone bath to −30 °C, and the LDA solution was added to the sodium-**8** solution dropwise over 30 min while maintaining the temperature below −20 °C. The resulting dark-red reaction mixture was stirred for 30 min. A solution of aldehyde **12** (60.0 g, 0.164 mol) in 120 mL of THF was charged to the dark-red dianion-**8** solution dropwise while maintaining the maximum temperature below −20 °C. The color stayed red throughout the addition. After the completion of the addition, the reaction mixture was stirred at −20 °C for an additional hour. Water (400 mL) was added to the reaction mixture dropwise. The cooling bath was removed, and the pH was adjusted to approximately 9 by addition of 120 mL of 5 N HCl. The mixture was transferred to a separatory funnel, and layers were separated. The aqueous layer was extracted with 300 mL of EtOAc. The combined organic layers were washed with 300 mL of water and then solvent switched to 1080 mL of heptane

and 60 mL of THF. The mixture was allowed to cool to rt slowly. The resulting slurry was stirred at rt for 15 h and then filtered to collect the solid. The solid was washed with 200 mL of heptane and dried in vacuo at 45–50 °C to afford alcohol **11** as a white solid (64.6 g, 0.102 mol, 62% yield).

Method B. Diisopropylamine (53.2 g, 0.526 mol) and 140 mL of THF were charged to a 5-L round-bottom flask equipped with mechanical stirring, a nitrogen inlet, an addition funnel, and a thermocouple. The solution was cooled to −25 °C in a dry ice/acetone bath, and *n*-BuLi (193 mL, 0.482 mol, 2.5 M solution in hexanes) was added over 30 min through an addition funnel. The addition funnel was rinsed with 10 mL of THF. The reaction was stirred for additional 5 min at −25 °C. A solution of nicotinamide **8** (57.0 g, 0.219 mol) dissolved in 350 mL of THF was charged to an addition funnel and was added to the reaction mixture over 30 min, while maintaining the reaction temperature below −20 °C. A red solution was formed upon the addition of nicotinamide **8**. The reaction mixture was stirred at −20 °C for 30 min. A solution of aldehyde **12** (80.0 g, 0.219 mol) dissolved in 150 mL of THF was added to the addition funnel and was added to the reaction over 30 min, again maintaining the reaction temperature below −20 °C. The solution was rinsed in with an additional 10 mL of THF. The reaction was stirred at −20 °C for 30 min and was quenched by slow addition of 500 mL of water. The cooling bath was removed, and the pH was adjusted to approximately 9 by adding 160 mL of 5 N HCl. After the layer separation, the aqueous layer was extracted with 500 mL of EtOAc. The organic layers were combined and washed with 500 mL of water. The organic portion was solvent switched into 1440 mL of heptane and 80 mL of THF. The mixture was allowed to cool slowly to 23 °C, and the resulting slurry was filtered. The solid was washed with 220 mL of heptane and dried in vacuo at 40–45 °C to a constant weight. The title compound was isolated as a white solid (77.0 g, 0.123 mol, 56% yield). The optical purity was assayed to be >99.5% ee. (ChiralPak AD-H 150 mm × 4.6 mm, 94% hexanes, 6% IPA, 1.0 mL/min, 25 °C, 230 nm, t_R = 3.9 min (undesired), 6.3 min (desired)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.26–7.18 (m, 10H), 6.97–6.87 (m, 3H), 6.48 (s, 1H), 4.50 (bs, 1H), 3.78–3.69 (m, 5H), 3.31 (m, 1H), 3.17 (m, 1H), 3.04 (m, 1H), 2.99–2.93 (m, 2H), 1.34 (s, 9H). ^{13}C (400 MHz, DMSO-d6) δ 166.6, 159.6, 158.7, 157.3, 156.3, 146.6, 146.3, 140.1, 138.1, 137.5, 130.8, 130.6, 128.7, 128.3, 127.0, 123.2, 120.4, 118.7, 118.4, 116.4, 116.2, 116.1, 114.2, 114.0, 69.7, 61.5, 53.8, 51.6, 42.1, 39.5, 28.7, 24.5. IR (KBr, cm –1) ν3432, 3244, 3071, 3031, 2168, 2848. MS (EI) *m*/*z* (rel intensity) 626 (M^+, 100). HRMS (ES^+) exact mass calcd for $C_{35}H_{37}F_5N_3O_2$ 626.2800, found 626.2801. Anal. Calcd for $C_{35}H_{36}F_5N_3O_2$ C, 67.19, H, 5.80, N, 6.72, found C, 66.91, H, 5.81, N, 6.81.

2-[3-Amino-4-(2,5-difluoro-phenyl)-2-hydroxy-butyl]-*N*-*tert*-butyl-6-trifluoromethyl-nicotinamide (1). To a 12-L three neck round-bottom flask equipped with a condenser, nitrogen inlet, mechanical stirring, and thermocouple was charged water wet 10% Pd/C (94 g), 5.9 L of EtOH, dibenzyl protected amino alcohol **11** (590 g, 0.94 mol), and a solution of ammonium formate (236 g, 3.7 mol) in 700 mL of water. The reaction mixture was heated to 40 °C and held for 3 h or until HPLC analysis indicated >99.5% conversion. The reaction mixture was allowed to cool to 20 °C and then filtered through water-wet Celite. The residual catalyst on the Celite was washed with 1 L of EtOH. The filtrate was then transferred to a 20-L evaporatory flask and concentrated in vacuo to remove EtOH. The concentrate was dissolved in 5.9 L of MTBE and was then transferred to a separatory funnel; 2.4 L of water was added, and layers were separated. Saturated aqueous NH_4OH (200 mL) was added to the aqueous layer, and the resulting aqueous layer was extracted with 2.9 L of MTBE. The combined organic layer was then washed with 1 L of water. The organic portion was then solvent switched into 3 L of IPA. The solution was stirred at 50 °C, and 2.2 L of water was added dropwise. The solution became cloudy during the addition, and the mixture was allowed to cool to rt. A slurry was formed upon cooling. The resulting slurry was stirred at rt for 3 h and then filtered to collect the solid. The solid was washed with 1.5 L of water and dried in vacuo at 45 °C to a constant weight. The title compound was obtained as a white solid (368 g, 0.83 mol, 88% yield). The optical purity was assayed to be >99.5% ee. (ChiralPak AD 250 mm × 4.6 mm, 85% hexanes, 15% IPA, 0.2% DEA, 1.0 mL/min, 30 °C, 225 nm, t_R = 5.2 min (desired), 6.5 min (undesired)). mp (DSC) (10 °C/min) onset 127.40 °C, peak 128.41 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, J = 7.7 Hz, 1 H), 7.58 (d, J = 7.7 Hz, 1 H), 7.45 (s, 1H), 7.03–6.89 (m, 3H), 4.08–4.05 (m, 1 H), 3.38–3.33 (m, 1 H), 3.14–3.08 (m, 3 H), 2.67–2.62 (m, 1 H), 1.47 (s, 9 H). ^{13}C ($CDCl_3$, 400 MHz) δ 166.5, 159.7, 158.5, 157.3, 156.9, 156.1, 148.5, 148.1, 147.8, 147.4, 137.9, 136.6, 127.8, 127.7, 127.6, 127.5, 125.2, 122.4, 119.7, 118.0, 117.8, 117.7, 117.5, 117.0, 116.5, 116.3, 116.2, 114.7, 114.6, 114.4, 114.3, 75.1, 55.8, 52.3, 37.9, 31.9, 28.5. Anal. Calcd for $C_{21}H_{24}F_5N_3O_2$: C, 56.63; H, 5.43; N, 9.43. Found: C, 56.72; H, 5.42; N, 9.40.

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