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Synthesis and characterization of 2,6-difluoro-4-carboxyphenylboronic acid and a biotin derivative thereof as captors of anionic aqueous [^{18}F]-fluoride for the preparation of [^{18}F/^{19}F]-labeled aryltrifluoroborates with high kinetic stability

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Abstract

Arylboronic esters are readily converted to aryltrifluoroborates in the presence of aqueous fluoride. As such these represent attractive synthetic precursors that afford one-step labeling with [^{18}F]-fluoride for the generation of PET reagents. Herein we present the synthesis of a heretofore undisclosed arylboronic ester that is converted to its corresponding trifluoroborate. Essential for contemplating its use in PET imaging is the demonstration of kinetic resistance to solvolytic defluoridation.
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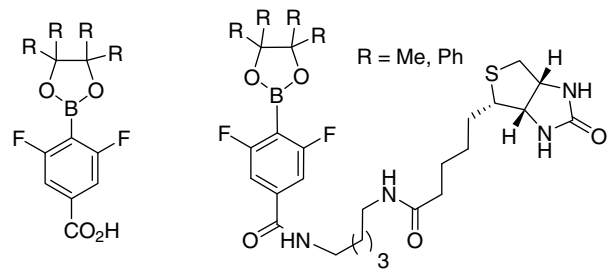
1. Introduction

Boronic acids have enjoyed widespread use, from serving as important building blocks for organic synthesis to acting as chemical sensors for carbohydrate recognition and components in pharmaceutically important enzyme inhibitors.[1] Their extensive use in synthetic and bioorganic chemistry led us to propose their use as precursors for the formation of PET (positron emission tomography) imaging agents based on their fluorophilicity for anionic [^{18}F]-fluoride to afford trifluoroborates with extraordinary chemoselectivity.[2] This potential is highlighted in a preliminary investigation of 2,4,6-trifluoro-3-carboxamidophenylboronic ester as a captor of aqueous [^{18}F]-fluoride in the preparation of an [^{18}F]-labeled aryltrifluoroborate PET radiotracer.[3] This particular electron-poor aryltrifluoroborate was discovered to be especially stable to solvolytic defluoridation and it was hypothesized that the electron-deficiency contributed to its stability. Extending that hypothesis, herein we describe the synthesis of protected 2,6-difluoro-4-carboxyphenylboronic acid (**1**) as a second and perhaps equally attractive candidate precursor for [^{18}F]-capture, as well as its biotin conjugate (**2**) which was prepared to demonstrate further potential for biomolecule labeling. Compounds **1** and **2** are shown in the next column.



1 **2**

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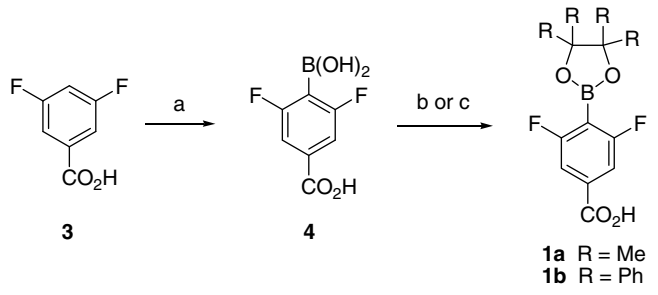
2. Results and discussion

Due to the lack of a commercially available, suitably functionalized electron-poor arylboronic acid, the synthesis of the carboxy-substituted compound **4** was envisaged by metallation of 3,5-difluorobenzoic acid (**3**) (Scheme 1).

Lithiation of **3** with *sec*-BuLi (or *n*-BuLi) in THF in the presence of TMEDA at −78 °C followed by trapping of the resultant dilithiated species with trimethylborate afforded 2,6-difluoro-4-carboxyphenylboronic acid **4** as the exclusive regiosiomer[4] in good yields on the gram scale.[5] The boronic acid **4** was easily converted to the pinacol ester **1a**[6] in quantitative yield.

Efforts were then undertaken to couple the pinacolate ester **1a** to a biotinylated derivative for the preparation of a radiotracer precursor with affinity for avidin and fusion constructs thereof. To this end, the Boc-protected amino-linked biotin **5**[7] was prepared and treated with TFA. The resultant TFA salt was then coupled to **1a** using standard EDC coupling conditions with DIPEA or triethylamine as base (Scheme 2).

Under these conditions, a significant proportion of protodeboronated product **6** (∼20–30% as determined by ^{1}H and ^{19}F NMR)[8] was obtained and this decomposition byproduct could not be easily separated from the desired boronate ester adduct **2a** by standard silica chromatography. As a result, other coupling conditions and isolation methods were explored. The commercially available *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS) resin[9] was employed in an attempt to immobilize the boronic acid **4** onto a solid support. As expected for electron-poor arylboronic acids, a low yield of immobilization (44%) was obtained and, upon examination of the remaining unbound material, it was discovered that a significant portion had also undergone protolytic deboronation.[10] Attempts to protect **2** with equimolar amounts of unbound *N*-methyldiethanolamine gave similar results.[11] Although this phenomenon has not been well characterized in the literature, arylboronic acids containing strong electron-withdrawing groups are known to be susceptible to this type of deboronation under basic conditions.[12] Consequently, the coupling of **1a** with the biotin-linked amine was repeated using pyridine as a milder base to avoid the formation of **6**. Notably, this minor modification provided the desired biotinylated adduct[13] cleanly in 60% yield with little formation of deboronated **6** (<5%) as observed by ^{1}H and ^{19}F NMR.

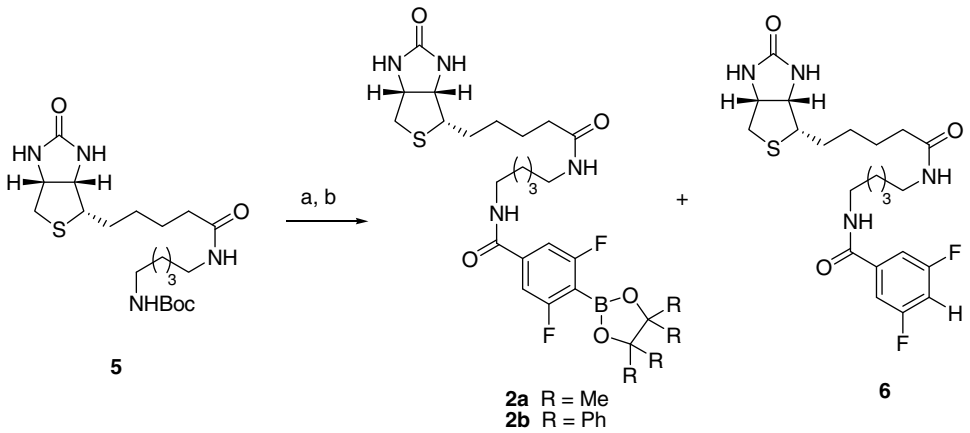


Scheme 1. Reagents and conditions: (a) *sec*-BuLi, TMEDA, THF, −78 °C then $B(OMe)_3$ then HCl, 75%; (b) R = Me, pinacol, THF/PhMe, 40 °C, quant.; (c) R = Ph, benzopinacol, THF/PhMe, reflux, 72%.

Given this concern, boronic acid **4** was subsequently protected by treatment with benzopinacol in refluxing THF/toluene using a Dean–Stark apparatus (Scheme 1).[14] Benzopinacolate **1b** proved to be considerably more robust than the corresponding pinacolate **1a** and afforded the biotin–boronate ester **2b** cleanly and in good yield after coupling with **5** (Scheme 2) and with considerably less protodeboronated material.[15]

The precursor carboxylic acid **1b** and the biotin–boronate ester conjugate **2b** were tested as captors for aqueous [^{18}F]-fluoride via the formation of [^{18}F]-labeled aryltrifluroborate PET imaging agents as described in the earlier report.[3] Briefly, [^{18}F]-labeled trifluoroborates were synthesized by incubating 5 μL of a 200 mM Boronic acid/ester solution in DMF with 5 μL 400 mM KHF_2 solution pH 3–4 (4 equiv of fluoride), containing a minimum of ∼20 μCi of [^{18}F]-fluoride (radioactivity at the start of reaction).

After 1 h of labeling at room temperature, a 1 μL aliquot of the labeling reaction was diluted 200-fold into 200 μL of a solution of 200 mM phosphate buffer pH 7.4 and 100 mM [^{19}F]-KF and allowed to solvolyze for a



Scheme 2. Reagents: (a) TFA, CH_2Cl_2; (b) **3** or **4**, EDC, HOBt, Base, CH_2Cl_2.

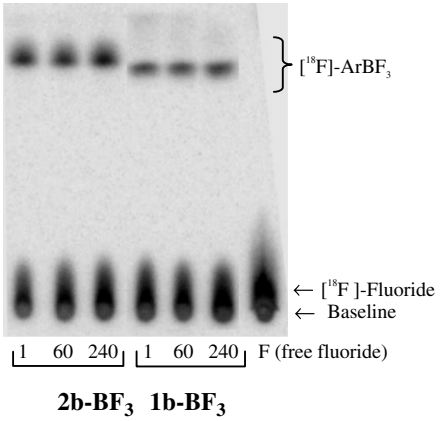


Fig. 1. Compounds **1b** and **2b** are converted to aryltrifluoroborates in the presence of [^{18}F]-fluoride in buffered KHF_2 pH 4.5. Following one hour of labeling, the fluoridation reaction is diluted 200-fold into 100 mM $K^{19}F$ pH 7.5 for various time periods 1, 60, or 240 min. The aryltrifluoroborate is resolved from free fluoride using 5:95 NH_4OH/EtOH and the TLC plate is subjected to autoradiography on a phosphor-storage screen. The relative autoradiographic density corresponding to the $ArBF_3$ and anionic fluoride can be quantified using the program IMAGEQUANT.

period of 240 min, 60 min, or 1 min. At the end point, a volume of 0.5 μL from each 'chase reaction' was spotted on a TLC plate and resolved in 5:95 NH_4OH/EtOH. The $ArBF_3$ cleanly separated from free fluoride with an R_f of 0.9, as shown in Figure 1.

Any solvolytic loss of fluoride results in the corresponding difluoroborane, which under aqueous conditions would either hydrolyze completely to the boronic acid, or revert to the unlabeled [^{19}F]-containing aryltrifluoroborate isotopolog. Furthermore, the large excess of [^{19}F]-KF added after labeling prevented any recapture of [^{18}F]-fluoride by a fully hydrolyzed boronic acid upon drying of the TLC plate dried.

Because thermodynamics dictate that at equilibrium the [^{18}F]-fluorine atom from the aryltrifluoroborate must completely exchange (>99%) in the presence of the large excess of [^{19}F]-KF, this isotopic exchange experiment followed by TLC separation and autoradiography effectively enables us to gauge a time-dependent increase in free fluoride and a concomitant decrease in the trifluoroborate.[2,3] Using IMAGEQUANT™ following autoradiography, the extent of isotopic exchange could be calculated using the method of initial rates or via a first-order decay fit shown in Figure 2 where the rate constants for solvolysis for the trifluoroborates of **1b** and **2b** are $1.6 \pm 0.4 \times 10^{-4}\ \mathrm{min}^{-1}$ and $2.8 \pm 0.9 \times 10^{-4}\ \mathrm{min}^{-1}$, respectively.

In this case, the trifluoroborates formed from compounds **1b** and **2b**, displayed very little fluoride exchange, following a 4-h incubation and TLC resolution.

The aqueous stability of **1b**–$\mathbf{BF_3}$ in phosphate buffer was also measured by ^{19}F NMR.[3b] This method allows one to quantitate the hydrolysis of an aryltrifluoroborate by measuring the rate of decrease of the trifluoroborate signal and the rate of increase in free fluoride over a sufficiently long time period compared to the half-life of ^{18}F. No other mono- or difluorinated intermediates were observed, thus allowing the total solvolysis of the $ArBF_3$ to be governed by dissociation of the first fluoride in a single rate-limiting step that is best approximated by a pseudo first-order rate constant. The kinetics of solvolysis for 10 mM **1b**–$\mathbf{BF_3}$ in 100 mM phosphate buffer pH 7.5 were thus measured at 5 min, 1 h, 4 h, 9 h, and 24 h, where the integration values for $ArBF_3$ (~56 ppm) and free fluoride (~43 ppm) were fit to the equation $([ArBF_3]/([ArBF_3]+[F]))_t = ([ArBF_3]+[F])_0 e^{-kt}$ and a rate constant of $6.8 \pm 0.4 \times 10^{-4}\ \mathrm{min}^{-1}$ was obtained (data not shown) and is in generally good agreement with the value obtained from the autoradiography. That the observed rate constant obtained from the autoradiographic analysis was a bit lower that obtained by ^{19}F NMR is due to the presence of 100 mM ^{19}F that reduces the k_{obs} value. The stability of 10 mM **1b**–**BF** in 200 mM phosphate buffer pH 5.7 was also measured to

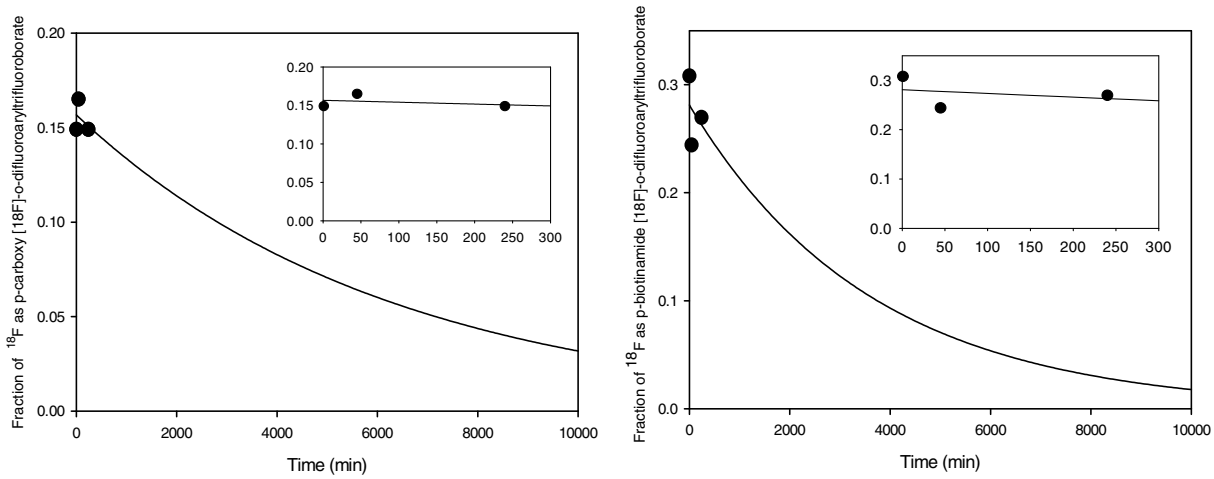


Fig. 2. Exponential decay fit for the trifluoroborates of compound A (left panel), and compound B (right panel), insets: relative amount of trifluoroborate over 240 min.

afford a rate constant of $3.5 \pm 1.5 \times 10^{-4}\,\mathrm{min}^{-1}$. This result demonstrates increased stability of **1b**–$\mathbf{BF_3}$ at lower pH, conditions which reflect certain intracellular localizations should such an aryltrifluoroborate cross the cell membrane.

These data, taken together, indicate that this particular aryltrifluoroborate is kinetically very stable with respect to solvolytic defluoridation.

3. Conclusions

In summary, 2,6-difluoro-4-carboxyphenylboronic acid was readily prepared and easily protected as either its pinacol or the benzopinacol boronate ester. Further derivatization of both boronates with a biotinylated amine was accomplished smoothly under mild conditions to afford PET imaging precursors suitable for [^{18}F]-labeling. This robust synthesis will allow for the attachment of **1** to other useful biomarkers besides biotin, examples of which will be reported in due course.

In order to demonstrate the kinetic stability of this aryltrifluoroborate with respect to solvolytic loss of fluoride, we used an isotopic exchange experiment that involved placing trace amounts of [^{18}F]-trifluoroborate in a solution containing a large excess of [^{19}F]-fluoride. This experiment measures the rate of loss of a single fluorine atom, as anionic fluoride, from the parent aryltrifluoroborate to afford the aryldifluoroborane, which is considered highly unstable in aqueous media. The resulting difluoroborane intermediate went undetected as it rapidly partitioned to either the fully hydrolyzed arylboronic acid/arylborate, or back to the aryltrifluoroborate, which is not radioactive as a consequence the large excess of [^{19}F]-fluoride present.

Although it is uncertain whether the aryldifluoroborane completely hydrolyzed to the unlabeled arylboronic/arylborate or reacted with 100 mM aqueous [^{19}F]-fluoride at pH 7.5 to regenerate the unlabeled aryltrifluoroborate isotopolog, nevertheless this experiment estimates the rate of loss of an atom of fluoride via a single rate-limiting step. Although only 3 time points were taken in this case leading to some error, it is clear that very little loss occurs over a period of 240 min, which is more than twice the half-life of the ^{18}F-fluoride (see Ref. 3a). This aqueous stability was independently supported by a more thorough analysis using ^{19}F NMR. Unless the presence of 100 mM free fluoride enhanced fluoride exchange, the same stability should be observed under physiological conditions (i.e., in vivo) and as such *this* trifluoroborate should be cleared from the blood stream to the bladder without solvolytic loss of [^{18}F]-fluoride to the bone.

Acknowledgments

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5. Preparation of 2,6-difluoro-4-carboxyphenylboronic acid **2**: To a solution of 3,5-difluorobenzoic acid (1.20 g, 7.59 mmol) and TMEDA (2.50 mL, 16.7 mmol) in THF (50 mL) at −78 °C was added a solution of *sec*-BuLi in cyclohexane (1.4 M, 13.0 mL, 18.2 mmol) and the reaction mixture was stirred at −78 °C for 75 min. Neat trimethyl borate (1.80 mL, 16.1 mmol) was then added to the reaction at −78 °C before warming the mixture to room temperature and stirring for 3 h. The reaction mixture was quenched with 3 N HCl (35 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated. The resultant gray solid was washed thoroughly with hexanes (3 × 50 mL) and dried in vacuo to afford the title compound (1.15 g, 75%) as a white solid. All nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 or 400 MHz instrument. ^{1}H NMR spectra are referenced to the tetramethylsilane peak (δ 0.00), ^{19}F NMR spectra are referenced to neat trifluoroacetic acid (δ 0.00, −78.3 ppm relative to $CFCl_3$) and ^{11}B NMR spectra are referenced to 15% $BF_3{\cdot}OEt_2$ in $CDCl_3$ (0.00 ppm). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 163.9 (dd, $J = 243$, 15 Hz), 134.6 (t, $J = 9$ Hz), 111.8 (d, $J = 29$ Hz), 111.8 (m); ^{19}F NMR (282 MHz, DMSO-d_6) δ −25.6 (d, $J = 6.5$ Hz, 2F); ^{11}B NMR (128 MHz, DMSO-d_6) δ 19.9; HRMS (ESI/MeOH) calcd for $C_9H_8BO_4F_2^-$ $(M-H)^-$ (dimethylboronate ester) 229.0484, found 229.0477.
6. Preparation of 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-bioxaborolan-2-yl)benzoic acid **3**: To a mixture of 2,6-difluoro-4-carboxyphenylboronic acid (114 mg, 0.56 mmol) and pinacol (66 mg, 0.56 mmol) were added THF (3 mL) and toluene (3 mL). The solvents were evaporated under reduced pressure at ~40 °C to dryness. This procedure of solvent addition and evaporation was repeated two more times and the residue dried in vacuo to afford the title compound (159 mg, quant.) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, $J = 7.4$ Hz, 2H), 1.40 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.2 (dd, $J = 252$, 12 Hz), 134.1 (t, $J = 9$ Hz), 112.7 (d, $J = 29$ Hz), 112.7 (m), 84.8, 24.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −22.5 (d, $J = 6.8$ Hz, 2F); HRMS (ESI) calcd for $C_{13}H_{14}BO_4F_2^-$ $(M-H)^-$ 283.0953, found 283.0947.
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13. Preparation of biotin–pinacolate **6**: A solution of *t*-butyl 5-biotinamidopentylcarbamate[7] (15 mg, 0.035 mmol) in CH_2Cl_2/TFA (3:1, 1.3 mL) was stirred at room temperature for 3 h then concentrated in vacuo. The resultant oil was diluted with CH_2Cl_2 (2 × 5 mL) and toluene (1 × 5 mL) and concentrated in vacuo for 5 h. To a solution of the resultant TFA salt in anhydrous DMF (1.5 mL) were added pyridine (15 μL, 0.19 mmol), HOBt hydrate (6.8 mg, 0.050 mmol), 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-bioxaborolan-2-yl)benzoic acid **3** (12.6 mg, 0.044 mmol) and EDC (9.2 mg, 0.048 mmol) sequentially. The reaction mixture was stirred for 16 h then diluted with $CHCl_3$ (20 mL) and H_2O (5 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated, and washed with Et_2O (5 × 3 mL) to afford adduct **6** (12.5 mg, 60% over 2 steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $J = 7.7$ Hz, 2H), 7.13 (m, 1H), 5.97 (m, 1H), 5.84 (br s, 1H), 4.83 (br s, 1H), 4.51 (m, 1H), 4.33 (m, 1H), 3.46–3.11 (m, 6H), 2.92 (dd, $J = 12.5$, 4.4 Hz, 1H), 2.90 (br s, 1H), 2.73 (d, $J = 12.8$ Hz, 1H), 2.24–2.18 (m, 2H), 1.68–1.45 (m, 10H), 1.43 (s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −22.8 (d, $J = 7.6$ Hz, 2F); HRMS (ESI) calcd for $C_{28}H_{41}BN_4O_5F_2SNa^+$ $(M+Na)^+$ 617.2756, found 617.2736.
14. Preparation of 2,6-difluoro-4-(4,4,5,5-tetraphenyl-1,3,2-bioxaborolan-2-yl)benzoic acid **4**: To a solution of 2,6-difluoro-4-carboxyphenylboronic acid (355 mg, 1.76 mmol) in toluene/THF (1:1, 30 mL) was added benzopinacol (709 mg, 1.93 mmol) and the mixture refluxed in a Dean–Stark apparatus for 16 h. The reaction mixture was cooled, concentrated, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH; 98:2 then 95:5 then 90:10) to afford the title compound (0.67 g, 72%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, $J = 6.7$ Hz, 2H), 7.26–7.21 (m, 8H); 7.10–7.08 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 166.7 (dd, $J = 253$, 12 Hz), 141.8, 134.9 (t, $J = 9$ Hz), 128.5, 127.3, 127.2, 113.0 (d, $J = 29$ Hz), 113.0 (m), 97.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −21.0 (s, 2F); HRMS (ESI) calcd for $C_{33}H_{22}BO_4F_2^-$ $(M-H)^-$ 531.1579, found 531.1594.
15. Preparation of biotin–benzopinacolate **8**: A solution of *t*-butyl 5-biotinamidopentylcarbamate[7] (15 mg, 0.035 mmol) in CH_2Cl_2/TFA (3:1, 1.3 mL) was stirred at room temperature for 3 h then concentrated in vacuo. The resultant oil was diluted with CH_2Cl_2 (2 × 5 mL) and toluene (1 × 5 mL) and concentrated in vacuo for 5 h. To a solution of the resultant TFA salt in anhydrous DMF (1.5 mL) were added pyridine (20 μL, 0.25 mmol), HOBt hydrate (7.5 mg, 0.056 mmol), 2,6-difluoro-4-(4,4,5,5-tetraphenyl-1,3,2-bioxaborolan-2-yl)benzoic acid **4** (25 mg, 0.047 mmol), and EDC (11.1 mg, 0.058 mmol) sequentially. The reaction mixture was stirred for 16 h then diluted with $CHCl_3$ (20 mL) and H_2O (5 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH; 96:4 then 90:10 then 85:15) to afford the boronate ester **8** (24 mg, 79% over 2 steps) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, $J = 7.8$ Hz, 2H), 7.37 (m, 1H), 7.25–7.20 (m, 8H), 7.09–7.06 (m, 12H), 6.45 (m, 1H), 6.19 (br s, 1H), 5.25 (br s, 1H), 4.36 (m, 1H), 4.22 (m, 1H), 3.48–3.41 (m, 2H), 3.25–3.21 (m, 2H), 3.04–3.01 (m, 1H), 2.78 (dd, $J = 12.5$, 4.6 Hz, 1H), 2.64 (d, $J = 13.0$ Hz, 1H), 2.22–2.16 (m, 2H), 1.63–1.36 (m, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −21.2 (d, $J = 7.3$ Hz, 2F); HRMS (ESI) calcd for $C_{48}H_{49}BN_4O_5F_2SNa^+$ $(M+Na)^+$ 865.3382, found 865.3374.