A Stereocontrolled Protocol to Highly Functionalized Fluorinated Scaffolds through a Fluoride Opening of Oxiranes

Attila Márió Remete [1], Melinda Nonn [2], Santos Fustero [3], Ferenc Fülöp [1,2] and Loránd Kiss [1,*]

[1] Institute of Pharmaceutical Chemistry, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary; remete.attila@pharm.u-szeged.hu (A.M.R.); fulop@pharm.u-szeged.hu (F.F.)

[2] MTA-SZTE Stereochemistry Research Group, Hungarian Academy of Sciences, Eötvös u. 6, H-6720 Szeged, Hungary; nonn.melinda@pharm.u-szeged.hu

[3] Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Av. Vicente Andrés Estellés, s/n 46100 Valencia, Spain; Santos.Fustero@uv.es

* Correspondence: kiss.lorand@pharm.u-szeged.hu; Tel.: +36-30-8904092 or +36-62-546809

Abstract: A novel selective and substrate-dependent synthetic protocol has been developed towards the synthesis of various fluorine-containing, highly functionalized cycloalkane derivatives. The method involves the stereoselective epoxidation of some unsaturated cyclic β-amino acid derivatives as model compounds, followed by a regioselective fluoride opening of oxiranes under various conditions with Deoxofluor and XtalFluor-E reagents, thereby offering an insight into this new epoxide opening methodology with fluoride.

Keywords: oxirane; fluorination; amino acids; stereoselectivity; regioselectivity

1. Introduction

Olefin epoxidation and the ring opening of epoxides with various nucleophiles is a widely used method for the creation of different functional groups on the skeleton of organic molecules [1–7].

Because of the increasing importance of fluorinated biomolecules, the introduction of one or more fluorine atoms into an organic molecule has received great interest in recent years. Besides the important fluorine-containing drugs [8,9], several fluorinated α- and acyclic β-amino acids are known as enzyme inhibitors, antitumoral agents, and antibiotics [10–13].

Taking into consideration the significance of fluorine in the structure of an organic molecule, an oxirane ring opening with fluoride is a substantially useful approach for the incorporation of a fluorine atom into a certain molecule [14–17]. However, the stereo- and regioselectivity in highly functionalized cyclic scaffolds is a major challenge, which is associated with this type of transformation. Various synthetic methods including asymmetric approaches for the oxirane ring opening with fluoride, using fluorine-containing reagents such as pyridine·HF [18,19], $Et_3N \cdot 3HF$ [20,21], $BF_3 \cdot OEt_2$ [22,23], $HBF_4 \cdot OEt_2$ or HBF_4 [24,25], KHF_2 [26], $TBAF/KHF_2$, $TBAF \cdot 3H_2O/KF$ [27], KHF_2/18-crown-6/chiral Jacobsen chromium complex [28,29], $AgHF_2$ with Ru catalyst [30], benzoyl fluoride, base, and HFIP [31,32], have been reported. However, despite the relatively large number of synthetic opportunities listed here, these molecular entities possessing the bicyclic oxirane fused ring system are still considered complicated substrates for ring openings with fluoride. Consequently, there might be a need for the development of novel synthetic techniques in view of this transformation.

2. Results and Discussion

Our goal has been the development of a novel synthetic approach for the introduction of a fluorine atom into the skeleton of a highly functionalized cycloalkane framework. We designed here a two-step protocol: first, selective epoxidation; second, a selective oxirane ring opening with appropriately selected fluoride reagents.

As a consequence of their important biological potential, highly functionalized amino acid derivatives play a significant role in medicinal and organic chemistry. Some functionalized alicyclic amino acid derivatives, such as oryzoxymycin, oseltamivir, peramivir, and icofungipen, exert relevant bioactive properties [33].

There are relatively few methods in the literature [5,10–13] for the access of fluorine-containing, highly functionalized β-amino acid derivatives. Therefore, the synthetic protocol for the access of various fluorine-containing functionalized scaffolds regarding these valuable bioactive derivatives was investigated here for the first time. The synthetic concept involves the stereoselective epoxidation of some unsaturated β-amino esters (derived from bicyclic β-lactams) as selected model compounds. In the next step, the regioselective fluoride opening of the formed oxiranes with both Deoxofluor and XtalFluor-E reagents is carried out for the creation of novel, potentially bioactive, fluorine-containing β-amino acid derivatives or heterocyclic systems.

First, the fluorination procedures were investigated with cyclopentane β-amino acid derivatives. For this reason, a number of experiments were performed with systematic variation in the fluorinating agent, the number of equivalents, the solvent, the temperature, the reaction time, and the usage of additives. The *all-cis* epoxy amino ester **(±)-2** (derived from bicyclic lactam **(±)-1** according to our earlier protocol) [34–36] was treated with XtalFluor-E [37] in dioxane at reflux (see Method D in the Materials and Methods section). The opening of the oxirane ring yielded an oxazolidine derivative **(±)-5** as the sole product through intramolecular nucleophilic cyclization by the amide *O*-atom (Scheme 1). It is noteworthy that the same reaction, when carried out in other common solvents such as PhMe, CH_2Cl_2, and THF, yielded no transformation; only starting epoxide could be detected after a day of reflux. Unfortunately, compound **(±)-5**, when reacted with Deoxofluor [38] under various conditions (in different solvents at room temperature, reflux, etc.), did not yield the corresponding fluorinated derivative. Next, the fluorination regent was changed from XtalFluor-E to Deoxofluor. When epoxide **(±)-2** was reacted with 6 equiv. of Deoxofluor in toluene (after some evaluation of various solvents such as THF, 1,4-dioxane, and CH_2Cl_2, this proved to be the most efficient) in the presence of one drop of EtOH at 20 °C for three days (see Method A in the Materials and Methods section), two products were isolated: One was an unsaturated fluorinated derivative **(±)-3** as a result of the elimination and rearrangement (see also Scheme 2). The other product was an amino ester **(±)-4** containing both fluorine and a hydroxyl group (Scheme 1). Derivatives **(±)-3** and **(±)-4** formed in a 2.3:1 ratio were separated and isolated by means of column chromatography. Although compound **(±)-2**, depending on the reagent, yielded different types of products, by reacting either with XtalFluor or Deoxofluor, the reactions with these reagents (analogously to the hydroxy–fluorine exchange; see [37] and references therein) most likely took place with different mechanisms. The exact elucidation of these mechanisms needs deeper evaluation, which is in progress in our laboratory.

The oxirane ring opening with both XtalFluor-E and Deoxofluor was studied in various solvents (e.g., THF, CH_2Cl_2, dioxane, and PhMe) and in the presence of certain additives activating the oxiranes. After some experimental investigations using different electrophilic additives (e.g., $BF_3 \cdot OEt_2$, NH_4Cl, $AlCl_3$, and Li salts), the ring opening of oxirane **(±)-2** was achieved with 4 equiv. of Deoxofluor in the presence of $TiCl_4$ (see Method C in the Material and Methods section), furnishing compound **(±)-4** as the only product, albeit in a modest yield (26%) (Scheme 1). It is noteworthy that, in all fluorination transformations, alongside with the desired fluorine-containing products, either a significant amount of starting epoxide or a polymeric material could be detected.

Similar studies have been carried out with "*trans*" epoxy amino ester **(±)-6** (synthetized analogously as reported earlier [34–36]), in which the ester and the carbamate groups are in a relative *trans*

arrangement. In the reaction with XtalFluor-E (reflux in dioxane), epoxy amino ester (±)-6 provided a cyclized derivative (±)-8 (see Method D in the Materials and Methods section). Deoxofluor, again, yielded two products in a 1.7:1 ratio. One is unsaturated amino ester (±)-3, the same product formed from *all-cis* amino esters (±)-2 (Scheme 1), while the second is a difluorinated derivative (±)-7 (see Method B in the Materials and Methods section) (Scheme 3).
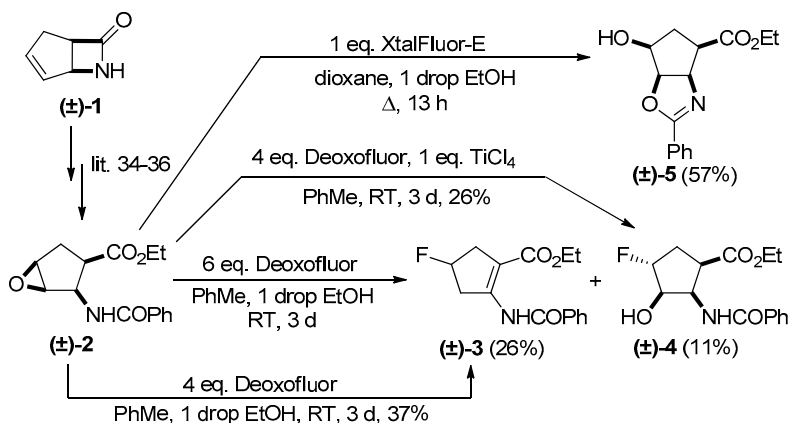
Scheme 1. Oxirane opening of *all-cis* epoxy amino ester (±)-2 with Deoxofluor and XtalFluor-E.
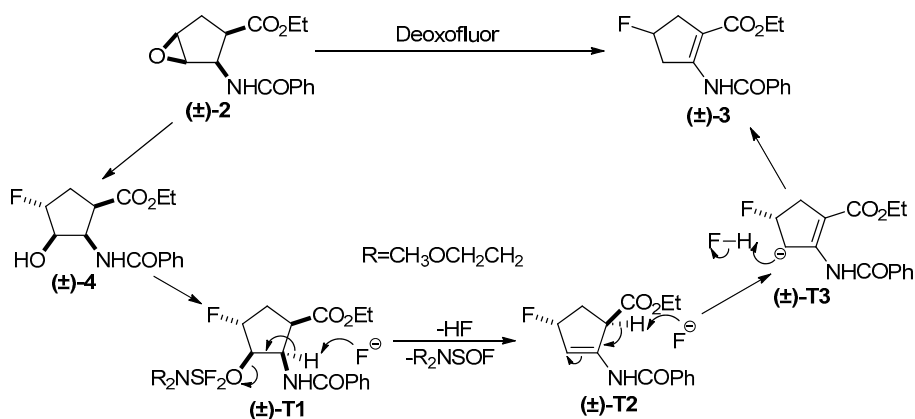

Scheme 2. A possible route for the formation of fluorinated amino ester (±)-3.
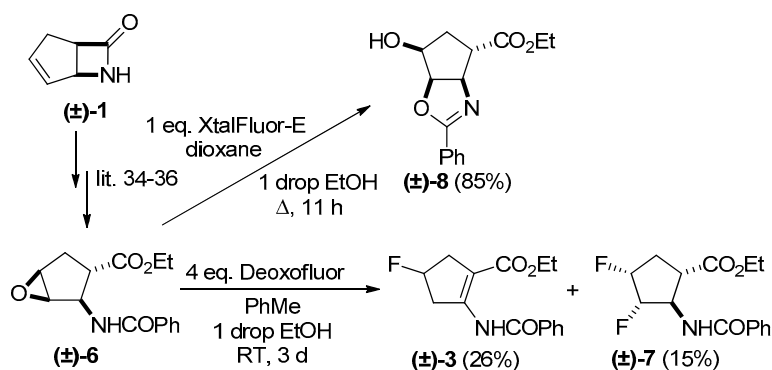
Scheme 3. Oxirane opening of the "*trans*" epoxy amino ester (±)-6 with Deoxofluor and XtalFluor-E.

Our synthetic investigations were further extended for larger ring systems, namely the six-membered analogues. Thus, *all-cis* epoxy amino ester (±)-10 (derived from bicyclic lactam (±)-9 according to a known method) [39,40] was subjected to fluorination. When the reaction was

accomplished with 2 equiv. of Deoxofluor (CH$_2$Cl$_2$ and reflux), difluorinated derivative (±)-**11** was obtained. Note that a similar product could not be detected in the transformation of cyclopentane derivative (±)-**2**. The yield of fluorinated amino ester (±)-**11** might be slightly increased (76%) by the addition of TiCl$_4$ (Method C). Furthermore, the reaction of compound (±)-**10** with XtalFluor-E afforded oxazine derivative (±)-**12**, formed via the intramolecular ring closing (Method D) (Scheme 4).
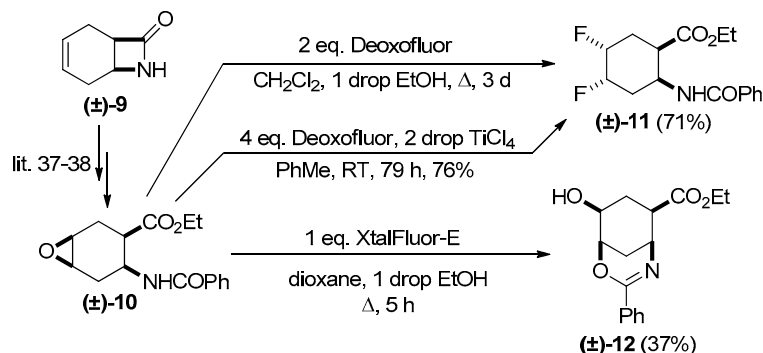
Scheme 4. Oxirane opening of cyclohexane *all-cis* epoxy amino ester (±)-**10** with Deoxofluor and XtalFluor-E.

However, rather surprisingly, the result of the fluorination of "*trans*" epoxy amino ester isomer (±)-**13** (for similar epoxidation see also reference [39,40]) is different from that of the *all-cis* isomer (±)-**10**. The reaction of (±)-**13** with Deoxofluor resulted in difluorinated amino ester (±)-**15** and fluoroalcohol derivative (±)-**16** formed in low yields (Method B). Next, the fluorination of (±)-**13** accomplished with XtalFluor-E (reflux in dioxane) furnished oxazine derivative (±)-**14**, as a single product, in a modest yield (Method D) (Scheme 5). It is noteworthy, however, that, contrary to epoxide (±)-**2**, fluorination of (±)-**10** in the presence of TiCl$_4$ yielded no identifiable product.
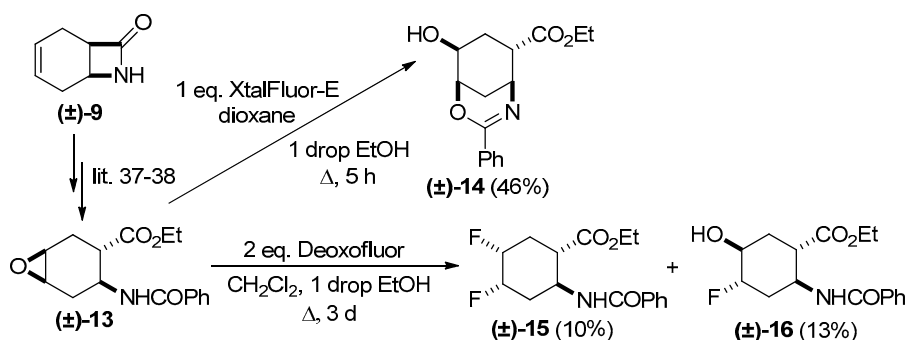
Scheme 5. Oxirane opening of cyclohexane "*trans*" amino ester (±)-**13** with Deoxofluor and XtalFluor-E.

3. Materials and Methods

Epoxidations of cycloalkene β-amino esters were performed according to procedures published previously [34,39]. The ^{1}H-NMR and ^{13}C-NMR spectra of all new compounds are available in the Supplementary Materials.

Experimental Procedures for the Oxirane Ring Openings

Method A: To a solution of epoxide (0.5–0.7 mmol) in anhydrous toluene (10 mL) under an Ar atmosphere, one drop of anhydrous EtOH and 50% Deoxofluor in toluene (4 equiv.) were added, and the solution was stirred at 20 °C for the time given in the schemes. The solution was then diluted with CH$_2$Cl$_2$ (30 mL), and the organic layer was washed with a saturated aqueous NaHCO$_3$

solution (2 × 20 mL), dried (Na$_2$SO$_4$), and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Method B: To a solution of epoxide (0.5 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) under an Ar atmosphere, one drop of anhydrous EtOH and 50% Deoxofluor in toluene (1 equiv.) were added, and the solution was kept at reflux temperature for 2 days. Then, 50% Deoxofluor in toluene (1 equiv.) was added again, and the solution was treated as above for one more day. The solution was then diluted with CH$_2$Cl$_2$ (30 mL), and the organic layer was washed with saturated aqueous NaHCO$_3$ solution (2 × 20 mL), dried (Na$_2$SO$_4$), and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Method C: To a solution of epoxide (0.5–0.75 mmol) in anhydrous toluene (10 mL) under an Ar atmosphere, 50% Deoxofluor in toluene (4 equiv.) and the given amount of TiCl$_4$ was added, and the solution was stirred at 20 °C for the time given in the schemes. The solution was then diluted with CH$_2$Cl$_2$ (30 mL), the organic layer was washed with a saturated aqueous NaHCO$_3$ solution (2 × 20 mL), dried (Na$_2$SO$_4$), and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Method D: To a solution of epoxide (0.5 mmol) in anhydrous 1,4-dioxane (10 mL) under an Ar atmosphere, one drop of anhydrous EtOH (or without the addition of EtOH, see the schemes) was added, followed by XtalFluor-E (1 equiv.). The reaction mixture was kept at a reflux temperature for the time given in the schemes. The solution after cooling was diluted with CH$_2$Cl$_2$ (30 mL), and the organic layer was washed with a saturated aqueous NaHCO$_3$ solution (2 × 20 mL), dried (Na$_2$SO$_4$), and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Ethyl (1R*,2R*,3R*,5S*) 2-benzamido-6-oxabicyclo[3.1.0]hexane-3-carboxylate **(±)-2**. White solid; yield 97%; R_f = 0.48 (*n*-hexane/EtOAc 1:2); m.p. 85–88 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.27 (t, *J* = 7.12 Hz, 3H, CH$_3$), 2.01–2.10 (m, 1H, CH$_2$), 2.75–2.83 (m, 2H, CH$_2$ and H-3), 3.49–3.53 (m, 1H, H-1), 3.67–3.71 (m, 1H, H-5), 4.10–4.26 (m, 2H, OCH$_2$), 4.89–4.96 (m, 1H, H-2), 7.42–7.55 (m, 3H, Ar-H), 7.85–7.91 (m, 2H, Ar-H), 8.63–8.79 (brs, 1H, N-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.4, 30.8, 37.5, 53.3, 54.0, 57.5, 61.6, 127.5, 129.0, 132.0, 134.4, 167.6, 174.8. MS (ESI, pos) *m/z* 298 (M + Na). Anal. Calcd. for C$_{15}$H$_{17}$NO$_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.11; H, 5.88; N, 4.81.

Ethyl (1R*,2R*,3S*,5S*) 2-benzamido-6-oxabicyclo[3.1.0]hexane-3-carboxylate **(±)-6**. White solid; yield 97%; R_f = 0.62 (*n*-hexane/EtOAc 1:2); m.p. 108–111 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.20 (t, *J* = 7.14 Hz, 3H, CH$_3$), 2.10–2.21 (m, 2H, CH$_2$), 2.40–2.52 (m, 1H, H-3), 3.56–3.62 (m, 1H, H-1), 3.69–3.76 (m, 1H, H-5), 4.07–4.22 (m, 2H, OCH$_2$), 4.83–4.92 (m, 1H, H-2), 6.34 (d, *J* = 7.64 Hz, 1H, N-H), 7.41–7.48 (m, 2H, Ar-H), 7.49–7.55 (m, 1H, Ar-H), 7.76–7.82 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.5, 30.7, 44.0, 55.3, 55.5, 58.1, 61.6, 127.4, 129.0, 132.1, 134.5, 167.9, 173.3. MS (ESI, pos) *m/z* 276 (M + 1). Anal. Calcd. for C$_{15}$H$_{17}$NO$_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.10; H, 6.86; N, 4.80.

Ethyl (1S*,3R*,4S*,6R*) 4-benzamido-7-oxabicyclo[4.1.0]heptane-3-carboxylate **(±)-10**. White solid; yield 69%; R_f = 0.47 (*n*-hexane/EtOAc 1:2); m.p. 100–109 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.31 (t, *J* = 7.12 Hz, 3H, CH$_3$), 2.16–2.26 (m, 1H, CH$_2$), 2.27–2.34 (m, 2H, CH$_2$), 2.57–2.65 (m, 1H, CH$_2$), 2.70–2.79 (m, 1H, H-3), 3.26–3.32 (m, 2H, H-1 and H-6), 4.12–4.27 (m, 2H, OCH$_2$), 4.60–4.69 (m, 1H, H-4), 7.34 (d, *J* = 9.20 Hz, 1H, N–H), 7.41–7.48 (m, 2H, Ar-H), 7.48–7.55 (m, 1H, Ar-H), 7.75–7.82 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.5, 25.1, 29.1, 40.6, 44.5, 51.5, 52.1, 61.4, 127.4, 128.9, 131.8, 134.9, 166.8, 173.4. MS (ESI, pos) *m/z* 290 (M + 1). Anal. Calcd. for C$_{16}$H$_{19}$NO$_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.09; H, 6.29; N, 4.50.

Ethyl (1S*,3S*,4S*,6R*) 4-benzamido-7-oxabicyclo[4.1.0]heptane-3-carboxylate **(±)-13**. White solid; yield 91%; R_f = 0.48 (*n*-hexane/EtOAc 1:2); m.p. 108–119 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.30 (t, *J* = 7.14 Hz, 3H, CH$_3$), 2.06–2.14 (m, 1H, CH$_2$), 2.22–2.30 (m, 1H, CH$_2$), 2.32–2.40 (m, 1H, CH$_2$), 2.45–2.54 (m, 1H, CH$_2$), 2.86–2.96 (m, 1H, H-3), 3.31–3.36 (m, 1H, H-6), 3.38–3.43 (m, 1H, H-1), 4.22

(q, J = 7.06 Hz, 2H, OCH$_2$), 4.61–4.70 (m, 1H, H-4), 7.04 (d, J = 9.44 Hz, 1H, N-H), 7.44–7.50 (m, 2H, Ar-H), 7.51–7.57 (m, 1H, Ar-H), 7.77–7.84 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.6, 23.7, 28.2, 40.9, 45.3, 51.8, 52.6, 61.5, 127.3, 129.0, 132.0, 134.6, 166.7, 173.4. MS (ESI, pos) *m/z* 290 (M + 1). Anal. Calcd. for C$_{16}$H$_{19}$NO$_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.11; H, 6.90; N, 4.49.

Ethyl 2-benzamido-4-fluorocyclopent-1-enecarboxylate (±)-**3**. Yellowish solid; yield 37%; R_f = 0.52 (*n*-hexane/EtOAc 5:1); m.p. 72–82 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.34 (t, J = 7.12 Hz, 3H, CH$_3$), 2.82–2.85 (m, 1H, H-5), 2.90–2.94 (m, 1H, H-5), 3.46–3.81 (m, 2H, H-3), 4.22–4.32 (m, 2H, OCH$_2$), 5.20–5.39 (m, 1 H, H-4), 7.47–7.53 (m, 2H, Ar-H), 7.54–7.60 (m, 1H, Ar-H), 7.92–7.98 (m, 2H, Ar-H), 11.26–11.36 (s, 1H, N-H). ^{19}F-NMR (376 MHz, CDCl$_3$) δ = −168.91. ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.8, 30.1, 37.05 and 37.29 (^2J = 24.00 Hz), 42.69 and 42.94 (^2J = 25.25 Hz), 60.7, 90.28 and 92.03 (^1J = 176.35 Hz), 105.7, 128.0, 129.3, 132.9, 133.7, 151.9, 165.2. MS (ESI, pos) *m/z* 577 (2M + Na). Anal. Calcd. for C$_{15}$H$_{16}$FNO$_3$: C, 64.97; H, 5.82; N, 5.05. Found: C, 64.66; H, 5.48; N, 4.77.

Ethyl (1R*,2R*,3R*,4R*) 2-benzamido-4-fluoro-3-hydroxycyclopentane-carboxylate (±)-**4**. Yellow solid; yield 26%; R_f = 0.62 (*n*-hexane/EtOAc 1:1); m.p. 96–104 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.13 (t, J = 7.14 Hz, 3H, CH$_3$), 2.19–2.36 (m, 1H, CH$_2$), 2.46–2.65 (m, 1H, CH$_2$), 3.58 (dt, J = 5.41 Hz and 8.91 Hz, 1H, H-1), 4.09 (q, J = 7.13 Hz, 2H, OCH$_2$), 4.26 (dd, J = 4.78 Hz and 10.22 Hz, 1H, H-3), 4.84–4.92 (m, 1H, H-2), 4.95–5.12 (m, 1H, H-4), 7.05 (d, J = 7.36 Hz, 1H, N-H), 7.39–7.46 (m, 2H, Ar-H), 7.47–7.54 (m, 1H, Ar-H), 7.73–7.79 (m, 2H, Ar-H). ^{19}F-NMR (376 MHz, CDCl$_3$) δ = −175.66. ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.4, 34.25 and 34.49 (^2J = 23.65 Hz), 44.78, 53.51, 62.36, 76.63 and 76.91 (^2J = 27.70 Hz), 96.10 and 97.88 (^1J = 179.42 Hz), 127.4, 129.1, 132.3, 177.4. MS (ESI, pos) *m/z* 296 (M + 1). Anal. Calcd. for C$_{15}$H$_{18}$FNO$_4$: C, 61.01; H, 6.14; N, 4.74. Found: C, 60.70; H, 5.79; N, 4.38.

Ethyl (3aR*,4R*,6S*,6aR*)-6-hydroxy-2-phenyl-4,5,6,6a-tetrahydro-3aH-cyclo-penta[d]oxazole-4-carboxylate (±)-**5**. White solid; yield 57%; R_f = 0.35 (*n*-hexane/EtOAc 1:2); m.p. 130–134 °C. ^{1}H-NMR (400 MHz, d_6-DMSO, TMS) δ = 1.23 (t, J = 7.08 Hz, 3H, CH$_3$), 1.51–1.63 (m, 1H, CH$_2$), 1.73–1.87 (m, 1H, CH$_2$), 2.97–3.06 (m, 1H, H-4), 4.00–4.16 (m, 3H, OCH$_2$ and H-3a), 4.74–4.84 (m, 2H, H-6 and H-6a), 5.05 (d, J = 7.12 Hz, 1H, O-H), 7.45–7.51 (m, 2H, Ar-H), 7.53–7.59 (m, 1H, Ar-H), 7.83–7.88 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.7, 31.9, 46.3, 61.2, 71.8, 74.2, 83.2, 127.1, 128.8, 129.0, 132.2, 165.0, 171.0. MS (ESI, pos) *m/z* 276 (M + 1). Anal. Calcd. for C$_{15}$H$_{17}$NO$_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.08; H, 5.87; N, 4.73.

Ethyl (1S*,2R*,3S*,4R*) 2-benzamido-3,4-difluorocyclopentanecarboxylate (±)-**7**. White solid; yield 15%; R_f = 0.39 (*n*-hexane/EtOAc 2:1); m.p. 152–161 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.26 (t, J = 7.12 Hz, 3H, CH$_3$), 2.31–2.46 (m, 1H, CH$_2$), 2.48–2.65 (m, 1H, CH$_2$), 3.40–3.49 (m, 1H, H-1), 4.19 (q, J = 7.06 Hz, 2H, OCH$_2$), 4.33–4.47 (m, 1H, H-2), 5.07–5.26 (m, 1H, H-4), 5.40–5.63 (m, 1H, H-3), 6.70 (d, J = 5.92 Hz, 1H, N-H), 7.42–7.48 (m, 2H, Ar-H), 7.50–7.56 (m, 1H, Ar-H), 7.73–7.78 (m, 2H, Ar-H). ^{19}F-NMR (376 MHz, CDCl$_3$) δ = −196.34, −203.13. ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.6, 31.01 and 31.22 (^2J = 21.04 Hz), 41.83 and 41.89 (^3J = 6.13 Hz), 57.96 and 58.20 (^{2}J = 24.37 Hz), 61.81, 89.52 and 89.68 and 91.36 and 91.52 (^1J = 185.10 Hz, ^2J = 15.14 Hz), 91.91 and 92.06 and 93.84 and 94.00 (^1J = 194.95 Hz, ^2J = 15.62 Hz), 127.3, 129.1, 132.4, 134.2, 168.5, 173.6. MS (ESI, pos) *m/z* 298 (M + 1). Anal. Calcd. for C$_{15}$H$_{17}$F$_2$NO$_3$: C, 60.60; H, 5.76; N, 4.71. Found: C, 60.25; H, 5.39; N, 4.40.

Ethyl (3aR*,4S*,6S*,6aR*)-6-hydroxy-2-phenyl-4,5,6,6a-tetrahydro-3aH-cyclo-penta[d]oxazole-4-carboxylate (±)-**8**. White solid; yield 85%; R_f = 0.57 (*n*-hexane/EtOAc 1:2); m.p. 54–64 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.29 (t, J = 7.14 Hz, 3H, CH$_3$), 1.74–1.84 (m, 1H, CH$_2$), 2.18–2.26 (m, 1H, CH$_2$), 3.09–3.16 (m, 1H, H-4), 4.19 (q, J = 7.14 Hz, 2H, OCH$_2$), 4.42–4.50 (m, 1H, H-6), 4.93–5.00 (m, 1H, H-3a), 5.01–5.08 (m, 1H, H-6a), 7.41–7.48 (m, 2H, Ar-H), 7.49–7.58 (m, 1H, Ar-H), 7.99–8.06 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.6, 34.0, 48.5, 61.5, 61.6, 73.1, 73.8, 83.6, 127.0, 127.5, 128.9, 132.4, 164.7, 174.1. MS (ESI, pos) *m/z* 276 (M + 1). Anal. Calcd. for C$_{15}$H$_{17}$NO$_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.07; H, 5.85; N, 4.74.

Ethyl (1R*,2S*,4S*,5R*) 2-benzamido-4,5-difluorocyclohexanecarboxylate **(±)-11**. White solid; yield 76%; R_f = 0.44 (*n*-hexane/EtOAc 2:1); m.p. 158–162 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.31 (t, *J* = 7.14 Hz, 3H, CH$_3$), 2.17–2.48 (m, 4H, CH$_2$), 3.16–3.24 (m, 1H, H-1), 4.17–4.30 (m, 2H, OCH$_2$), 4.61–4.86 (m, 2H, H-5 and H-2), 4.88–5.09 (m, 1H, H-4), 6.99 (d, *J* = 6.68 Hz, 1H, N-H), 7.42–7.49 (m, 2H, Ar-H), 7.50–7.57 (m, 1H, Ar-H), 7.74–7.80 (m, 2H, Ar-H). ^{19}F-NMR (376 MHz, CDCl$_3$) δ = −192.2, −201.8. ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.5, 27.48 and 27.70 (^2J = 22.10 Hz), 31.99 and 32.19 (^2J = 20.16 Hz), 42.0, 44.2, 61.8, 86.83 and 87.01 and 88.64 and 88.82 (^1J = 182.07 Hz, ^2J = 18.31 Hz), 87.2 and 87.42 and 89.03 and 89.21 (^1J = 179.59 Hz, ^2J = 17.45 Hz), 127.3, 129.0, 132.1, 134.6, 167.1, 173.7. MS: (ESI, pos) *m/z* = 312 (M +1). Anal. Calcd. for C$_{16}$H$_{19}$F$_2$NO$_3$: C, 61.73; H, 6.15; N, 4.50. Found: C, 61.40; H, 5.79; N, 4.16.

Ethyl (1R*,5S*,6R*,8S*) 8-hydroxy-3-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene-6-carboxylate **(±)-12**. Yellow oil; yield 37%; R_f = 0.49 (*n*-hexane/EtOAc 1:3). ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.34 (t, *J* = 7.12 Hz, 3H, CH$_3$), 1.58–1.71 (m, 1H, CH$_2$), 1.78–1.85 (m, 1H, CH$_2$), 2.15–2.27 (m, 2H, CH$_2$), 2.75–2.83 (m, 1H, H-6), 3.80–3.87 (m, 1H, H-8), 4.27 (q, *J* = 7.10 Hz, 2H, OCH$_2$), 4.34–4.38 (m, 1H, H-5), 4.70–4.74 (m, 1H, H-1), 7.37–7.43 (m, 2H, Ar-H), 7.43–7.50 (m, 1H, Ar-H), 7.93–7.97 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.6, 27.1, 28.3, 30.1, 47.2, 48.2, 61.3, 73.3, 74.8, 127.7, 128.4, 131.1, 131.8, 133.5, 157.9, 172.3. MS (ESI, pos) *m/z* 290 (M + 1). Anal. Calcd. for C$_{16}$H$_{19}$NO$_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.09; H, 6.92; N, 4.50.

Ethyl (1S*,2S*,4S*,5R*) 2-benzamido-4,5-difluorocyclohexanecarboxylate **(±)-15**. Yellowish brown solid; yield 10%; R_f = 0.53 (*n*-hexane/EtOAc 2:1); m.p. 42–51 °C. ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.16 (t, *J* = 7.12 Hz, 3H, CH$_3$), 1.83–2.14 (m, 1H, CH$_2$) 2.15–2.38 (m, 1H, CH$_2$) or 1.83–2.38 (m, 1H, CH$_2$), 2.42–2.58 (m, 1H, CH$_2$), 2.80–2.95 (m, 1H, H-1), 4.05–4.20 (m, 2H, OCH$_2$), 4.43–4.57 (m, 1H, H-2), 4.75–4.97 (m, 2H, H-4 and H-5), 6.31 (d, *J* = 7.56 Hz, 1H, N-H), 7.36–7.45 (m, 2H, Ar-H), 7.46–7.53 (m, 1H, Ar-H), 7.69–7.78 (m, 2H, Ar-H). ^{19}F-NMR (376 MHz, CDCl$_3$) δ = −192.71. ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.5, 28.66 and 28.86 (^2J = 19.67 Hz), 32.67 and 32.87 (^2J = 20.27 Hz), 43.4, 46.0, 61.7, 84.78 and 85.08 and 86.47 and 86.78 (^1J = 170.33 Hz, ^2J = 30.58 Hz), 85.95 and 86.29 and 87.69 and 88.03 (^1J = 175.08 Hz, ^2J = 34.96 Hz), 127.3, 129.0, 132.0, 134.7, 167.3, 172.9. MS (ESI, pos) *m/z* 312 (M + 1). Anal. Calcd. for C$_{16}$H$_{19}$F$_2$NO$_3$: C, 61.73; H, 6.15; N, 4.50. Found: C, 61.39; H, 5.81; N, 4.87.

Ethyl (1R*,5S*,6S*,8S*) 8-hydroxy-3-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene-6-carboxylate **(±)-14**. Yellow oil; yield 46%; R_f = 0.47 (*n*-hexane/EtOAc 2:3); ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.29 (t, *J* = 7.14 Hz, 3H, CH$_3$), 1.39–1.50 (m, 1H, CH$_2$), 1.84–1.91 (m, 1H, CH$_2$), 1.98–2.06 (m, 1H, CH$_2$), 2.30–2.38 (m, 1H, CH$_2$), 3.09–3.15 (m, 1H, H-6), 4.05–4.12 (m, 1H, H-8), 4.15–4.24 (m, 3H, OCH$_2$ and H-5), 4.67–4.73 (m, 1H, H-1), 7.35–7.42 (m, 2H, Ar-H), 7.42–7.47 (m, 1H, Ar-H), 7.92–7.98 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ =14.6, 24.5, 27.9, 45.8, 47.6, 61.4, 70.6, 75.4, 127.6, 128.5, 131.3, 133.5, 158.4, 173.3. MS (ESI, pos) *m/z* 290 (M + 1). Anal. Calcd. for C$_{16}$H$_{19}$NO$_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.07; H, 6.29; N, 4.51.

Ethyl (1S*,2S*,4S*,5S*) 2-benzamido-4-fluoro-5-hydroxycyclohexanecarboxylate **(±)-16**. Brown oil; yield 13%; R_f = 0.53 (*n*-hexane/EtOAc 1:2). ^{1}H-NMR (400 MHz, CDCl$_3$, TMS) δ = 1.16 (t, *J* = 7.10 Hz, 3H, CH$_3$), 1.91–2.40 (m, 4H, CH$_2$), 2.97–3.07 (m, 1H, H-1), 4.03–4.16 (m, 3H, OCH$_2$ and H-5), 4.45–4.56 (m, 1H, H-2), 4.62–4.81 (m, 1H, H-4), 6.47 (d, *J* = 7.96 Hz, 1H, N-H), 7.34–7.43 (m, 2H, Ar-H), 7.43–7.51 (m, 1H, Ar-H), 7.68–7.76 (m, 2H, Ar-H). ^{19}F-NMR (376 MHz, CDCl$_3$) δ = −187.14. ^{13}C-NMR (100 MHz, CDCl$_3$, TMS) δ = 14.5, 30.5, 32.11 and 32.31 (^2J = 20.31 Hz), 43.2, 46.6, 61.5, 65.94 and 66.21 (^2J = 27.35 Hz), 89.60 and 91.32 (^1J = 172.66 Hz), 127.3, 128.9, 131.9, 134.8, 167.5, 173.9. MS (ESI, pos) *m/z* 310 (M + 1). Anal. Calcd. for C$_{16}$H$_{20}$FNO$_4$: C, 62.12; H, 6.52; N, 4.53. Found: C, 61.81; H, 6.21; N, 4.17.

4. Conclusions

A novel synthetic procedure has been developed for the access of some highly functionalized fluorine-containing alicyclic scaffolds. The synthetic procedure was based on the ring opening reaction

of functionalized cycloalkane-fused oxiranes with both XtalFluor-E and Deoxofluor as fluoride sources. Through an investigation with various experimental conditions, the opening of the three-membered heterocyclic ring with fluoride was found to be highly substrate-dependent. However, this substrate directable synthetic investigation of an epoxide opening with fluoride using XtalFluor-E or Deoxofluor needs further study in order to achieve higher yields. Synthetic investigations using other highly functionalized model compounds under various experimental conditions are currently being studied in our laboratory.

Supplementary Materials: Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/21/11/1493/s1.

Author Contributions: L.K., S.F., and F.F. designed and planned the research, and interpreted the results. A.M.R. and M.N. performed the synthetic work. All authors discussed the results and prepared and commented on the manuscript.

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Sample Availability: Samples of all compounds are available in mg amounts from the authors.