Tetrahedron: *Asymmetry* 20 (2009) 1515–1520

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric syntheses of (1*r*,3*R*,4*S*)- and (1*s*,3*R*,4*S*)-(3,4-difluorocyclopentyl)-alanine derivatives

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ARTICLE INFO

Article history:
Received 6 May 2009
Accepted 20 May 2009
Available online 24 June 2009

ABSTRACT

By employing a sequence of epoxide opening, asymmetric alkylation, and fluorination, polyfluorinated cyclopentylamino acids with defined stereochemistries were prepared.

1. Introduction

The synthesis of non-natural amino acids for use in molecular biology and drug discovery remains an active field of research. Amino acids containing varying degrees of fluorination are an important set of these structures.[1] Substitution of hydrogen for fluorine imparts dramatic changes on the physical properties of compounds; these changes can thus have dramatic effects on drug distributions and other PK and PD-related effects. The incorporation of fluorine into drugs may increase lipophilicity and thus promote passive diffusion across membranes. This is particularly true for CNS drugs, which are required to traverse the blood–brain barrier. Diminished metabolism by hydroxylation and other oxidative processes is also commonly observed.[2] This increased metabolic stability often leads to increased duration of action and greater bioavailability.[3]

The majority of non-aromatic-fluorinated amino acids reported in the literature contain trifluoromethyl[4] or difluoromethylene[5] subunits. There are fewer examples of amino acids containing intermediate degrees of fluorination in the backbone and only scant examples of amino acids containing CHF groups.[6] Given the polarity of the C–F bonds and the stereoelectronic effects this imparts, we believed that compounds possessing intermediate levels of fluorination might possess unusual conformations and physicochemical properties.[7]

Cyclopentyl alanine has been incorporated in a number of recent drug targets, most prominently inhibitors of HCV protease,[8a] DPPIV,[8b] and cathepsin S.[8c] Given the propensity for aliphatic amino acids to be metabolized by oxidative processes, we hoped that modification of this hydrophobic amino acid by incorporation of fluorine into defined regions may alter the biological activities of similar compounds. Herein we report efficient stereospecific syntheses of (1*r*,3*R*,4*S*)- and (1*s*,3*R*,4*S*)-(3,4-difluorocyclopentyl) (compounds **5** and **10**, Schemes 1 and 2) alanine derivatives.

Unnatural amino acids are readily prepared by the asymmetric alkylation of a chiral template or by asymmetric hydrogenation of the enamide. The former proved to be a convenient starting point for the synthesis. We envisioned that a suitably substituted cyclopentane derivative could be further manipulated to provide the required amino acid. The relative stereochemistry between the fluorine atoms and the ring attachment point could be installed in a predictable manner by oxidation of a cyclopentene carboxylic acid derivative. The *syn*-dihydroxylation of cyclopent-3-ene-alanine derivative was an obvious starting point for the synthesis. A literature search showed that the reaction of vicinal diols with fluorinating reagents is often substrate dependent. While acyclic diols may be converted to vicinal difluorides with traditional SF_4-derived reagents, treatment of cyclic diols under similar conditions gives low yields (<10%) of the desired products.[9] Thus, we sought a more predictable and higher yielding method for this transformation. We envisioned that the fluorides could be installed stepwise, via an epoxide opening with an HF reagent, then conversion of the intermediate fluorohydrin to a vicinal difluoride with a fluorinating reagent. A similar approach was previously employed by O'Hagan et al. to prepare a series of 3- and 4-vicinal fluorides with defined stereochemistry.[10]

2. Results and discussion

The required *trans*-epoxide **1**[11] was prepared following the literature procedures. Using a procedure originally described by Muelbacher and Poulter,[12] the racemic fluorohydrin **2** was produced in 85% yield by treatment of **1** with $NEt_3(HF)_3$ at 115 °C for 12 h (Scheme 1). A single signal is observed in the ^{19}F NMR spectrum at −178.2 ppm.[12] The ^{13}C spectrum of this material was examined rigorously and no evidence for the presence of a diastereomeric fluorohydrin was observed. Protection of the alcohol as a TBS ether, reduction of the ester, and conversion of the alcohol to an iodide with I_2/PPh_3 gave the required racemic iodide **3** in 57% yield for the sequence. Alkylation of the (*R*)-Schülkopf reagent[13] with **3**, followed by cleavage of the pyrazine and

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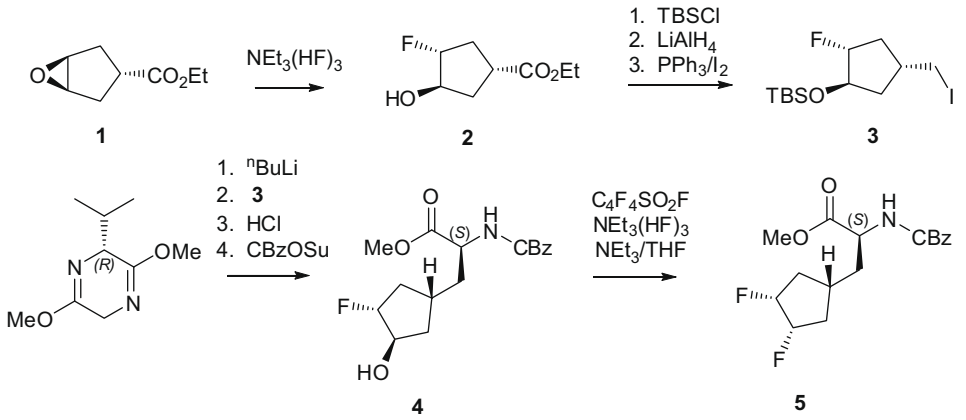
doi:10.1016/j.tetasy.2009.05.024



Scheme 1.

proteo-desilylation with HCl and protection of the amine with CBzOSu gave the amino acid methyl ester **4** as a mixture of pseudoenantiomers about the cyclopentane ring in 88% yield after flash chromatography.

A variety of fluorinating agents were investigated for the conversion of **4** to the final difluoride. Employing SF_4-derived fluorinating agents (Deoxo-Fluor or DAST) gave very low yields of impure difluoride.[14,15] The highest yields and chemical purity were achieved using the $C_4F_9SO_2F/NEt_3(HF)_3$ system recently reported by the Merck Process group.[16] Employment of this set of reagents afforded the required difluoride **5** in 40–60% yield. Examination of the crude reaction mixture by LC/MS showed varying amounts of a side product, whose mass is consistent with a cyclopentanone as the major impurity.[9,15] The crude amino acid was purified by conventional flash chromatography on silica.

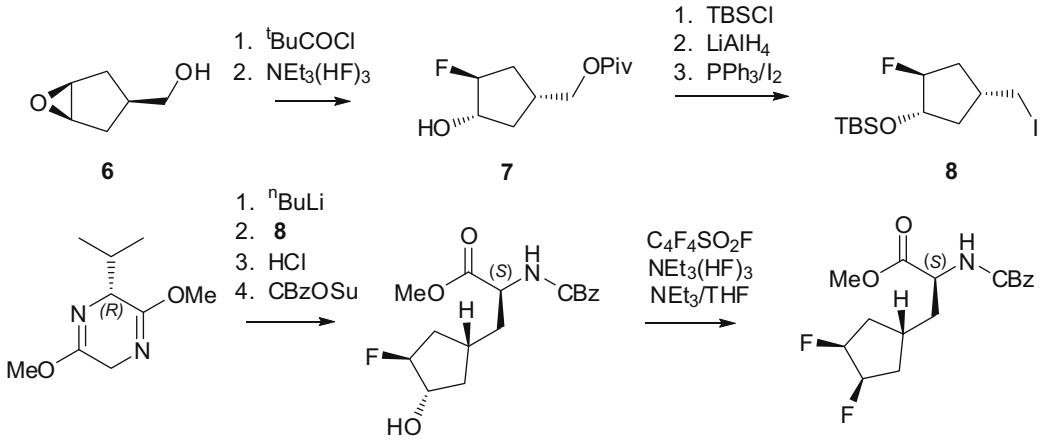
The NMR spectra of this compound are consistent with a symmetrical cyclopentyl group. The methine protons bearing the fluorine substituent are observed as a doublet of multiplets, at 4.82 ppm in the ^1H NMR spectra with an averaged H–F coupling constant of 47.3 Hz. The three cyclopentyl signals in the ^{13}C NMR spectra display coupling to two magnetically inequivalent fluorine atoms. The vicinal fluorine atoms display a complex multiplet at −196.9 ppm in the ambient temperature ^{19}F NMR spectrum, which sharpens to a more symmetrical signal as the sample temperature is increased. This behavior may be indicative of hindered conformational mobility about the cyclopentane ring but a full conformational analysis was not carried out.

This approach required modification to prepare the (1*s*,3*R*,4*S*)-epimer (Scheme 2). The *cis*-isomer of epoxide **1**[17] was consumed during its reaction with $NEt_3(HF)_3$, however only a small amount of impure fluorohydrin was produced. Examination of the crude reaction mixture by NMR spectroscopy showed the loss of the ethyl group. This may arise from lactonization of the intermediate alcohol during the epoxide-opening reaction. Using this observation as a guide we envisioned that reduction of the exocyclic carbonyl would eliminate this side reaction. The requisite substrate was prepared as follows: directed epoxidation of 3-cyclopentenylmethanol with $VO(acac)_2/^tBuOOH$ gives the previously described *cis*-epoxide **6**,[18] which was then protected as the pivalate ester. This compound underwent smooth fluorohydrin formation using the previously described conditions. Iodide **8** and amino acid **10** were prepared using the chemistry described above.

The spectroscopy associated with the protected amino acid **10** is similar to that of **5**. The methine protons are shifted downfield by 0.15 ppm relative to **5**, yet bear identical H–F couplings while the ^{19}F NMR signal occurs at −201.2 ppm. The ^{19}F NMR chemical shifts are useful in establishing the stereochemistry of the intermediates and final amino acids. In all cases, the fluorine *cis*- to the 1-substituent resonates ca 2 ppm downfield relative to the *trans*-isomer. The trend is even more pronounced in the final vicinal difluorides (−201.2 for the *trans* vs −196.9 ppm for the *cis*-isomer).

3. Conclusion

In conclusion, the stereoselective syntheses of the epimeric (1*r*,3*R*,4*S*)- and (1*s*,3*R*,4*S*)-(3,4-difluorocyclopentyl) alanine derivatives **5** and **10** were carried out using epoxidation to establish the stereochemistry of the alkyl fluorides, then use of standard chiral



Scheme 2.

template chemistry to form the amino acid. The fluorine atoms were installed sequentially by epoxide opening, then S_N2 displacement of the alcohol at a later stage. This allowed for the use of the high-yielding epoxide opening with HF to install the first fluorine substituent. The absolute stereochemistry of these intermediates[19] do not need to be addressed since the final vicinal difluorides are more symmetrical structures than the fluorohydrin intermediates **4** and **9**. This produced the desired products with complete control of stereochemistry about the ring systems and avoided the use of more hazardous fluorinating reagents. The biological behavior of derivatives of these compounds will be reported in subsequent publications.

4. Experimental

4.1. General

^{1}H NMR, ^{13}C NMR spectra were acquired on Bruker AM-400. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane and referenced to the signal of the solvent. ^{19}F NMR spectra were obtained at 376 MHz and referenced to external trifluoroacetic acid. Optical rotations were measured on a Perkins-Elmer Polarimeter 341 with a sodium lamp and are reported as follows $[\alpha]_D^{23}$ (c g/100 mL, CH_2Cl_2). Flash chromatography was performed with the aid of an Isco CombiFlash system. LC/MS were obtained on a Waters system. All starting materials, reagents, and solvents were obtained from conventional suppliers and used as received.

4.2. Ethyl-3-fluoro-4-hydroxycyclopentanecarboxylate[19] 2

A 100 mL flask was charged with 7.2 g (50.7 mol) of the *trans*-epoxide **1**[11] and 12.3 (76 mmol, 1.5 equiv) of $NEt_3(HF)_3$ (CAUTION).[20] The mixture was heated to 120 °C for 16 h. After this time TLC analysis showed consumption of the starting epoxide. The mixture was cooled to 0 °C and quenched by addition of saturated $NaHCO_3$. The mixture was allowed to stir for 1 h, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with additional EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The fluorohydrin was purified by flash chromatography on silica, eluting with 0–47% EtOAc in hexanes. This afforded 6.73 g (75% yield) of the fluorohydrin. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.70 (d of m, J_{HF} = 51.9 Hz, 1H), 4.32 (d of m, $^3J_{HF}$ = 9.2 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.02 (quin, J = 8.2 Hz, 1H), 2.34 (m, 1H), 2.15–2.0 (m, 2H), 1.88 (m, 1H), 1.22 (t, J = 7.0 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 175.1, 98.4 (d, $^1J_{CF}$ = 179.4 Hz), 76.3 (d, $^2J_{CF}$ = 27.6 Hz), 60.5, 39.9, 35.4, 33.4 (d, $^2J_{CF}$ = 21.5 Hz), 25.6, 17.8, 14.0, −5.04. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −178.4.

4.3. Ethyl 3-(*tert*-butyldimethylsilyloxy)-4-fluorocyclopentanecarboxylate

A solution of the above fluorohydrin (6.73 g, 38.2 mmol, 1.0 equiv), TBSCl (11.5 g, 76.4 mmol, 2.0 equiv) and imidazole (12 g, 0.17 mol, 4.0 equiv) in DMF (10 mL) was stirred at ambient temperature for 4 h. After this time the free alcohol was consumed by TLC analysis. The DMF was removed in vacuo and the residue was partitioned between ether/water. The layers were separated and the organic layer washed with brine, dried over Na_2SO_4, filtered, and evaporated. The silyl ether was isolated in >99% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.81 (d of m, J_{HF} = 51.5 Hz, 1H), 4.32 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.05 (ms, 1H), 2.7 (br s, 1H), 2.39 (m, 1H), 2.25–2.1 (m, 2H), 1.92 (m, 1H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 175.4, 98.0 (d, *JCF* = 177.9 Hz), 75.3 (d, JCH = 27.6 Hz), 60.6, 39.6, 34.7, 33.2 (d, J = 22.2 Hz), 13.8. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −178.3.

4.4. 3-(*tert*-Butyldimethylsilyloxy)-4-fluorocyclopentyl)methanol

A slurry of $LiAlH_4$ (2.99 g, 78.5 mmol, 2.0 equiv) in THF (100 mL) was cooled to −78 °C. A solution of the above ester in THF (50 mL) was added over a 20-min period, and the mixture stirred at −78 °C for 0.5 h. Analysis by TLC showed consumption of the ester. The mixture was allowed to warm to 0 °C, then 10 mL of brine was added dropwise over a 15-min period, followed by ~20 g of Celite. The thick slurry was diluted with EtOAc and allowed to stir for 0.5 h. After this time, the mixture was filtered through a pad of Celite. The filter cake was washed with additional EtOAc. The resulting clear solution was dried over Na_2SO_4, filtered, and evaporated. This afforded 7.24 g (76% yield) of the primary alcohol. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.69 (d of m, J_{HF} = 52.3 Hz, 1H), 4.18 (d of m, J_{HF} = 7.8 Hz, 1H), 3.48 (d, J = 6.6 Hz, 2H), 2.37 (m, 1H), 2.15 (m, 1H), 2.0 (m, 2H), 1.70–1.40 (m, 3H), 0.81 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 99.5 (d, J_{CF} = 177.0 Hz), 76.4 (d, J_{CF} = 27.4 Hz), 67.0, 37.7, 35.3, 33.0 (d, J_{CF} = 20.2 Hz), 25.6, 17.9, −4.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −176.0.

4.5. *tert*-Butyl-2-fluoro-4-(iodomethyl)cyclopentyloxy)-dimethylsilane 3

The above alcohol (7.24 g, 29.1 mmol, 1.0 equiv), triphenylphosphine (9.2 g (35 mmol, 1.2 equiv), and imidazole (4.0 g, 58.3 mmol, 2.0 equiv) were dissolved in 100 mL of THF and cooled to 0 °C. Iodine (8.15 g, 32.4 mmol, 1.1 equiv) was added in 3 equal portions over a 20-min period. The mixture was stirred for 1 h at 0 °C. After this time an additional 0.125 equiv of triphenylphosphine was added, followed by an additional 0.125 equiv of iodine. After stirring for 20 min, TLC analysis showed no remaining alcohol. The mixture was filtered through a pad of silica. The silica was washed with ether and the filtrate evaporated. The iodide was isolated by flash chromatography on silica, eluting with 0–9% EtOAc in hexanes. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.72 (d of m, J_{HF} = 51.9 Hz, 1H), 4.22 (d of m, J_{HF} = 10.1 Hz, 1H), 3.12 (d, J = 6.6 Hz, 2H), 2.51 (m, 1H), 2.26 (m, 1H), 1.82 (m, 1H), 1.58–1.40 (m, 2H), 0.81 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 99.2 (d, J_{CF} = 177.9 Hz), 76.6 (d, J_{CF} = 10.1 Hz), 40.2, 38.7, 37.4 (d, J_{CF} = 20.7 Hz), 25.7, 17.9, 13.3, −4.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −174.7.

4.6. (*S*)-Methyl 2-(benzyloxycarbonylamino)-3-(3-fluoro-4-hydroxycyclopentyl)propanoate 4

An oven-dried 250 mL flask was charged with 75 mL of dry THF and 4.02 g (21.8 mmol, 1.5 equiv) of (*R*)-2,5-dihydro-3,6-dimethoxyl-2-isopropylpyrazine. The mixture was cooled to −78 °C (dry ice/IPA) and ^{n}BuLi (2.5 M, 8.72 mL, 21.8 mmol, 1.5 equiv) added dropwise over a 20-min period. After addition was complete the flask was maintained at −78 °C for 1 h. After this time a solution of the iodide **3**, (5.2 g, 14.5 mmol, 1.0 equiv) in 25 mL of THF was added over a 10-min period. The mixture was stirred at −78 °C for 2 h, then tightly stoppered and the dry ice/IPA bath placed in a −15 C freezer for 19 h. After this time LC/MS analysis showed consumption of the iodide and formation of the desired product. The reaction was quenched by addition of 10 mL of saturated NH_4Cl and THF removed in vacuo. The residue was partitioned between EtOAc/H_2O. The water layer was extracted with additional EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The disubstituted pyrazine, contaminated with the starting pyrazine, was used directly in the next step.

The above residue was dissolved in 200 mL of 1:1 acetonitrile/1.0 M aqueous HCl. The mixture was stirred for 7 h at ambient temperature. After this time, the volatile components were

removed in vacuo. The residue was dissolved in 100 mL of 1:1 acetonitrile/water. To this solution were added K_2CO_3 (15.2 g, 0.110 mol, 5.0 equiv) and CBzOSu (10.9 g, 43.6 mmol, 3.0 equiv) and the resulting mixture was allowed to stir for 17 h. After this time, the volatile materials were removed and the residue was partitioned between EtOAc/water. The layers were separated and the organic layer was washed with saturated $NaHCO_3$, brine, then dried over Na_2SO_4, filtered, and evaporated. The desired amino acid derivative was purified by flash chromatography, on silica, eluting with 0 to 47% EtOAc in hexanes. This afforded 4.4 g (89% yield) of the desired protected amino acid as a mixture of pseudoenantiomers about the cyclopentyl ring. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (m, 5H), 5.54 (t, J = 9.0 Hz, 1H), 5.08 (s, 2H), 4.79 (d of m, J_{HF} = 51.5 Hz, 1H), 4.34 (m, 1H), 4.25 (d of m, J_{HF} = 18.3 Hz, 1H), 3.71 (s, 3H), 2.74 (br s, 1H), 2.32–2.20 (m, 2H), 1.90–1.25 (m, 1H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −175.6.

4.7. (*S*)-Methyl 2-(benzyloxycarbonylamino)-3-((1*r*,3*R*,4*S*)-3,4-difluorocyclopentyl)propanoate 5

The above protected amino acid (4.4 g, 12.9 mmol, 1.0 equiv) was dissolved in 50 mL of THF and cooled to 0 °C. To this solution was added $C_4F_9SO_2F$ (7.86 g, 25.93 mmol, 2.0 equiv), $NEt_3(HF)_3$ (4.18 g, 25.93 mmol, 2.0 equiv), and NEt_3 (7.84 g, 77.8 mmol, 6.0 equiv). The resulting mixture was allowed to stir for 72 h. After this time, the solution was filtered through a pad of silica. The silica was washed with additional THF and the filtrate transferred to a separatory funnel. The solution was washed with saturated $NaHCO_3$ and brine and evaporated. The desired vicinal difluoride was purified by flash chromatography on silica. This afforded 3.0 g (68% yield) of the difluoride. An additional 818 mg of the starting alcohol was recovered. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (m, 5H), 5.29 (db, J = 8.6 Hz, 1H), 5.11 (s, 2H), 4.82 (d of m, $^1J_{HF}$ = 47.3 Hz, 2H), 4.37 (m, 1H), 3.73 (s, 3H), 2.32–2.07 (m, 2H), 2.05–1.90 (m, 2H), 1.80–1.60 (m,3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 172.8, 155.9, 136.1, 128.5. 128.2, 128.1, 92.1 (d of q, $^1J_{CF}$ = 187.9 Hz, $^2J_{CF}$ = 10.0 Hz), 67.1, 34.1 (d of d, $^2J_{CF}$ = 19.9 Hz, $^3J_{CF}$ = 3.2 Hz), 28.7 (t, $^3J_{CF}$ = 2.2 Hz. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −196.9. HRMS (EI) calcd. for $C_{17}H_{21}F_2NO_4Na$ (M+23) 364.1336. Found: 364.1323.

4.8. (1*R*,3*r*,5*S*)-6-Oxabicyclo[3.1.0]hexan-3-ylmethyl pivalate

The previously reported *cis*-epoxide **6**[14] (3.95 g, 26.3 mmol, 1.0 equiv) was dissolved in 50 mL of THF. The solution was cooled to 0 °C and NEt_3 (6.64 g, 9.2 mL, 65.7 mmol, 2.5 equiv) was added, followed by pivaloyl chloride (4.76 g, 4.85 mL, 39.5 mmol, 1.5 equiv). The solution was stirred at 0 °C until the starting alcohol was consumed by TLC analysis. The mixture was allowed to warm to ambient temperature, added to a separatory funnel, washed with 1.0 M HCl, brine, then dried over Na_2SO_4, filtered, and evaporated. The required ester was purified by flash chromatography, eluting with 0–19% EtOAc in hexanes. This afforded 2.78 g (53% yield) of the pivalate ester. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84 (d of m, J = 3.9 Hz, 2H), 3.44 (br s, 2H), 2.33 (m, 1H), 1.82 (m, 4H), 1.14 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 178.1, 69.7, 58.2. 38.6. 34.0, 30.0, 27.0.

4.9. (3-Fluoro-4-hydroxycyclopentyl)methyl pivalate 7

The above ester (2.78 g, 14.03 mmol, 1.0 equiv) was dissolved in 3.4 mL of $NEt_3(HF)_3$ (21.0 mmol, ~1.5 equiv) and the mixture was heated to 119 °C for 17 h. After this time the dark solution was cooled to 0 °C and quenched by the addition of saturated $NaHCO_3$. The mixture was allowed to stir for 1 h, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with additional EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The fluorohydrin was purified by flash chromatography on silica, eluting with 0–27% EtOAc in hexanes. This afforded 1.88 g (61% yield) of the fluorohydrin. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.82 (d of m, J_{HF} = 52.3 Hz, 1H), 4.25 (d of m, J_{HF} = 15.6 Hz, 1H), 3.99 (t, J = 7.0 Hz, 2H), 3.0 (br s, 1H), 2.49 (m, 1H), 2.20 (m, 1H), 1.99 (m, 1H), 1.73 (m, 1H), 1.36 (m, 1H), 1.16 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 178.7. 99.4 (d, J_{CF} = 175.6 Hz), 76.2, 67.7, 38.7, 35.1, 34.6, 33.6, 33.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ m, −181.2.

4.10. (3-(*tert*-Butyldimethylsilyloxy)-4-fluorocyclopentyl)-methyl pivalate

The above fluorohydrin (3.99 g, 18.3 mmol), TBSCl (5.52 g, 36.6 mmol, 2.0 equiv) and imidazole (4.99 g, 73.2 mmol, 4.0 equiv) were dissolved in 10 mL of DMF. The mixture was stirred for 4 h at ambient temperature; after this time TLC analysis showed consumption of the starting fluorohydrin. The volatile materials were removed in vacuo and the residue was portioned between hexanes and 1.0 M HCl. The layers were separated and the hexane layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The resulting TBS ether (6.1 g, >99% yield) was of sufficient purity to carry on to subsequent transformations. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.76 (d of m, J_{HF} = 51.9 Hz, 1H), 4.21 (d of m, J_{HF} = 14.8 Hz, 1H), 3.99 (d, J = 7.0 Hz, 2H), 2.47 (sept, J = 7.8 Hz, 1H), 2.12 (m, 1H), 1.99 m, 1H), 1.72 (m, 1H), 1.37 (m, 1H), 1.19 (s, 9H), 0.83 (s, 9H), 0.08 (s, 6). ^{13}C NMR ($CDCl_3$, 100 MHz): 178.3. 99.8 (d, J_{CF} = 176.4 Hz), 76.7, 68.0, 38.7, 34.8 33.9, 33.7, 27.1, 25.7, 17.9, −4.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −179.7.

4.11. (3-(*tert*-Butyldimethylsilyloxy)-4-fluorocyclopentyl)-methanol

The above TBS ether (6.1 g, 18.3 mmol, 1.0 equiv) was dissolved in 50 mL of THF and the solution cooled to 0 °C under nitrogen. A solution of $LiAlH_4$ (1.0 M in THF, 9.2 mL, 9.2 mmol, 1.5 equiv) was added via syringe over a 15-min period, then the solution was stirred for 0.5 h. TLC analysis showed consumption of the pivalate ester. The excess $LiAlH_4$ was quenched by the dropwise addition of ~7 mL of brine, followed by ~10 g of Celite. The resulting suspension was filtered through a pad of Celite and the filter cake washed with EtOAc. The solution was evaporated and the desired alcohol purified by flash chromatography, eluting with 0–27% EtOAc in hexanes. This afforded 3.0 g (66% yield) of the free alcohol. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.69 (d of m, J_{HF} = 53.1 Hz, 1H), 4.11 (d of m, J_{HF} = 11.7 Hz, 1H), 3.47 (m, 2H), 2.37 (m, 1H), 2.11 (m, 1H), 1.84 (m, 2H), 1.35 (d of m, J_{HF} = 14.1 Hz, 1H), 0.78 (s, 9H), 0.01 (s, 6). ^{13}C NMR ($CDCl_3$, 100 MHz): 99.8 (d, J_{CF} = 175.6 Hz), 76.4 (d, J_{CF} = 27.6 Hz), 66.1, 37.8, 36.2, 32.6 (d, J_{CF} = 21.4 Hz), 25.7, 17.9, −4.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −178.4.

4.12. *tert*-Butyl(2-fluoro-4-(iodomethyl)cyclopentyloxy)-dimethylsilane 8

The aforementioned alcohol (3.02 g, 12.2 mmol, 1.0 equiv), PPh_3 (4.0 g, 15.2 mmol, 1.25 equiv) and imidazole (2.1 g, 30.4 mmol, 2.5 equiv) were dissolved in THF (50 mL) and the solution was cooled to 0 °C. Iodine (4.6 g, 18.3 mmol, 1.5 equiv) was added in ~0.5 g portions over 0.5 h. After the addition was completed the solution was warmed to ambient temperature for 1 h, during which time the starting alcohol was consumed. Hexanes (~50 mL) were added and the mixture was filtered through a pad of silica gel. The silica was washed with additional hexanes and the pale yellow filtrate was evaporated. The residue

was dissolved in hexanes and filtered through a fresh pad of silica. The silica was washed with additional hexanes. The filtrate was evaporated to yield the iodide as a pale pink liquid (3.63 g, 84% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.76 (d of m, J_{HF} = 52.3 Hz, 1H), 4.19 (d of m, J_{HF} = 15.0 Hz, 1H), 3.16 (m, 2H), 2.43 (m, 1H), 2.14 (m, 1H), 2.04 (m, 1H), 1.64 (m, 1H), 1.32 (m, 1H), 0.80 (s, 9H), 0.01 (s, 6). ^{13}C NMR ($CDCl_3$, 100 MHz): 100.1 (d, J_{CF} = 177.1 Hz), 77.1 (d, J_{CF} = 27.6 Hz), 40.2, 38.2, 37.9 (d, J_{CF} = 21.5 Hz), 25.7 (d, J_{HF} = 2.3 Hz), 25.7, 17.9, −4.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −177.8.

4.13. (*S*)-Methyl 2-(benzyloxycarbonylamino)-3-(3-fluoro-4-hydroxycyclopentyl)propanoate 9

An oven-dried 250 mL flask was charged with 75 mL of dry THF and 2.33 g (21.8 mmol, 1.25 equiv) of (*R*)-2,5-dihydro-3,6-dimethoxyl-2-isopropylpyrazine. The mixture was cooled to −78 °C (dry ice/IPA) and ^{n}BuLi (2.5 M, 4.4 mL, 11.2 mmol, 1.1 equiv) was added dropwise over a 20-min period. After the addition was complete the flask was maintained at −78 °C for 1 h. After this time a solution of the above iodide, (3.63 g, 10.13 mmol, 1.0 equiv) in 25 mL of THF was added over a 10-min period. The mixture was stirred at −78 C for 2 h, then tightly stoppered and the dry ice/IPA bath was placed in a −15 °C freezer for 19 h. After this time LC/MC analysis showed consumption of the iodide and formation of the desired product ($M+H^+$). The reaction was quenched by addition of 10 mL of saturated NH_4Cl and THF removed in vacuo. The residue was partitioned between EtOAc/H_2O. The water layer was extracted with additional EtOAc and the combined organic layers were washed with brine, dried over dried over Na_2SO_4, filtered, and evaporated. The disubstituted pyrazine, contaminated with the starting pyrazine, was used directly in the next step.

The above residue was dissolved in 200 mL of 1:1 acetonitrile/1.0 M aqueous HCl. The mixture was stirred for 7 h at ambient temperature. After this time the volatile components were removed in vacuo. The residue was dissolved in 100 mL of 1:1 acetonitrile/water. To this solution were added K_2CO_3 (50 mL of a 15% solution), acetonitrile (50 mL), and CBzOSu (6.31 g, 25.3 mmol, 2.5 equiv), and the resulting mixture was stirred for 17 h. After this time the volatile materials were removed and the residue was partitioned between EtOAc/water. The layers were separated and the organic layer was washed with saturated $NaHCO_3$, brine, then dried over Na_2SO_4, filtered, and evaporated. The desired amino acid derivative was purified by flash chromatography, on silica, eluting with 0–61% EtOAc in hexanes. The fifth set of UV active fractions were collected and evaporated to yield 2.33 g (68% yield) of the desired protected amino acid as a mixture of pseudoenantiomers about the cyclopentyl ring. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (m, 5H), 5.50 (b, 1H), 5.08 (s, 2H), 4.81 (d of m, J_{HF} = 52.3 Hz, 1H), 4.33 (m, 1H), 4.24 (d of m, J_{HF} = 18.3.0 Hz, 1H), 3.71 (s, 3H), 2.38–1.45 (m, 6H), 1.24 (m, 1H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −180.3.

4.14. (*S*)-Methyl 2-(benzyloxycarbonylamino)-3-((1*s*,3*R*,4*S*)-3,4-difluorocyclopentyl)propanoate 10

The above fluorohydrin (2.33 g, 6.87 mmol, 1.0 equiv) was dissolved in 30 mL of THF and the solution cooled to 0 °C. To this solution were added $C_4F_9SO_2F$ (4.15 g, 2.5 mL, 13.7 mmol, 2.0 equiv), $NEt_3(HF)_3$ (2.21 g, 2.23 mL, 13.7 mmol, 2.0 equiv), and NEt_3 (4.17 g, 5.8 mL, 41.2 mmol, 6.0 equiv). The resulting mixture was allowed to stir for 72 h. After this time the solution was filtered through a pad of silica. The silica was washed with additional THF and the filtrate transferred to a separatory funnel. The solution was washed with saturated $NaHCO_3$ and brine and evaporated. The desired vicinal difluoride was purified by flash chromatography on silica, eluting with 0–41% EtOAc in hexanes. This afforded 1.27 g, 54% yield, of the required difluoride as colorless syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (m, 5H), 5.29 (db, J = 7.8 Hz, 1H), 5.11 (s, 2H), 4.97 (d of m, $^1J_{HF}$ = 47.3 Hz, 1H), 4.35 (m, 1H), 3.75 (s, 3H), 2.52 (m, 1H), 2.22 (m, 2H), 1.82–1.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): 172.6, 155.7, 136.0, 128.5. 128.2, 128.1, 92.5 (d of q, $^1J_{CF}$ = 187.9 Hz, $^2J_{CF}$ = 15.3 Hz), 39.7, 34.5 (d of d, $^2J_{CF}$ = 22.2 Hz, $^3J_{CF}$ = 5.4 Hz), 30.5 (t, $^3J_{CF}$ = 2.3 Hz. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −201.2. HRMS (EI) calcd for $C_{17}H_{21}F_2NO_4Na$ (M+23) 364.1336. Found: 364.1340.

Acknowledgments

The authors wish to thank Dr. Marisa Kozlowski and Elizabeth Linton of the University of Pennsylvania for the use of their polarimeter.

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