Towards Optically Pure Mono- and Difluorinated Amino Acids: Common Methodology Based on \((R)-2,3-O\)-Isopropylideneglyceraldehyde

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Abstract: The stereocontrolled synthesis of N-protected \((2S,3R)-2\)-amino-3-fluoroundecanoic and \((3R)-3\)-amino-2,2-difluoroundecanoic acids, as representative examples, from commercially available optically pure \((R)-2,3-O\)-isopropylideneglyceraldehyde is described. Key steps involve the Mitsunobu reaction for the introduction of amino function, and incorporation of fluorine atom(s) by the fluorinating agent, morpholinotrifluorosulfurane.

Key words: nucleophilic fluorination, 1,2-diols, the Mitsunobu reaction, protecting group, fluorine-containing amino acids

Modification of amino acids by introduction of fluorine atom(s) into the molecules quite often leads to the generation of novel and potent biochemical tools and chemotherapeutic agents due to the influence of fluorine.1 The strength of C–F bond (485.7 kJ mol–1) and high electronegativity of fluorine (4.0) are factors which impact strongly the chemical and physical properties of amino acids making the fluorinated analogues more metabolically stable. Similarity of the van der Waals radii of H (1.20 Å) and F (1.47 Å) leads only to small steric perturbations in the molecules and usually allows them to follow the metabolic pathway of the corresponding nonfluorinated compounds. Fluorine-containing amino acids (FAAs) are known to show antibacterial activity, to act as antihypertensive agents, and to exhibit promising properties as candidates for peptide modification.2 In particular, \(\beta\)-fluorinated amino acids are potential inhibitors of pyridoxal phosphate–depending enzymes.3 In this respect it is not surprising that strong efforts were stimulated for the development of the synthetic routes to FAAs. In view of their possible applications, elaboration of methods for preparing pure enantiomers became one of the main requirements.

In recent years, our research group has shown the possibility to prepare various \(\beta\)-amino acids in general and FAAs in particular with high enantiomeric purity (>95% ee) and good yields by Penicillin acylase (from \(E.\) coli) resolution of their racemic \(N\)-phenylacetyl derivatives.4 Our further studies have resulted in the development of preparative three-step route to racemic \(\alpha,\alpha\)-difluoro-\(\beta\)-amino acids and detailed study of the Mitsunobu amination as the key step.5 To the best of our knowledge, to date only a few examples have been reported on the Mitsunobu methodology in the synthesis of FAAs, namely 4-amino-5,6,6-trifluorohex-5-enioic acid,6 2-(chlorofluoromethyl)ornithine7 and \((S)-2\)-amino-3-fluoropropanoic acid.8

Taking into account the importance of the Mitsunobu reaction in the synthesis and transformations of various classes of natural products, as being conducted under mild conditions, it appeared desirable to extend this methodology for the preparation of optically active FAAs.

In our previous paper on the Mitsunobu amination we have used the building block strategy for the introduction of fluorine (CF2-synthon).5 As a part of an ongoing study of the selective fluorination9 by means of diethylaminotri fluorosulfurane (DAST) and morpholinotrifluorosulfurane (Morpho-DAST) and in context with our interest in FAAs we decided to combine the Mitsunobu methodology for the introduction of amino function and incorporation of fluorine by fluorinating agent (Morpho-DAST) in the synthesis of optically active FAAs. Such an approach can be evaluated on the basis of requirements of the diastereomeric alcohols we used for the synthesis of a number of optically active target molecules,10 The presence of aldehyde and protected diol fragments in \(I\) opens wide range of possibilities for functionalizations.

Here we wish to present the synthetic routes to optically pure 2-amino-3-fluoroundecanoic (type \(A\)) and 3-amino-2,2-difluoroundecanoic acids (type \(B\)), as representative examples of mono- and difluorinated amino acids available from \((R)-2,3-O\)-isopropylideneglyceraldehyde \((I)\) (Figure 1). Preparation of amino acids of types \(C\) and \(D\) is currently underway in our laboratory.

The reaction of organometallic reagents with aldehyde \(I\) is known to result in an isomeric mixture with predominance of anti-product.10c In our case, addition of \(n\)-octylmagnesium bromide to aldehyde \((R)-I\) afforded a mixture of diastereomeric alcohols \(2a,b\) in 2.5:1 \((2R,3S)/(2R,3R)\) ratio and 80% yield (Scheme 1).

For the conversion of carbon-oxygen to carbon-fluorine moiety (fluorodehydroxylation) we used commercially

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available Morpho-DAST. This reagent was reported to give higher yields than DAST under similar reactions,\textsuperscript{12} and is known to be more stable than the latter. Fluorination of alcohols 2a,b afforded fluorides 4a,b in low yields (10–25%). To increase the yield of the fluorination step we converted alcohols 2a,b to fluorides 4a,b through the trimethylsilyl ethers 3a,b. Compounds 3a,b, obtained from alcohols 2a,b in quantitative yield, were fluorinated with Morpho-DAST in CH\textsubscript{2}Cl\textsubscript{2} at –25 °C affording a mixture of isomeric fluorides 4a,b in 50% yield in 5:1 (2R,3R)/(2R,3S) ratio (determined by \textsuperscript{1}H and \textsuperscript{19}F NMR). Fluorination of individual stereoisomers 3a and 3b studied separately showed, that anti-isomer 3a gave three times higher yield of 4 than syn-isomer 3b. It was previously found by a number of groups, that fluorination of hydroxy derivatives occurred with inversion of the con-

Figure 1 The four possible fluorinated amino acids obtainable from 1

configuration.\textsuperscript{13} In our case, under fluorination of the mixture of diastereomeric ethers 3a,b, the different reactivity of 3a and 3b led to the mixture of fluorides 4a,b with syn-isomer 4a predominating. It is known, that replacement of the OH groups of an alcohol with fluorine may be accompanied by carbocationic rearrangements as well as dehydration.\textsuperscript{14} Utilization of Morpho-DAST or DAST makes the rearrangements less likely than with other fluorinating agents.\textsuperscript{14} It is also known, that the yields of dehydrated byproducts are decreased in less polar solvents.\textsuperscript{14,15} Whereas fluorides 4a,b were the only fluorine-containing products obtained, formation of olefin 5 lowered the yield at this step even in CH\textsubscript{2}Cl\textsubscript{2}.\textsuperscript{12a} Therefore, the crude reaction mixture was treated with m-CPBA to transform olefin 5 to more polar corresponding epoxide for subsequent efficient chromatographic separation of fluorides 4a,b.

1,2-Diols 6a,b were obtained after hydrolysis of 4a,b with 4 N HCl in 90% yield in the same diastereomeric ratio. To perform the Mitsunobu reaction at the C\textsubscript{2}-hydroxy group it was necessary to protect the hydroxy group at C\textsubscript{1}-carbon atom. The choice of protecting group was limited to those that being deprotected at further steps were unlikely to cleave the C–F bond. Hence, diols 6a,b were converted to protected derivatives 7a,b upon treatment with t-BuMe\textsubscript{2}SiCl in the presence of 4-dimethylaminopyridine (DMAP) in 83% yield, and after chromatographic separation the major diastereomer (2R,3R)-7a was used for further transformation. The Mitsunobu reaction was performed with hydroxy derivative 7a, utilizing as reagents Ph\textsubscript{3}P, diethyl azodicarboxylate (DEAD) and phthalimide (PhthNH) (Scheme 2).

Scheme 1 Reagents and conditions: a) n-C\textsubscript{4}H\textsubscript{9}MgBr, THF, –30 °C to r.t., 1 h; b) Me\textsubscript{3}SiCl, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, 15 °C to r.t., 1 h; c) Morpho-DAST, CH\textsubscript{2}Cl\textsubscript{2}, –25 °C, 2 h; d) 4 N HCl, THF, r.t., 24 h; e) t-BuMe\textsubscript{2}SiCl, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 16 h

Scheme 2 Reagents and conditions: a) PhthNH, DEAD, Ph\textsubscript{3}P, toluene, 0 °C, 1 h, then r.t., 24 h; b) dioxane/HCl/H\textsubscript{2}O (93:5:2), r.t., 20 h; c) NaO\textsubscript{2}, RuCl\textsubscript{3}·H\textsubscript{2}O, CCl\textsubscript{4}–MeCN–H\textsubscript{2}O, r.t., 3.5 h

It is worth noting that, in general the Mitsunobu reaction has proven to be sensitive to the steric environment of the alcohol.\textsuperscript{16} The reaction with more stericly encumbered secondary substrates may result in low yields or recovery of starting material. Based on our previous studies\textsuperscript{4} of the Mitsunobu amination we carried out the reaction at 0 °C to room temperature in anhydrous toluene using three equivalents of Ph\textsubscript{3}P, DEAD and PhthNH (0.2 M DEAD solution in toluene was added to the mixture of other reagents) and obtained derivative (2S,3R)-8 in 88% yield as individual diastereomer (\textsuperscript{1}H and \textsuperscript{19}F NMR) with
inversion of the configuration at C2-carbon atom. The tert-butyl(dimethyl)silyl protecting group was removed in dioxane/HCl system affording alcohol (2S,3R)-9 in 85% yield. Further oxidation of alcohol moiety in 9 with NaOCl/RuCl3 gave N-protected amino acid (2S,3R)-10 in 71% yield. The diastereomeric purity (de >99%) of compound 10 was confirmed by 1H and 19F NMR spectroscopy.

First step of the synthetic route to the next target copy. (Figure 1) was the Mitsunobu amination of alcohols 11a,b in 87% yield as a mixture of diastereomers in 2.5:1 (2R,3R)/(2R,3S) ratio.

After hydrolysis with 4 N HCl accomplished in 93% yield, diols 12a,b were converted to protected derivatives 13a,b by treatment with tert-BuMe2SiCl in the presence of DMAP in 85% yield. Major diastereomer (2R,3R)-13a after the chromatographic separation was used for further transformation. Swern oxidation18 of alcohol 13a at -60 °C led to ketone 14 in 76% yield (Scheme 4). The reaction conditions for the next step (fluorination) were examined in details.

Usually, ketones react with DAST at temperatures ranging from 20 to 80 °C to give the corresponding gem-difluorides. However, the yields of difluorides may be lowered because of formation of vinyl fluorides as side products. Taking into account the effect of solvent polarity on the outcome of the reaction, and in order to minimize possible side reactions, CH2Cl2 was used as the solvent. The reaction of ketone 14 with Morpho-DAST (2.5 equiv) in anhyd CH2Cl2 at room temperature for 75 hours resulted in low conversion with formation of monofluoride 16 (14%) and only 13% of the desired product 15. The same reaction accomplished in hexane at 50 °C led to partial decomposition of ketone 14. Substitution of tert-butyl(dimethyl)silyl group with tert-butyl(diphenyl)silyl group in ketone 14 and subsequent fluorination with Morpho-DAST (5 equiv) in CH2Cl2 at 30 °C for 65 hours afforded difluoride 15 (R = t-BuMe2Si) in 19% yield, traces of monofluoride and unconverted starting material. The best results were achieved by treatment of ketone 14 (R = t-BuMe2Si) with Morpho-DAST (2.5 equiv) in CH2Cl2 at 30 °C for 45 hours, furnishing product 15 (R = t-BuMe2Si) in 34% yield. These results clearly indicate that the low conversion was observed because of steric hindrance in substrate. Prolongation of the reaction time led to the deprotection of hydroxy group near C1-carbon atom and fluorodehydroxylation of primary alcohol thus obtained with formation of monofluoride 16. tert-Butyldiphenylsilyl protecting group was more stable under the fluorination conditions, however, the increased steric hindrance lowered the reactivity.

Difluoride 15 was deprotected in dioxane/HCl system to give alcohol (3R)-17 in 64% yield. After oxidation of alcohol moiety in 17 with NaOCl/RuCl3, N-protected amino acid (3R)-18 was isolated in 69% yield. Taking into account that chiral C1-carbon atom of alcohol 13a remains untouched in the above transformations, the 3R-configuration of difluorinated amino acid 18 was assumed.

In conclusion, optically and diastereomerically pure N-protected (2S,3R)-2-amino-3-fluoroundecanoic and (3R)-3-amino-2,2-difluoroundecanoic acids were synthesized in 14 and 5% overall yields, respectively. The developed approach to enantiomeric α-amino-β-fluorocarboxylic and α,α-difluoro-β-amino acids from the commercially available chiral substrate 1 demonstrates the utility of this ‘chiral pool’ for the synthesis of a wide variety of fluorinated amino acids by introduction of different substituents into the side chain.
THF was freshly distilled under argon from sodium benzophenone ketyl. Diethyl azodicarboxylate and CDCI₃ were dried over molecular sieves. Toluene and CH₂Cl₂ were dried by distillation from P₂O₅. DMSO was distilled from BaO. Morpho-DAST was prepared according to the procedure described in the literature.³⁰ Hexane was distilled from CaH₂. All other reagents were obtained from Aldrich, Fluka and Merck and used without further purification. Reactions were monitored by TLC using Merck silica gel 60 F₂54 plates. Flash chromatography was performed using Merck silica gel 60 (0.040–0.063 mm). ¹H NMR (299.9 MHz, CDCl₃): δ = 0.13 (s, 9 H, (CH₃)₃Si), 0.88 (t, 3 H, J₆₋₇ = 6.6 Hz, CH₃), 1.18–1.60 (m, 14 H, CH₃CH₂), 1.37 (s, 3 H, CCH₃), 1.43 (s, 3 H, CCH₃), 2.07 (d, 1 H, J₃₋₄ = 3.0 Hz, OCH₃), 3.72–3.82 (m, 1 H, CHOCHOH), 3.87–4.06 (m, 6 H, CHO, CH₂O). Anal. Calcd for C₁₄H₂₇FO₂ (246.36): C, 68.25; H, 11.05. Found: C, 68.25; H, 11.05.

3-(2,2-Dimethyl-1,3-dioxolan-4-yl)mono-1-ols (2a,b)

Octyl bromide (0.89 g, 4.61 mmol) was added under stirring to a mixture of activated Mg (2.58 g, 106.04 mmol) in anhyd THF (10 mL) under argon. After the reaction had started, anhyd THF (330 mL) was added dropwise during 30 min, and the mixture was refluxed for 1 h. After cooling to –30°C, a solution of aldehydes 1 (9.20 g, 70.69 mmol) in anhyd THF (40 mL) was added dropwise, and the mixture was stirred for 1 h. After completion of the reaction, monitored by TLC (eluents: hexane–Et₂O, 2:1; hexane–EtOAc, 2.5:1), the mixture was diluted with sat. aq NH₄Cl (100 mL) and the reaction mixture was quenched with sat. aq NaHCO₃ (15 mL), left to stir for 15 min and extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with H₂O, brine and dried (MgSO₄). After removal of the solvent, the residue was distilled to give 2a,b as a colorless liquid; yield: 14.34 g (83%); bp 93–94°C/0.06 mm Hg.

[1-(2,2-Dimethyl-1,3-dioxolan-4-yl)monoxo]trimethylsilanes (3a,b)

DMAP (1.96 g, 16.04 mmol) were added to a stirred solution of alcohols 2a,b (1.96 g, 8.02 mmol) in anhyd CH₂Cl₂ (33 mL) at 15°C under argon. The reaction mixture was stirred at r.t. for 1 h, diluted with sat. aq NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with H₂O, brine and dried (MgSO₄). After removal of the solvent, the residue was passed through a short silica gel column (hexane–Et₂O, 25:1; 10:1) to give 3a,b as a colorless oil; yield: 2.41 g (95%).
6a

\[ ^{1}H\text{ NMR (299.9 MHz, CDCl}_{3}): \delta = 0.08 \text{ (t, } 3 \text{ H, } J_{HH} = 6.6 \text{ Hz, CH}_{3}) \]

\[ 1.15–1.70 \text{ (m, } 14 \text{ H, CH}_{2} \text{CH}_{3}) \]

\[ 3.60–3.82 \text{ (m, } 3 \text{ H, CH}_{2} \text{CHOH}) \]

\[ 4.49 \text{ (dm, } 1 \text{ H, } J_{HH} = 47.8 \text{ Hz, CHF}) \]

\[ ^{19}F\text{ NMR (282.2 MHz, CDCl}_{3}): \delta = -194.05–193.53 \text{ (m, CF)} \]

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\[ 3.60–3.82 \text{ (m, } 3 \text{ H, CH}_{2} \text{CHOH}) \]

\[ 4.39 \text{ (dm, } 1 \text{ H, } J_{HH} = 48.6 \text{ Hz, CHF}) \]

\[ ^{19}F\text{ NMR (282.2 MHz, CDCl}_{3}): \delta = -196.90 \text{ to } -196.30 \text{ (m, CF)} \]

6b

\[ ^{1}H\text{ NMR (299.9 MHz, CDCl}_{3}): \delta = 0.08 \text{ (t, } 3 \text{ H, } J_{HH} = 6.6 \text{ Hz, CH}_{3}) \]

\[ 1.15–1.70 \text{ (m, } 14 \text{ H, CH}_{2} \text{CH}_{3}) \]

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The combined organic layers were washed with brine and dried (MgSO₄). The residue after evaporation of the solvent to half was purified by flash chromatography on silica gel (hexane–Et₂O, 10:1, 5:1, hexane–EtOAc, 1:1) to give 11a,b as a colorless oil; yield: 0.73 g (61%) and 13b as a colorless oil; yield: 0.28 g (24%).

11a

IR (CCL₃): 3080–2800, 1735, 1647, 1400 cm⁻¹.

11b

IR (CCL₃): 2995–2840, 1740, 1400, 1220 cm⁻¹.

12a,b

A mixture of diols 12a,b (0.89 g, 2.67 mmol), t-BuMe₂SiCl (0.48 g, 3.2 mmol) and DMAP (0.78 g, 6.41 mmol) in anhyd CH₂Cl₂ (8 mL) was stirred at r.t. for 16 h. After the completion of the reaction, monitored by TLC (eluent: hexane–EtOAc, 2.5:1), the reaction mixture was diluted with H₂O (5 mL) and extracted with CH₂Cl₂ (3 × 3 mL). The combined organic layers were washed with brine and dried (MgSO₄). After removal of the solvent, the residue was separated by flash chromatography on silica gel (hexane–Et₂O, 25:1, 10:1, 5:1) to give 13a as a colorless oil; yield: 0.73 g (61%) and 13b as a colorless oil; yield: 0.28 g (24%).

13a

IR (CCL₃): 3080–2800, 1740, 1400, 1220 cm⁻¹.

13b

IR (CCL₃): 2995–2830, 1740, 1400, 1220 cm⁻¹.

Anal. Calcd for C₁₉H₂₇NO₄ (333.43): C, 67.32; H, 8.98; N, 3.01. Found: C, 67.35; H, 8.98; N, 3.01.

(2R,3R)-2-[1-(2-tert-Butyldimethylsilyloxy)-1-hydroxyethyl]nonyl]isoindole-1,3-dione (13a)

Morpho-DAST (2.83 mL, 23.27 mmol) was added to a stirred solution of oxalyl chloride (0.18 mL, 2.09 mmol) in anhyd CH₂Cl₂ (4.4 mL) at –60 °C. After stirring for 15 min, a solution of alcohol 13a (0.85 g, 1.9 mmol) in anhyd CH₂Cl₂ (1.9 mL) was added; the mixture was stirred for 45 min and Et₃N (1.32 mL, 9.5 mmol) was added. After warming to r.t., H₂O (10 mL) was added. The aqueous phase was separated and extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with H₂O (4 mL), brine and dried (MgSO₄). After removal of the solvent, the residue was purified by flash chromatography on silica gel (hexane–EtOAc, 100:1, 30:1, 10:1) to give 14 as a colorless oil; yield: 0.64 g (76%); [α]₂⁰D –7.73 (c = 0.05, CHCl₃).

IR (CCL₃): 2980–2810, 1730, 1460, 1390, 1200 cm⁻¹.


(3R)-2-[1-(2-tert-Butyldimethylsilyloxy)acetyl]nonyl]isoindole-1,3-dione (14)

DMSO (0.3 mL, 4.18 mmol) was added to a stirred solution of oxalyl chloride (0.18 mL, 2.09 mmol) in anhyd CH₂Cl₂ (4.4 mL) at –60 °C. After stirring for 15 min, a solution of alcohol 13a (0.85 g, 1.9 mmol) in anhyd CH₂Cl₂ (1.9 mL) was added; the mixture was stirred for 45 min and Et₃N (1.32 mL, 9.5 mmol) was added. After warming to r.t., H₂O (10 mL) was added. The aqueous phase was separated and extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with H₂O (4 mL), brine and dried (MgSO₄). After removal of the solvent, the residue was purified by flash chromatography on silica gel (hexane–EtOAc, 100:1, 30:1, 10:1) to give 14 as a colorless oil; yield: 0.64 g (76%); [α]₂⁰D –7.73 (c = 0.05, CHCl₃).

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(3R)-2-[1-(2-tert-Butyldimethylsilyloxy)acetyl]nonyl]isoindole-1,3-dione (14)

Morpho-DAST (2.83 mL, 23.27 mmol) was added to a stirred solution of oxalyl chloride (0.18 mL, 2.09 mmol) in anhyd CH₂Cl₂ (4.4 mL) at –60 °C. After stirring for 15 min, a solution of alcohol 13a (0.85 g, 1.9 mmol) in anhyd CH₂Cl₂ (1.9 mL) was added; the mixture was stirred for 45 min and Et₃N (1.32 mL, 9.5 mmol) was added. After warming to r.t., H₂O (10 mL) was added. The aqueous phase was separated and extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with H₂O (4 mL), brine and dried (MgSO₄). After removal of the solvent, the residue was purified by flash chromatography on silica gel (hexane–EtOAc, 100:1, 30:1, 10:1) to give 14 as a colorless oil; yield: 0.64 g (76%); [α]₂⁰D –7.73 (c = 0.05, CHCl₃).

IR (CCL₃): 2980–2810, 1730, 1460, 1390, 1200 cm⁻¹.

glycine (hexane-EtOAc, 50:1; 30:1; 10:1) to give **15** as a colorless oil; yield: 1.48 g (34%); [α]D25 = +29.25 (c = 0.07, CHCl3).

**IR** (CCl4): 2990–2800, 1740, 1460, 1380, 1210 cm

1H NMR (299.9 MHz, CDCl3); δ = 0.01 (s, 3 H, CH3), 0.03 (s, 3 H, CH3), 0.85 (t, 3 H, J=7.2 Hz, CH3), 0.86 (s, 9 H, t-CH3), 1.15–1.37 (m, 12 H, C2H5CH2), 1.77–1.90 (m, 1 H, CHCH2CH2CH2), 2.51–2.66 (m, 1 H, CHCH2CH2CH2), 3.76–3.97 (m, 2 H, CH2CF3), 4.68–4.84 (m, 1 H, CHN), 7.70–7.79 (m, 2 H), 8.72–9.71 (m, 2 H)

**19F NMR** (282.2 MHz, CDCl3); δ = −112.91 to −110.15 (m, CF3).

Anal. Calcd for C25H39F2NO3Si (467.66): C, 64.21; H, 8.41; N, 3.00. Found: C, 64.45; H, 8.44; N, 3.41.

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**References**


