Tetrahedron 66 (2010) 9996–10001

Contents lists available at ScienceDirect

Tetrahedron

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

Efficient synthesis of fluorobenzyloxoimidazolidinone derivatives: precursors for the radiosynthesis of [^{18}F]fluorophenylamino acids

Johnny Castillo Meleán, Johannes Ermert *, Heinz H. Coenen

Forschungszentrum Jülich GmbH, Institut für Neurowissenschaften und Medizin, INM-5: Nuklearchemie, D-52425 Jülich, Germany

ARTICLE INFO

Article history:
Received 16 August 2010
Received in revised form 13 October 2010
Accepted 14 October 2010
Available online 17 November 2010

Keywords:
Amino acid
Oxoimidazolidinone
Fluorine-18
^{18}[F]Fluorophenylamino acid
Radiopharmaceutical

ABSTRACT

This paper describes an efficient synthesis of fluorobenzyloxoimidazolidinone derivatives. The title compounds **1a**, **1b** and **1c** could be prepared with high diasteromeric purity (>99%) and overall yields of 19%, 48% and 41% in a ten or six-step synthetic procedure, respectively. These compounds are used as precursors for isotopic ^{18}F-labelling.

1. Introduction

In nuclear medicine diagnosis ^{18}F-labelled aromatic amino acids are widely employed as radiopharmaceuticals for in vivo imaging using Positron Emission Tomography (PET).[1] The most representative of this class of compounds is 6-[^{18}F]fluoro-L-DOPA, one of the few established radiopharmaceuticals, which is used for the diagnosis of central motor disorders and also of brain and peripheral endocrine tumours with PET.[2]

Two general pathways have been developed for the radiofluorination of arene-derivatives of high electron density. Due to the necessary generation of elemental [^{18}F]fluorine, the currently used methods for routine preparation of aromatic amino acids via electrophilic labelling[3] are limited to low amounts of activity at high costs.[4] Alternatively developed nucleophilic syntheses using the advantage of large scale production of [^{18}F]fluoride, however, result either in insufficient enantiomeric purity or in a need of multi-step-syntheses that are difficult to automate, due to their complexity.[5]

Recently, an isotopic exchange approach made the radiosynthesis of 6-[^{18}F]fluoro-L-DOPA available in three-steps.[6] In this radiochemical process the precursor (2*S*,5*S*)-*tert*-butyl 5-(4-benzyloxy-2-fluoro-formylbenzyl)-2-*tert*-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate **1a** at first was radiofluorinated and subsequently the formyl group was converted into the formate derivative by Baeyer–Villiger oxidation. Finally, an acid hydrolysis generated two hydroxyl groups and unmasked the amino acid 6-[^{18}F]fluoro-L-DOPA **4a** (Scheme 1). When using (2*S*,5*S*)-*tert*-butyl-5-(5-acetyl-2-fluorobenzyl)-2-*tert*-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate **1b** as precursor, the Bayer–Villiger oxidation yielded 6-[^{18}F]fluoro-L-*m*-tyrosine **4b**,[7] a radiopharmaceutical with similar pharmacological properties as 6-[^{18}F]fluoro-L-DOPA.[8]

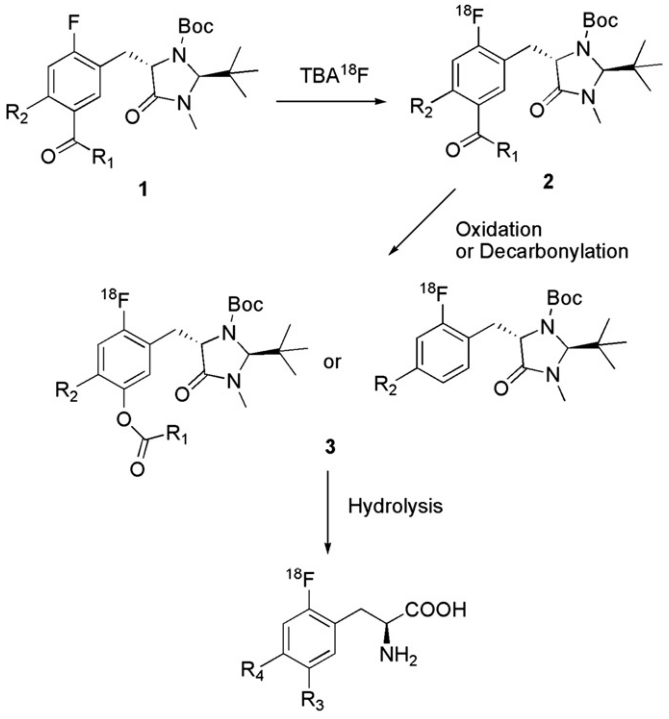
In a second pathway the formyl group is removed by a reductive decarbonylation reaction.[9] This has been exemplified with the synthesis of 2-[^{18}F]fluoro-L-phenylalanine **4c** from **1c**.[10] Similarly by decarbonylation, 2-[^{18}F]fluoro-L-tyrosine **4d**, a radiotracer for the quantitation of cerebral protein synthesis,[11] becomes available also from precursor **1a**.[12]

Both three-step methods, using the conversion of the activating carbonyl-group after isotopic ^{18}F-exchange either by Baeyer–Villiger oxidation or by reductive decarbonylation, are not only more efficient than known nucleophilic methods for the synthesis of [^{18}F]fluorophenylamino acids, but furthermore, they are capable of being implemented in existing automated ^{18}F-synthesizer modules offering a reliable large scale production method.

Isotopic substitution reactions for the synthesis of ^{18}F-labelled radiopharmaceuticals can only be used for non-toxic fluoro compounds, which are applied as in vivo probes of non-saturable processes, i.e., where a high specific activity [activity per unit mass] is not needed. In isotopic exchange procedures the specific activity obtained depends of course on both, the starting amount of the fluoro compound and the quantity of [^{18}F]fluoride used for labelling. In the recently realised radiosynthesis of 6-[^{18}F]fluoro-L-DOPA,

* Corresponding author. Tel.: +49 2461613110; fax: +49 2461612119; e-mail address: j.ermert@fz-juelich.de (J. Ermert).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.10.036



Scheme 1. Radiosynthesis of aromatic amino acids labelled with [^{18}F]fluoride.

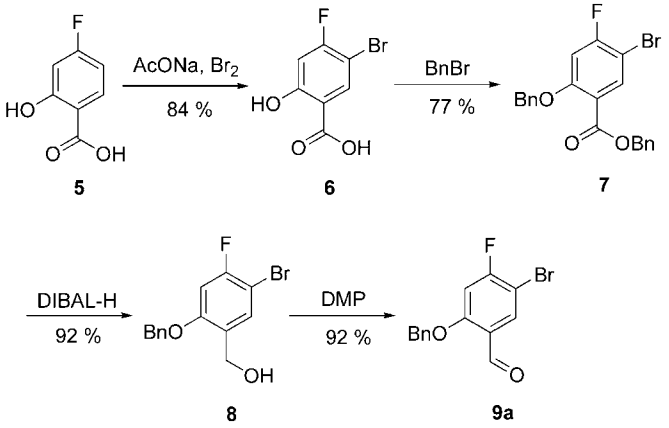
for example, a maximum of 2.0 mg carrier is formed corresponding to the amount of precursor **1a** sufficient for an effective synthesis.[6] This is considerably lower than that obtained by the state-of-the-art electrophilic preparation where up to 15 mg of 6-fluoro-L-DOPA are produced for human injection, which is tolerated by, for example, the European Pharmacopoeia.[13] Considering the much higher starting activity of [^{18}F]fluoride available for substitution reactions under production conditions, a five times higher specific activity can easily be achieved than by electrophilic labelling procedures. Because of the importance of this general ^{18}F-labelling procedure an efficient synthesis of the labelling precursors is needed.

An earlier reported synthesis of **1a** involved eleven reaction steps in a total chemical yield of $<$1%. Here an optimized synthesis of **1a** is presented, where one reaction step is saved and the yield of most others is considerably improved, leading to a total yield of about 19%. Additionally, the preparation of the derivatives **1b** and **1c** is described.

2. Results and discussion

2-(Benzyloxy)-5-bromo-4-fluorobenzaldehyde **9a**, 1-(3-bromo-4-fluorophenyl)ethanone **9b** and 3-bromo-4-fluorobenzaldehyde **9c** were used as starting materials for precursors **1a**, **1b** and **1c**, respectively. The latter two are commercially available. The aldehyde **9a** was prepared as shown in Scheme 2.

4-Fluoro-salicylic acid was brominated in basic alcoholic medium using molecular bromine as brominating agent. The reaction produced the desired 3-bromo-4-fluoro-salicylic acid **6** in a yield of 82%. Benzylation of **6** with benzyl bromide in basic media yielded the compound **7** in 77%. The ester functionality of **7** was then reduced to the alcohol **8** with 92% yield using 2.1 equiv of DIBAL-H.

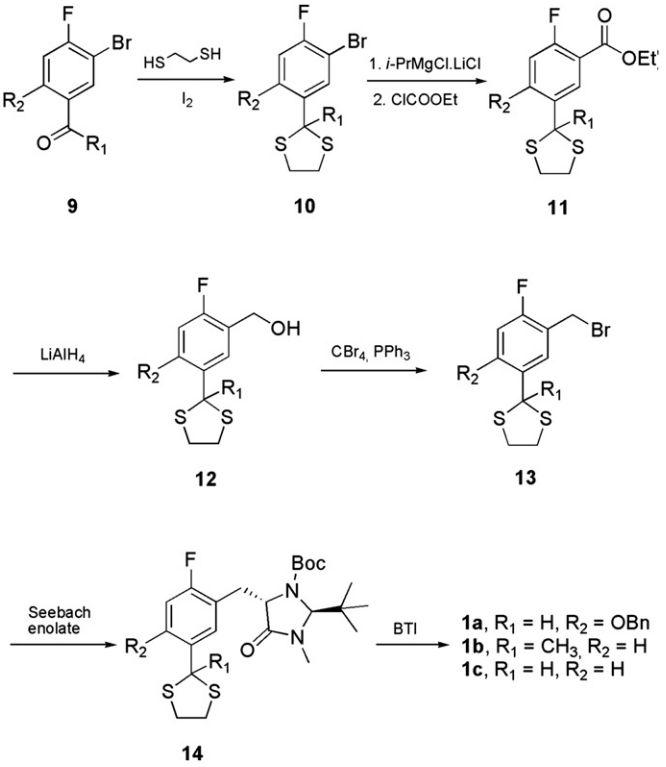


Scheme 2. Synthesis of 2-(benzyloxy)-5-bromo-4-fluorobenzaldehyde.

The first intention was to reduce the ester just to the corresponding aldehyde, however, after several trials using 1 equiv of the reducing agent at different temperatures the result was always a mixture of 1:1 of the starting material and the benzyl alcohol derivative **8**. Red-Al-pyrrolidine, which has been earlier successfully employed in this kind of reduction,[14] produced similar results. Reduction of the ester to the alcohol using $LiAlH_4$, on the other hand, generates a mixture of the desired alcohol **8** plus the debrominated alcohol.

Oxidation of alcohol **8** with Dess–Martin periodinane (DMP) in dichloromethane at room temperature provides the aldehyde **9a** in a yield of 92%.[15]

Scheme 3 resumes the general synthetic pathway for **1a**, **1b** and **1c**. In the first step the carbonyl function was protected as 1,3-dithiolane derivative.[16] The selection of the protecting group was based on the bigger stability showed by the 1,3-dithiolane with respect to the corresponding 1,3-dioxolane derivative. The latter has shown moderate lability during the following synthetic steps.



Scheme 3. General synthetic pathway to precursors **1a**,**b**,**c**.

The compounds **11** were achieved using the two-step one pot coupling reaction proposed by Krasovskiy et al.[17] The first-step is the bromo-magnesium exchange between **10** and a diisopropylmagnesium chloride lithium chloride complex followed by the coupling with ethyl chloroformate. The use of ethyl chloroformate as electrophile was preferred over DMF due to its higher electrophilic character. This reaction represents a mild and regioselective alternative to the low yielding bromo-lithium exchange formylation reaction using BuLi (20% in this case).[18] Attempts to prepare the benzyl alcohol **12** directly by means of coupling of organo-magnesium species with *para*-formaldehyde provided the desired compound in poor yields of 10–20%.

Reduction of **11** with $LiAlH_4$ provided the benzyl alcohol **12** in yields around 92% after 1 h at room temperature. The conversion of the benzyl alcohol to the benzyl bromide was performed using the Appel reaction with good yields.[19] The stability of this group of benzyl bromides has been a problematic issue. Immediate decomposition is observed when solutions of the benzyl bromide in dichloromethane or ethyl acetate are heated above room temperature. In order to avoid this problem, the reaction solvent (CH_2Cl_2) was partially evaporated under vacuo without application of external heating.

Freshly prepared lithium diisopropylamide (LDA), product of the reaction of diisopropylamine and BuLi at −78 °C during 15 min, was used to generate the enolate derivative of the chiral auxiliary (*S*)-(−)-1-BOC-2-*tert*-butyl-3-imidazolidinone (Seebach reagent).[20] Use of commercially available LDA leads to poor yields (20–30%). On the other hand the synthesis of LDA at −78 °C provides better alkylation yields compared with LDA prepared at 0 °C. After optimization, the alkylated product **14** was obtained in a range of 75–89% yield. Deprotection of the 1,3-dithiolane was performed following the procedure described by Stork and Zhao using [bis(trifluoroacetoxy)iodo]benzene regenerates the carbonyl functionality to afford the desired series of compounds **1** Table 1.[21]

Table 1
Yields of the reaction steps to fluorobenzyloxoimidazolidinone derivatives **1a**, **1b** and **1c** (cf. Scheme 3)

Compound	**a** (%)	**b** (%)	**c** (%)
10	96	95	97
11	77	81	81
12	90	91	91
13	74	84	74
14	75	89	84
1	92	91	93
Overall yield	34[a]	48	41

[a] Including the synthesis of **9a** the overall yield for **1a** is 19%.

In summary, the synthesis of (2*S*,5*S*)-*tert*-butyl 5-(4-(benzyloxy)-2-fluoro-5-formylbenzyl)-2-*tert*-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate **1a** has been optimized. The 10 steps procedure achieved the desired compound with an overall yield of 19%. In addition, the derivatives **1b** and **1c** have been synthesized in six steps with overall yields of 48% and 41%, respectively.

3. Experimental part

3.1. General techniques

All the reactions sensitive to moisture were carried out under argon atmosphere and, prior to use, the reaction flasks were dried over night in an oven at 95 °C. All liquids sensitive to moisture were transferred into the reaction flask, equipped with a septum, through syringes. All the reaction mixtures were magnetically stirred. Flash chromatography was performed following the procedure proposed by Still et al.[22] on silica gel (Merck 60 mesh for flash chromatography).

Dry solvents dichloromethane, tetrahydrofurane, dioxane and methanol were purchased from Fluka, Germany. Diethylether, petroleum ether, acetonitrile, ethyl acetate and ethanol were obtained from Merck, Germany. All solvents were used without further purification.

1-(3-bromo-4-fluorophenyl)ethanone, isopropylmagnesium chloride, lithium chloride complex, lithium aluminium hydride, diisobutylaluminium hydride, carbontetrabromide, triphenylphosphine, diisopropylamine, butyllithium, [bis(trifluoroacetoxy) iodo]benzene and Dess–Martin periodinane were purchased from Aldrich, Germany. Iodine, sodium acetate, benzyl bromide, ethanedithiol and ethyl chloroformate from Fluka, Germany and molecular bromine, (*S*)-Boc-BMI were acquired from Merck, Germany. All the reagents were used without purification.

3.2. Compounds

*3.2.1. 5-Bromo-4-fluoro-2-hydroxybenzoic acid (**6**).* 4-Fluorosalicilyc acid (1.00 g, 6.4 mmol) was dissolved in methanol (10 mL). Sodium acetate (2.2 g, 26.88 mmol) was added and the mixture was cooled to −78 °C. Molecular bromine (0.33 mL, 6.4 mmol) dissolved in 10 mL of methanol was slowly added and the mixture was allowed to warm to room temperature. After 5 h the solvent was removed under vacuum and the remnants treated with a solution of 10% HCl. The residue was filtered under vacuum, washed with water and dissolved in EtOAc. After drying over Na_2SO_4 the solvent was removed in vacuo to give 1.23 g (82%) of the desired product **6**. Mp 205–207 °C (lit. 203–205 °C[23]).

*3.2.2. Benzyl 2-(benzyloxy)-5-bromo-4-fluorobenzoate (**7**).* K_2CO_3 (7.06 g, 51.08 mmol) and benzyl bromide (3.34 mL, 28.08 mmol) were added to a solution of the acid **6** (3.00 g, 12.77 mmol) in acetone (100 mL). The mixture was stirred under reflux. After 3 h the reaction was cooled down to room temperature. Water was added and the mixture extracted with CH_2Cl_2 (3×30 mL). The organic fractions were combined and washed with brine. The organic layer was separated, dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was purified by flash chromatography (5% EtOAc/petroleum ether) to give 1.76 g of **7** (77%). R_f=0.33 (5% EtOAc/petroleum ether); mp 77–78 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J=8.0 Hz, 1H), 7.41–7.29 (m, 10H), 6.79 (d, J=10.4 Hz, 1H), 5.17 (s, 2H), 5.31(s, 2H); ^{13}C NMR ($CDCl_3$) δ 164.1, 161.9 (J=253.4 Hz), 159.2 (J=10.4 Hz), 136.6 (J=2.5 Hz) 135.7, 135.4, 128.7, 128.6, 128.3, 128.24, 128.18, 127.1, 118.0 (J=3.4 Hz), 102.8 (J=26.2 Hz), 99.3 (J=22.0 Hz), 71.2, 67.1; ^{19}F NMR ($CDCl_3$) δ −97.7; HRMS $C_{21}H_{17}BrFO_3$ m/z $[M+H]^+$ calculated 415.0345, found 415.0341.

*3.2.3. (2-(Benzyloxy)-5-bromo-4-fluorophenyl)methanol (**8**).* Ester **7** (3.06 g, 7.36 mmol) was dissolved in dry dichloromethane (50 mL) and cooled to 0 °C. 16.19 mL (1.0 M, 16.19 mmol) of a solution of DIBAL was added dropwise. The reaction was stirred during 10 min at 0 °C and then was allowed to warm to room temperature. After 30 min the reaction mixture was quenched with water. The organic layer was separated and the aqueous phase extracted with dichloromethane, the organic fractions were combined and washed with brine, separated and dried over Na_2SO_4. The solvent was removed and the crude product purified by flash chromatography (15% AcOEt/petroleum ether) yielded the product **8** in 90%. R_f=0.60 (20% EtOAc/petroleum ether); mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J=7.8 Hz, 1H), 7.31–7.38 (m, 5H), 6.73 (d, J=10.2 Hz, 1H), 5.09 (s, 2H), 4.65 (s, 2H), 2.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 158.9

(J=245.7 Hz), 156.4 (J=8.5 Hz), 135.6 (J=2.5 Hz), 132.4, 128.8, 128.4, 127.3, 127.1 (J=4.2 Hz), 101.3 (J=27.0 Hz), 99.1 (J=21.1 Hz), 70.7, 60.6; ^{19}F NMR ($CDCl_3$) δ −105.9; E.A. calculated C: 54.04, H: 3.89, found C: 53.6H: 4.24.

*3.2.4. 2-(Benzyloxy)-5-bromo-4-fluorobenzaldehyde (**9a**).* DMP (1.50 g, 3.42 mmol) was added to a solution of the alcohol **8** (0.97 g, 3.13 mmol) in methylene chloride (20 mL) under stirring. After 20 min the reaction mixture was diluted with 50 mL of ether and poured into saturated aqueous $NaHCO_3$ containing a sevenfold excess of $Na_2S_2O_3$. The mixture was stirred to dissolve the solid, and the layers were separated. The organic layer was washed with water, separated, dried over Na_2SO_4, filtrated and the solvent evaporated in vacuo. The crude product was purified by flash chromatography (5% EtOAc/petroleum ether) to give the desired compound in 95% of yield. R_f=0.45 (5% EtOAc/petroleum ether); mp 89–91 °C; ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 7.98 (d, J=8.2 Hz, 1H), 7.31–7.38 (m, 5H), 6.78 (d, J=9.9 Hz, 1H), 5.10 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 186.9, 163.3 (J=255.9 Hz), 161.4 (J=10.1 Hz), 134.8, 133.5 (J=3.4 Hz), 128.9, 128.7, 127.4, 122.9 (J=3.4 Hz), 102.4 (J=26.2 Hz), 101.1 (J=22.0 Hz), 71.2; ^{19}F NMR ($CDCl_3$) δ −93.6; HRMS $C_{14}H_{11}BrFO_2$ m/z $[M+H]^+$ calculated 308.9926, found 308.9905.

*3.2.5. 2-(2-(Benzyloxy)-5-bromo-4-fluorophenyl)-1,3-dithiolane (**10a**).* 1,3-Ethanedithiol (0.29 mL, 3.55 mmol) was added to a solution of **9a** (1.00 g, 3.23 mmol) and iodine (0.082 g, 0.32 mmol) in dichloromethane (10 mL) and the mixture was stirred at room temperature. After 1 h the reaction was quenched with NaS_2O_3 (0.1 M, 25 mL) and NaOH (10%, 25 mL). Then 25 mL of dichloromethane were added and the organic layer was separated, dried over $MgSO_4$ and filtrated. The solvent was removed in vacuo and the crude product purified by flash chromatography (3% AcOEt/petroleum ether) to give 1.21 g of **10a** (97%). R_f=0.49 (% EtOAc/petroleum ether); mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J=8.0 Hz, 1H), 7.14–7.39 (m, 5H), 6.63 (d, J=10.2 Hz, 1H), 5.03 (s, 2H), 5.90 (s, 1H), 3.25 (m, 2H), 3.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 159.9 (J=247.4 Hz), 156.8 (J=8.9 Hz), 136.8, 133.3, 129.9, 129.4, 128.4, 129.2 (J=3.2 Hz), 102.4 (J=27.0 Hz), 100.3 (J=21.1 Hz), 72.0, 49.4, 40.5; ^{19}F NMR ($CDCl_3$) δ −105.9; HRMS $C_{16}H_{15}BrFOS_2$ m/z $[M+H]^+$ calculated 384.9732, found 384.9726.

*3.2.6. 2-(3-Bromo-4-fluorophenyl)-2-methyl-1,3-dithiolane (**10b**).* 1,3-Ethanedithiol (0.435 mL, 5.07 mmol) was added to a solution of 1-(3-bromo-4-fluorophenyl)ethanone (1.00 g, 4.60 mmol) and iodine (0.117 g, 0.46 mmol) in dichloromethane (10 mL) and the mixture was stirred under reflux. After 3.5 h the reaction was cooled to room temperature and quenched with NaS_2O_3 (0.1 M, 25 mL) and NaOH (10%, 25 mL). Then 25 mL of dichloromethane were added and the organic layer was separated, dried over $MgSO_4$ and filtrated. The solvent was removed in vacuo and the crude product purified by flash chromatography (3% AcOEt/petroleum ether) to give **10b** (95%) as pale yellow oil. R_f=0.35 (3% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.94 (dd, J=6.4, 2.6 Hz, 1H), 7.65 (ddd, J=8.8, 4.5, 2.5 Hz, 1H), 7.02 (t, J=8.5 Hz, 1H), 3.29–3.49 (m, 4H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.9 (J=248.8 Hz), 143.8 (J=3.3 Hz), 132.1, 127.7 (J=7.6 Hz), 115.7 (J=22.8 Hz), 108.3 (J=24.7 Hz), 67.4, 40.5, 33.6; ^{19}F NMR ($CDCl_3$) δ −110.1; HRMS $C_{10}H_{11}BrFS_2$ m/z $[M+H]^+$ calculated 292.9470, found 292.9466.

*3.2.7. 2-(3-Bromo-4-fluorophenyl)-1,3-dithiolane (**10c**).* Compound **10c** was prepared following the procedure described for compound **10a**. Yield 97%; R_f=0.51 (5% EtOAc/petroleum ether); mp 51–53 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (dd, J=7.2, 2.2 Hz, 1H), 7.39 (ddd, J=8.5, 4.5, 2.3 Hz, 1H), 7.03 (t, J=8.2 Hz, 1H), 5.53 (s, 1H), 3.47 (m, 2H), 3.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.6 (J=248.3 Hz), 138.1 (J=3.4 Hz), 133.0, 128.6 (J=7.6 Hz), 116.3 (J=22.8 Hz), 108.9 (J=22.0 Hz), 54.8, 40.3; ^{19}F NMR ($CDCl_3$) δ −108.4; HRMS $C_9H_9BrFS_2$ m/z $[M+H]^+$ calculated 278.9313, found 278.9133.

*3.2.8. Ethyl 4-(benzyloxy)-5-(1,3-dithiolan-2-yl)-2-fluorobenzoate (**11a**).* Dioxane (0.3 mL) was added to a solution of isopropylmagnesium chloride lithium chloride complex in THF (1.3 M, 3.14 mL 4.08 mmol) and the mixture was cooled to 0 °C. After 5 min 1.21 g (3.14 mmol) of compound **5** was added and the mixture stirred during 1.0 h at 0 °C. Then 0.61 mL (6.28 mmol) of ethyl chloroformate was added and the mixture was allowed to reach room temperature. The solution was stirred for 2 h and then quenched with saturated aqueous NH_4Cl solution (4 mL). The reaction mixture was partitioned in H_2O/ether (30:30) the organic layer separated and the aqueous phase was extracted with ether (2×20 mL), the organic fractions were combined dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (10% AcOEt/petroleum ether) yielding compound **6** (77%). R_f=0.39 (10% EtOAc/petroleum ether); mp 83–85 °C; ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J=8.4 Hz, 1H), 7.29–7.42 (m, 5H), 6.63 (d, J=12.1 Hz, 1H), 5.13 (s, 2H), 4.35 (q, J=7.1 Hz, 2H), 5.95 (s, 2H), 3.30 (m, 2H), 3.38 (m, 2H), 1.36 (s, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.1 (J=4.2 Hz), 162.7 (J=260.9 Hz), 159.8 (J=10.1 Hz), 135.4, 131.6 (J=2.5 Hz), 128.7, 128.4, 127.3, 126.5 (J=3.4 Hz), 110.7 (J=9.3 Hz), 100.8 (J=27.9 Hz), 70.9, 61.0, 48.4, 39.3, 14.3; ^{19}F NMR ($CDCl_3$) δ −106.4; HRMS $C_{19}H_{20}FO_3S_2$ m/z $[M+H]^+$ calculated 379.0838, found 379.0830.

*3.2.9. Ethyl 2-fluoro-5-(2-methyl-1,3-dithiolan-2-yl)benzoate (**11b**).* Compound **11b** was prepared following the procedure described for compound **11a**. The crude residue was purified by flash chromatography (10% AcOEt/petroleum ether) yielding compound **11a** (81%) as pale yellow oil. R_f=0.57 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 8.26 (dd, J=6.8, 2.7 Hz, 1H), 7.91 (ddd, J=8.8, 4.5, 2.7 Hz, 1H), 7.04 (dd, J=8.8, 10.0 Hz, 1H), 4.38 (q, J=7.2 Hz, 2H), 3.31–3.50 (m, 4H), 2.12 (s, 3H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4 (J=3–9 Hz), 160.8 (J=261.3 Hz), 142.1 (J=3.8 Hz), 133.2 (J=9.5 Hz), 130.3, 118.1 (J=10.0 Hz), 116.5 (J=22.5 Hz), 67.5, 61.4, 40.5, 33.5, 14.3; ^{19}F NMR ($CDCl_3$) δ −112.2; HRMS $C_{13}H_{16}FO_2S_2$ m/z $[M+H]^+$ calculated 287.0576, found 287.0570.

*3.2.10. Ethyl 5-(1,3-dithiolan-2-yl)-2-fluorobenzoate (**11c**).* Compound **11c** was prepared following the procedure described for compound **11a**. Yield 81%; R_f=0.42 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.67 (ddd, J=8.4, 4.4, 2.6 Hz, 1H), 7.99 (dd, J=6.8, 2.4 Hz, 1H), 7.04 (dd, J=8.7, 10.2 Hz, 1H), 4.35 (q, J=7.1 Hz, 2H), 5.59 (s, 1H), 3.47 (m, 2H), 3.34 (m, 2H), 2.12, 1.37 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.0 (J=4.2 Hz), 161.4 (J=260.9 Hz), 136.5 (J=3.4 Hz), 133.9 (J=9.3 Hz), 131.5, 118.7 (J=10.1 Hz), 117.2 (J=22.8 Hz), 61.4, 55.0, 40.3, 14.2; ^{19}F NMR ($CDCl_3$) δ −110.5; HRMS $C_{12}H_{14}FO_2S_2$ m/z $[M+H]^+$ calculated 273.0419, found 273.0414.

*3.2.11. (4-(Benzyloxy)-5-(1,3-dithiolan-2-yl)-2-fluorophenyl)methanol (**12a**).* $LiAlH_4$ 1.21 mL in dry THF (2.0 M, 2.42 mmol) was added dropwise to a solution of the ester **6** (0.81 g, 2.42 mmol) dissolved in dry THF (25 mL). The reaction was stirred for 1 h at room temperature. The mixture was quenched with water and acidified with concentrated H_2SO_4 until the solid was dissolved. The mixture was extracted with CH_2Cl_2, the organic phase separated and dried over Na_2SO_4. The solvent was removed and the crude purified by flash chromatography (25% AcOEt/petroleum ether) yielded product **7** in 90%. R_f=0.44 (30% EtOAc/petroleum ether); mp 114–117 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J=8.6 Hz, 1H), 7.32–7.45 (m, 5H), 6.58 (d, J=11.5 Hz, 1H), 5.06 (s, 2H), 4.63 (s, 2H), 6.00 (s, 1H) 3.28 (m, 2H), 3.37 (m, 2H); ^{13}C NMR ($CDCl_3$)

δ 160.6 (J=247.4 Hz), 156.1 (J=10.1 Hz), 136.0, 129.2 (J=5.9 Hz), 128.6, 128.1, 127.2, 125.8 (J=3.4 Hz), 119.5 (J=15.2 Hz), 100.1 (J=26.2 Hz), 70.6, 59.2 (J=4.0 Hz), 48.6, 39.4; ^{19}F NMR ($CDCl_3$) δ −117.8; E.A. calculated C: 60.69, H: 5.09, S: 19.06, found C: 60.4, H: 5.45, S: 21.1.

*3.2.12. (2-Fluoro-5-(2-methyl-1,3-dithiolan-2-yl)phenyl)methanol (**12b**).* Compound **12b** was prepared following the procedure described for compound **12a**. Yield 91%; R_f=0.52 (20% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J=7.0, 2.5 Hz, 1H), 7.66 (ddd, J=8.2, 4.9, 2.7 Hz, 1H), 6.95 ('t', J=9.0 Hz, 1H), 4,73 (s, 2H), 3.32–3.44 (m, 4H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5 (J=247.2 Hz), 142.0 (J=3.8 Hz), 128.0 (J=8.2 Hz), 127.9, 127.0 (J=14.5 Hz), 114.7 (J=21.5 Hz), 67.9, 59.5 (J=3.9 Hz), 40.4, 33.9; ^{19}F NMR ($CDCl_3$) δ −112.4; E.A. calculated C: 54.07, H: 5.36, S: 26.3, found C: 53.9, H: 5.84, S: 26.3.

*3.2.13. (5-(1,3-Dithiolan-2-yl)-2-fluorophenyl)methanol (**12c**).* Compound **12c** was prepared following the procedure described for compound **12a**. Yield 91%; R_f=0.40 (20% EtOAc/petroleum ether); mp 60–61 °C; ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 1H), 7.53 (dd, J=6.9, 1.9 Hz, 1H), 6.92 ('t', J=9.0 Hz, 1H), 4.67 (s, 2H), 5.56 (s, 1H) 3.44 (m, 2H), 3.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 160.0 (J=247.4 Hz), 136.2 (J=3.4 Hz), 128.78 (J=14.3 Hz), 128.76, 127.8 (J=15.2 Hz), 115.2 (J=22.0 Hz), 59.2 (J=4.2 Hz), 55.5, 40.2; ^{19}F NMR ($CDCl_3$) δ −120.6; E.A. calculated C: 52.15, H: 4.81, S: 27.84, found C: 52.0, H: 4.95, S: 28.5.

*3.2.14. 2-(2-(Benzyloxy)-5-(bromomethyl)-4-fluorophenyl)-1,3-dithiolane (**13a**).* A magnetically stirred solution of the alcohol **12a** (1.25 g, 3.71 mmol) and 1.37 g (4.09 mmol) of carbontetrabromide in 10 mL of dichloromethane was cooled to 0 °C. A solution of triphenylphosphine (1.46 g, 5.57 mmol) in 5 mL of dichloromethane was added dropwise. After the addition the mixture was stirred for further 5 min, whereupon the solvent was partially removed in vacuo at room temperature. Ether (20 mL) was added and the mixture filtered. The filter cake was washed with ether (2×20 mL). The combined filtrates and washings were concentrated and the residue purified via flash chromatography to give 1.10 g (74%) of the bromide as a white solid. R_f=0.46 (3% EtOAc/petroleum ether); mp 114–115 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J=8.7 Hz, 1H), 7.31–7.44 (m, 5H), 6.61 (d, J=11.2 Hz, 1H), 5.09 (s, 2H), 4.48 (s, 2H), 5.97 (s, 1H) 3.40–3.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 160.7 (J=250.9 Hz), 156.9 (J=9.8 Hz), 135.7, 130.5 (J=4.9 Hz), 128.7, 128.3, 127.2, 126.5 (J=3.5 Hz), 116.6 (J=14.9 Hz), 100.3 (J=25.6 Hz), 70.7, 48.5, 39.3, 29.3 (J=3.6 Hz); ^{19}F NMR ($CDCl_3$) δ −114.6; HRMS $C_{17}H_{17}BrFOS_2$ $[M+H]^+$ calculated 298.9888, found 298.9708.

*3.2.15. 2-(3-(Bromomethyl)-4-fluorophenyl)-2-methyl-1,3-dithiolane (**13b**).* Compound **13b** was prepared following the procedure described for compound **13a**. Yield 84%; R_f=0.51 (3% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.76 (dd, J=7.1, 2.1 Hz, 1H), 7.66 (ddd, J=8.0, 4.5, 2.5 Hz, 1H), 6.95 ('t', J=7.5 Hz, 1H), 4,49 (s, 2H), 3.51–3.28 (m, 4H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6 (J=250.9 Hz), 142.4 (J=3.4 Hz), 129.8 (J=3.2 Hz), 128.3 (J=8.2 Hz), 124.3 (J=14.6 Hz), 115.2 (J=21.5 Hz), 67.7, 40.5, 33.7, 25.9 (J=4.3 Hz); ^{19}F NMR ($CDCl_3$) δ −119.5; MS $C_{22}H_{24}BrF_2S_4$ $[2M+H-HBr]^+$ calculated 532.9912, found 532.9908.

*3.2.16. 2-(3-(Bromomethyl)-4-fluorophenyl)-1,3-dithiolane (**13c**).* Compound **13c** was prepared following the procedure described for compound **13a**. Yield 74%; R_f=0.49 (3% EtOAc/petroleum ether); mp 63–64 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (dd, J=7.1, 2.4 Hz, 1H), 7.50 (ddd, J=8.4, 4.8, 2.3 Hz, 1H), 7.04 ('t', J=9.0 Hz, 1H), 5.63 (s, 1H), 4.53 (s, 2H) 3.60–3.33 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 160.2 (J=249.7 Hz), 136.7 (J=3.6 Hz), 130.8 (J=3.5 Hz), 130.2 (J=8.4 Hz), 125.1 (J=14.9 Hz), 115.9 (J=21.7 Hz), 55.3, 40.3, 25.5 (J=4.4 Hz); ^{19}F NMR ($CDCl_3$) δ −117.7; HRMS $C_{10}H_{10}FS_2$ $[M+H-HBr]^+$ calculated 213.0208, found 213.0203.

*3.2.17. (2S,5S)-tert-Butyl 5-(4-(benzyloxy)-5-(1,3-dithiolan-2-yl)-2-fluorobenzyl)-2-tert-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate (**14a**).* A stirred solution of diisopropylamine (0.47 mL, 3.30 mmol) in dry THF (2 mL) was cooled down to −78 °C, then BuLi (2.5 M/hexane, 1.32 mL, 3.30 mmol) was added dropwise. The resulting solution was stirred during 15 min. A solution of (*S*)-Boc-BMI (0.71 g, 2.75 mmol) in dry THF (2 mL) was added slowly and stirring was maintained for 40 min. The benzyl bromide **7** (1.10 g, 2.75 mmol) in THF (3 mL) was then added. The reaction mixture was kept at room temperature and stirring was continued over 3 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), 30 mL of water were added and the reaction was extracted with CH_2Cl_2 (3×25 mL). The organic layer was dried over sodium sulfate and evaporated to give the crude product, which was purified by flash chromatography (20% EtOAc/petroleum ether) (1.19 g, 75%, pale yellow solid). R_f=0.42 (25% EtOAc/petroleum ether); mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J=7.2 Hz, 1H), 7.32–7.45 (m, 5H), 6.54 (d, J=11.5 Hz, 1H), 4.95 (br, H), 5.03 (s, 2H), 4.30 (br, 1H), 5.99 (s, 1H), 3.29 (m, 2H), 3.41 (m, 2H), 2.89 (s, 3H), 1.34 (s, 9H), 3.18 (d, J=15.8 Hz, 1H), 3.60 (br, 1H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.5, 160.9 (J=246.6 Hz), 154.8 (J=10.1 Hz), 152.8 (br), 136.3, 129.3 (J=4.3 Hz), 128.6, 128.0, 127.2, 125.0 (br), 115.1 (J=16.0 Hz), 100.0 (J=27.0 Hz), 81.0, 80.9, 70.5, 58.9 (J=4.0 Hz), 48.7, 40.9, 39.4, 39.4, 39.2, 32.3, 28.0, 26.5, 26.6; ^{19}F NMR ($CDCl_3$) δ −113.6; HRMS $C_{30}H_{40}FN_2O_4S_2$ $[M+H]^+$ calculated 575.2414, found 575.2413.

*3.2.18. (2S,5S)-tert-Butyl 2-tert-butyl-5-(2-fluoro-5-(2-methyl-1,3-dithiolan-2-yl)benzyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (**14b**).* Compound **14b** was prepared following the procedure described for compound **14a**. Yield 89%; R_f=0.52 (25% EtOAc/petroleum ether); mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (ddd, J=8.6, 4.9, 2.7 Hz, 1H), 7.37 (dd, J=7.0, 2.3 Hz, 1H), 6.88 ('t', J=9.4 Hz, 1H), 5.04 (br, 1H), 4.33 (br, 1H) 3.25–3.41 (m, 4H), 3.27 (br, 2H), 2.03 (s, 3H), 2.97 (s, 3H), 1.25 (s, 9H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.6, 154.9 (J=248.6 Hz), 152.9 (br), 141.6 (br), 127.7 (br), 126.3 (J=8.0 Hz), 123.0 (J=15.1 Hz), 114.5 (J=23.1 Hz), 81.0, 80.9, 68.6 (br), 58.2 (br), 40.8, 40.0, 39.9 (br), 33.7 (br), 32.4, 27.9, 26.7 (br), 26.5; ^{19}F NMR ($CDCl_3$) δ −118.5; HRMS $C_{24}H_{36}FN_2O_3S_2$ *m/z* $[M+H]^+$ calculated 483.2151, found 483.2148.

*3.2.19. (2S,5S)-tert-Butyl-5-(5-(1,3-dithiolan-2-yl)-2-fluorobenzyl)-2-tert-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate (**14c**).* Compound **14c** was prepared following the procedure described for compound **14a**. Yield 84%; R_f=0.33 (25% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.19–7.26 (m, 2H), 6.87 ('t', J=9.3 Hz, 1H), 4.90 (br, 1H), 4.32 (br, 1H), 5.52 (s, 1H), 3.70 (br, 1H), 3.24 (d, J=15.1 Hz, 1H), 3.46 (m, 2H), 3.30 (m, 2H), 2.88 (s, 3H), 1.33 (s, 9H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.5, 160.7 (J=247.4 Hz), 152.7 (br), 135.2 (br), 129.7, 127.5 (J=8.7 Hz), 123.8 (J=15.8 Hz), 115.0 (J=23.4 Hz), 81.2, 81.0, 58.8, 55.9, 40.9, 40.0, 40.1, 32.2, 28.0, 27.0 (br), 26.5; ^{19}F NMR ($CDCl_3$) δ −116.3; HRMS $C_{23}H_{34}FN_2O_3S_2$ *m/z* $[M+H]^+$ calculated 469.1995, found 469.1994.

*3.2.20. (2S,5S)-tert-Butyl 5-(4-(benzyloxy)-2-fluoro-5-formylbenzyl)-2-tert-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate (**1a**).* [Bis (trifluoroacetoxy)iodo]benzene (1.37 g, 3.09 mmol) was added in one portion to 1.19 g of **9** (2.06 mmol) dissolved in 10 mL of 9:1 MeOH/H_2O. The reaction mixture was stirred at room temperature during 5 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The product was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash

chromatography (30% EtOAc/petroleum ether) yields the desired aldehyde **10** in 92%. R_f=0.42 (25% EtOAc/petroleum ether); mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 7.51 (d, J=8.8 Hz, 1H), 7.32–7.39 (m, 5H), 6.67 (d, J=11.5 Hz, 1H), 4.88 (br, 1H), 5.10 (s, 2H), 4.29 (br, 1H), 2.98 (s, 3H), 3.28 (d, J=14.9 Hz, 1H), 3.60 (br, 1H), 1.33 (s, 9H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 187.9, 171.7, 165.8 (J=256.7 Hz), 160.9 (J=11.0 Hz), 152.5 (br), 135.4, 130.1 (J=8.4 Hz), 128.8, 128.4, 127.2, 121.4 (br), 117.0 (J=18.1 Hz), 100.9 (J=27.0 Hz), 81.2, 81.1, 70.7, 58.4 (br), 40.9, 32.1, 29.7, 27.9, 26.5; ^{19}F NMR ($CDCl_3$) δ-101.2; HRMS $C_{28}H_{36}FN_2O_5$ $[M+H]^+$ calculated 499.2608, found 499.2602.

*3.2.21. (2S,5S)-tert-Butyl-5-(5-acetyl-2-fluorobenzyl)-2-tert-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate (**1b**).* Compound **1b** was prepared following the procedure described for compound **1a**. Yield 91%; R_f=0.29 (25% EtOAc/petroleum ether); mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (ddd, J=8.4, 5.2, 2.4 Hz, 1H), 7.66 (dd, J=7.4, 2.3 Hz, 1H), 6.88 ('t', J=8.7 Hz, 1H), 4.85 (br, 1H), 4.34 (br, 1H), 3.68 (br, 1H), 3.38 (d, J=14 Hz, 1H), 2.94 (s, 3H), 2.52 (s, 3H), 1.33 (s, 9H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 196.6, 171.6, 164.3 (J=255.7 Hz), 152.7 (br), 130.9 (J=5.4 Hz), 128.8 (J=9.0 Hz), 124.3 (J=14.4 Hz), 115.5, 113.0 (J=3.0 Hz), 81.3, 81.1, 58.5, 40.9, 32.2, 27.9, 26.6, 26.5; ^{19}F NMR ($CDCl_3$) δ −107.4; HRMS $C_{22}H_{32}FN_2O_4$ m/z $[M+H]^+$ calculated 469.1995, found 469.1994.

*3.2.22. (2S,5S)-tert-Butyl-2-tert-butyl-5-(2-fluoro-5-formylbenzyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (**1c**).* Compound **1c** was prepared following the procedure described for compound **1a**. Yield 93%; R_f=0.34 (25% EtOAc/petroleum ether); mp 92–93 °C; ^{1}H NMR ($CDCl_3$) δ 9.81 (s, H), 7.69 (m, 1H), 7.58 (dd, J=7.0, 1.4 Hz, 1H), 7.10 ('t', J=9.2 Hz, 1H), 4.84 (br, 1H), 4.33 (br, 1H), 3.65 (br, 1H), 3.41 (d, J=15.2 Hz, 1H), 2.92 (s, 3H), 1.34 (s, 9H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 190.5, 171.4, 165.0 (J=257.0 Hz), 152.5 (br), 132.5, 132.3 (J=6.2 Hz), 130.2 (J=10.0 Hz), 125.4 (J=16.7 Hz), 116.2 (J=24.4 Hz), 81.3, 81.1, 58.5, 40.9, 32.2, 28.0, 27.6 (br), 26.5; ^{19}F NMR ($CDCl_3$) δ −104.3; HRMS $C_{21}H_{30}FN_2O_4$ m/z $[M+H]^+$ calculated 393.2190, found 393.2183.

Acknowledgements

The authors want to thank Dr. S. Willbold, Dr. D. Hofmann and Dr. M. Holschbach for recording the spectroscopic data. This work was supported by a Grant of the Technology Transfer Bureau of FZ-Jülich.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.036.

References and notes

1. (a) Laverman, P.; Boerman, O. C.; Costens, F. H. M.; Oyen, W. J. G. *Eur. J. Nucl. Med.* **2002**, *29*, 681; (b) Coenen, H. H. PET Studies on Amino Acid Metabolism and Protein Synthesis. In; Mazoyer, B. M., Heiss, W. D., Comar, D., Eds.; Kluwer Academic Publishers: Dordrecht, Boston, London, 2003; pp 109–129.
2. (a) Mohnike, K.; Blankenstein, O.; Minn, H.; Mohnike, W.; Füchtner, F.; Otonkoski, T. *Horm. Res.* **2008**, *70*, 65; (b) Jager, P. L.; Chirakal, R.; Marriott, C. J.; Brouwers, A. H.; Koopmans, K. P.; Gulenchyn, K. Y. *J. Nucl. Med.* **2008**, *49*, 573.
3. (a) de Vries, E. F. J.; Luurtsema, G.; Brüssermann, M.; Elsinga, P. H.; Vaalburg, W. *Appl. Radiat. Isot.* **1999**, *51*, 389; (b) Hess, E.; Sichler, S.; Kluge, A.; Coenen, H. H. *Appl. Radiat. Isot.* **2002**, *57*, 185; (c) VanBrocklin, H. F.; Blagoev, M.; Hoepping, A.; O'Neil, J. P.; Klose, M.; Schubiger, P. A.; Ametamey, S. *Appl. Radiat. Isot.* **2004**, *61*, 1289.
4. Hess, E.; Blessing, G.; Coenen, H. H.; Qaim, S. M. *Appl. Radiat. Isot.* **2000**, *52*, 1431.
5. Lemaire, C.; Gillet, S.; Guillouet, S. P.; Plenevaux, A.; Aerts, J.; Luxen, A. *Eur. J. Org. Chem.* **2004**, 2899.
6. Wagner, F. M.; Ermert, J.; Coenen, H. H. *J. Nucl. Med.* **2009**, *50*, 1724.
7. Castillo, J.; Ermert, J.; Coenen, H. H. *Eur. J. Nucl. Med.* **2009**, *36*, S221.
8. DeJesus, O.; Endres, C. J.; Shelton, S.; Nickles, J.; Holden, J. J. *J. Nucl. Med.* **1997**, *38*, 630.
9. Plenevaux, A.; Lemaire, C.; Palmer, A. J.; Damhaut, P.; Comar, D. *Appl. Radiat. Isot.* **1992**, *43*, 1035.
10. Castillo, J.; Ermert, J.; Wagner, F. M.; Coenen, H. H. *J. Label. Compd. Radiopharm.* **2009**, *52*, S163.
11. Coenen, H. H.; Kling, P.; Stöcklin, G. *J. Nucl. Med.* **1989**, *30*, 1367.
12. Castillo, J.; Ermert, J.; Coenen, H.H. *Org. Biomol. Chem.* **2010**, doi:10.1039/C0OB00440E.
13. Fluorodopa (18F) (prepared by electrophilic substitution) injection *European Pharmacopoeia* **2008**, *6*, 990.
14. Ahrendt, K.; Bergman, R.; Ellman, J. *Org. Lett.* **2003**, *5*, 1301.
15. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
16. Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527.
17. Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.
18. For selected literature of the use bromo-lithium exchange reactions for the synthesis of aromatics fluoro-amino acids see: (a) Ref. 6. (b) Monclus, M.; Masson, C.; Luxen, A. *J. Fluorine Chem.* **1995**, *70*, 39.
19. Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
20. Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.
21. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *3*, 287.
22. Still, W.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.
23. Shiraishi, M.; Hashiguchi, S.; Watanabe, T. Patent 5,270,308, **1993**.