Synthesis and ^{19}F NMR parameters of a perfluoro-*tert*-butoxy tagged L-DOPA analogue

Simonetta Orlandi[a], Marco Cavazzini[a], Silvia Capuani[b], Andrea Ciardello[c], Gianluca Pozzi[a]*

[a] *CNR Institute of Chemical Sciences and Technologies "Giulio Natta" (CNR SCITEC), UOS Golgi, via Golgi 19, 20133 Milan, Italy*

[b] *CNR Institute for Complex Systems (CNR ISC), UOS Roma Sapienza Department of Physics, 00185 Rome, Italy*

[c] *Sapienza University of Rome, 00185 Rome, Italy*

* Corresponding author. Tel.: +39 02 50314163; e-mail addresss: gianluca.pozzi@scitec.cnr.it

Abstract: The robust multistep synthesis of a perfluoro-*tert*-butoxy (PFTB) tagged analogue of the non-proteinogenic amino acid 3,4-dihydroxy-L-phenylalanine (L-DOPA) via diastereoselective benzylation of Oppolzer's sultam glycinate was developed. The new compound is characterized by a flexible alkoxy linker connecting PFTB to the biochemically and pharmacologically relevant L-DOPA scaffold, which facilitates the free motion of the fluorinated moiety. Therefore, the nine chemically equivalent fluorine atoms give rise to an intense and sharp ^{19}F NMR singlet signal that is easily detected in an aqueous environment. In addition, the kinetics of ^{19}F NMR relaxation processes in blood solution fit the requirements for the potential use of the new compound as a probe in ^{19}F magnetic resonance imaging applications in translational clinical field.

Keywords: Amino acids; Chiral auxiliaries; Fluorinated probes; Mitsunobu reaction; NMR relaxation times

1. Introduction

Magnetic resonance imaging (MRI) is a powerful, non-invasive diagnostic tool that does not require the use of radioactive nuclides or ionizing radiations, while providing physiological and anatomical information with high spatial resolution and excellent soft tissue contrast [1, 2, 3]. The majority of MRI clinical applications are currently based on responsive MR agents that modulate magnetic effects on the ^{1}H nuclei of water present in biological systems, but there is an ongoing search for imaging agents containing responsive heteronuclei, which can provide complementary information and expand MRI's options. Fluorinated compounds are mostly appealing in view of the intrinsic favorable properties of the ^{19}F nucleus, including its 100% natural abundance, high signal sensitivity, wide chemical shift range, and negligible endogenous presence in living organisms that produces a background signal below the ^{19}F NMR detection limit. Several fluorine-labelled dendrimers and polymers, organic molecules, paramagnetic metal complexes, and nanoparticle systems have been consequently proposed as imaging agents for in vitro and in vivo MRI applications [4, 5, 6, 7, 8]. However, to leverage the full potential of ^{19}F MRI, highly sensitive, specific probes of defined biological processes are needed. A possible approach would involve the incorporation of a fluorinated moiety producing a single ^{19}F NMR signal into the structure of a target biomolecule, in a manner that is minimally disruptive of its structure and functions. This strategy has been already successfully employed in the investigation of a wide range of biological processes by means of non-imaging ^{19}F NMR [9], as in the case of molecular interactions and conformational changes of proteins, which can be elucidated by ^{19}F NMR when appropriate synthetic fluorinated amino acids are encoded within proteins of interest [10, 11, 12, 13]. Moreover, ^{19}F-labelled metabolites or drugs are extremely useful for pharmacokinetic studies, precisely because it is possible, by monitoring the ^{19}F signal, to follow the metabolic path of a specific molecule with high precision, without problems due to the background signal of other molecules [14, 15].

Both in imaging and non-imaging applications, useful information is collected thanks to the variation of relevant NMR parameters, including chemical shift, scalar coupling, chemical exchange and relaxation processes. In particular, to carry out ^{19}F MRI experiments in times acceptable for future clinical applications, the transverse relaxation time, or T_2, of ^{19}F should not be less than about 4 ms and the spin-lattice relaxation time, or T_1, possibly not higher than 3 s in in vivo applications. In general, ^{19}F-labelled molecules with small T_2/T_1 ratios [16] and with not so rapid T_2 relaxation time [17, 18] in tissues require $10^{-3}<T_2/T_1 \leq 1$ in liquid solutions.

The non-proteinogenic amino acid 3,4-dihydroxy-L-phenylalanine (L-DOPA) plays an important role in the biosynthesis of chatecolamine neurotransmitters being the direct precursor of dopamine (DA) [19]. Based on this, L-DOPA analogues labelled on the aromatic ring with a ^{18}F nuclide (^{18}F-DOPA) have been long time used as radiotracers to monitor the dopaminergic brain system [20]. Indeed, ^{18}F-DOPA retain the parent molecule's ability to cross the hematoencephalic barrier (BBB) and to enter into nerve cells, where they are converted to the corresponding ^{18}F-labelled dopamine by the action of the enzyme L-aromatic amino acid decarboxylase (AAAD). The ^{18}F-DOPA bearing ^{18}F in the 6-position of the aryl ring, often referred to as fluorodopa, is an approved radioactive diagnostic agent applied in positron emission tomography (PET) imaging of dopaminergic nerve terminals in the striatum for the evaluation of adult patients with suspected Parkinson disease (PD). PET imaging using fluorodopa as radiotracer is also employed in the study of brain and neuroendocrine tumors, pancreatic cell hyperplasia and congenital hyperinsulinemic hypoglycaemia [21].

In order to overcome the well-known downsides of diagnostic tools based on the use of radiopharmaceuticals, Tooyama and coworkers have recently explored the alternative use of nonradioactive fluorodopa as a ^{19}F MRI probe for evaluating dopaminergic presynaptic function in the striatum [22]. The molecule obviously maintained the useful functional characteristics of fluorodopa (e.g. BBB permeability, specific cell uptake, accumulation in dysfunctional dopaminergic terminals), but its sensitivity as a ^{19}F MRI reporter was too low to ensure short acquisition times as those required by ^{19}F MRI experiments in vivo. Nevertheless, the results obtained showed the potential of L-DOPA as a platform for fluorinated NMR probes that target specific neurological processes, provided that a higher signal-to-noise ratio (SNR) could be achieved. This demand might be accomplished by the incorporation of a larger amount of chemically equivalent fluorine atoms into the L-DOPA structure, leading to a more intense, well-resolved single spectral peak. At the same time, the modified probes should still exhibit sufficient water solubility and suitable NMR parameters, such as relaxation times, which could be impaired by an excessive fluorine loading. The use of perfluoro-*tert*-butoxy (PFTB) tags that can be attached to the L-DOPA aryl ring through tunable linkers might offer a good compromise solution, as previously shown by Yu and coworkers in the case of macrocyclic ligands for lanthanide MRI contrast agents [23, 24]. More recently, Tressler and Zondo have described the synthesis of *para*-PFTB-L-phenyalanine and its incorporation in a short peptide sequence that was next examined by

^{19}F NMR in water. The PFTB tag generated a single peak that was readily detected at peptide concentration as low as 200 nM [25]. Another advantage of PFTB in comparison with

On these premises, we have now designed and synthesized **PFTB-DOPA** (Figure 1), an analogue of L-DOPA bearing an ether-bonded PFTB tag at the 5-position of the phenyl ring. The assessment of the ^{19}F NMR parameters revealed that the **PFTB-DOPA** is a promising candidate for biological ^{19}F NMR and ^{19}F MRI applications.

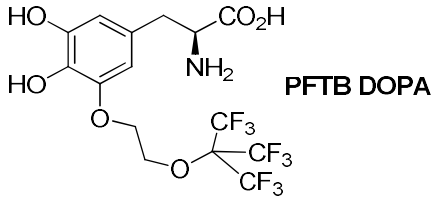
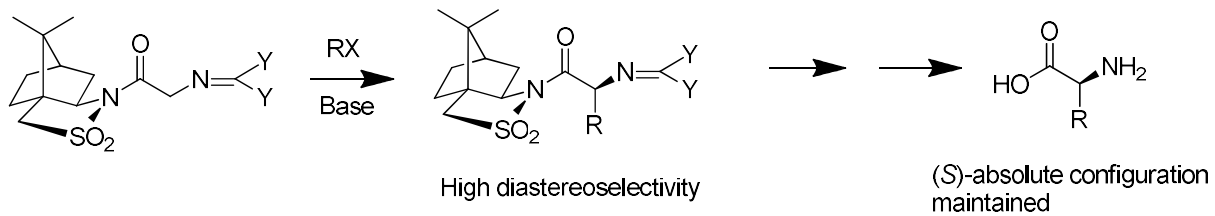


Figure 1. Structure of the new L-DOPA analogue with nine chemically equivalent fluorine atoms

2. Results and Discussion

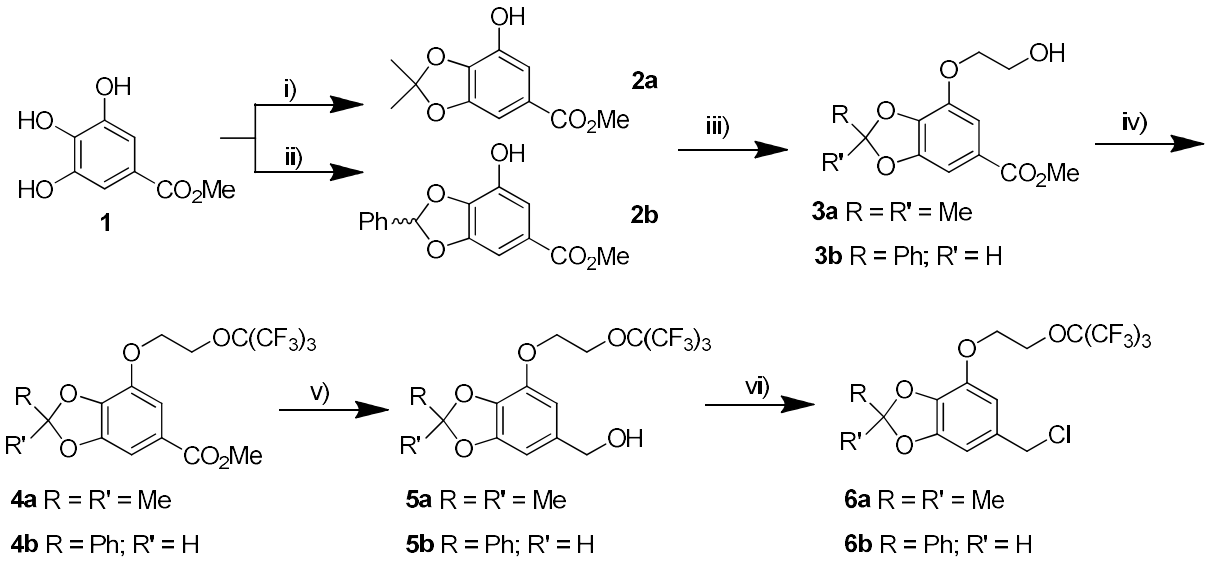
*2.1 Synthesis of **PFTB-DOPA***

The design of **PFTB-DOPA** is aimed at maintaining both the key catechol pattern typical of endogenous neurotransmitters and the absolute configuration of the amino acid moiety of L-DOPA. This thwarted the application of direct amino acids functionalization methods, including the introduction of PFTB onto the aryl ring via diazonium coupling that works in the case of L-phenylalanine [25]. After various attempts, the multistep synthesis of **PFTB-DOPA** was achieved by resorting to a well-proven strategy for the preparation of enantiopure α-amino acids, which relies on the diastereoselective C-alkylation of readily accessible chiral glycine synthons derived from Oppolzer's sultam (Scheme 1) [26]. The subsequent removal of the amine protecting group and of the sultam chiral auxiliary can be performed without racemization under mild hydrolysis conditions that do not affect the absolute configuration of the newly created stereogenic center. Thus, when the levorotatory enantiomer of Oppolzer's sultam is employed, α-amino acids with (S) configuration, similar to that of L-DOPA, are obtained in e.e. > 95% [26, 27].



Scheme 1. Synthesis of enantiopure α-amino acids via diastereoselective alkylation of glycine derivatives of levorotatory Oppolzer's sultam.

We built the PFTB tagged benzyl moiety of **PFTB-DOPA**, starting from commercially available gallic acid methyl ester **1** as sketched in Scheme 2. Initially, two of the three equivalent hydroxyl groups of **1** were protected by reaction with acetone in the presence of PCl_3, and the resulting phenol **2a** was then O-alkylated with 2-bromoethanol in DMSO in the presence of potassium carbonate as a base to give the alcohol **3a** in good yield after chromatographic purification. The introduction of the PFTB group was achieved in the next step by reaction of **3a** with nonafluoro *tert*-butanol under Mitsunobu conditions. Lithium aluminium hydride reduction of the methyl ester group of **4a** gave the corresponding benzyl alcohol **5a** that was finally converted into benzyl chloride **6a** by thionyl chloride in the presence of pyridine.

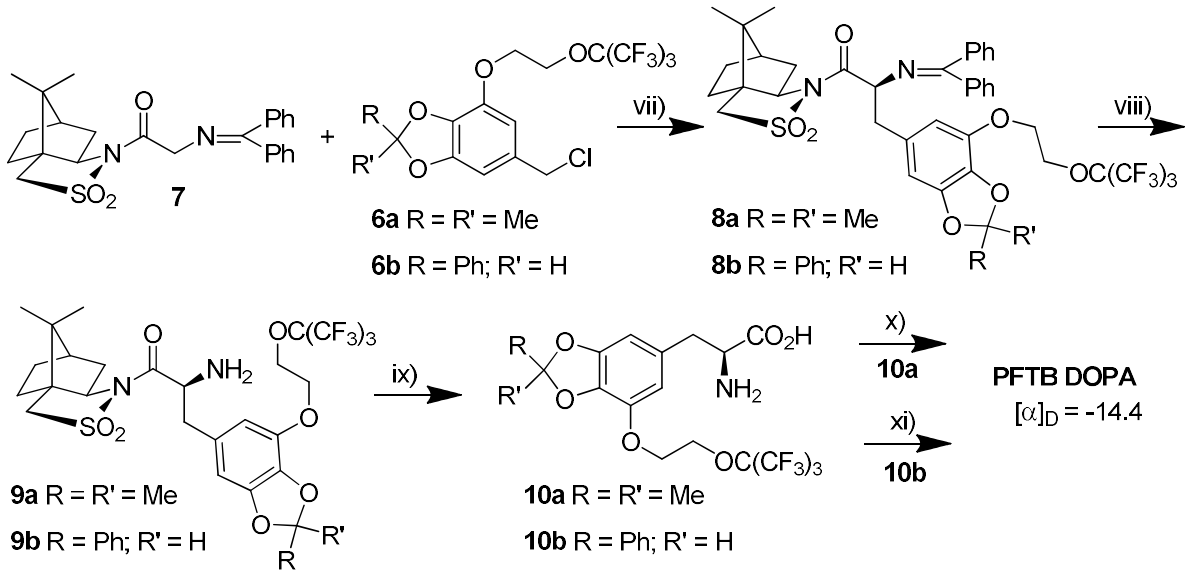


Reagents and conditions: i) PCl_3, toluene, acetone, reflux (73%); ii) $PhCHCl_2$, Pyridine, 110 °C (34%); iii) $Br(CH_2)_2OH$; K_2CO_3; DMSO, 80 °C (**3a** = 81%; **3b** = 73%); iv) $(CF_3)_3COH$, PPh_3, DIAD, Et_2O (**4a** = 95%; **4b** = 92%); v) LAH, THF (5a = 85%; 5b = 87%); vi) $SOCl_2$, Pyridine, toluene (**6a** = 89%, **6b** =76%).

Scheme 2. Synthesis of **PFTB-DOPA** benzylic precursors.

The readily available Oppolzer's sultam N-(diphenylmethylene)glycine derivative **7** (Scheme 3) had been previously used as chiral synthon for the successful preparation of enantiopure monofluorinated L-DOPA derivatives [27], leading to the intermediate protected aminoacids with excellent diastereoselectivities and high yields. Similarly, the reaction of **7** with **6a** in DMF in the presence of cesium carbonate as a base proceeded smoothly with more than 90% diastereomeric excess (d.e.) as calculated by ^1H NMR analysis of the crude product. The fully protected L-DOPA derivative **8a** was then isolated as a single diastereoisomer (d.e. > 98%) in 56% yield after final chromatographic separation. The free amino- and carboxylic groups were next restored by

standard mild acidic and basic hydrolysis conditions, respectively, but the final removal of the acetonide protecting group still present in the free amino acid **10a** turned out to be tricky. Indeed, after several attempts we were able to obtain **PFTB-DOPA** in modest yields (up to 34%) upon treatment of **10a** with aqueous acid chloride in THF, but reaction time and yield observed using different batches of starting material varied in an unpredictable way.



Reagents and conditions: vii) Cs_2CO_3, DMF (**8a** = 56%; **8b** = 66%); viii) 10% HClaq, DCM (**9a** = 76%, **9b** = 71%); ix) LiOH aq, THF (**10a** = 80%; **10b** = 90%); x) 10% HClaq, THF (34%); xi) H_2, Pd/C, MeOH (92%).

Scheme 3. Synthesis of **PFTB-DOPA** via diastereoiselective benzylation of Oppolzer's sultam glycinate.

This limitation was circumvented by converting gallic acid methyl ester **1** into the corresponding benzylidene acetal **2b** (Scheme 2) that was then employed to generate the benzylating agent **6b** according to the same procedure described for **6a**.

Due to the presence of a stereogenic center in **6b**, its subsequent reaction with the chiral synthon **7** (Scheme 3) afforded the alkylated product **8b** as a 1:1 diastereoisomeric mixture that was subjected as such to the mild hydrolytic cleavage of the imine function and elimination of the sultam chiral auxiliary as described in the case of **8a**. The configuration of the additional stereocenter of **6b** had no influence on the stereochemical outcome of the benzylation step. Indeed, when the benzylidene acetal protective group of **10b** was finally removed by catalytic hydrogenation at atmospheric pressure and room temperature, **PFTB-DOPA** was obtained in high yield, with optical rotatory power identical to that of the compound obtained from **10b**. This

confirmed that the two **8b** diastereoisomers generated in the electrophilic addition of **6b** to **7** differ for the configuration of the stereocenter in the 1,3-benzodioxole ring, while the N-substituted carbon stereocenter formed in the reaction has the usual (S)-configuration, wich is maintained during the cleavage of the sultam chiral auxiliary and of the other protecting groups. [26, 27]

2.2 NMR relaxation times measurement

PFTB-DOPA was found to be soluble in water up to 0.5 mg/ml (1 mM), and the intense singlet signal at -74.4 ppm generated by the nine chemically equivalent fluorine atoms of the PFTB tag was readily detected by ^{19}F NMR in aqueous solutions. The potential of **PFTB-DOPA** was further highlighted by T_1 and T_2 relaxation times measurement of fluorine that was performed in 0.4 mM water solution and in rat blood (with heparin), using a 9.4T Bruker Avance spectrometer.
To quantify T_1, an inversion recovery (IR) acquisition sequence with 48 IR times, t_{IR} from 0.1 ms to 10 s were used, number of averaged scans NA=64 (for the water solution sample) and NA=128 (for blood solution sample), repetition time TR=10 s. Data were fitted to the mono-exponential function [28]:

$$S(t_{IR}) = S(0)[1 - 2\exp\left(-\frac{t_{IR}}{T1}\right)] \quad (1)$$

Where S(0) is proportional to the total magnetization, S(IR) is the signal amplitude at the inversion time t_{IR}.
T_2 values were obtained using a Carr-Purcell Meiboom-Gill (CPMG) pulse sequence with 100 echo times TE from 2 to 400 ms, TR=10 s, NA=128. CPMG data were fitted to the bi-exponential function [28]:

$$S(TE) = S_1(0)\exp\left(-\frac{TE}{T_{21}}\right) + S_2(0)exp\left(-\frac{TE}{T_{22}}\right) + c \quad (2)$$

Where S(TE) is the signal amplitude at TE, $S_1(0)$ is proportional to the magnetization associated to the transversal relaxation time T_{21}, $S_2(0)$ is proportional to the magnetization associated to the transversal relaxation time T_{22}, and c is a constant to take into account of the noise floor.
T_1 and T_2 results are reported in Table 1. T_1 in rat blood is shorter than in aqueous solution due to the paramagnetic compounds present in the blood that normally give rise to a considerable

decrease of T_1. Moreover, T_2 measured in rat blood is considerably shorter than in aqueous solution and, differently from water solution, it assumes two principal components, T_{21} and T_{22}. In blood, T_2 decreases either for the paramagnetic effects or for the interaction with macromolecules that, contributing to the slow motion, decrease the T_2 value. The two components of the fluorine transverse relaxation T_{21} and T_{22} (Tab. 1, associated to the 40% and 60% of the total magnetization, respectively) found in blood sample indicate that PFTB-DOPA molecules are in a heterogeneous environments that provide a different restricted molecular motion.

The experimental **PFTB-DOPA** fluorine relaxation times suggest that it can be imaged through ^{19}F MRI, being T2/T1 approximately equal to 0.01 in blood solution.

Table 1. Fluorine relaxation times

	PFTB-DOPA in water	**PFTB-DOPA in blood**
T1	(2700±200) ms	(1290±70) ms
T2	(41±2) ms	(10.6±0.2) ms [a] (17.8±0.2) ms [b]

[a] T_{21}; the associated magnetization is about 40% of the total
[b] T_{22}; the associated magnetization is about 60% of the total

3. Conclusions

Ideal probes for ^{19}F NMR and MRI biological applications should fulfil some basic requirements. Among them are a high content of fluorine atoms that are chemically equivalent so that they produce a single NMR signal, an efficient mobility and limited association of the fluorinated region resulting in suitable relaxation times (i.e. $10^{-3}<T_2/T_1\leq1$, with $T_2>4$ ms) and an adequate solubility in water. We have here suggested a synthetic strategy for the incorporation of these characteristics into the biochemically and pharmacologically relevant L-DOPA platform. The strategy is amenable to further refinements of the original design of the **PFTB-DOPA** molecule, characterized by nine equivalent ^{19}F nuclei and T_2/T_1~0.01 in blood. In particular, the robust sequence leading to the benzylating agents **6** allows for the introduction of PFTB end-capped alkoxy chains of different length and hydrophilic/lipophilic balance, such as oligo ethylene glycols [29], thus providing a viable access to fluorinated L-DOPA probes with tunable NMR and biochemical characteristics. The assessment of the cytotoxicity and genotoxicity profiles, which is crucial for future in vivo applications

The ideal probes should thus possess both high density of chemically equivalent ^{19}F nuclei per molecule, with suitable relaxation times T1 and T2 that allow for a large accumulation of ^{19}F per image voxel, [9] and

selective affinity for either amyloid plaques or dopaminergic agents. In addition, their toxicity profile should be fully compatible with clinical use

Some of the newly-synthesized fluorous compounds were cytotoxic to the tested cell lines, but with the exception of one compound, these effects were observed at concentrations approximately 3–30 times greater than those reported for widely used C_8-perfluorinatedcompounds (new ref. Horvath) New products will be analyzed at a toxicological level to assess their cytotoxic potential on human lymphocytes, hepatic and kidney cells. The investigation of the genotoxic activity associated with any chemical substance is of primary importance for the risk assessment, especially considering that the effects are severe and irreversible. This evaluation is essential for substances with future expected human exposure and especially for potential in vivo diagnostic agents and drugs. The investigation of the toxicological and metabolic profiles of the new probes

4. Experimental Section

General remarks. All available reagents were purchased from commercial sources and were used without any further purification. Solvents were purified by standard methods and dried if necessary. Oppolzer's sultam glycinate **7** was prepared as described in the literature [30]. An improved method for the preparation of the known compound **2a** [31] is here reported. Reactions were monitored by thin layer chromatography (TLC) that was conducted on plates precoated with silica gel Si 60-F254 (Merck, Germany). Column chromatography was carried out on silica gel SI 60 (Merck, Germany), mesh size 0.063 – 0.200 mm (gravimetric) or 0.040 – 0.063 mm (flash). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 400 spectrometer (400 and 100.6 MHz, respectively). Chemical shifts are reported in ppm downfield from $SiMe_4$, with the residual proton ($CHCl_3$: δ=7.26 ppm, DMSO: δ=2.50 ppm, CH_3OD: δ=3.31 ppm,) and carbon ($CDCl_3$: δ=77.0 ppm, DMSO-d_6: δ=39.5 ppm, CD_3OD: δ=49.2 ppm) solvent resonances as internal references.^{19}F NMR spectra were recorded on a Bruker AV 400 spectrometer (377 MHz). Chemical shifts are reported in ppm relative to an external standard ($CFCl_3$, δ=0). T_1 and T_2 relaxation times measurement was performed on a BrukerAvance-400 spectrometer operating at 9.4 T. Melting points were determined with a capillary melting point apparatus Büchi B-540. HPLC was performed on a chiral phase column Crownpak® CR (Diacel Ltd., 250×4 mm, equipped with a precolumn 80×4 mm, aq. HClO4 pH=1.6, flow rate 1.0 mL/min). Elemental analyses were carried out by the Departmental Service of Microanalysis (University of Milan).

*Methyl 7-hydroxy-2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate (**2a**)*

To a suspension of the gallic acid methyl ester **1** (5.20 g, 28.2 mmol) in a mixture of toluene (20 mL) and acetone (13 mL), PCl_3 (1.90 mL, 21.7 mmol) was added and the mixture was left stirring at room temperature overnight. The mixture was then quenched carefully with saturated aqueous $NaHCO_3$ and the phases were separated. The aqueous phase was extracted with AcOEt and the combined organic phases were washed with water and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure giving the title compound as an off-white solid (4.60 g, 73% yield) that was used without any further purification.

Mp 116-117 °C (lit. [31] 114-115 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.6 Hz, 1H), 7.05 (d, *J* = 1.5 Hz, 1H), 3.87 (s, 3H), 1.70 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.33, 148.59, 139.26, 138.71, 123.43, 120.29, 113.74, 103.21, 52.41, 25.97. Anal. calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39; found: C, 59.05; H, 5.42.

*Methyl 7-hydroxy-2-phenylbenzo[d][1,3]dioxole-5-carboxylate (**2b**)*

In a two necked round bottomed flask equipped with a reflux condenser and a stir bar, gallic acid methyl ester **1** (4.99 g, 27.1 mmol) was dissolved in pyridine (15 mL) under inert atmosphere. After the addition of α,α-dichlorotoluene (5.20 mL, 40.5 mmol) the mixture was heated in an oil bath at 110°C and left stirring overnight. After cooling, the mixture was diluted with water and AcOEt. The phases were separated, and the organic phase was washed with 10% HCl and was dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude purified by crystallization from DCM:hexane to obtain the title compound as a white powder (2.52 g, 34% yield).

Mp 134-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 2H), 7.48 – 7.42 (m, 3H), 7.41 (d, *J* = 1.5 Hz, 1H), 7.17 (d, *J* = 1.5 Hz, 1H), 7.04 (s, 1H), 5.98 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.95, 148.92, 138.99, 138.65, 135.33, 130.64, 128.78, 126.45, 124.24, 114.29, 111.83, 103.10, 52.38. Anal. calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44; found: C, 66.01; H, 4.48.

*Methyl 7-(2-hydroxyethoxy)-2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate (**3a**)*

In a two-necked round bottom flask equipped with a reflux condenser and a magnetic stirrer K_2CO_3 (0.85 g, 6.1 mmol) and a solution of **2a** (0.69 g, 3.1 mmol) in DMSO (20 mL) were introduced. After the addition of 2-bromoethanol (0.24 mL, 3.4 mmol) the mixture was heated at 80°C in an oil bath and left stirring overnight. The mixture was cooled to room temperature and water was added. The solution was extracted with AcOEt and the organic phase was washed thoroughly with water and dried over $MgSO_4$. After filtration, the solvent was removed under

reduced pressure and the crude was purified by column chromatography (silica gel, hexane:AcOEt 7:3) affording the title compound as a white solid (0.67 g, 81 % yield).

Mp 89-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.5 Hz, 1H), 7.13 (d, *J* = 1.5 Hz, 1H), 4.21 (dd, *J* = 5.1, 3.9 Hz, 2H), 3.96 (dd, *J* = 5.1, 3.9 Hz, 2H), 3.86 (s, 3H), 1.71 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.49, 148.51, 142.03, 139.79, 123.65, 120.10, 111.08, 104.26, 71.00, 61.31, 52.14, 25.91. Anal. calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01; found: C, 58.11; H, 6.22.

*Methyl 7-(2-hydroxyethoxy)-2-phenylbenzo[d][1,3]dioxole-5-carboxylate (**3b**)*

The title compound was obtained from **2b** according to the procedure described for the preparation of **3a**. The crude was purified by flash column chromatography (silica gel, hexane:AcOEt 1:1). White solid (73% yield)

Mp 102-103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2H), 7.49 – 7.41 (m, 3H), 7.37 (s, 1H), 7.26 (s, 1H), 7.06 (s, 1H), 4.24 (t, *J* = 4.5 Hz, 2H), 3.95 (t, *J* = 4.5 Hz, 2H), 3.89 (s, 3H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.35, 148.99, 141.97, 139.87, 135.30, 130.64, 128.85, 126.15, 124.43, 112.10, 104.49, 71.10, 61.31, 52.15. Anal. calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10; found: C, 64.52; H, 5.16.

*Methyl 7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate (**4a**)*

In a Schlenk tube PPh_3 (1.14 g, 4.4 mmol) was introduced under inert atmosphere and solubilised in dry Et_2O (5 mL), followed by the addition of a solution of **3a** (0.97 g, 3.6 mmol) in dry Et_2O (10 mL). The mixture was cooled to 0°C in an ice-water bath and nonafluoro-*tert*-butyl alcohol (0.52 mL, 3.7 mmol) was added, followed by the dropwise addition of a solution of DIAD (0.86 mL, 4.4 mmol) in dry Et_2O (5 mL). After 5 minutes the cooling bath was removed and the mixture was allowed to return to room temperature and left stirring overnight. The mixture was filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (silica gel, hexane:AcOEt 9:1) to give the title compound as a white solid (1.55 g, 88% yield).

Mp 91-92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 1.5 Hz, 1H), 7.14 (d, *J* = 1.5 Hz, 1H), 4.35 (s, 4H), 3.87 (s, 3H), 1.71 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.43, 148.71, 141.54, 139.92, 123.65, 120.26 (q, J_{CF} = 293 Hz, C(*C*F_3)$_3$), 120.11, 111.79, 104.42, 68.11, 67.79, 52.12, 25.83. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.2. Anal. calcd for $C_{17}H_{15}F_9O_6$: C, 41.99; H, 3.11; found: C, 42.11; H, 3.20.

*Methyl 7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2-phenyl-benzo[d][1,3]dioxole-5-carboxylate (**4b**)*

The title compound was obtained from **3b** according to the procedure described for the preparation of **4a**. The crude was purified by flash column chromatography (silica gel, hexane:AcOEt 95:5). Colorless oil that solidifies on standing (92% yield).

Mp 52-53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.55 (m, 2H), 7.48 – 7.41(m, 3H), 7.36 (d, *J* = 1.4 Hz, 1H), 7.26 (d, *J* = 1.2 Hz, 1H), 7.06 (s, 1H), 4.43 – 4.29 (m, 4H), 3.89 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.25, 149.13, 141.50, 139.94, 135.39, 130.58, 128.74, 126.42, 124.45, 120.25 (q, J_{CF} = 293 Hz, C(CF_3)$_3$), 112.59, 111.75, 104.30, 68.17, 67.95, 52.21. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.3. Anal. calcd for $C_{21}H_{15}F_9O_6$: C, 47.20; H, 2.83; found: C, 47.09; H, 2.91.

*6-(Hydroxymethyl)-4-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2,2-dimethylbenzo[d][1,3]dioxole (**5a**)*

A three-necked round bottom flask equipped with a reflux condenser, a stir bar and a dropping funnel was charged under inert atmosphere with $LiAlH_4$ (0.48 g, 12.6 mmol) and dry THF (30 mL). The suspension was cooled to 0°C in an ice-water bath and a solution of **4a** (6.10 g, 13.3 mmol) in dry THF (30 mL) was added dropwise. The mixture was kept at low temperature for 30 min, then it was allowed to return to room temperature and left stirring overnight. The mixture was then cooled to 0°C and quenched by the careful addition of water. After the filtration over a short plug of silica, the solution was extracted with AcOEt and the organic phase was washed with water and dried over $MgSO_4$. The solution was filtered, the solvent removed under vacuum and the crude was purified by flash column chromatography (silica gel, hexane:AcOEt 7:3) to give the title compound as a white solid (4.90 g, 85% yield).

Mp 62-63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, *J* = 1.4, 1H), 6.49 (d, *J* = 1.5 Hz, 1H), 4.54 (s, 2H), 4.33 (s, 4H), 1.68 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.21, 141.95, 135.25, 134.92, 120.41 (q, J_{CF} = 293 Hz, C(CF_3)$_3$), 118.96, 108.70, 102.18, 68.40, 68.02, 65.50, 25.84. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.3. Anal. calcd for $C_{16}H_{15}F_9O_5$: C, 41.93; H, 3.30; found: C, 41.97; H, 3.22.

*6-(Hydroxymethyl)-4-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2-phenylbenzo[d][1,3]dioxole (**5b**)*

The title compound was obtained from **4b** according to the procedure described for the preparation of **5a**. The crude was purified by column chromatography (silica gel, DCM). Colorless oil (87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.53 (m, 2H), 7.48 – 7.41 (m, 3H), 6.96 (s, 1H), 6.61 (s, 1H), 6.58 (s, 1H), 4.57 (s, 2H), 4.40– 4.35 (m, 2H), 4.35-4.30 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.59 141.89, 135.96, 135.77, 135.34, 130.51, 128.79, 126.60, 120.25 (q, J_{CF} = 293 Hz, C(CF_3)$_3$), 110.99, 109.49, 102.04, 68.44, 68.20, 65.38. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.3. Anal. calcd for $C_{20}H_{15}F_9O_5$: C, 47.44; H, 2.99; found: C, 47.63; H, 3.14.

6-(Chloromethyl)-4-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2,2-dimethylbenzo[d][1,3]dioxole (**6a**)

To a solution of **5a** (0.92 g, 2.0 mmol) in dry toluene (12 mL), pyridine (0.15 mL, 1.9 mmol) was added under inert atmosphere. The solution was cooled to 0°C in an ice-water bath and $SOCl_2$ (0.20 mL, 2.7 mmol) was added. The ice-water bath was removed and the mixture was allowed to return to room temperature and left stirring overnight. The mixture was quenched with water and the phases were separated. The aqueous phase was extracted with AcOEt and the combined organic phase was washed with saturated aqueous $NaHCO_3$, water and then dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude was purified by column chromatography (silica gel, hexane:AcOEt 9:1) to give the title compound as a white solid (0.85 g 89% yield).

Mp 57-59 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, *J* = 1.6 Hz, 1H), 6.51 (d, *J* = 1.6 Hz, 1H), 4.47 (s, 2H), 4.33 (s, 4H), 1.69 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.10, 141.67, 135.85, 131.06, 120.28 (q, J_{CF} = 293 Hz, C(CF_3)$_3$), 119.25, 110.53, 103.57, 68.24, 68.00, 46.70, 25.80. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.3. Anal. calcd for $C_{16}H_{14}ClF_9O_4$: C, 40.31; H, 2.96; found: C, 40.11; H, 2.99.

*6-(Chloromethyl)-4-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2-phenylbenzo[d][1,3]dioxole (**6b**)*

The title compound was obtained from **5b** according to the procedure described for the preparation of **6a**. The crude was purified by column chromatography (silica gel, hexane:AcOEt 95:5). Colorless oil that solidifies on standing (76% yield).

Mp 43-44 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 2H), 7.49 – 7.41 (m, 3H), 6.98 (s, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.60 (d, *J* = 1.6 Hz, 1H), 4.50 (s, 2H), 4.41 – 4.35 (m, 2H), 4.35 – 4.29 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.63, 141.73, 136.08, 135.76, 132.04, 130.60, 128.78, 126.57, 120.29 (q, J_{CF} = 293 Hz, C(CF_3)$_3$), 111.52, 111.32, 103.61, 68.48, 68.31, 46.62. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.3. Anal. calcd for $C_{20}H_{14}ClF_9O_4$: C, 45.78; H, 2.69; found: C, 45.66; H, 2.83.

(2R)-N-[(2S)-2-((Diphenylmethylidene)amino)-3-(7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)-propan-1-

*oyl]bornane-10,2-sultam (**8a**)*

In a two-necked round bottom flask equipped with a dropping funnel and a stir bar, Cs_2CO_3 (1.17 g, 3.6 mmol) was suspended in dry DMF (5 mL) under inert atmosphere. To the suspension cooled to 0°C a solution of **7** (0.78 g, 1.8 mmol) in dry DMF (5 mL) was added dropwise. The reaction mixture was stirred 10 min followed by the dropwise addition of a solution of chloride **6a** (0.95 g, 2.0 mmol) in dry DMF (5 mL). Stirring was continued at low temperature until TLC analysis showed a complete conversion of the starting material. The mixture was then quenched with water and diluted with AcOEt. After phase separation, the aqueous phase was extracted with AcOEt. The combined organic phase was washed thoroughly with water and then dried over MgSO4. After filtration, the solvent was removed under vacuum and the crude was purified with column chromatography (silica gel, DCM:Et_2O 100:1) to afford the title compound (single diastereoisomer) as a white foam (0.79 g, 56% yield).

$[\alpha]_D$ = -77.4 ($CHCl_3$ *c* 0.005 g/mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.30 (m, 8H), 7.17 – 7.02 (m, 2H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.86 (d, *J* = 1.3 Hz, 1H), 4.84 (t, *J* = 7.0 Hz, 1H), 4.30 (t, *J* = 4.1 Hz, 2H), 4.14 – 3.96 (m, 2H), 3.79 (s, 1H), 3.71 – 3.45 (m, 2H), 3.04 (dd, *J* = 12.8, 8.3 Hz, 1H), 2.65 (dd, *J* = 12.8, 5.8 Hz, 1H), 1.90 – 1.64 (m, 3H), 1.64 – 1.47 (m, 8H), 1.39 (t, *J* = 9.3 Hz, 1H), 1.29 – 1.10 (m, 1H), 0.82 (s, 3H), 0.58 (s, 3H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 170.85, 169.31, 147.81, 141.18, 138.91, 135.26, 133.69, 130.45, 129.60, 128.54, 128.22, 128.15, 128.05, 127.64, 119.93 (q, J_{CF} = 294 Hz, C(CF_3)$_3$), 118.13, 109.73, 103.41, 79.13 (m, $C(CF_3)_3$), 69.01, 67.44, 66.66, 64.08, 52.31, 48.09, 46.95, 44.23, 40.62, 37.64, 31.75, 25.82, 25.34, 19.91, 19.41. ^{19}F NMR (377 MHz, DMSO-d_6) δ -70.9. Anal. calcd for $C_{41}H_{41}F_9N_2O_7S$: C, 56.16; H, 4.71; N, 3.19; found: C, 56.27; H, 4.78; N 3.08.

*(2R)-N-[(2S)-2-((Diphenylmethylidene)amino)-3-(7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2-phenylbenzo[d][1,3]dioxol-5-yl)-propan-1-oyl]bornane-10,2-sultam (**8b**)*

In a two necked round bottomed flask equipped with a dropping funnel and a magnetic stirrer Cs_2CO_3 (1.17 g, 3.6 mmol) was suspended in dry DMF (5 mL) under inert atmosphere. To the suspension cooled to 0°C a solution of **7** (0.78 g, 1.8 mmol) in dry DMF (7 mL) was added dropwise. The reaction mixture was stirred 10 min followed by the dropwise addition of a solution of chloride **6b** (1.10 g, 2.1 mmol) in dry DMF (7 mL), then it mixture was allowed to warm up to room temperature and left stirring overnight. The mixture was then filtered, diluted with AcOEt and treated with water. After phase separation, the organic phase was thoroughly washed with water and dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude

material was purified by flash column chromatography (silica gel, hexane:AcOEt 8:2) to afford the title compound (1:1 diastereoisomeric mixture) as a white foam (1.10 g, 66% yield).
$[\alpha]_D$ = -70.0 ($CHCl_3$ *c* 0.004 g/mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.34 (m, 26H), 7.12 – 6.98 (m, 6H), 6.07 (s, 1H), 6.04 (s, 1H), 6.01 (s, 1H), 5.99 (s, 1H), 4.86 (m, 2H), 4.32 (m, 4H), 4.09 (m, 4H), 3.80 (m, 2H), 3.65 (dd, *J* = 14.1, 8.1 Hz, 2H), 3.54 (dd, *J* = 14.2, 5.1 Hz, 2H), 3.09 (m, 2H), 2.79 – 2.61 (m, 2H), 1.92 – 1.11 (m, 10H), 0.82 (s, 3H), 0.80 (s, 3H), 0.60 (s, 3H), 0.54 (s, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -70.9. Anal. calcd for $C_{45}H_{41}F_9N_2O_7S$: C, 58.44; H, 4.47; N, 3.03; found: C, 58.42; H, 4.59; N 3.09.

*(2R)-N-[(2S)-2-Amino-3-(7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)-propan-1-oyl]bornane-10,2-sultam (**9a**)*
To a solution of **8a** (750 mg, 0.85 mmol) in DCM (3 mL) aqueous 1 M HCl (3 mL) was added and the mixture left stirring until TLC analysis showed complete consumption of the substrate. After phase separation the organic layer was washed with saturated aqueous $NaHCO_3$, water and dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude was purified by column chromatography (silica gel, AcOEt:hexane 3:2) to afford the title compound as a white foam (464 mg, 76% yield).
$[\alpha]_D$ = -6.2 ($CHCl_3$ *c* 0.005 g/mL). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 1.4 Hz, 1H), 6.38 (d, *J* = 1.5 Hz, 1H), 4.35-4.25 (m, 5H), 3.87 (s, 1H), 3.45 (s, 2H), 2.98 (dd, *J* = 13.2, 7.3 Hz, 1H), 2.85-2.72 (m, 1H), 2.09 – 1.70 (m, 5H), 1.65 (d, *J* = 1.9 Hz, 6H), 1.45 – 1.22 (m, 2H), 0.92 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.51, 148.83, 141.86, 134.57, 130.12, 120.41 (q, J_{CF} = 293 Hz, C(CF_3)$_3$), 118.96, 110.22, 104.42, 79.78 (m, *C*(CF_3)$_3$), 68.29, 67.66, 65.11, 56.12, 53.16, 48.70, 47.76, 44.88, 41.39, 38.28, 32.94, 26.54, 25.94, 25.90, 20.56, 19.91. ^{19}F NMR (377 MHz, DMSO-d_6) δ -70.9. Anal. calcd for $C_{28}H_{33}F_9N_2O_7S$: C, 47.19; H, 4.67; N, 3.93; found: C, 47.30; H, 4.75; N 3.78.

*(2R)-N-[(2S)-2-Amino)-3-(7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2-phenylbenzo[d][1,3]dioxol-5-yl)-propan-1-oyl]bornane-10,2-sultam (**9b**)*
The title compound (diastereoisomeric mixture) was obtained from **8b** according to the procedure described for the preparation of **9a**. The crude was purified by column chromatography (silica gel, DCM:MeOH 99:1). White foam (71% yield).
$[\alpha]_D$ = -10.0 ($CHCl_3$ *c* 0.003 g/mL). ^{1}H NMR (400 MHz, DMSO) δ 7.76 – 7.58 (m, 10H), 7.26 (m, 2H), 6.65 – 6.55 (m, 4H), 4.55-4.50 (m, 4H), 4.45-4.41 (m, 4H), 4.23 – 4.12 (m, 2H), 3.99-3.87 (m, 4H), 3.85-3.73 (m, 2H), 2.99-2.88 (m, 2H), 2.87-2.77 (m, 2H), 2.09 – 1.66 (m, 10H), 1.62-1.49 (m, 2H), 1.44

– 1.26 (m, 2H), 1.03 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.89 (s, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -70.8. Anal. calcd for $C_{32}H_{33}F_9N_2O_7S$: C, 50.53; H, 4.37; N, 3.68; found: C, 50.58; H, 4.46; N 3.63.

*(S)-2-Amino-3-(7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)propanoic acid (**10a**)*

To a solution of **9a** (467 mg, 0.65 mmol) in THF (3 mL) a 2.57 M aqueous solution of LiOH H_2O (0.7 mL, 1.80 mmol) was added and the mixture stirred at room temperature until TLC analysis showed the complete consumption of the substrate. The solvent was removed by evaporation under vacuum and the residue was taken up in water (1 mL). Aqueous 10% HCl was added until pH =2 (litmus paper). A solid separated out which was filtered on a Büchner funnel and dried under vacuum. The crude was purified by gradient chromatography on a short pad of silica (0% to 50% of MeOH in AcOEt) to afford the title compound as a white solid (270 mg, 80% yield).

$[\alpha]_D$ = - 14.3 (MeOH *c* 0.002 g/mL). ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.49 (d, *J* = 1.5 Hz, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 4.58 – 4.26 (m, 4H), 3.70 (dd, *J* = 8.7, 4.3 Hz, 1H), 3.18 (dd, *J* = 14.5, 4.3 Hz, 1H), 2.89 (dd, *J* = 14.5, 8.7 Hz, 1H), 1.65 (s, 6H). ^{13}C NMR (100.6 MHz, Methanol-d_4) δ 172.35, 149.32, 142.09, 134.76, 129.31, 120.35 (q, J_{CF} = 294 Hz, C(CF_3)$_3$), 118.35, 110.50, 103.31, 79.66 (m, C(CF_3)$_3$), 69.02, 67.94, 56.19, 36.69, 24.44. ^{19}F NMR (377 MHz, Methanol-d_4) δ -72.6. Anal. calcd for $C_{18}H_{18}F_9NO_6$: C, 41.95; H, 3.52; N, 2.72; found: C, 41.79; H, 3.49; N 2.70.

*(2S)-2-Amino-3-(7-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-2-phenylbenzo[d][1,3]dioxol-5-yl)propanoic acid (**10b**)*

The title compound (diastereoisomeric mixture) was obtained from **9b** according to the procedure described for the preparation of **10a**. Major impurities were eliminated by gradient chromatography on a short pad of silica (0% to 20% of MeOH in DCM). Trace impurities were finally eliminated by a second gradient chromatography on a short pad of silica (0% to 50% of MeOH in AcOEt). White solid (90% yield).

$[\alpha]_D$ = - 15.1 (MeOH *c* 0.001 g/mL). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 – 7.51 (m, 2H), 7.44 (m, 3H), 7.00 (s, 1H), 6.57 (s, 2H), 4.38 (s, 4H), 3.72 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.20 (dd, *J* = 14.5, 4.4 Hz, 1H), 2.92 (dd, *J* = 14.6, 8.6, 2.1 Hz, 1H). ^{19}F NMR (377 MHz, Methanol-d_4) δ -72.5. Anal. calcd for $C_{22}H_{18}F_9NO_6$: C, 46.90; H, 3.22; N, 2.49; found: C, 46.80; H, 3.34; N 2.37.

*(S)-2-Amino-3-(3-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)ethoxy)-4,5-dihydroxyphenyl)propanoic acid (**PTFB-DOPA**)*

A solution of **10a** (220 mg, 0.43 mmol) in a 2:1 mixture of THF:10% aqueous HCl (3 mL) was stirred at room temperature until NMR analysis of an aliquot of the reaction mixture showed a complete conversion of the substrate (up to 7 days). The solvent was removed under vacuum, then saturated aqueous $NaHCO_3$ was added dropwise to the recovered crude solid product until the pH of the liquid phase reached 5-6 (litmus paper). The solid material was filtered on a Büchner funnel, washed with a minimal amount of water and dried under vacuum to give the title compound as a beige solid material (70 mg, 34% yield).

Mp (decomp.) > 215 °C. $[\alpha]_D$ = - 14.4 (MeOH, *c* 0.002 g/mL). ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.44 (s, 2H), 4.42 (t, *J* = 4.5 Hz, 2H), 4.26 (t, *J* = 4.6 Hz, 2H), 3.68 (dd, *J* = 8.9, 4.0 Hz, 1H), 3.14 (dd, *J* = 14.6, 3.9 Hz, 1H), 2.81 (dd, *J* = 14.5, 8.7 Hz, 1H). ^{13}C NMR (100.6 MHz, Methanol-d_4) δ 173.83, 148.57, 147.43, 135.38, 127.72, 121.78 (q, J_{CF} = 294 Hz, C(CF_3)$_3$), 111.63, 107.93, 70.24, 69.10, 57.64, 38.00. ^{19}F NMR (377 MHz, Methanol-d_4) δ -72.6. Anal. calcd for $C_{15}H_{14}F_9NO_6$: C, 37.91; H, 2.97; N, 2.95; found: C, 37.84; H, 3.01; N 2.89.

PTFB-DOPA *from* ***10b***

To a solution of **10b** (425 mg, 0.75 mmol) in MeOH (20 mL) 10% Pd/C (43 mg) was added. The reaction mixture was stirred at room temperature under atmospheric pressure of hydrogen until NMR analysis showed complete cleavage of the acetal protection (3 hours). The catalyst was eliminated by filtration of the mixture on a short pad of Celite under inert atmosphere. The colorless liquid phase evaporated to dryness under vacuum to afford the title compound as a white solid that tends to darken in air (330 mg, 92% yield).

Physical data were identical in all respects to those of PTFB-DOPA obtained from **10a**.

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