Synthesis and Radiofluorination of Iodophenyl Esters as Tool for the Traceless Staudinger Ligation

Marc Pretze[a], Anke Flemming[b], Martin Köckerling[b], and Constantin Mamat[a]

[a] Institut für Radiopharmazie am Forschungszentrum Dresden-Rossendorf e.V., Postfach 51, 01 19, 01314 Dresden, Germany
[b] Institut für Chemie der Universität Rostock, Albert-Einstein-Straße 3a, 18059 Rostock, Germany

Reprint requests to Dr. Constantin Mamat. Fax: +49 (0) 351-260 3232. E-mail: c.mamat@fzd.de

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A new synthetic pathway for the preparation of ω-functionalized 2-iodophenyl esters as starting materials for the synthesis of substituted phosphanes is described. A radiolabeling of these esters with fluorine-18 has led to building blocks which were reacted with $HPPh_2$ in a Pd-catalyzed P-C cross coupling to establish new phosphanes. These compounds can be applied as mild and bioorthogonal radiolabeling agents by means of the traceless Staudinger ligation. A route to access this class of compounds has been established.

Key words: Staudinger Ligation, Traceless, Bioorthogonal, Radiofluorination, PET, X-Ray Structure

Introduction

Imaging techniques like PET and SPECT are based on the application and detection of decaying radionuclides which are connected to a biologically active molecule to form the radiotracer. Both techniques have been used extensively for non-invasive diagnosis, staging and therapy control of diseases at the cellular and molecular level [1]. The availability of radiotracers is limited by the speed of synthetic methods. Moreover, the introduction of fluorine-18 ($t_{1/2}$ = 109.8 min) remains a special challenge due to harsh reaction conditions [2]. Normally, peptides, proteins, antibodies or oligonucleotides can not be labeled directly. Therefore, bifunctional labeling agents have been developed for the radiofluorination of these compounds under mild conditions [3].

Several bioconjugation techniques, including acylation, imidation or thioether formation, are known [4]. However, every method has its limitations. True bioorthogonal ligations are rarely applied [5]. One of these methods is the Cu-catalyzed Huisgen cycloaddition, which proved to be a valuable tool for an efficient ^{18}F labeling of peptides [6]. Furthermore, the traceless/non-traceless Staudinger ligation was established as a powerful bioconjugation approach for the labeling of small organic and bioactive molecules under mild conditions and in the absence of cytotoxic copper salts [7, 8]. Phosphane derivatives and azides act as bioorthogonal conjugation partners in this ligation. To obtain such phosphanes, building blocks with good leaving groups for the introduction of radiofluorine or for the insertion of other labels and a coupling position for the azide moiety are essential. Thus, we have developed an easy and convenient synthesis route to fluoro- and tosyl-functionalized 2-iodophenyl esters, that were used as building blocks for the construction of phosphane-containing bifunctional labeling agents for the traceless Staudinger ligation. In this paper we show the preparation and radiofluorination of these ester derivatives and the synthesis of sample phosphanes.

Results and Discussion

2-Iodophenyl esters with good leaving groups (*e. g.* tosylate, mesylate, nosylate) were the initial point of our studies. These leaving groups are important for the introduction of radiofluorine. Moreover, other labels can still be introduced into the target molecule. Direct esterifications of 2-(phosphano)phenol with ω-haloalkyl group-containing acid derivatives were not amenable due to the formation of phosphonium salts with the ω-haloalkyl residue. Therefore, several tosylated and mesylated acetic and propionic acids have been synthesized in one step from the corresponding iodo compounds. Acetate and propionate scaffolds with tosyl or mesyl leaving groups are important key intermediates and are used as building blocks *e. g.*

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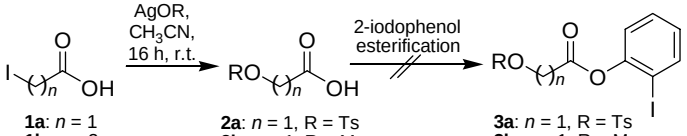


Scheme 1. Synthesis of several tosylated and mesylated acids **2a**–**d**.

Table 1. Crystal structure data for **2c**.

Formula	$C_{10}H_{12}O_5S$
M_r	244.26
Crystal size, mm^3	0.43 × 0.41 × 0.36
Crystal system	triclinic
Space group	$P\bar{1}$
a, Å	7.1056(1)
b, Å	9.4319(2)
c, Å	10.0013(2)
α, deg	114.669(1)
β, deg	97.466(1)
γ, deg	108.346(1)
V, Å^3	550.98(2)
Z	2
D_{calcd}, g cm^{-3}	1.47
μ (MoK_α), cm^{-1}	0.3
F(000), e	256
hkl range	$-10 \le h \le +11$, $-14 \le k \le +13$ $-12 \le l \le +15$
Refl. measured / unique	12449 / 3696
Param. refined	145
$R(F)$ / $wR(F^2)$[a] (all refl.)	0.033 / 0.100
GoF (F^2)[a]	1.03
$\Delta\rho_{fin}$ (max / min), e Å^{-3}	+0.43 / −0.32

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2)+(AP)^2+BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0)+2F_c^2)/3$ and A and B are constants adjusted by the program; GoF = $[\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$, where n_{obs} is the number of data and n_{param} the number of refined parameters.

in medicinal chemistry [9], for the synthesis of biologically active molecules [10], for labeling strategies [11], or in polymer and material sciences [12]. Typically, the preparation of these carboxylic acids and their derivatives involves multistep syntheses with often small yields [13]. These tosylated and mesylated carboxylic acids **2a**–**d** were prepared by the reaction of ω-iodoalkyl carboxylic acids **1a**,**b** with silver tosylate or mesylate in acetonitrile, as shown in Scheme 1. The reaction mixture was stirred at ambient temperature for 8 h in the dark. Afterwards, a simple cleaning step followed, that involved the separation of the silver iodide from the product. After the removal of the solvent, the crude product was washed 3 times with ethyl acetate to yield the sulfonated acid derivatives **2a**–**d** as colorless solids in excellent purity and nearly quantitative yield. Unfortunately, a direct esterification of

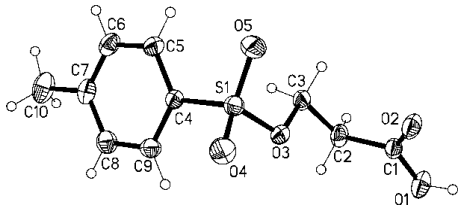


Fig. 1. Molecular structure of **2c** in the crystal (ORTEP, ellipsoids at the 50 % probability level).

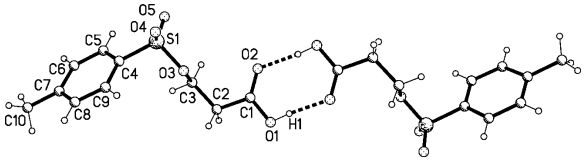
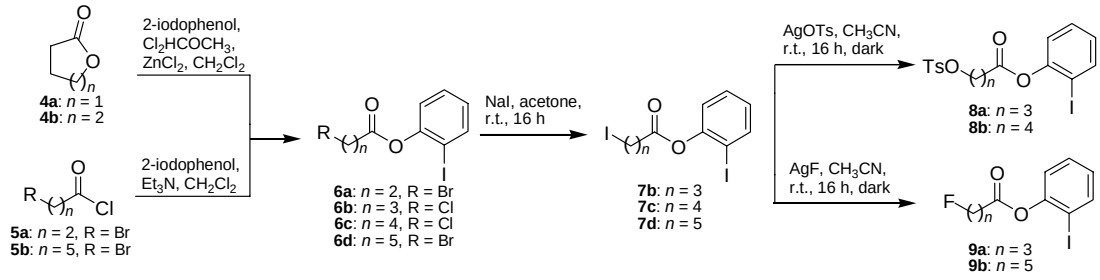


Fig. 2. View of the hydrogen-bonded dimers of **2c** in the solid state.

compounds **2a**–**d** with 2-iodophenol failed. Several attempts were made, and various esterification techniques were applied, but the desired 2-iodophenyl esters **3a**–**d** could not be obtained. Therefore a different reaction path was developed.

In addition, it was possible to obtain single crystals of compound **2c** suitable for an X-ray crystal structure determination from a saturated ethyl acetate solution. Crystallographic data are given in Table 1. A view of the molecular structure of compound **2c** in the crystal is shown in Fig. 1. The compound crystallizes in the triclinic space group $P\bar{1}$ with $Z = 2$. In the solid state hydrogen-bonded dimers are present, which are arranged around a center of inversion with distances of 2.628 Å between the oxygen atoms O1 and O2$^{\#}$ (symmetry operation for the generation of O2$^{\#}$: $2 - x$, y, $1 - z$). These dimers are arranged in the crystalline material such that all the planar tosyl groups are parallel to each other (Fig. 2).

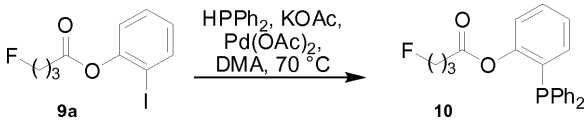
Two different starting materials for the preparation of 2-iodophenylesters were found (Scheme 2). In the first path ω-bromoalkylcarboxylic esters **6a** and **6d** could be obtained in high yields (77 and 99 %) from the reaction of respective acid chlorides **5a**,**b** with 2-iodophenol in the presence of Et_3N as a



Scheme 2. Synthetic route to fluorinated and tosylated iodophenyl esters **8a**, **b** and **9a**, **b**.

base in anhydrous dichloromethane. The crude products were distilled in high vacuum for purification. In the second path, ω-chloroalkylcarboxylic esters **6b** and **6c** were obtained by conversion of lactones **4a**,**b** into the appropriate ω-chloroalkyl acid chlorides with dichloromethyl methyl ether [14] followed by the treatment with 2-iodophenol in dry dichloromethane in a one-pot synthesis procedure as shown in Scheme 2. Purification was done *via* distillation in high vacuum.

Compounds **6b**–**d** were converted into the respective ω-iodoalkyl derivatives **7b**–**d** using NaI in acetone at ambient temperature under Finkelstein conditions overnight. A preparation of the respective propyl derivative **7a** from bromo compound **6a** was not successful due to an elimination reaction yielding 2-iodophenyl acrylate [15]. To introduce fluorine-18, good leaving groups are required in the precursor. The syntheses of the appropriate tosylate-containing compounds **8a**,**b** were accomplished by the reaction of ω-iodoalkyl esters **7b**,**c** with silver tosylate in acetonitrile at ambient temperature for 16 h in the dark with excellent yields (94 % for **8a** and 95 % for **8b**). In the same manner, the respective ω-fluoroalkyl compounds **9a**,**b** as non-radioactive analogs were prepared using silver fluoride under the reaction conditions used for the tosylate compounds with yields of 89 % (**9a**) and 90 % (**9b**). Finally, the fluorinated iodophenyl ester **9a** was reacted with $HPPh_2$ in a Pd-catalyzed P-C coupling to the desired phosphane **10** which can be used in traceless Staudinger ligation reactions as a (radio)labeling agent for azide-functionalized small organic and bioactive molecules. The cross-coupling of diphenylphosphane with the fluoro compound **9a** yielded phosphane **10** in 51 % yield as a colorless syrup (Scheme 3). ^{31}P NMR investigations of compound **10** showed a signal at $\delta = -15.0$ ppm indicative of an aromatic organophosphane in the oxidation state +3. Additionally, a signal at $\delta = -220.2$ ppm in the ^{19}F NMR was found for **10**, which is comparable with the signal found for compound **9a** ($\delta = -220.7$ ppm).



Scheme 3. Pd-catalyzed P-C coupling to phosphane **10**.

*Radiofluorination of iodophenyl ester **8a***

The tosylated butyric ester **8a** represents an ideal sample for radiolabeling purposes. Optimal labeling conditions with [^{18}F]fluoride were achieved by the variation of the solvent, the temperature and the base. Results are shown in Table 2. The temperature and the reaction time seem to have only little influence on the radiochemical yield (RCY). No radiofluorination product was obtained using DMF or DMSO as solvents. Only low-yield conversion to **[^{18}F]9a** was observed when acetonitrile was used as solvent (entries 1 and 2). The use of *n*-Bu_4NOH instead of K_2CO_3 as base is important. Best results were obtained using a mixture of acetonitrile and *t*-BuOH (v : v = 1 : 4) at 100 °C and a reaction time of 10 min [16]. The radio-TLC (Fig. 3) showed 58 % conversion into the desired 2-iodophenyl ester **[^{18}F]9a** (see entry 6 in Table 2 and Scheme 4).

Entry	Solvent	Base	T (°C)	t (min)	$m_{precursor}$ (mg)	RCY (%)[a]
1	CH_3CN	K_2CO_3	80	10	7	1
2	CH_3CN	K_2CO_3	90	30	15	5
3	*t*-BuOH:CH_3CN (9:1)	*n*-Bu_4NOH	100	10	20	19
4	*t*-BuOH:CH_3CN (4:1)	*n*-Bu_4NOH	100	20	20	36
5	*t*-BuOH:CH_3CN (7:3)	*n*-Bu_4NOH	100	10	20	18
6	*t*-BuOH:CH_3CN (4:1)	*n*-Bu_4NOH	100	10	17.5	58

Table 2. Conditions and radiochemical yield (RCY) for the preparation of **[^{18}F]9a**.

[a] Conversion determined *via* radio-TLC.

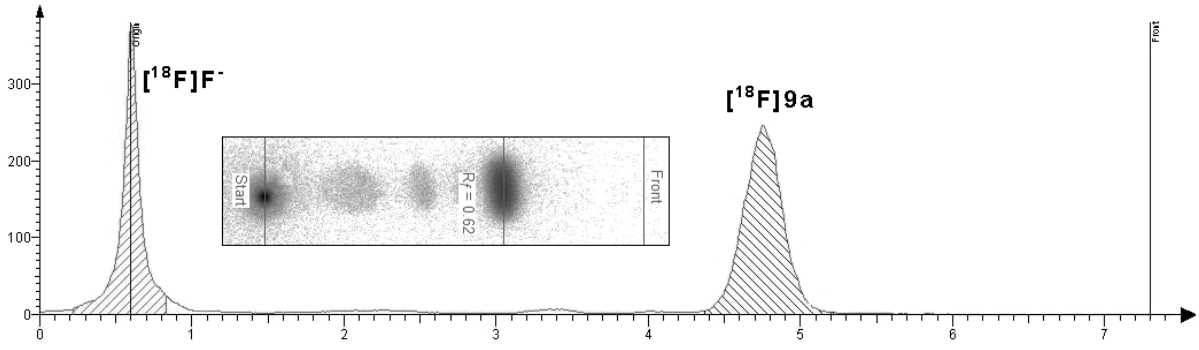
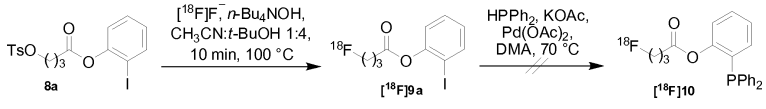


Fig. 3. Radio-TLC chromatogram of compound **[^{18}F]9a** (entry 6).



Scheme 4. Radiolabeling strategy for the preparation of **[^{18}F]10**.

Finally, it was tried to convert the radiolabeled analog **[^{18}F]9a** with $HPPh_2$ in a Pd-catalyzed P-C cross-coupling reaction. In contrast to compound **9a**, the reaction of $HPPh_2$ with the radiolabeled **[^{18}F]9a** failed (Scheme 4). Unfortunately, no fluorine-18-labeled phosphane **[^{18}F]10** was found.

Conclusion

In this paper we demonstrated an easy and convenient route to 2-iodophenyl carboxylic esters ω-functionalized with good leaving groups, which were successfully labeled with fluorine-18. The respective non-radioactive analog was obtained in high yields. Furthermore, the fluorinated iodophenyl esters were applied as starting materials for the preparation of fluoro-containing phosphanes in a Pd-catalyzed P-C cross-coupling reaction. An approach to the respective radiolabeled phosphane with fluorine-18 was not yet successful.

Experimental Section

Reagents and techniques

NMR spectra were recorded on a Varian Inova-400 spectrometer; chemical shifts of the ^{1}H, ^{13}C, ^{19}F, and ^{31}P spectra are reported in parts per million (ppm) using the solvent shifts for ^{1}H and ^{13}C, $CFCl_3$ for ^{19}F, and H_3PO_4 for ^{31}P spectra as internal standard. Mass spectra (MS) were obtained on a Quattro/LC mass spectrometer (MICROMASS) by electron spray ionization or on a Bruker autoflex II TOF/TOF mass spectrometer (Matrix: DHB, reflector mode). The melting points were determined on a Galen III (Cambridge Instruments) apparatus (Leica, Vienna, Austria) and are uncorrected. Microanalyses were carried out with a Hekatech CHNS elemental analyzer EuroEA 3000. Dry solvents (*N,N*-dimethyl acetamide, acetonitrile, CH_2Cl_2) were purchased from Fluka (anhydrous, over molecular sieves, 99.7 %). Other chemicals were purchased from Sigma-Aldrich, Fluka or Acros and were used as received. Chromatographic separations and TLC detections were carried out with Merck silica gel 60 (63 – 200 μm) and Merck silica gel 60 F254 sheets, respectively. TLCs were developed by visualization under UV light (λ = 254 nm). All reactions concerning the Pd-catalyzed coupling of $HPPh_2$ and the borane-phosphane adduct formation were carried out under an argon atmosphere using Schlenk techniques.

The radioactive compound was identified with analytical radio-TLC by comparison of the retention factor of the reference compound. Decay-corrected radiochemical yields (RCYs) were quantified by integration of radioactive peaks on a radio-TLC, which was developed in a solution of petroleum ether and EtOAc (v : v = 8 : 1), using a radio-TLC scanner (Fuji, BAS2000). [^{18}F]Fluoride was produced utilizing the PET cyclotron Cyclone 18/9 (IBA, Belgium). [^{18}O]H_2O was irradiated with protons (18 MeV, 30 μA) exploiting the ^{18}O(*p,n*)^{18}F nuclear reaction.

Crystal structure determination of ***2c***

Diffraction data were collected with a Bruker-Nonius Apex-X8 CCD-diffractometer using graphite-monochromatized MoK_α radiation (λ = 0.71073 Å), and the diffraction measurement was done at −100 °C. The unit cell dimensions were recorded and refined by using the angular settings of 8783 reflections, and the structure was solved by Direct Methods using SHELXS-97 and refined against F^2 on all data

by full-matrix least-squares with SHELXL-97 [17]. All non-hydrogen atoms were refined anisotropically; all hydrogen atoms bonded to C atoms were placed on geometrically calculated positions and refined using a riding model. Table 1 summarizes the crystallographic data.

CCDC 748404 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

*General synthesis procedure for compounds **2a – d***

1 eq. of ω-iodocarboxylic acid **1a**, **b** was dissolved in dry acetonitrile, and 1.38 eq. of the respective silver salt was added. The reaction mixture was stirred at r. t. overnight in the dark. Afterwards, the solution was filtered, the solvent was removed *in vacuo*, and the residue was washed three times with ethyl acetate. Finally, the ethyl acetate was removed *in vacuo*, and the final product was obtained without further purification.

*(Tosyloxy)acetic acid (**2a**)*

Iodoacetic acid (1.0 g, 5.38 mmol) and silver tosylate (2.07 g, 7.42 mmol) in acetonitrile (20 mL) were reacted according to the general procedure. Yield 1.23 g (99 %) of **2a**. M. p. 134 °C. – ^{1}H NMR (400 MHz, CD_3CN): δ = 2.45 (s, 3 H, CH_3), 4.57 (s, 2 H, CH_2), 7.44 (d, ^3J = 8.0 Hz, 2 H, H_{meta}), 7.80 (d, ^3J = 8.0 Hz, 2 H, H_{ortho}). – ^{13}C NMR (101 MHz, CD_3CN): δ = 21.7 (CH_3), 65.8 (CH_2), 128.9 (C_{ortho}), 131.1 (C_{meta}), 146.8 (C_{para}), 178.8 (C=O). – MS ((+)-ESI): *m/z* (%) = 253 (48) $[M+Na]^+$. – $C_9H_{10}O_5S$ (230.24): calcd. C 46.95, H 4.38, S 13.93; found C 46.88, H 4.40, S 14.13.

*(Methanesulfonyloxy)acetic acid (**2b**)*

Iodoacetic acid (1.0 g, 5.38 mmol) and silver methanesulfonate (1.51 g, 7.42 mmol) in acetonitrile (25 mL) were reacted according to the general procedure. Yield: 807 mg (97 %) of **2b**. M. p. 113 °C. – ^{1}H NMR (400 MHz, CD_3CN): δ = 3.12 (s, 3 H, CH_3), 4.73 (s, 2 H, CH_2), 7.44 (br. s, 1 H, OH). – ^{13}C NMR (101 MHz, CD_3CN): δ = 38.5 (CH_3), 65.8 (CH_2), 168.3 (C=O). – MS ((+)-ESI): *m/z* (%) = 177 (32) $[M+Na]^+$. – $C_3H_6O_5S$ (154.14): calcd. C 23.38, H 3.92, S 20.80; found C 23.00, H 3.84, S 21.00.

*3-(Tosyloxy)propionic acid (**2c**)*

3-Iodopropionic acid (1.0 g, 5.0 mmol) and silver tosylate (1.93 g, 6.9 mmol) in acetonitrile (25 mL) were reacted according to the general procedure. Yield: 1.2 g (95 %) of **2c**. M. p. 105 °C. – ^{1}H NMR (400 MHz, CD_3CN): δ = 2.45 (s, 3 H, CH_3), 2.62 (t, ^3J = 6.1 Hz, 2 H, CH_2CH_2CO), 4.19 (t, ^3J = 6.1 Hz, 2 H, CH_2CH_2CO), 7.44 (d, ^3J = 8.0 Hz, 2 H, H_{meta}), 7.78 (d, ^3J = 8.0 Hz, 2 H, H_{ortho}). – ^{13}C NMR (101 MHz, CD_3CN): δ = 21.6 (CH_3), 34.0 (CH_2CH_2CO), 67.2 (CH_2CH_2CO), 128.8 (C_{ortho}), 131.0 (C_{meta}), 133.5 (C_{ipso}), 146.5 (C_{para}), 178.6 (C=O). – MS ((+)-ESI): *m/z* (%) = 267 (97) $[M+Na]^+$, 245 (10) $[M+H]^+$. – $C_{10}H_{12}O_5S$ (244.26): calcd. C 49.17, H 4.95, S 13.13; found C 49.17, H 4.92, S 13.13.

*3-(Methanesulfonyloxy)propionic acid (**2d**)*

3-Iodopropionic acid (1.5 g, 7.5 mmol) and silver methanesulfonate (2.1 g, 10.35 mmol) in acetonitrile (25 mL) were reacted according to the general procedure. Yield: 1.2 g (95 %) of **2d**. M. p. 63 °C. – ^{1}H NMR (400 MHz, CD_3CN): δ = 2.73 (t, ^3J = 5.8 Hz, 2 H, CH_2CH_2CO), 3.03 (s, 3 H, CH_3), 4.38 (t, ^3J = 5.8 Hz, 2 H, CH_2CH_2CO), 7.41 (br. s, 1 H, OH). – ^{13}C NMR (101 MHz, CD_3CN): δ = 34.2 (CH_2CH_2CO), 37.3 (CH_3), 67.1 (CH_2CH_2CO), 171.9 (C=O). – MS ((+)-ESI): *m/z* (%) = 191 (81) $[M+Na]^+$. – $C_4H_8O_5S$ (168.17): calcd. C 28.57, H 4.79, S 19.07; found C 28.05, H 4.72, S 19.34.

*2-Iodophenyl 3-bromopropanoate (**6a**)*

2-Iodophenol (300 mg, 1.36 mmol) was dissolved in dry dichloromethane (5 mL), and 3-bromopropanoyl chloride **5a** (0.2 mL, 1.50 mmol) was added dropwise at 0 °C. The mixture was stirred at r. t. for 2 h, the solvent was removed, and the residue was purified *via* bulb tube distillation to yield **6a** as a pale-yellow liquid (548 mg, 82 %). B. p. 130 °C/5 × 10^{-3} mbar. R_f = 0.76 (petroleum ether/EtOAc 8:1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 2.61 (t, ^3J = 7.0 Hz, 2H, H-α), 3.11 (t, ^3J = 7.0 Hz, 2H, H-β), 6.39 (dt, $^3J_{3,4}$ = 7.8 Hz, $^3J_{4,5}$ = 7.0 Hz, $^4J_{4,6}$ = 1.6 Hz, 1H, H-4), 6.81 (dt, $^3J_{5,6}$ = 7.8 Hz, $^3J_{4,5}$ = 7.0 Hz, $^4J_{3,5}$ = 1.6 Hz, 1H, H-5), 6.88 (dd, $^3J_{5,6}$ = 7.8 Hz, $^4J_{4,6}$ = 1.6 Hz, 1H, H-6), 7.46 (dd, $^3J_{3,4}$ = 7.8 Hz, $^4J_{3,5}$ = 1.6 Hz, 1H, H-3). – ^{13}C NMR (100 MHz, C_6D_6): δ = 25.6 (C-β), 37.9 (C-α), 90.7 (C-2), 123.4 (C-6), 127.7 (C-4), 129.5 (C-5), 139.6 (C-3), 151.5 (C-1), 167.8 (C=O). – MS ((+)-ESI): *m/z* (%) = 377 (100) $[M+Na, {}^{79}Br]^+$, 379 (99) $[M+Na, {}^{81}Br]^+$. – $C_9H_8BrIO_2$ (354.97): calcd. C 30.45, H 2.27; found C 30.36, H 2.15.

*2-Iodophenyl 4-chlorobutanoate (**6b**)*

Zinc chloride (47 mg, 0.35 mmol) was added to a solution of γ-butyrolactone **4a** (0.3 mL, 3.48 mmol) in dichloromethyl methyl ether (0.5 mL, 4.53 mmol), and the resulting mixture was stirred at 60 °C for 2 h. Then a solution of 2-iodophenol (766 mg, 3.48 mmol) and Et_3N (1 mL, 6.97 mmol) in dichloromethane (5 mL) was added dropwise at 0 °C, and the mixture was stirred at r. t. overnight. The mixture was washed with 3 × 15 mL of a 1 M KOH solution, and the organic layer was dried over Na_2SO_4. After the removal of the sol-

vent the residue was purified *via* bulb tube distillation to yield **6b** as pale-yellow liquid (405 mg, 36 %). B. p. 120 °C/5 × 10^{-3} mbar. R_f = 0.69 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.75 – 1.82 (m, 2 H, H-β), 2.41 (t, ^3J = 7.2 Hz, 2 H, H-α), 3.14 (t, ^3J = 6.3 Hz, 2 H, H-γ), 6.38 – 6.42 (m, 1 H, 4-H), 6.82 – 6.83 (m, 2 H, 5-H, 6-H), 7.49 (d, $^3J_{3,4}$ = 7.8 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, C_6D_6): δ = 27.7 (C-β), 31.3 (C-α), 43.8 (C-γ), 90.9 (C-2), 123.3 (C-6), 127.6 (C-4), 129.4 (C-5), 139.6 (C-3), 151.7 (C-1), 169.8 (C=O). – MS ((+)-ESI): *m/z* (%) = 347 (75) $[M+Na]^+$. – $C_{10}H_{10}ClIO_2$ (324.54): calcd. C 37.01, H 3.11; found C 36.72, H 3.32.

*2-Iodophenyl 5-chloropentanoate (**6c**)*

Zinc chloride (70 mg, 0.51 mmol) was added to a solution of δ-valerolactone **4b** (0.5 mL, 5.11 mmol) in dichloromethyl methyl ether (0.6 mL, 6.39 mmol), and the resulting mixture was stirred at 60 °C for 2 h. Then a solution of 2-iodophenol (750 mg, 3.41 mmol) and Et_3N (1 mL, 6.82 mmol) in dichloromethane (5 mL) was added dropwise at 0 °C, and the mixture was stirred at r. t. overnight. The mixture was washed with 3 × 15 mL of a 1 M KOH solution, and the organic layer was dried over Na_2SO_4. After the removal of the solvent the residue was purified *via* bulb tube distillation to yield **6c** as a pale-yellow liquid (1.10 g, 96 %). B. p. 120 °C/5 × 10^{-3} mbar. R_f = 0.72 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.39 – 1.47 (m, 2 H, H-β), 1.55 – 1.62 (m, 2 H, H-γ), 2.20 (t, ^3J = 7.8 Hz, 2 H, H-α), 3.03 (t, ^3J = 6.3 Hz, 2 H, H-δ), 6.40 (dt, $^3J_{3,4}$ = 7.8 Hz, $^4J_{4,6}$ = 2.3 Hz, 1 H, 4-H), 6.82 – 6.88 (m, 2 H, 5-H, 6-H), 7.50 (d, $^3J_{3,4}$ = 7.8 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, C_6D_6): δ = 22.3 (C-β), 31.9 (C-α), 33.5 (C-γ), 44.3 (C-δ), 91.0 (C-2), 123.4 (C-6), 127.5 (C-4), 129.4 (C-5), 139.6 (C-3), 151.8 (C-1), 170.2 (C=O). – MS ((+)-ESI): *m/z* (%) = 361 (100) $[M+Na]^+$. – $C_{11}H_{12}ClIO_2$ (338.57): calcd. C 39.02, H 3.57; found C 39.50, H 3.78.

*2-Iodophenyl 6-bromohexanoate (**6d**)*

6-Bromohexanoyl chloride **5b** (0.8 mL, 3.75 mmol) was added dropwise to a solution of 2-iodophenol (0.75 mg, 3.41 mmol) and Et_3N (1 mL, 6.82 mmol) in dry dichloromethane (5 mL) and stirred at r. t. overnight. The mixture was washed with 3 × 15 mL of a 1 M KOH solution, and the organic layer was dried over Na_2SO_4. After the removal of the solvent the residue was purified *via* column chromatography (petroleum ether/ EtOAc 20 : 1) or *via* bulb tube distillation to yield **6d** as a pale-yellow liquid (1.05 g, 77 %). B. p. 150 °C/1 × 10^{-3} mbar. R_f = 0.82 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.14 – 1.20 (m, 2 H, H-γ), 1.31 – 1.38 (m, 2 H, H-β), 1.41 – 1.49 (m, 2 H, H-δ), 2.26 (t, ^3J = 7.4 Hz, 2 H, H-α), 3.04 (t, ^3J = 6.6 Hz, 2 H, H-ε), 6.42 (t, $^3J_{3,4}$ = 8.6 Hz, $^3J_{4,5}$ = 7.0 Hz, 1 H, 4-H), 6.85 (t, $^3J_{5,6}$ = 7.8 Hz, $^3J_{4,5}$ = 7.0 Hz, 1 H, 5-H), 6.91 (d, $^3J_{5,6}$ = 7.8 Hz, 1 H, 6-H), 7.51 (d, $^3J_{3,4}$ = 8.6 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, C_6D_6): δ = 24.2 (C-β), 26.5 (C-γ), 32.4 (C-δ), 34.1 (C-ε), 34.2 (C-α), 95.1 (C-2), 123.4 (C-6), 127.5 (C-4), 129.4 (C-5), 139.6 (C-3), 151.9 (C-1), 170.5 (C=O). – MS ((+)-ESI): *m/z* (%) = 419 (10) $[M+Na, {}^{79}Br]^+$, 421 (10) $[M+Na, {}^{81}Br]^+$. – $C_{12}H_{14}BrIO_2$ (397.05): calcd. C 36.30, H 3.55; found C 36.74, H 3.58.

*2-Iodophenyl 4-iodobutanoate (**7b**)*

NaI (1.74 g, 11.59 mmol) was added to a solution of **6b** (0.94 g, 2.89 mmol) in acetone (10 mL), and the mixture was stirred at 50 °C overnight. After the removal of the solvent the residue was purified *via* bulb tube distillation to yield **7b** as a pale-yellow liquid (1.08 g, 90 %). B. p. 160 °C/3 × 10^{-3} mbar. R_f = 0.67 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.77 – 1.84 (m, 2 H, H-β), 2.32 (t, ^3J = 7.0 Hz, 2 H, H-α), 2.74 (t, ^3J = 6.8 Hz, 2 H, H-γ), 6.38 – 6.39 (m, 1 H, H-4), 6.80 – 6.83 (m, 2 H, 5-H, 6-H), 7.48 (d, $^3J_{3,4}$ = 7.0 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, C_6D_6): δ = 5.1 (C-γ), 28.5 (C-β), 34.9 (C-α), 91.0 (C-2), 123.3 (C-6), 127.6 (C-4), 129.4 (C-5), 139.6 (C-3), 150.2 (C-1), 169.9 (C=O). – MS ((+)-ESI): *m/z* (%) = 439 (20) $[M+Na]^+$. – $C_{10}H_{10}I_2O_2$ (415.99): calcd. C 28.87, H 2.42; found C 29.13, H 2.57.

*2-Iodophenyl 5-iodopentanoate (**7c**)*

NaI (1.91 g, 12.75 mmol) was added to a solution of **6c** (1.08 g, 3.19 mmol) in acetone (10 mL), and the mixture was stirred at 50 °C overnight. After the removal of the solvent the residue was purified *via* bulb tube distillation to yield **7c** as a yellow liquid (1.21 g, 88 %). B. p. 140 °C/3 × 10^{-3} mbar. R_f = 0.72 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.43 – 1.52 (m, 4 H, H-β, γ), 2.17 (t, ^3J = 7.0 Hz, 2 H, H-α), 2.62 (t, ^3J = 6.6 Hz, 2 H, H-δ), 6.41 (dt, ^3J = 6.3 Hz, ^4J = 2.34 Hz, 1 H, 4-H), 6.82 – 6.88 (m, 2 H, 5-H, 6-H), 7.50 (d, $^3J_{3,4}$ = 7.8 Hz, 1 H, H-3). – ^{13}C NMR (101 MHz, C_6D_6): δ = 5.4 (C-δ), 25.8 (C-β), 32.8 (C-γ), 33.2 (C-α), 91.0 (C-2), 123.4 (C-6), 127.6 (C-4), 129.4 (C-5), 139.6 (C-3), 151.8 (C-1), 170.2 (C=O). – MS ((+)-ESI): *m/z* (%) = 453 (100) $[M+Na]^+$. – $C_{11}H_{12}I_2O_2$ (430.02): calcd. C 30.72, H 2.81; found C 31.34, H 2.92.

*2-Iodophenyl 6-iodohexanoate (**7d**)*

NaI (1.13 g, 7.56 mmol) was added to a solution of **6d** (1.00 g, 2.52 mmol) in acetone (5 mL), and the mixture was stirred at 50 °C overnight. After the removal of the solvent the residue was purified *via* bulb tube distillation to yield **7d** as a yellow liquid (0.82 g, 74 %). B. p. 120 °C/3 × 10^{-3} mbar. R_f = 0.82 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.07 – 1.13 (m, 2 H, H-γ),

1.33 – 1.38 (m, 2 H, H-β), 1.41 – 1.48 (m, 2 H, H-δ), 2.24 (t, ^3J = 7.5 Hz, 2 H, H-α), 2.64 (t,^3J = 7.0 Hz, 2 H, H-ε), 6.41 (dt, $^3J_{3,4}$ = 7.5 Hz, $^4J_{4,6}$ = 1.6 Hz, 1 H, 4-H), 6.85 (t, $^3J_{4,5}$ = 7.8 Hz, 1 H, 5-H), 6.92 (d, $^3J_{5,6}$ = 7.8 Hz, 1 H, 6-H), 7.50 (d, $^3J_{3,4}$ = 7.8 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, C_6D_6): δ = 6.0 (C-ε), 23.6 (C-β), 29.8 (C-γ), 33.1 (C-δ), 33.9 (C-α), 90.9 (C-2), 123.2 (C-6), 127.3 (C-4), 129.2 (C-5), 139.4 (C-3), 151.7 (C-1), 170.2 (C=O). – MS ((+)-ESI): *m/z* (%) = 467 (10) $[M+Na]^+$. – $C_{12}H_{14}I_2O_2$ (444.05): calcd. C 32.46, H 3.18; found C 35.88, H 3.63.

*2-Iodophenyl 4-(tosyloxy)butanoate (**8a**)*

AgOTs (1.02 g, 3.64 mmol) was added to a solution of **7b** (1.08 g, 2.60 mmol) in dry acetonitrile (2 mL) under an argon atmosphere, and the mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified *via* column chromatography (petroleum ether/EtOAc 40 : 1 → 10 : 1 → 1 : 1) to yield **8a** as a pale-yellow liquid (1.13 g, 94 %). R_f = 0.20 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.61 – 1.68 (m, 2 H, H-β), 1.81 (s, 3H, CH_3), 2.29 (t, ^3J = 7.0 Hz, 2 H, H-α), 3.86 (t, ^3J = 6.3 Hz, 2 H, H-γ), 6.38 (dt, $^3J_{3,4}$ = 7.8 Hz, $^4J_{4,6}$ = 1.6 Hz, 1 H, 4-H), 6.67 (d, ^3J = 7.8 Hz, 2H, H_{meta}), 6.80 – 6.88 (m, 2 H, 5-H, 6-H), 7.47 (d, $^3J_{3,4}$ = 7.8 Hz, 1H, 3-H), 7.74 (d, ^3J = 8.6 Hz, 2H, H_{ortho}). – ^{13}C NMR (101 MHz, C_6D_6): δ = 21.1 (CH_3), 24.3 (C-β), 30.2 (C-α), 68.9 (C-γ), 90.9 (C-2), 123.3 (C-6), 127.6 (C-4), 128.2 (C_{ortho}), 129.4 (C-5), 129.9 (C_{meta}), 134.3 (C_{ipso}), 139.5 (C-3), 144.3 (C_{para}), 151.8 (C-1), 169.8 (C=O). – MS ((+)-ESI): *m/z* (%) = 289 (20) $[M–TsO]^+$, 483 (100) $[M+Na]^+$. – $C_{17}H_{17}IO_5S$ (460.28): calcd. C 44.36, H 3.72; found C 44.19, H 3.79.

*2-Iodophenyl 5-(tosyloxy)pentanoate (**8b**)*

AgOTs (1.06 g, 3.79 mmol) was added to a solution of **7c** (1.17 g, 2.71 mmol) in dry acetonitrile (10 mL) under an argon atmosphere, and the mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified *via* column chromatography (petroleum ether/EtOAc 20 : 1 → 8 : 1) to yield **8b** as a pale-yellow liquid (1.22 g, 95 %). R_f = 0.26 (petroleum ether/EtOAc 8:1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.31 – 1.36 (m, 2 H, H-β), 1.42 – 1.49 (m, 2 H, H-γ), 1.82 (s, 3 H, CH_3), 2.14 (t, ^3J = 7.4 Hz, 2 H, H-α), 3.77 (t, ^3J = 6.0 Hz, 2 H, H-δ), 6.38 (dt, $^3J_{3,4}$ = 7.8 Hz, $^4J_{4,6}$ = 2.3 Hz, 1 H, 4-H), 6.69 (d, ^3J = 7.8 Hz, 2 H, H_{meta}), 6.83 – 6.85 (m, 2 H, 5-H, 6-H), 7.49 (d, $^3J_{3,4}$ = 8.6 Hz, 1 H, 3-H), 7.76 (d, ^3J = 8.6 Hz, 2 H, H_{ortho}). – ^{13}C NMR (101 MHz, C_6D_6): δ = 20.9 (C-β), 21.2 (CH_3), 28.3 (C-γ), 33.5 (C-α), 69.6 (C-δ), 91.0 (C-2), 123.4 (C-6), 127.5 (C-4), 128.2 (C_{ortho}), 129.4 (C-5), 129.9 (C_{meta}), 134.5 (C_{ipso}), 139.6 (C-3), 144.2 (C_{para}), 151.8 (C-1), 170.1 (C=O). – MS ((+)-ESI): *m/z* (%) = 303 (50) $[M–TsO]^+$, 497 (100) $[M+Na]^+$. – $C_{18}H_{19}IO_5S$ (474.31): calcd. C 45.58, H 4.04; found C 45.56, H 4.01.

*2-Iodophenyl 4-fluorobutanoate (**9a**)*

AgF (112 mg, 0.88 mmol) was added to a solution of **7b** (91 mg, 0.22 mmol) in dry acetonitrile (2 mL) under an argon atmosphere, and the mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified *via* bulb tube distillation to yield **9a** as a pale-yellow liquid (60 mg, 89 %). B. p. 100 °C C/5 × 10^{-3} mbar. R_f = 0.63 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.69 – 1.78 (m, 2 H, H-β), 2.29 (t, ^3J = 7.3 Hz, 2 H, H-α), 4.08 (dt, $^3J_{H,F}$ = 46.9 Hz, ^3J = 5.7 Hz, 2 H, H-γ), 6.40 (dt, $^3J_{3,4}$ = 7.5 Hz, $^4J_{4,6}$ = 2.3 Hz, 1 H, 4-H), 6.82 – 6.84 (m, 2H, 5-H, 6-H), 7.49 (d, $^3J_{3,4}$ = 7.8 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, C_6D_6): δ = 30.1 (d, $^2J_{C,F}$ = 19.6 Hz, C-β), 34.2 (d, $^3J_{C,F}$ = 4.7 Hz, C-α), 82.3 (d, $^1J_{C,F}$ = 165.3 Hz, C-γ), 93.6 (C-2), 123.4 (C-6), 126.7 (C-4), 130.0 (C-5), 139.6 (C-3), 152.2 (C-1), 170.9 (C=O). – ^{19}F NMR (376 MHz, C_6D_6): δ = −220.7. – MS ((+)-ESI): *m/z* (%) = 332 (10) $[M+Na+H]^+$. – $C_{10}H_{10}FIO_2$ (308.09): calcd. C 38.98, H 3.27; found C 38.66, H 3.09.

*2-Iodophenyl 6-fluorohexanoate (**9b**)*

AgF (205 mg, 1.62 mmol) was added to a solution of **7b** (362 mg, 0.81 mmol) in dry acetonitrile (2 mL) under an argon atmosphere, and the mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified *via* bulb tube distillation to yield **9b** as a colorless liquid (137 mg, 90 %). B. p. 95 °C/5 × 10^{-3} mbar. R_f = 0.52 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.17 – 1.22 (m, 2 H, H-γ), 1.31 – 1.36 (m, 2 H, H-β), 1.49 – 1.55 (m, 2 H, H-δ), 2.29 (t, ^3J = 7.6 Hz, 2 H, H-α), 4.04 (dt,$^3J_{H,F}$ = 47.7 Hz, ^3J = 5.9 Hz, 2 H, H-ε), 6.41 (dt, $^3J_{3,4}$ = 7.5 Hz, $^4J_{4,6}$ = 1.6 Hz, 1 H, 4-H), 6.83 – 6.92 (m, 2 H, 5-H, 6-H), 7.51 (d, $^3J_{3,4}$ = 7.1 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, C_6D_6): δ = 24.5 (C-β), 25.0 (d, $^3J_{C,F}$ = 5.2 Hz, C-γ), 30.3 (d, $^2J_{C,F}$ = 19.6 Hz, C-δ), 34.2 (C-α), 83.4 (d, $^1J_{C,F}$ = 165.9 Hz, C-ε), 91.0 (C-2), 123.4 (C-6), 127.5 (C-4), 129.4 (C-5), 139.6 (C-3), 151.9 (C-1), 170.5 (C=O). – ^{19}F NMR (376 MHz, C_6D_6): δ = −218.4. – MS ((+)-ESI): *m/z* (%) = 359 (80) $[M+Na]^+$. – $C_{12}H_{14}FIO_2$ (336.14): calcd. C 42.88, H 4.20; found C 43.04, H 4.29.

*2-(Diphenylphosphano)phenyl 4-fluorobutanoate (**10**)*

KOAc (38 mg, 0.39 mmol), $HPPh_2$ (60 μL, 0.32 mmol) and $Pd(OAc)_2$ in catalytical amount were added to a solution of 2-iodophenyl benzoate (**9a**) (100 mg, 0.32 mmol) in dry DMA (2 mL) under an argon atmosphere. The mixture was stirred at 90 °C for 3 h. Afterwards water (15 mL) and CH_2Cl_2 (15 mL) were added, the organic layer was separated, and the aqueous layer was extracted with 3× 10 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced

pressure. The crude product was purified by column chromatography (petroleum ether/EtOAc 20 : 1 → 10 : 1) to yield **10** as a colorless syrup (60 mg, 51 %). R_f = 0.37 (petroleum ether/EtOAc 8 : 1). – ^{1}H NMR (400 MHz, C_6D_6): δ = 1.47 – 1.61 (m, 2 H, H-β), 2.10 (t, ^3J = 7.3 Hz, 2 H, H-α), 3.92 (dt,$^3J_{H,F}$ = 47.5 Hz, ^3J = 6.0 Hz, 2 H, H-γ), 6.74 (t, $^3J_{3,4}$ = 7.4 Hz, 1 H, 4-H), 6.94 – 6.98 (m, 7 H, 3-H, 5-H, 6-H, H_{meta}, H_{para}), 7.26 – 7.33 (m, 4 H, H_{ortho}). – ^{13}C NMR (101 MHz, C_6D_6): δ = 30.1 (d, $^2J_{C,F}$ = 19.7 Hz, C-β), 34.2 (d, $^3J_{C,F}$ = 4.7 Hz, C-α), 82.4 (d, $^1J_{C,F}$ = 165.0 Hz, C-γ), 123.2 (C-6), 126.3 (C-4), 128.5 (d, $^1J_{C,P}$ = 12.4 Hz, C-2), 129.0 (d, $^3J_{C,P}$ = 24.9 Hz, C_{meta}), 130.0 (C_{para}), 130.8 (C-5), 130.9 (d, $^2J_{C,P}$ = 15.7 Hz, C-3), 134.2 (d, $^2J_{C,P}$ = 20.5 Hz, C_{ortho}), 136.7 (d, $^1J_{C,P}$ = 11.5 Hz, C_{ipso}), 153.9 (d, $^2J_{C,P}$ = 18.0 Hz, C-1), 171.0 (C=O). – ^{19}F NMR (376 MHz, C_6D_6): δ = −220.2. – ^{31}P NMR (162 MHz, C_6D_6): δ = −15.0. – MS ((+)-ESI): *m/z* (%) = 406 (8) $[M+K]^+$. – $C_{22}H_{20}FO_2P$ (366.37): calcd. C 72.12, H 5.50; found C 72.18, H 5.24.

*2-Iodophenyl 4-[^{18}F]fluorobutanoate ([^{18}F]**9a**)*

An anion-exchanger cartridge (Waters, Sep-Pak® Light Accell™ Plus QMA) was activated by rinsing with 5 mL of a 1 M $NaHCO_3$ solution and 10 mL of deionized water. It was charged with [^{18}F]fluoride (500 – 800 MBq) and eluted with 1 mL of a 4.5 % TBAOH solution. The solvents were evaporated azeotropically by subsequent addition of three portions of 1 mL each of dry acetonitrile under a stream of nitrogen at 100 °C. 17.5 mg of **6b** was dissolved in 0.5 mL dry acetonitrile, and the mixture was added to the [^{18}F]fluoride-containing sealed vial. The resulting solution was heated to 100 °C for 10 min. Samples for analytical radio-TLC were taken after 10 min. Analytical radio-TLC: R_f = 0.62 (petroleum ether/EtOAc 8 : 1).

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