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Synthesis, structure determination, and (radio-)fluorination of novel functionalized phosphanes suitable for the traceless Staudinger ligation

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ABSTRACT

An elegant and efficient synthesis approach for the preparation of novel benzoate and nicotinate containing phosphanes is presented. This reaction path has a broad substrate scope. Thus, various functionalized phosphanes were obtained in high yields using an esterification procedure under Steglich conditions. A facile blocking of the phosphorus atom with BH_3 was carried out. BH_3 as easily insertable and removable protecting group enables a further derivatization of the benzoate residue. The prepared phosphane derivatives proved to be valuable labeling building blocks for the implementation of a bioorthogonal (radio-)fluorination strategy and were applied for labeling purposes using the traceless Staudinger ligation. For this purpose, a selection of azide-functionalized small organic and bioactive sample molecules was prepared. Furthermore, a mild and selective (radio-)fluorination of these derivatives is demonstrated adopting this bioorthogonal ligation method.

1. Introduction

In recent years, both the traceless and the non-traceless Staudinger ligation[1] have become important coupling methods for the bioorthogonal interconnection of bioactive molecules[2] as well as in material sciences.[3] Additionally, this ligation was developed as an important approach for the attachment of functional groups like radioactive[4] as well as non-radioactive labels[5] to organic and bioactive molecules. The chemoselective (radio-)labeling of biomacromolecules like peptides, proteins or antibodies still remains a special challenge. Specific attention should be paid to the implementation of fast and highly selective labeling reactions, which tolerate other functional groups of the respective molecule. Therefore, selective ligation reactions were evaluated. The traceless Staudinger ligation is similar to the Cu(I) catalyzed Huisgen cycloaddition[6] a powerful conjugation reaction. Beneficially, ligations using the Staudinger approach proceed without the application of cytotoxic Cu-salts in contrast to the Huisgen reaction. The bioorthogonal character[7] of azides[8] and phosphanes, which were used as starting material for the Staudinger ligation as well as the mild reaction conditions of this method remain the most important advantages. Unpropitiously, primary amines, e.g., in peptides show that unexpected side reactions with phosphanes used in Staudinger ligations may occur.[2b]

To exploit the Staudinger ligation for labeling purposes easily available fluorine-18 containing building blocks are required. Thus, we decided to evaluate various new benzoate and nicotinate functionalized phosphanes. The convenient access to biologically active (radio-)fluorinated pyridine compounds was previously shown[9] and a wide variety of fluoropyridine containing compounds was applied as radiotracers.[10] Furthermore, nicotinic acid as precursor for NADH, NAD^+ and other cofactors play an essential metabolic role in living cells.[11] In this case, direct fluorination reactions of heteroaromatic systems were exemplified due to the electron-deficient pyridine ring capable for nucleophilic aromatic fluorinations.[12] Herein, we have demonstrated a facile and adequate access to novel functionalized phosphane derivatives based on benzoate and nicotinate moieties as versatile fluorine-18 labeling building blocks with the potential for mild and bioorthogonal radiolabeling of diverse bioactive small organic molecules as well as biomacromolecules with fluorine-18 using the traceless Staudinger ligation. Advantageously, this method provides access to compounds with a wide variety of substitution patterns. Moreover, it was possible to prepare phosphanes with a trimethylammonium-benzoate residue using alkylating agents due to the protection of the central phosphorus atom with BH_3. The structures of all compounds were confirmed by NMR and MS. Furthermore, crystals suitable for X-ray structure determinations of key compounds were grown and the structures were assigned.

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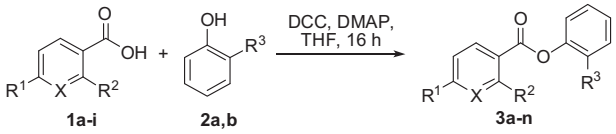
2. Results and discussion

Acylated phosphanes are of great interest as building blocks for the Staudinger ligation, e.g., for the preparation of *N*-glycosides,[13] the fluorescence labeling of cells,[5b] the interconnection of amides,[14] peptides, and proteines[15] or the intramolecular ring closure to form medium size lactames.[16] Most of these derivatives were prepared using carboxylic acid chlorides or anhydrides with phosphanophenol **2b** under basic conditions that led to the corresponding esters.[13] In the majority of cases, non-functionalized carboxylic acid derivatives were used. Benzoate compounds were rarely applied.[17] Recently, we described a valuable synthesis path using the Pd-catalyzed P–C cross-coupling strategy in which diphenylphosphane was reacted with respective *o*-iodophenyl esters.[5a] Unfortunately, the preparation of derivatives containing a iodo- or nitrobenzoate function was not amenable using this method. In contrast, the esterification under Steglich conditions represented a valuable and adjuvant option consisting of the reaction between phosphanophenol **2b** and respective carboxylic acids **1b**–**i** and led to the favored phosphanes in good to high yields. Scope and limitations of this esterification procedure are shown in Scheme 1 and Table 1. A broad incorporation of various radioactive and non-radioactive labels is feasible using these benzoate-functionalized phosphanes.



Scheme 1. Esterification of **1a**–**i** with **2a**,**b** under Steglich conditions.

Table 1
Scope and limitations for the preparation of various 2-iodophenyl esters and phosphanes

1	2	R^1	R^2	R^3	X	Product	Yield [%]
a	**a**	NO_2	H	I	CH	**3a**	83
b	**a**	NMe_2	H	I	CH	**3b**	42
c	**a**	I	H	I	CH	**3c**	74
d	**a**	OH	H	I	CH	**3d**	39
e	**a**	Me	H	I	CH	**3e**	40
f	**a**	Br	H	I	N	**3f**	58
b	**b**	NMe_2	H	PPh_2	CH	**3g**	75
c	**b**	I	H	PPh_2	CH	**3h**	76
d	**b**	OH	H	PPh_2	CH	**3i**	73
e	**b**	Me	H	PPh_2	CH	**3j**	98
f	**b**	Br	H	PPh_2	N	**3k**	87
g	**b**	F	H	PPh_2	N	**3l**	21
h	**b**	H	Br	PPh_2	N	**3m**	76
i	**b**	H	F	PPh_2	N	**3n**	36

Accessorily, several functionalized 2-iodophenyl esters **3a**–**f**, which were used as starting material for the alternative Pd-catalyzed cross-coupling strategy, were prepared by the reaction of 2-iodophenol (**2a**) with various benzoic acids **1a**–**f** using DCC/DMAP in dry THF. The desired esters **3a**–**f** were obtained in yields ranging from 39 to 83%.

Beside the benzoate derivatives **3a**–**j**, novel halo-nicotinate compounds **3k**–**n** were synthesized (yield 21–98%). Substituted pyridines served as important precursors for radiofluorination purposes due to their electron-depleted aromatic system. It was possible to obtain single crystals of the nitro compound **3a** and nicotinate **3m** suitable for an X-ray structure determination.[18] Figs. 1 and 2 depict the molecular structure of these two compounds.

The nucleophilic introduction of (radio-)fluorine into aromatic compounds requires an electron-deficient aromatic system. This

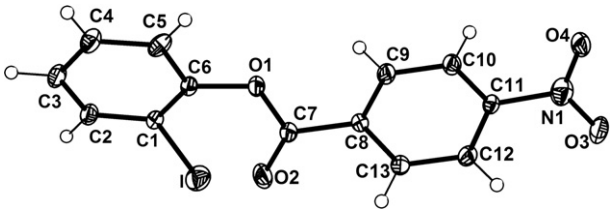


Fig. 1. Molecular structure and atom labeling scheme of 2-iodophenyl benzoate **3a**. Displacement ellipsoids are drawn at the 50% probability level.

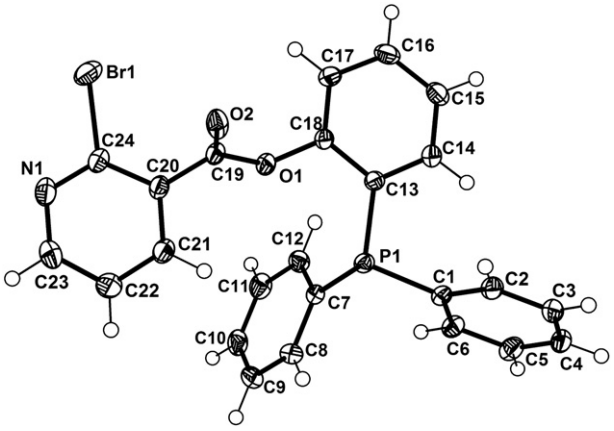
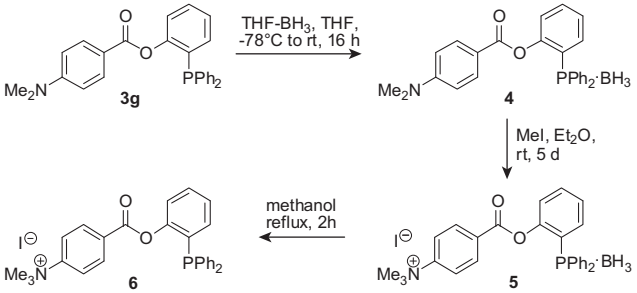


Fig. 2. Molecular structure and atom labeling scheme of phosphane **3m**. Displacement ellipsoids are drawn at the 50% probability level.

can be achieved on the one hand using electron withdrawing groups like aldehydes, ester functions, nitriles or halogens attached to the benzene residue and on the other hand by the introduction of good leaving groups like I, NO_2 or Me_3N^+. Benzoates functionalized with a trimethylammonium group proved to be suitable precursors and are widely used for radiofluorination purposes.[19] Therefore, compound **6** was synthesized using a three step procedure starting from **3g**. Alkylation reactions necessitate the blocking of the central phosphorus atom to prevent the formation of phosphonium salts with the alkylating agent. Thus, phosphane **3g** was converted into phosphane borane adduct **4** by direct transfer of BH_3 from the weaker THF·BH_3 adduct [5a] at −78 °C (Scheme 2).



Scheme 2. Preparation of trimethylammonium precursor **6**.

The existence of the BH_3 group in **4** and **5** was evidenced by ^1H, ^{31}P NMR as well as MS analyses. In addition, crystals suitable for an X-ray structure determination of compound **4** were obtained from a saturated ethyl acetate/petroleum ether solution. The corresponding molecular structure is shown in Fig. 3.[18] The three molecular structures, as derived from X-ray structure experiments, are in complete accordance with those expected from the synthetic procedures and spectroscopic properties.

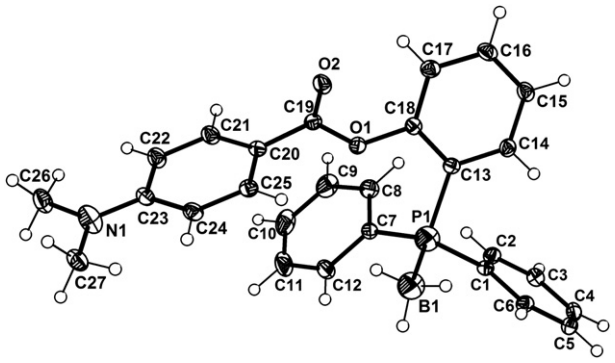
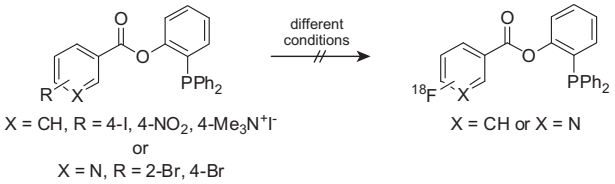


Fig. 3. Molecular structure and atom labeling scheme of compound **4**. Displacement ellipsoids are drawn at the 50% probability level.

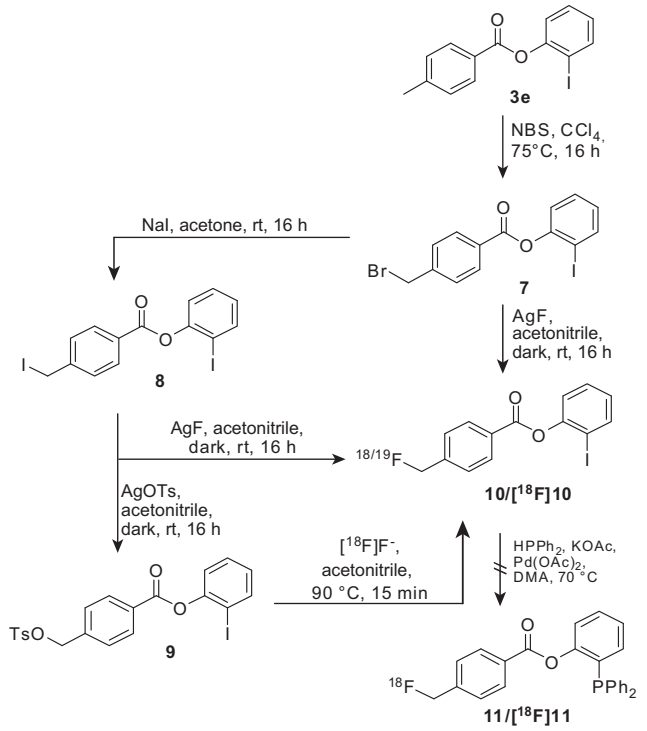
3. Radiolabeling

A multitude of biomacromolecules, such as proteins, peptides or antibodies labeled with the positron emitting radionuclide fluorine-18 function as radioactive probes to image physiological and pathological processes within humans. Usually, these compounds cannot be labeled directly with ^{18}F due to the required harsh reaction conditions. Thus, various ^{18}F-labeled prosthetic groups,[19] such as *N*-[6-(4- [^{18}F]fluorobenzylidene)-aminooxyhexyl]-maleimide ([^{18}F]FBAM)[20] or *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB)[21] originally developed by Vaidyanathan and Zalutsky[22a] and modified by Wester et al.[22b] were used. However, due to the wide variety of functional groups in peptides and proteins a specific labeling strategy for each of the above mentioned macromolecules has to be developed. In this context, novel precursor molecules were created consisting of activated benzoates **3a**,**h**, **6** or nicotinates **3k**,**m**, which represent ideal substrates for a nucleophilic introduction of [^{18}F]fluoride (Scheme 3). Different classical as well as microwave conditions were tested for the radiofluorination of these phosphanes, but no radiolabeled product was found. Radio-HPLC and radio-TLC evaluations pointed out that the precursor either led to decomposition or the phosphorus atom of the precursor building block core was oxidized during the labeling procedure.



Scheme 3. Radiolabeling trials of various phosphane derivatives under different conditions.

These results prompted us to develop a second, new approach adopting 4-halomethyl-functionalized 2-iodophenyl benzoates. The 4-fluoromethylbenzoate moiety was recently used as prosthetic group for labeling purposes.[23] Thereby, it was found out that bromide is rapidly displaced by fluoride at the benzylic position instead of a direct substitution at the aromatic system. Moreover, the resulting benzyl fluoride is relatively stable in aqueous medium and benzyl halides are not subject to elimination, which has been noted as side reaction with other methods of introducing fluorine-18.[23] Additionally, the use of precursors with leaving groups like mesyl, tosyl or iodide were preferred for the introduction of radiofluorine and the preparation of non-radioactive reference compounds (Scheme 4).



Scheme 4. Functionalization, radiolabeling, and P–C cross-coupling to (radio-)fluorinated compounds **10**/[^{18}F]**10** and **11**.

A direct bromination of compound **3j** using NBS in CCl_4 was not amenable. However, the reaction of iodophenyl benzoate **3e** with NBS proved to be successful and led to the desired bromomethyl compound **7** in 81% yield. Subsequently, the iodinated compound **8** was prepared from **7** in 79% yield using a Finkelstein exchange with NaI in acetone at room temperature. Afterward, **8** was successfully reacted with AgOTs in anhydrous acetonitrile in the dark and yielded **9** (89%), whereas reaction of **7** or **8** with AgF gave the desired fluoro compound **10** in 41% (starting from **7**) or 57% yield (starting from **8**), respectively. Besides, the fluoromethyl derivative **10** could be obtained in 46% yield when tosylate **9** was reacted with CsF in *t*-BuOH (experimental procedure not shown).

Optimal reaction conditions for the preparation of [^{18}F]**10** were evaluated using different leaving groups (Table 2) and various solvents. In this context, precursor amounts as well as reaction times were changed. All labeling reactions were carried out at 100 °C. The application of labeling conditions from entry 6 in Table 2

Table 2
RCY and scope of the labeling reaction

	Leaving Group	Precursor amount [mg]	Solvent	Time	Yield [%][a]
1	Br	3.34	Acetonitrile	30 min	1
2	Br	4.31[b]	Acetonitrile	15 min	7
3	Br	3.34	Acetonitrile	MW[c]	1
4	I	2.33	Acetonitrile	15 min	1
5	I	5.21[c]	Acetonitrile	20 min	46
6	OTs	3.21	Acetonitrile	30 min	25
7	OTs	5.20	Acetonitrile	30 min	33
8	OTs	5.20	Acetonitrile	MW[d]	36
9	OTs	9.52	Acetonitrile/*t*-BuOH 1:4	15 min	2
10	OTs	10.3	Acetonitrile	15 min	66

[a] Conversion determined via evaluation of radio-TLC.
[b] $AgNO_3$ (3.37 mg) was added.
[c] AgOMs (5.12 mg) was added.
[d] Microwave conditions: 5 min/50 W.

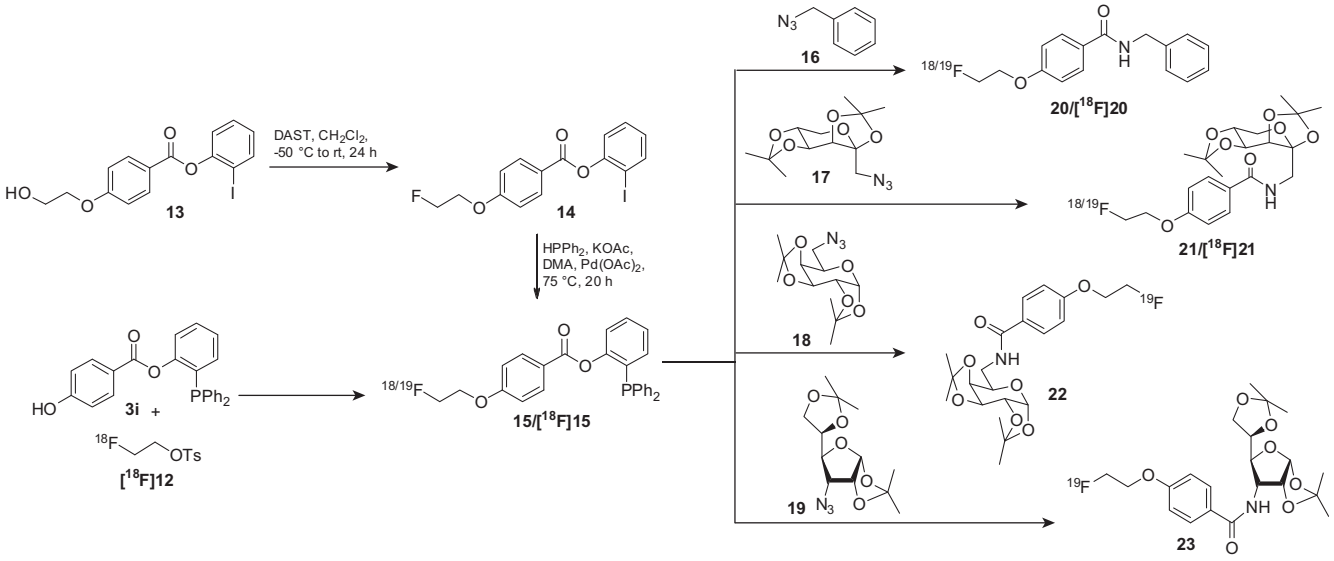
(Kryptofix K 2.2.2./K_2CO_3 in acetonitrile) delivered the highest conversion of 66% (decay corrected, d.c.)[24] (average of 5 runs) to [^{18}**F**]**10** when tosyloxymethyl compound **8** was used as precursor at a synthesis time of 15 min.

Finally, the radiolabeled phosphane as well as the non-radioactive reference compound should be prepared using the Pd-catalyzed P–C cross-coupling. For this purpose, 2-iodophenyl ester **10** was reacted with diphenylphosphane in dry DMA. The desired fluoro-containing phosphane **11** was obtained in 30% yield, whereas the synthesis of the radiofluorinated phosphane [^{18}**F**]**11** failed under the same conditions. An application of other solvents, a variation of temperature as well as the base was not successful. Based on these results, we developed another labeling strategy.

The third and successful approach involved the indirect incorporation of radiofluorine into 4-hydroxybenzoate-functionalized phosphane **3i** with [^{18}F]fluoroethyl tosylate ([^{18}**F**]**12**), which served as alkylating agent. This building block is known to be an excellent tool for the labeling of compounds bearing a hydroxyl or an amine function[25] and can be easily prepared from ethylene ditosylate. Thus, a one pot procedure was developed for the radiolabeling of **3i** with [^{18}**F**]**12** followed by the Staudinger ligation with several model compounds. (Scheme 5) For this purpose, 4-(fluoroethoxy)benzoate-functionalized phosphane **15** to yield the respective Staudinger products **20** (95%), **21** (60%), **22** (66%), and **23** (50%). The ligation was performed in a mixture of acetonitrile/water (v:v, 10:1) at 60 °C for 2 h.

Finally, the radiofluorinated phosphane [^{18}**F**]**15** was reacted with benzyl azide (**16**) in a 'one pot' synthesis. Therefore, a solution of **16** in 300 μL of an acetonitrile/water mixture (v:v, 10:1) was added. After 15 min heating at 90 °C, the ligation reaction was complete and yielded [^{18}**F**]**20** (17%, d.c., after three steps starting from [^{18}F]fluoride).[24] Fig. 4 shows the respective radio-TLC chromatogram of [^{18}**F**]**20**. Accessorily, Fig. 6 shows the HPLC chromatogram with a mixture of non-radioactive starting materials **3i** and **16** as well as product **20** (UV-trace), whereas Fig. 7 shows the appropriate radio-HPLC with radiofluorinated [^{18}**F**]**20** (γ-trace).

Furthermore, it was possible to label the azide-functionalized carbohydrate **17** successfully with fluorine-18 to yield [^{18}**F**]**21** (12%, d.c., after three steps starting from [^{18}F]fluoride).[24] For this purpose, [^{18}**F**]**15** was prepared in dry acetonitrile and treated with **17** in an acetonitrile/water mixture (300 μL; v:v, 10:1) for 15 min at 90 °C. Verification of all resulting Staudinger products was done using radio-HPLC as well as radio-TLC analyses.[24] A radio-TLC chromatogram of [^{18}**F**]**21** is shown in Fig. 5.



Scheme 5. Radiofluorination using 2-[^{18}F]fluoroethyl tosylate [^{18}**F**]**12** and subsequent traceless Staudinger ligation.

[^{18}**F**]**12** was prepared and subsequently treated with 2–3 mg of **3i** dissolved in 300 μL of acetonitrile. The resulting mixture was heated at 90 °C for another 15 min to yield [^{18}**F**]**15**.

4. Traceless Staudinger ligation

Non-radioactive reference compounds **15** and **20**–**23**, which were used for the identification of all radiolabeled derivatives, were prepared starting from 2-iodophenyl ester **13**. (Scheme 5) Thus, **13** was treated with DAST to obtain the fluorinated 2-iodophenyl ester **14**. Subsequently, **14** was reacted with diphenylphosphane under Pd-catalysis in a P–C cross-coupling reaction to yield the desired non-radioactive phosphane **15** (60%).

To prove the applicability of the traceless Staudinger ligation for labeling purposes with fluorine-18, various azides **16**–**19** were synthesized. Subsequently, benzyl azide (**16**) and three different carbohydrates **17**, **18**, and **19** with azide function were reacted with

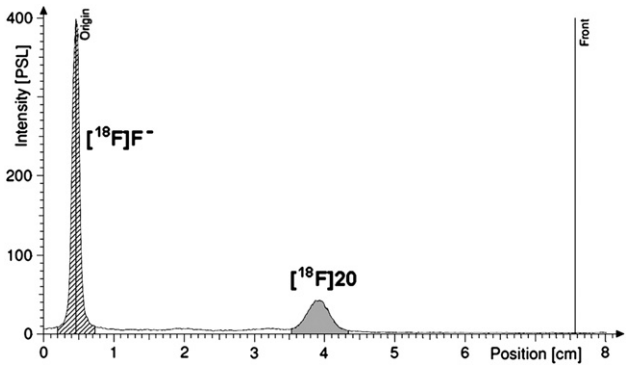


Fig. 4. Radio-TLC chromatogram of Staudinger product [^{18}**F**]**20**, R_f=0.51 (petroleum ether/ethyl acetate, 2:3).

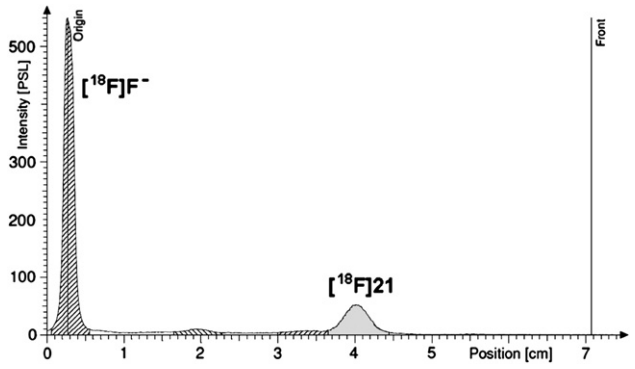


Fig. 5. Radio-TLC chromatogram of Staudinger product [^{18}F]**21**, R_f=0.44 (petroleum ether/ethyl acetate, 1:1).

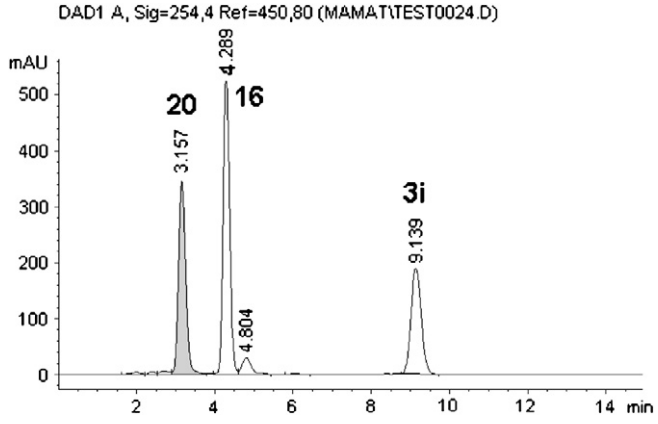


Fig. 6. HPLC chromatogram (UV-trace) of starting materials **3i**, **16**, and non-radioactive Staudinger product **20** (t_R=3.16 min).

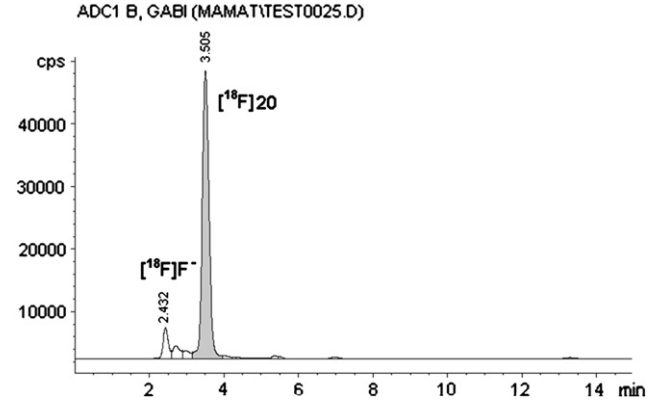


Fig. 7. Radio-HPLC chromatogram (γ-trace) of Staudinger product [^{18}F]**20** (t_R=3.58 min).

5. Conclusion

In conclusion, we demonstrated an easy and convenient synthesis route for the preparation of benzoate and nicotinate functionalized phosphanes with various functional groups. These groups allow either the fast introduction of labels, such as fluorine-18 or the alkylation of the benzoate residue when the phosphorus atom is protected with BH_3. Furthermore, we described a 'one pot' procedure for the successful introduction of radiofluorine into a phosphane for a further application as radiolabeled building block using the traceless Staudinger ligation. In this context, it was possible to label different model azides with fluorine-18. The respective non-radioactive fluorinated reference compounds were prepared to prove the feasibility of the traceless Staudinger ligation as radiolabeling procedure.

6. Experimental section

6.1. Reagents and techniques

All chemicals were purchased from Sigma–Aldrich, abcr or Acros and were used as received, dry solvents (THF, DMA, toluene, and acetonitrile) were obtained from Fluka (anhydrous, over molecular sieves, 99.7%). Phosphanol **2b**[5a] and compounds **4**, **13**,[5a] and **16**–**19**[26] were synthesized according to literature methods. The reaction with BH_3·THF, the Pd-catalyzed P–C cross-coupling and the deprotection using MeOH/toluene were carried out using Schlenk technique under an argon atmosphere. NMR spectra were recorded on a Varian Inova-400 and chemical shifts of the ^{1}H, ^{13}C, ^{19}F, and ^{31}P spectra were 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 spectrometric (MS) data was 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) melting point apparatus (Leica, Vienna, Austria) and are uncorrected. Crystallographic data were collected with a Bruker-Nonius Apex-X8 CCD-diffractometer with Mo Kα radiation (λ=0.71073 Å). The structures were solved by direct methods using SHELXS-97 and refined against F^2 on all data by full-matrix least-squares with SHELXL-97.[27] All non-hydrogen atoms were refined anisotropically; all hydrogen atoms bonded to carbon atoms were placed on geometrically calculated positions and refined using a riding model. The three hydrogen atoms of the BH_3 group in **4** were refined isotropically. Microanalyses were carried out with a Hekatech CHNS elemental analyzer EuroEA 3000. Chromatographic separations and TLC detections were carried out with Merck Silica Gel 60 (63–200 μm) and Merck Silica Gel 60 F_{254} sheets, respectively. TLCs were visualized under UV light (λ=254 nm). All reactions concerning the borane–phosphane-adduct formation were carried out under an Argon atmosphere using Schlenk techniques. Analytical HPLC was performed on a Hewlett Packard HP 1050 series HPLC system, equipped with a reverse phase column (Supelco Discovery C-18; 150×4.6 mm; 5 μm), a UV-diode array detector (230 nm) and a scintillation radiodetector (Raytest, Gabi Star). The radioactive compounds were identified with analytical radio-HPLC by comparison of the retention time of the reference compounds. Decay-corrected RCYs were quantified by integration of radioactive peaks on a radio-TLC using a radio-TLC scanner (Fuji, BAS2000).[24] [^{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.

6.2. General synthetic procedure for the preparation of 3a–n

The respective benzoic acid **1a**–**i** (1.1 equiv) and *o*-iodophenol (**2a**) or phosphanol **2b** (1 equiv) with a catalytic amount of DMAP were dissolved in dry THF and DCC (1.5–2 equiv) was added at room temperature. The mixture was allowed to stir overnight at 60 °C. Afterward, the precipitate was filtered off and the filtrate was concentrated in vacuo. Purification was done via column chromatography (silica gel, petroleum ether/EtOAc). The preparation and analytical data of **3a**–**d** and **3g**,**h** was previously published.[5a]

*6.2.1. 2-Iodophenyl 4-methylbenzoate (**3e**).* *p*-Tolylic acid (**1e**) (2 g, 14.7 mmol), *o*-iodophenol (**2a**) (3.55 g, 16.2 mmol), DCC (4.55 g, 22.0 mmol), and DMAP (100 mg) in dry THF (30 mL) yielded **3e** as colorless solid (2 g, 40%); mp=61 °C; R_f=0.64 (petroleum

ether/EtOAc=5:1); ^{1}H NMR (400 MHz, C_6D_6): δ 1.97 (s, 3H, CH_3), 6.44 (t, $^3J_{3,4}$=7.8 Hz, 1H, H-4), 6.87 (t, $^3J_{5,6}$=7.0 Hz, 1H, H-5), 6.91 (d, $^3J_{o,m}$=8.5 Hz, 2H, H_{meta}), 6.99 (d, $^3J_{5,6}$=7.0 Hz, 1H, H-6), 7.54 (d, $^3J_{3,4}$=7.8 Hz, 1H, H-3), 8.26 (d, $^3J_{o,m}$=8.5 Hz, 2H, H_{ortho}); ^{13}C NMR (101 MHz, C_6D_6): δ 21.5 (CH_3), 91.1 (C-2), 123.7 (C-6), 127.3 (C_{ipso}), 127.5 (C-4), 129.4 (C-5), 129.6 (C_{meta}), 130.9 (C_{ortho}), 139.6 (C-3), 144.6 (C_{para}), 152.1 (C-1), 164.2 (C=O); MS (ESI$^+$): *m*/*z* 339 (M+H$^+$); Anal. Calcd for: $C_{14}H_{11}IO_2$ (338.1): C 49.73, H 3.28; found: C 50.32, H 3.45.

*6.2.2. 2-Iodophenyl 6-bromonicotinate (**3f**).* 6-Bromonicotinic acid (500 mg, 2.47 mmol), *o*-iodophenol (599 mg, 2.72 mmol), DCC (1.02 g, 4.95 mmol), and DMAP (50 mg) in dry THF (30 mL) yielded **3f** as colorless solid (584 mg, 58%); mp=93 °C; R_f=0.49 (petroleum ether/EtOAc=3:1); ^{1}H NMR (400 MHz, C_6D_6): δ 6.43 (t, $^3J_{3,4}$=7.4 Hz, 1H, H-4), 6.79–6.93 (m, 3H, H-3, H-5, H-6), 7.48 (d, $^3J_{4',5'}$=8.6 Hz, H-5′), 7.63 (d, $^3J_{4',5'}$=8.6 Hz, H-4′), 9.11 (s, 1H, H-2′); ^{13}C NMR (101 MHz, C_6D_6): δ 90.5 (C-2), 123.2 (C-6), 124.7 (C-3′), 127.9 (C-5′), 129.5 (C-5), 139.4 (C-4′), 139.7 (C-3), 148.0 (C-6′), 151.3 (C-1), 152.2 (C-2′), 162.3 (C=O); MS (ESI$^+$): *m*/*z* 427 (M+Na$^+$); Anal. Calcd for: $C_{12}H_7BrINO_2$ (404.0): C 35.68, H 1.75, N 3.47; found: C 35.88, H 1.94, N 3.41.

*6.2.3. 2-(Diphenylphosphano)phenyl 4-hydroxybenzoate (**3i**).* 4-Hydroxybenzoic acid (186 mg, 1.35 mmol), phosphanol **2b** (250 mg, 0.90 mmol), DCC (278 mg, 1.35 mmol), and DMAP (25 mg) in dry THF (15 mL) yielded **3i** as colorless solid (276 mg, 73%). Analytical data are in accordance with the previously published.[5a]

*6.2.4. 2-(Diphenylphosphano)phenyl 4-methylbenzoate (**3j**).* *p*-Tolylic acid (318 mg, 2.34 mmol), phosphanol **2b** (591 mg, 2.12 mmol), DCC (657 mg, 3.19 mmol), and DMAP (50 mg) in dry THF (15 mL) yielded **3j** as colorless solid (825 mg, 98%); mp=144 °C; R_f=0.48 (petroleum ether/EtOAc=3:1); ^{1}H NMR (400 MHz, C_6D_6): δ 1.91 (s, 3H, CH_3), 6.80 (d, $^3J_{o,m}$=8.6 Hz, 2H, $H_{meta'}$), 6.84 (t, $^3J_{3,4}$=7.0 Hz, 1H, H-4), 6.98–7.08 (m, 8H, H-5, H-6, H_{meta}, H_{para}), 7.28 (dd, $^3J_{3,4}$=7.8 Hz, $^4J_{H,P}$=4.7 Hz, 1H, H-3), 7.36–7.42 (m, 4H, H_{ortho}), 8.01 (d, $^3J_{o,m}$=8.6 Hz, 2H, $H_{ortho'}$); ^{13}C NMR (101 MHz, C_6D_6): δ 21.4 (CH_3), 123.3 (C-6), 127.4 ($C_{ipso'}$), 128.8 (d, $^3J_{C,P}$=7.4 Hz, C_{meta}), 129.1 ($C_{meta'}$), 129.3 (C-5), 130.1 ($C_{ortho'}$), 130.6 (C_{para}), 131.4 (d, $^2J_{C,P}$=16.4 Hz, C-3), 134.0 (C-4), 134.5 (d, $^2J_{C,P}$=20.6 Hz, C_{ortho}), 136.6 (d, $^1J_{C,P}$=11.8 Hz, C_{ipso}), 144.0 ($C_{para'}$), 154.0 (d, $^2J_{C,P}$=17.6 Hz, C-1), 164.3 (C=O); ^{31}P NMR (162 MHz, C_6D_6): δ=−14.7; MS (ESI$^+$): *m*/*z* 397 (M+H$^+$); Anal. Calcd for: $C_{26}H_{21}O_2P$ (396.4): C 77.78, H 5.34; found: C 77.74, H 5.47.

*6.2.5. 2-(Diphenylphosphano)phenyl 6-bromonicotinate (**3k**).* 6-Bromonicotinic acid (248 mg, 1.23 mmol), phosphanol **2b** (310 mg, 1.11 mmol), DCC (460 mg, 2.23 mmol), and DMAP (30 mg) in dry THF (15 mL) yielded **3k** as colorless solid (446 mg, 87%); mp=105 °C; R_f=0.62 (petroleum ether/EtOAc=3:1); ^{1}H NMR (400 MHz, C_6D_6): δ 6.73 (d, $^3J_{4',5'}$=8.7 Hz, 1H, H-5′), 6.83 (t, $^3J_{3,4}$=7.7 Hz, 1H, H-4), 6.95–7.01 (m, 7H, H-3, H_{meta}, H_{para}), 7.05 (t, $^3J_{5,6}$=7.8 Hz, 1H, H-5), 7.19 (dd, $^3J_{5,6}$=7.8 Hz, 1H, H-6), 7.28–7.36 (m, 4H, H_{ortho}), 7.48 (dd, $^3J_{4',5'}$=8.7 Hz, $^4J_{2',4'}$=2.4 Hz, 1H, H-4′), 8.81 (d, $^4J_{2',4'}$=2.4 Hz, H-2′); ^{13}C NMR (101 MHz, C_6D_6): δ 122.9 (d, $^3J_{C,P}$=1.5 Hz, C-6), 124.8 (C-3′), 127.9 (C-5′), 129.0 (d, $^3J_{C,P}$=7.3 Hz, C_{meta}), 129.4 (C_{para}), 130.1 (C-5), 131.4 (d, $^2J_{C,P}$=16.2 Hz, C-3), 132.0 (d, $^1J_{C,P}$=9.9 Hz, C-2), 134.1 (d, $^3J_{C,P}$=1.9 Hz, C-4), 134.4 (d, $^2J_{C,P}$=21.0 Hz, C_{ortho}), 135.8 (d, $^1J_{C,P}$=10.9 Hz, C_{ipso}), 139.2 (C-4′), 147.6 (C-6′), 152.0 (C-2′), 153.0 (d, $^2J_{C,P}$=17.0 Hz, C-1), 162.4 (C=O); ^{31}P NMR (162 MHz, C_6D_6): δ −14.5; MS (ESI$^+$): *m*/*z* 465 (M+H$^+$; ^{81}Br), 463 (M+H$^+$; ^{79}Br); Anal. Calcd for: $C_{24}H_{17}BrNO_2P$ (462.3): C 62.36, H 3.71, N 3.03; found: C 62.16H 3.91, N 2.94.

*6.2.6. 2-(Diphenylphosphano)phenyl 6-fluoronicotinate (**3l**).* 6-Fluoronicotinic acid (247 mg, 1.75 mmol), phosphanol **2b** (536 mg, 1.93 mmol), DCC (722 mg, 3.50 mmol), and DMAP (30 mg) in dry THF (15 mL) yielded **3l** as colorless oil (150 mg, 21%); R_f=0.56 (petroleum ether/EtOAc=3:1); ^{1}H NMR (400 MHz, C_6D_6): δ 6.07 (dd, $^3J_{H,F}$=3.1 Hz, $^3J_{4',5'}$=8.6 Hz, 1H, H-5′), 6.84 (t, $^3J_{3,4}$=7.0 Hz, 1H, H-4), 6.95–7.03 (m, 7H, H-3, H_{meta}, H_{para}), 7.07 (t, $^3J_{5,6}$=7.8 Hz, 1H, H-5), 7.22 (dd, $^3J_{5,6}$=7.8 Hz, 1H, H-6), 7.29–7.37 (m, 4H, H_{ortho}), 7.79 (dd, $^3J_{4',5'}$=8.6 Hz, $^4J_{2',4'}$=2.3 Hz, 1H, H-4′), 8.76 (d, $^4J_{2',4'}$=2.3 Hz, H-2′); ^{13}C NMR (101 MHz, C_6D_6): δ=109.2 (d, $^2J_{C,F}$=38.1, C-5′), 123.0 (d, $^3J_{C,P}$=1.5 Hz, C-6), 123.9 (d, $^4J_{C,F}$=4.4 Hz, C-3′), 128.9 (d, $^3J_{C,P}$=7.4 Hz, C_{meta}), 129.4 (C_{para}), 130.1 (C-5), 131.4 (d, $^2J_{C,P}$=16.2 Hz, C-3), 134.1 (d, $^3J_{C,P}$=1.9 Hz, C-4), 134.4 (d, $^2J_{C,P}$=20.5 Hz, C_{ortho}), 135.9 (d, $^1J_{C,P}$=10.8 Hz, C_{ipso}), 142.7 (d, $^3J_{C,F}$=9.5 Hz, C-4′), 151.1 (d, $^3J_{C,F}$=17.3 Hz, C-2′), 153.0 (d, $^2J_{C,P}$=16.9 Hz, C-1), 162.0 (C=O), 166.3 (d, $^1J_{C,F}$=244.8 Hz, C-6′); ^{19}F NMR (376 MHz, C_6D_6): δ −61.1; ^{31}P NMR (162 MHz, C_6D_6): δ −14.4; MS (ESI$^+$): *m*/*z* 424 (M+Na$^+$), 402 (M+H$^+$); Anal. Calcd for: $C_{24}H_{17}FNO_2P$ (401.4): C 71.82, H 4.27, N 3.49; found: C 71.92, H 4.67, N 3.04.

*6.2.7. 2-(Diphenylphosphano)phenyl 2-bromonicotinate (**3m**).* 2-Bromonicotinic acid (279 mg, 1.38 mmol), phosphanol **2b** (350 mg, 1.26 mmol), DCC (519 mg, 2.52 mmol), and DMAP (30 mg) in dry THF (15 mL) yielded **3m** as colorless solid (441 mg, 76%); mp=105 °C; R_f=0.69 (petroleum ether/EtOAc=1:2); ^{1}H NMR (400 MHz, C_6D_6): δ 6.25 (dd, $^3J_{4',5'}$=4.7 Hz, $^3J_{5',6'}$=7.7 Hz, 1H, H-5′), 6.83 (t, $^3J_{4,5}$=7.6 Hz, 1H, H-4), 6.99–7.02 (m, 7H, H-3, H_{meta}, H_{para}), 7.05 (t, $^3J_{4,5}$=7.6 Hz, $^3J_{5,6}$=8.0 Hz, 1H, H-5), 7.18 (dd, $^3J_{5,6}$=8.0 Hz, 1H, H-6), 7.30–7.36 (m, 4H, H_{ortho}), 7.65 (ddd, $^3J_{5',6'}$=7.7 Hz, $^4J_{4',6'}$=2.0 Hz, 1H, H-6′), 7.81 (d, $^3J_{4',5'}$=4.7 Hz, $^4J_{4',6'}$=2.0 Hz, 1H, H-4′); ^{13}C NMR (101 MHz, C_6D_6): δ 121.8 (C-5′), 123.1 (d, $^3J_{C,P}$=1.8 Hz, C-6), 126.8 (C-3′), 129.0 (d, $^3J_{C,P}$=7.2 Hz, C_{meta}), 129.3 (C_{para}), 130.4 (C-5), 131.0 (d, $^2J_{C,P}$=16.0 Hz, C-3), 134.3 (d, $^2J_{C,P}$=20.5 Hz, C_{ortho}), 134.4 (d, $^3J_{C,P}$=0.9 Hz, C-4), 136.1 (d, $^1J_{C,P}$=10.9 Hz, C_{ipso}), 139.6 (C-6′), 141.7 (C-2′), 152.0 (C-4′), 153.5 (d, $^2J_{C,P}$=17.8 Hz, C-1), 162.6 (C=O); ^{31}P NMR (162 MHz, C_6D_6): δ −15.5.; MS (ESI$^+$): *m*/*z* 485 (M+H+Na$^+$); Anal. Calcd for: $C_{24}H_{17}BrNO_2P$ (462.3): C 62.36, H 3.71, N 3.03; found: C 62.81, H 4.07, N 2.93.

*6.2.8. 2-(Diphenylphosphano)phenyl 2-fluoronicotinate (**3n**).* 2-Fluoronicotinic acid (247 mg, 1.75 mmol), phosphanol **2b** (536 mg, 1.93 mmol), DCC (722 mg, 3.50 mmol), and DMAP (30 mg) in dry THF (15 mL) yielded **3n** as colorless oil (280 mg, 36%); R_f=0.20 (petroleum ether/EtOAc=4:1); ^{1}H NMR (400 MHz, C_6D_6): δ 6.25 (ddd, $^3J_{4',5'}$=4.8 Hz, $^3J_{5',6'}$=7.6 Hz, $^5J_{H,F}$=1.6 Hz, 1H, H-5′), 6.84 (t, $^3J_{3,4}$=7.5 Hz, 1H, H-4), 6.98–7.02 (m, 7H, H-3, H_{meta}, H_{para}), 7.05 (t, $^3J_{4,5}$=7.5 Hz, $^3J_{5,6}$=8.0 Hz, 1H, H-5), 7.18 (dd, $^3J_{5,6}$=8.0 Hz, 1H, H-6), 7.31–7.37 (m, 4H, H_{ortho}), 7.76 (ddd, $^3J_{4',5'}$=4.8 Hz, $^4J_{4',6'}$=2.0 Hz, $^4J_{H,F}$=3.2 Hz, 1H, H-4′), 7.89 (d, $^3J_{5',6'}$=7.6 Hz, $^4J_{4',6'}$=2.0 Hz, $^4J_{H,F}$=3.7 Hz, 1H, H-6′); ^{13}C NMR (101 MHz, C_6D_6): δ 113.1 (d, $^2J_{C,F}$=24.1, C-3′), 121.0 (d, $^4J_{C,F}$=5.0 Hz, C-5′), 123.2 (C-6), 128.9 (d, $^3J_{C,P}$=7.1 Hz, C_{meta}), 129.2 (C_{para}), 130.2 (C-5), 131.2 (d, $^2J_{C,P}$=16.5 Hz, C-3), 133.9 (d, $^1J_{C,P}$=19.2 Hz, C-2), 134.3 (d, $^3J_{C,P}$=1.7 Hz, C-4), 134.4 (d, $^2J_{C,P}$=20.7 Hz, C_{ortho}), 136.1 (d, $^1J_{C,P}$=11.1 Hz, C_{ipso}), 143.6 (d, $^3J_{C,F}$=15.8 Hz, C-4′), 152.2 (d, $^3J_{C,F}$=15.9 Hz, C-6′), 153.2 (d, $^2J_{C,P}$=17.7 Hz, C-1), 160.5 (d, $^3J_{C,F}$=8.7 Hz, C=O), 162.4 (d, $^1J_{C,F}$=251.1 Hz, C-2′); ^{19}F NMR (376 MHz, C_6D_6): δ −61.1; ^{31}P NMR (162 MHz, C_6D_6): δ −14.7; MS (ESI$^+$): *m*/*z* 402 (M+H$^+$); Anal. Calcd for: $C_{24}H_{17}FNO_2P$ (401.4): C 71.82, H 4.27, N 3.49; found: C 72.01, H 4.19, N 3.51.

*6.2.9. 4-(2-(Diphenylphosphano)phenoxy)carbonyl-N,N,N-trimethylanilinium iodide borane adduct (**5**).* Compound **4** (480 mg, 1.09 mmol) was dissolved in methyl iodide (4 mL), and the mixture was stirred for 7 days at room temperature. Afterward, the precipitate was filtered and washed with diethyl ether (3×10 mL) and ethyl acetate (10 mL) to yield **5** as pale yellow solid (367 mg, 58%); mp=142 °C (decomp.); ^{1}H NMR (400 MHz, acetone-d_6): 0.80–1.70

(m, 3H, BH_3), 4.03 (s, 9H, NMe_3), 7.20–7.98 (m, 14H, Ar–H), 7.78 (d, $^3J_{o,m}$=8.5 Hz, 2H, H_{meta}), 8.23 (d, $^3J_{o,m}$=8.5 Hz, 2H, H_{ortho}); ^{31}P NMR (162 MHz, acetone-d_6): δ 19.1 (m); MS (ESI^+): m/z 454 (M^+–I), 440 (M^+–I–BH_3); MS (ESI^-): m/z 126 (I^-); Anal. Calcd for: $C_{28}H_{30}BINO_2P$ (581.23): C 57.86, H 5.20, N 2.41; found: C 57.88, H 5.51, N 2.44.

*6.2.10. 4-(2-(Diphenylphosphano)phenoxy)carbonyl-N,N,N-trimethylanilinium iodide (**6**).* Compound **5** (100 mg, 0.17 mmol) was dissolved in methanol (5 mL) and was refluxed for 2 h. Afterward, the solvent was removed and the residue was decanted with diethyl ether (3×3 mL) to yield **6** as colorless syrup (86 mg, 88%); ^{1}H NMR (400 MHz, acetone-d_6): 4.04 (s, 9H, NMe_3), 6.88–6.93 (m, 1H, Ar–H), 7.27–7.98 (m, 13H, Ar–H), 8.02 (d, ^3J=9.2 Hz, 2H, H_{meta}), 8.39 (d, ^3J=9.2 Hz, 2H, H_{ortho}); ^{13}C NMR (101 MHz, acetone-d_6): δ 57.9 (NMe_3), 122.4 ($C_{meta'}$), 123.7 (d, $^3J_{C,P}$=1.6 Hz, C-6), 127.4 (C-4), 129.7 (d, $^3J_{C,P}$=7.4 Hz, C_{meta}), 131.0 (C-5), 132.4 ($C_{ortho'}$), 134.3 (d, $^2J_{C,P}$=1.6 Hz, C-3), 134.7 (d, $^2J_{C,P}$=21.0 Hz, C_{ortho}), 136.1 (d, $^1J_{C,P}$=10.1 Hz, C_{ipso}), 152.1 ($C_{para'}$), 153.6 (d, $^2J_{C,P}$=17.4 Hz, C-1), 163.3 (C=O); ^{31}P NMR (162 MHz, acetone-d_6): δ –15.2; MS (ESI^+): m/z 440 (M^+–I); MS (ESI^-): m/z 126 (I^-); Anal. Calcd for: $C_{28}H_{27}INO_2P$ (567.40): C 59.27, H 4.80, N 2.47; found: C 59.06, H 4.81, N 2.21.

*6.2.11. 2-Iodophenyl 4-(bromomethyl)benzoate (**7**).* Compound **3e** (1.7 g, 5.03 mmol) and NBS (1.16 g, 6.54 mmol) were dissolved in CCl_4 (15 mL), benzoyl peroxide (100 mg) was added and the resulting mixture stirred at 60 °C overnight. Afterward, the solvent was removed in vacuo. After purification of the crude product via column chromatography (silica gel, petroleum ether/EtOAc=20:1) **7** was obtained as a pale yellow solid (1.06 g, 81%); mp=117 °C; R_f=0.51 (petroleum ether/EtOAc=6:1); ^{1}H NMR (400 MHz, C_6D_6): δ 3.79 (s, 2H, CH_2), 6.43 (t, $^3J_{3,4}$=7.0 Hz, 1H, H-4), 6.86 (t, $^3J_{5,6}$=7.0 Hz, 1H, H-5), 6.93 (d, $^3J_{o,m}$=8.1 Hz, 2H, H_{meta}), 6.97 (d, $^3J_{5,6}$=7.0 Hz, 1H, H-6), 7.52 (d, $^3J_{3,4}$=7.0 Hz, 1H, H-3), 8.14 (d, $^3J_{o,m}$=8.1 Hz, 2H, H_{ortho}); ^{13}C NMR (101 MHz, C_6D_6): δ 31.9 (CH_2), 90.9 (C-2), 123.6 (C-6), 127.7 (C-4), 129.4 (C_{meta}), 130.0 (C_{ipso}), 131.1 (C_{ortho}), 139.6 (C-3), 143.8 (C_{para}), 151.9 (C-1), 163.6 (C=O); MS (ESI^+): m/z 455 ($M+K^+$); Anal. Calcd for: $C_{14}H_{10}BrIO_2$ (417.0): C 40.32, H 2.42; found: C 40.30, H 2.76.

*6.2.12. 2-Iodophenyl 4-(iodomethyl)benzoate (**8**).* Compound **6** (816 mg, 1.92 mmol) was dissolved in acetone (5 mL), NaI (1.15 g, 7.67 mmol) was added and the mixture was allowed to stir at room temperature overnight. Afterward, the mixture was filtered and the solvent was removed. After purification of the crude product via column chromatography (silica gel, petroleum ether/EtOAc=20:1) **8** was obtained as a yellow solid (721 mg, 79%); mp=86 °C; R_f=0.51 (petroleum ether/EtOAc=6:1); ^{1}H NMR (400 MHz, C_6D_6): δ 3.75 (s, 2H, CH_2), 6.43 (t, $^3J_{3,4}$=7.8 Hz, 1H, H-4), 6.83–6.90 (m, 3H, H-5, H_{meta}), 6.97 (d, $^3J_{5,6}$=7.8 Hz, 1H, H-6), 7.52 (d, $^3J_{3,4}$=7.8 Hz, 1H, H-3), 8.09 (d, $^3J_{o,m}$=7.8 Hz, 2H, H_{ortho}); ^{13}C NMR (101 MHz, C_6D_6): δ 3.4 (CH_2), 90.9 (C-2), 123.6 (C-6), 127.6 (C-4), 129.1 (C_{meta}), 129.4 (C_{ipso}), 131.1 (C_{ortho}), 139.6 (C-3), 145.6 (C_{para}), 152.0 (C-1), 163.6 (C=O); MS (ESI^+): m/z 465 ($M+H^+$); Anal. Calcd for: $C_{14}H_{10}I_2O_2$ (464.04): C 36.24, H 2.17; found: C 36.04, H 2.17.

*6.2.13. 2-Iodophenyl 4-(tosyloxymethyl)benzoate (**9**).* Compound **8** (700 mg, 1.51 mmol) and silver tosylate (447 mg, 1.96 mmol) were dissolved in 10 mL acetonitrile and stirred at room temperature overnight. Afterward, the solvent was removed and purification was done via column chromatography (silica gel, petroleum ether/EtOAc=6:1) to obtain **9** as a colorless solid (683 mg, 89%); mp=91 °C; R_f=0.19 (petroleum ether/EtOAc=6:1); ^{1}H NMR (400 MHz, C_6D_6): 1.83 (s, 2H, CH_3), 4.74 (s, 2H, CH_2), 6.44 (t, $^3J_{3,4}$=7.6 Hz, 1H, H-4), 6.68 (d, $^3J_{o,m}$=8.0 Hz, 2H, OTs_{meta}), 6.83–6.97 (m, 4H, H-5, H-6, H_{meta}), 7.52 (d, $^3J_{3,4}$=8.0 Hz, 1H, H-3), 7.72 (d, $^3J_{o,m}$=8.0 Hz, 2H, OTs_{ortho}), 8.11 (d, $^3J_{o,m}$=8.5 Hz, 2H, H_{ortho}); ^{13}C NMR (101 MHz, C_6D_6): δ 21.2 (CH_3),70.4 (CH_2), 90.8 (C-2), 123.6 (C-6), 127.7 (C-4), 128.4 (C_{meta}), 129.4, 129.9 ($C_{Ar,\ OTs}$), 130.0 (C_{ipso}), 130.9 (C_{ortho}), 134.2 ($C_{q,OTs}$), 139.6 (C-3), 139.8 ($C_{q,OTs}$), 144.6 (C_{para}), 151.9 (C-1), 163.6 (C=O); MS (ESI^+): m/z 509 ($M+H^+$); Anal. Calcd for: $C_{21}H_{17}IO_5S$ (508.33): C 49.62, H 3.37, S 6.31; found: C 49.70, H 3.13, S 6.12.

*6.2.14. 2-Iodophenyl 4-(fluoromethyl)benzoate (**10**).* Compound **7** (300 mg, 0.72 mmol) and silver fluoride (228 mg, 1.80 mmol) were dissolved in acetonitrile (8 mL) and the resulting mixture stirred at room temperature in the dark overnight. Afterward, precipitate was filtered and the solvent was removed in vacuo. After purification of the crude product via column chromatography (silica gel, petroleum ether/EtOAc=20:1) **10** was obtained as a colorless solid (106 mg, 41%); mp=72 °C; R_f=0.45 (petroleum ether/EtOAc=6:1); ^{1}H NMR (400 MHz, C_6D_6): δ 4.83 (d, 2H, $^2J_{H,F}$=47.2 Hz, CH_2), 6.45 (t, $^3J_{3,4}$=6.9 Hz, 1H, H-4), 6.88 (t, $^3J_{4,5}$=6.9 Hz, $^3J_{5,6}$=7.9 Hz, 1H, H-5), 6.98 (d, $^3J_{5,6}$=7.9 Hz, 1H, H-6), 7.01 (d, $^3J_{o,m}$=7.9 Hz, 2H, H_{meta}), 7.53 (d, $^3J_{3,4}$=6.9 Hz, 1H, H-3), 8.23 (d, $^3J_{o,m}$=7.9 Hz, 2H, H_{ortho}); ^{13}C NMR (101 MHz, C_6D_6): δ 83.3 (d, $^1J_{C,F}$=169.3 Hz, CH_2), 90.9 (C-2), 123.6 (C-6), 126.9 (d, $^3J_{C,F}$=7.0 Hz, C_{meta}), 127.7 (C-4), 129.5 (C-5), 129.7 (C_{ipso}), 130.9 (C_{ortho}), 139.6 (C-3), 142.6 (d, $^2J_{C,F}$=17.3 Hz, C_{para}), 151.9 (C-1), 163.8 (C=O); ^{19}F NMR (376 MHz, C_6D_6): δ –214.2; MS (ESI^+): m/z 357 ($M+H^+$); Anal. Calcd for: $C_{14}H_{10}FIO_2$ (356.1): C 47.22, H 2.83; found C 47.55, H 2.96.

*6.2.15. 2-(Diphenylphosphano)phenyl 4-(fluoromethyl)-benzoate (**11**).* 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 **10** (100 mg, 0.32 mmol) in dry DMA (2 mL) under an argon atmosphere. The mixture was stirred at 90 °C for 3 h. Afterward, 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. Purification was done via column chromatography (silica gel, petroleum ether/EtOAc=6:1) to obtain **11** as a colorless solid (102 mg, 30%); mp=164 °C; R_f=0.79 (petroleum ether/EtOAc=1:1); ^{1}H NMR (400 MHz, C_6D_6): δ 4.77 (d, $^3J_{H,F}$=47.3 Hz, 2H, CH_2F), 6.84 (t, $^3J_{3,4}$=7.8 Hz, 1H, H-4), 6.89 (d, ^3J=8.0 Hz, 2H, $H_{meta'}$), 6.99–7.04 (m, 8H, H_{ortho}, H_{meta}), 7.06 (t, ^3J=7.6 Hz, 1H, H-5), 7.26 (dd, $^3J_{3,4}$=7.8 Hz, $^3J_{H,P}$=4.1 Hz, 1H, H-3), 7.34–7.41 (m, 4H, H_{para}), 7.99 (d, ^3J=8.0 Hz, 2H, $H_{ortho'}$); ^{13}C NMR (101 MHz, C_6D_6): δ 83.3 (d, $^1J_{C,F}$=169.8 Hz, CH_2), 123.2 (d, J=1.7 Hz, C-6), 126.4 (C-4), 126.6 (d, $^3J_{C,F}$=6.6 Hz, $C_{meta'}$), 128.9 (d, $^3J_{C,P}$=7.2 Hz, C_{meta}), 129.1 (C_{para}), 130.2 (C-5), 130.7 ($C_{ortho'}$), 132.2 (d, $^1J_{C,P}$=9.9 Hz, C-2), 134.1 (d, $^2J_{C,P}$=0.9 Hz, C-3), 134.5 (d, $^2J_{C,P}$=20.7 Hz, C_{ortho}), 136.4 (d, $^1J_{C,P}$=11.0 Hz, C_{ipso}), 142.1 (d, $^2J_{C,F}$=17.6 Hz, $C_{para'}$), 153.8 (d, $^2J_{C,P}$=17.7 Hz, C-1), 163.9 (C=O); ^{19}F NMR (376 MHz, C_6D_6): δ –214.0; ^{31}P NMR (162 MHz, C_6D_6): δ –14.3; MS (ESI^+): m/z (%)=415 ($M+H^+$); Anal. Calcd for: $C_{26}H_{20}FO_2P$ (414.41): C 75.36, H 4.86; found: C 70.41, H 5.31.

*6.2.16. 2-Iodophenyl 4-(2-fluoroethoxy)benzoate (**14**).* Under an Argon atmosphere compound **13** (208 mg, 0.54 mmol) was dissolved in dry dichloromethane (5 mL) and cooled to –78 °C. Afterward, diethylaminosulfurtrifluoride (DAST) (0.11 mL, 0.84 mmol) was added and the mixture was warmed slowly to room temperature overnight. Saturated hydrogencarbonate solution (20 mL) was added, the mixture was extracted with dichloromethane (3×15 mL), the combined organic layers were dried over Na_2SO_4, the solvent was removed, and the crude product was purified via column chromatography (silica gel, petroleum ether/EtOAc=20:1) to obtain **14** as a colorless solid (114 mg, 55%); Analytical data are in accordance to the previously published.[5a]

*6.2.17. 2-(Diphenylphosphano)phenyl 4-(2-fluoroethoxy)-benzoate (**15**).* Diphenylphosphane (188 mg, 1.01 mmol) and $Pd(OAc)_2$ in

catalytical amount were added to a solution of 2-iodophenyl 4-(2-fluoroethoxy)benzoate **14** (390 mg, 1.01 mmol) and KOAc (119 mg, 1.45 mmol) in 5 mL dry DMA at room temperature under an argon atmosphere. The mixture was allowed to stir at 70 °C overnight. Afterward, water (10 mL) and CH_3Cl (10 mL) were added, the organic layer was separated and the aqueous layer was extracted with CH_3Cl (3×10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/EtOAc=20:1→10:1) to obtain **15** as a colorless solid (270 mg, 60%). Analytical data are in accordance to the previously published.[5a]

*6.2.18. N-Benzyl-4-(2-fluoroethoxy)benzamide (**20**).* Compounds **15** (155 mg, 0.35 mmol) and **16** (56 mg, 0.42 mmol) were dissolved in a 10:1 mixture of DMF/water (3 mL) and heated at 60 °C for 2 h. Afterward, the solvent was removed and the residue was purified via column chromatography (petroleum ether/EtOAc=1:1) to obtain **20** as a colorless solid (100 mg, 95%); mp=215 °C; R_f=0.52 (petroleum ether/EtOAc=1:2); ^{1}H NMR (400 MHz, C_6D_6): δ 3.40 (dt, 2H, ^3J=3.7 Hz, $^3J_{H,F}$=27.1 Hz, CH_2CH$_2$F), 4.10 (dt, 2H, $^2J_{H,F}$=48.4 Hz, ^3J=3.7 Hz, CH$_2$CH_2F), 4.48 (d, 2H, ^3J=3.7 Hz, CH$_2$), 5.71 (br s, 1H, NH), 6.60 (d, $^3J_{3,4}$=6.6 Hz, H$_{meta}$), 6.90–7.20 (m, 5H, Bn), 7.57 (d, ^3J=8.6 Hz, 2H, H$_{ortho}$); ^{13}C NMR (101 MHz, C_6D_6): δ 44.0 (CH$_2$), 67.0 (d, $^2J_{C,F}$=20.6 Hz, CH_2CH$_2$F), 81.4 (d, $^2J_{C,F}$=170.6 Hz, CH$_2$CH_2F), 114.4 (C$_{meta}$), 127.5, 128.1, 128.8, 129.3 (C$_{Ar}$), 132.2, 139.6 (C$_q$), 161.2 (C$_{para}$), 166.0 (C=O); ^{19}F NMR (376 MHz, C_6D_6): δ −123.8; MS (ESI$^+$): *m*/*z* 296 (M$^+$+Na), 273 (M$^+$+H); Anal. Calcd for: $C_{16}H_{16}FNO_2$ (273.30): C 70.31, H 5.90, N 5.12; found: C 70.30, H 6.00.

*6.2.19. 1-Deoxy-2,3:4,5-di-O-isopropylidene-1-(4-[2-fluoroethoxy]benzamidyl)-α-D-fructopyranose (**21**).* Compounds **15** (122 mg, 0.27 mmol) and **17** (94 mg, 0.33 mmol) were dissolved in a 10:1 mixture of DMF/water (1 mL) and heated at 60 °C for 2 h. Afterward, the solvent was removed and the residue was purified via column chromatography (petroleum ether/EtOAc=1:2) to obtain **21** as a pale yellow syrup (68 mg, 60%); R_f=0.37 (petroleum ether/EtOAc=1:2); ^{1}H NMR (400 MHz, C_6D_6): δ 1.09 (s, 3H, CH$_3$), 1.21 (s, 3H, CH$_3$), 1.31 (s, 3H, CH$_3$), 1.35 (s, 3H, CH$_3$), 3.44 (dt, ^3J=3.9 Hz, $^3J_{H,F}$=28.1 Hz, 2H, CH_2CH$_2$F), 3.66–3.79 (m, 3H, H-5, H-6a, H-6b), 4.02–4.19 (m, 4H, CH$_2$CH_2F, H-1a, H-1b), 4.38 (dd, ^3J=7.8 Hz, ^3J=2.3 Hz, 1H, H-4), 4.43 (d, ^3J=2.3 Hz, 1H, H-3), 6.60–3.63 (m, 3H, H-m, NH), 7.78 (d, ^3J=7.8 Hz, H-o); ^{13}C NMR (101 MHz, C_6D_6): δ 24.1, 25.0, 26.3 (CH$_3$), 47.6 (C-1), 61.9 (C-6), 67.1 (d, $^2J_{C,F}$=20.6 Hz, CH_2CH$_2$F), 70.9 (C-5), 71.0 (C-4), 72.4 (C-3), 81.5 (d, $^1J_{C,F}$=172.3 Hz, CH$_2$CH$_2$F), 103.6, 108.3, 109.0 (C-2, C$_q$), 114.3 (C-m), 129.6 (C-o), 161.1 (C-p), 166.7 (C=O); ^{19}F NMR (376 MHz, C_6D_6): δ −223.8; MS (MALDI-TOF): *m*/*z* 426 (M$^+$+H), 425 (M$^+$); Anal. Calcd for: $C_{21}H_{28}FNO_7$ (425.45): C 59.28, H 6.63; found: C 59.30, H 6.70.

*6.2.20. 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(4-[2-fluoroethoxy]benzamidyl)-α-D-galactofuranose (**22**).* Compounds **15** (150 mg, 0.34 mmol) and **18** (116 mg, 0.41 mmol) were dissolved in a 10:1 mixture of DMF/water (1 mL) and heated at 60 °C for 2 h. Afterward, the solvent was removed and the residue was purified via column chromatography (petroleum ether/EtOAc=1:2) to obtain **22** as a colorless solid (95 mg, 66%); mp=155 °C; R_f=0.33 (petroleum ether/EtOAc=1:2); ^{1}H NMR (400 MHz, C_6D_6): δ 1.02 (s, 3H, CH$_3$), 1.13 (s, 3H, CH$_3$), 1.42 (s, 3H, CH$_3$), 1.48 (s, 3H, CH$_3$), 3.41 (dt, ^3J=4.1 Hz, $^3J_{H,F}$=27.6 Hz, 2H, CH_2CH$_2$F), 3.52–3.59 (m, 1H, H-6a), 3.83 (dd, $^3J_{4,5}$=1.6 Hz, $^3J_{3,4}$=7.9 Hz, H-4), 4.01–4.18 (m, 4H, H-2, H-6b, CH$_2$CH_2F), 4.26–4.36 (m, 1H, H-5), 4.43 (dd, $^3J_{2,3}$=2,3 Hz, $^3J_{3,4}$=7.9 Hz, 1H, H-3), 5.49 (d, ^3J=5.0 Hz, 1H, H-1), 6.29 (br s, 1H, NH), 6.57 (d, ^3J=8.7 Hz, 2H, H-m), 7.67 (d, ^3J=8.7 Hz, H-o); ^{13}C NMR (101 MHz, C_6D_6): δ 24.3, 25.0, 26.2, 26.3 (4× CH$_3$), 41.7 (C-6), 67.0 (C-5), 67.0 (d, $^2J_{C,F}$=20.5 Hz, CH_2CH$_2$F), 71.2 (C-2), 71.4 (C-3), 72.0 (C-4), 81.4 (d, $^1J_{C,F}$=172.2 Hz, CH$_2$CH$_2$F), 96.9 (C-1), 108.8, 109.3 (2× C$_{quart}$), 114.4 (C-m), 128.2 (C-i), 129.2 (C-o), 161.1 (C-p), 166.7 (C=O); ^{19}F NMR (376 MHz, C_6D_6): δ −223.7; MS (ESI$^+$): *m*/*z* 448 (M$^+$+Na), 426 (M$^+$+H); Anal. Calcd for: $C_{21}H_{28}FNO_7$ (425.45): C 59.28, H 6.63; found: C 59.73, H 6.73.

*6.2.21. 3-Deoxy-1,2:5,6-di-O-isopropylidene-3-(4-[2-fluoroethoxy]benzamidyl)-α-D-allofuranose (**23**).* Compounds **15** (122 mg, 0.27 mmol) and **19** (94 mg, 0.33 mmol) were dissolved in a 10:1 mixture of DMF/water (1 mL) and heated at 60 °C for 2 h. Afterward, the solvent was removed and the residue was purified via column chromatography (petroleum ether/EtOAc=1:2) to obtain **23** as a pale yellow syrup (58 mg, 50%); R_f=0.32 (petroleum ether/EtOAc=1:2); ^{1}H NMR (400 MHz, C_6D_6): δ 1.09 (s, 3H, CH$_3$), 1.29 (s, 3H, CH$_3$), 1.41 (s, 3H, CH$_3$), 1.50 (s, 3H, CH$_3$), 3.42 (dt, ^3J=3.9 Hz, $^3J_{H,F}$=28.0 Hz, 2H, CH_2CH$_2$F), 4.04–4.25 (m, 6H, H-3, H-5, H-6a, H-6b, CH$_2$CH_2F), 4.39–4.46 (m, 2H, H-2, H-4), 5.52 (d, ^3J=3.2 Hz, 1H, H-1), 6.48 (d, ^3J=8.6 Hz, 1H, NH), 6.58 (d, ^3J=8.6 Hz, 2H, H-m), 7.76 (d, ^3J=8.3 Hz, H-o); ^{13}C NMR (101 MHz, C_6D_6): δ 25.5, 26.3, 26.7, 26.8 (4× CH$_3$), 54.3 (CH), 65.4 (CH), 67.1 (d, $^2J_{C,F}$=20.4 Hz, CH$_2$CH$_2$F), 76.4 (CH), 79.5 (CH), 79.7 (CH), 81.3 (d, $^1J_{C,F}$=172.0 Hz, CH$_2$CH$_2$F), 104.8 (C-1), 109.7, 112.4 (2× C$_{quart}$), 114.6 (C-m), 127.6 (C-i), 129.3 (C-o), 161.4 (C-p), 166.1 (C=O); ^{19}F NMR (376 MHz, C_6D_6): δ −223.8; MS (ESI$^+$): *m*/*z* 448 (M$^+$+Na), 426 (M$^+$+H); Anal. Calcd for: $C_{21}H_{28}FNO_7$ (425.45): C 59.28, H 6.63; found: C 59.71, H 6.72.

6.3. Radiochemistry

An anion-exchanger cartridge (Waters, Sep-Pak® Light Accell™ Plus QMA) was activated by rinsing with 10 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 1.5 mL of a solution of Kryptofix 2.2.2. (10 mg/mL) and K_2CO_3 (13 mM) in 7 mL of acetonitrile and 43 mL of water. The solvents were evaporated azeotropically by subsequent addition of three 1 mL portions of dry acetonitrile under a stream of nitrogen at 120 °C.

*6.3.1. N-Benzyl-4-(2-[^{18}**F**]fluoroethoxy)benzamide ([^{18}**F**]**20**).* Ethylene ditosylate (3–4 mg in 300 μL of acetonitrile) was added to the dry [^{18}F]fluoride containing vial and the mixture was heated at 90 °C for 15 min. Subsequently, a solution of **3i** (1–2 mg in 300 μL of acetonitrile) was added and the mixture was heated another 15 min at 90 °C. In the final step, azide **16** (1–2 mg in 300 μL of acetonitrile) was added and the resulting solution was heated for 15 min at 90 °C. Samples for analytical radio-TLC/radio-HPLC were taken after cooling to room temperature. Analytical radio-TLC: R_f=0.51 (petroleum ether/EtOAc=2:3); analytical radio-HPLC: t_R=3.58 min (acetonitrile/water=60:40).

*6.3.2. 1-Deoxy-2,3:4,5-di-O-isopropylidene-1-(4-[2-[^{18}F]fluoroethoxy]benzamidyl)-α-D-fructopyranose ([^{18}**F**]**21**).* Ethylene ditosylate (2–3 mg in 300 μL of acetonitrile) was added to the dry [^{18}F] fluoride containing vial and the mixture was heated at 90 °C for 15 min. Subsequently, a solution of **3i** (1–2 mg in 300 μL of acetonitrile) was added and the mixture was heated another 15 min at 90 °C. In the final step, azide **17** (1–2 mg in 300 μL of acetonitrile) was added and the resulting solution was heated for 15 min at 90 °C. Samples for analytical radio-TLC/radio-HPLC were taken after cooling to room temperature. Analytical radio-TLC: R_f=0.44 (petroleum ether/EtOAc=1:1); analytical radio-HPLC: t_R=3.11 min (acetonitrile/water=40:60).

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18. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC–809415 (compound **3a**), CCDC–809414 (compound **3m**) and CCDC–809413 (compound **4**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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