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**Research Article**

# Carbon-14 labeling of a trifluoromethoxy group: synthesis of a substance P antagonist

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## Summary

Synthesis of a carbon-14 labeled trifluoromethoxy group has been accomplished using the stepwise oxidative fluorination–desulfurization of a readily prepared [$^{14}$C]xanthate (**5**). This novel labeling procedure allowed a rapid synthesis of substance P antagonist candidate **1** that avoided potentially more complex ring-labeling procedures. Similar procedures have been used to prepare C-14 labeled trifluoromethyl and trifluoromethylamine groups. 

**Key Words:** [$^{14}$C]trifluoromethoxy; substance P antagonist; synthesis

## Introduction

Substance P, a peptide neurotransmitter which binds preferentially to the $NK_1$ receptor, is widely distributed in the central and peripheral nervous systems, as well as in gastrointestinal tissue.[1] Substance P receptor antagonists may be of significant therapeutic use in the treatment of a wide range of clinical conditions, including migraine, pain, nausea and depression.[2] During the development of compounds of this type at Merck,[3–5] synthesis of a carbon-14 labeled analog (**1**) for animal metabolism studies was required.

With the exception of the cyclopropyl ring (due to potential *O*-dealkylation), all carbon positions of **1** appeared to be metabolically stable and suitable for labeling (Scheme 1). Since labeling of the

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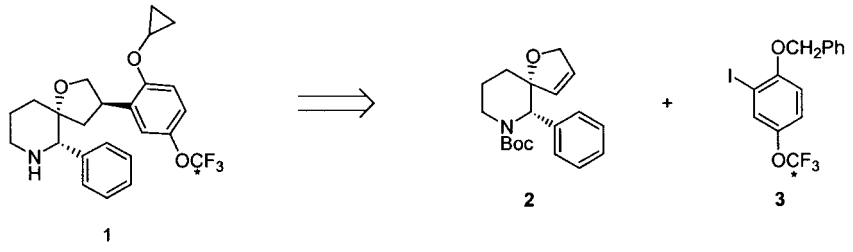



**Scheme 1.**

spirobicyclic ring system or aryl rings of **1** would probably require multiple steps, a shorter route to the target molecule was envisioned through labeling of the trifluoromethoxy group. Considering the metabolic inertness of $CF_3O$ groups,[6] as well as the availability of spiroalkene **2** from Merck Process Research for use in a Heck coupling reaction, synthesis of the [$^{14}$C]trifluoromethoxy-labeled aryl iodide **3** was initiated.

Trifluoromethoxy groups can be prepared by a number of means: (1) halogen exchange of $CCl_3O$ with $SbF_3/SbCl_5$ [7] or HF,[8] (2) alkylation of phenols with $CCl_4$/HF,[9] (3) fluorination of ArOC(O)F or ArOC(S)Cl with $SF_4$ [10] or $MoF_6$,[11] respectively, and (4) the oxidative desulfurization–fluorination of dithiocarbonates (xanthates), ArOC(S)SMe, with HF/pyridine and 1,3-dibromo-5,5-dimethylhydantoin.[12] Since xanthates are readily prepared by the reaction of phenoxides with carbon disulfide[13] (a commercially available carbon-14 source) the Kuroboshi approach,[12] known for high yields and mild conditions, appeared to be the most convenient for the rapid synthesis of the $^{14}CF_3O$ group.

There have been no previous reports of $^{14}CF_3O$-containing compounds, and only a handful of other $^{14}CF_3$-containing compounds was found in the literature. These include [$^{14}CF_3$]Trifluralin and related herbicides prepared by fluorination of the [$^{14}$C]trichloromethylated precursors with $SbF_3$,[14] and several 5-[$^{14}CF_3$]-substituted uracil derivatives.[15,†] Given the frequency with which $CF_3$ groups are represented in pharmaceutical compounds, it is surprising that there have been so few previous reports of C-14 labeling of this functionality.

[†][$^{14}$C]5-Trifluoromethyluracil is available commercially from Moravek.

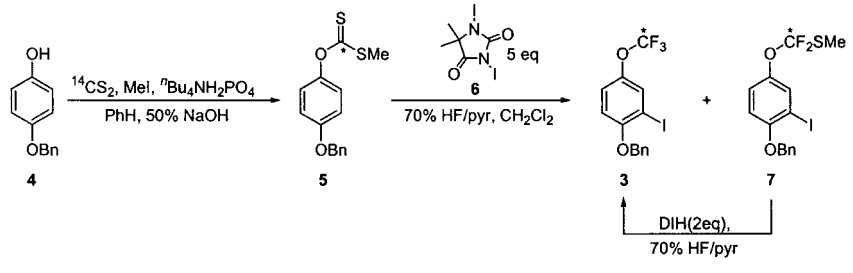
 

## Results and Discussion

The synthesis of key labeled trifluoromethoxy intermediate **3** was initiated with the formation of [$^{14}$C]xanthate **5** in 43% radiochemical yield (>99% radiochemical purity without chromatographic purification) by reaction of [$^{14}$C]carbon disulfide (1.2 eq, 150 mCi) with 4-benzyloxyphenol **4** (1.0 eq) and methyl iodide under phase transfer conditions (Scheme 2).[13] The moderate radiochemical yield is assumed to be due to loss of $^{14}CS_2$ in transfer. Kuroboshi *et al.*[12] proposed that the mechanism of their fluorination–desulfurization procedure involved serial oxidation of the xanthate sulfur atoms by $Br^+$ followed by nucleophilic attack of $F^-$at the carbon center, leading to stepwise replacement of each C–S bond with a C–F bond.

For the conversion of [$^{14}$C]xanthate **5** to [$^{14}$C]trifluoromethyl ether **3**, it was envisaged that replacing the bromonium ion source with an analogous iodonium ion source would allow conversion of the dithiocarbonate group to the trifluoromethoxy group whilst iodinating the aromatic ring *ortho* to the electron-rich benzyloxy group at the same time, to yield **3**. The oxidant 1,3-diiodo-5,5-dimethylhydantoin (DIH, **6**) was thus prepared by iodination of 5,5-dimethylhydantoin with ICl.[16] It was found that the effectiveness of **6** in the trifluoromethylation reaction was dependent on how thoroughly the final, solid DIH was washed with water and EtOAc (Table 1). DIH washed with large excesses of water and EtOAc, as described in the experimental section, resulted in the highest yields of products **3** and **7**. Variation of the DIH/$F^-$ ratio (Table 1) allowed optimization of the yields of **3** and **7**, and reduction in the amounts of radioactive byproducts.

Using the optimum conditions, reaction of 62 mCi of **5** with DIH and HF/pyridine gave 17.1 mCi (28%) of [$^{14}$C]aryl iodide and 6.5 mCi (11%) of [$^{14}$C]thioether **7** after purification to remove radioactive byproducts.



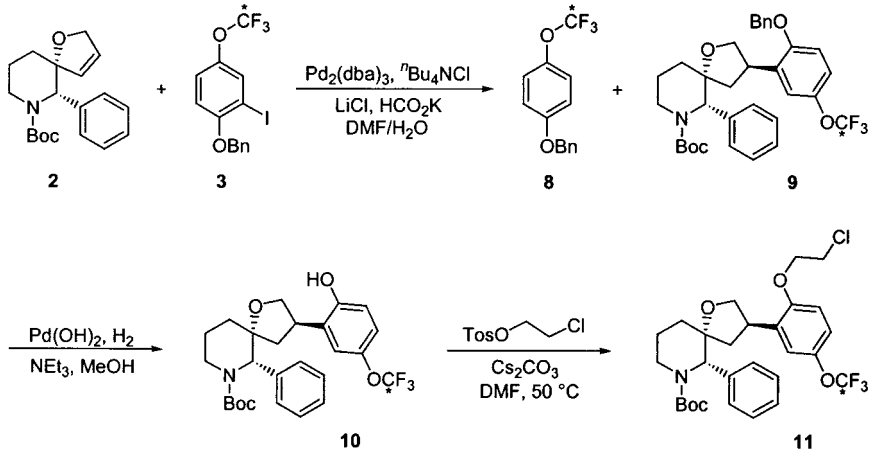

**Scheme 2.**

**Table 1.**

| Equiv of $F^-$ | Equiv of DIH (**6**) | Area % of **3**[†] | Area % of **7**[†] |
|---|---|---|---|
| 80 | 4[‡] | 7 | 25 |
| 300 | 4[‡] | 18 | 17 |
| 80 | 4[§] | 20 | 24 |
| 100 | 5[§] | 48 | 20 |
| 120 | 7[§] | 19 | 28 |

[†]Area % determined by radioactive HPLC.
[‡]DIH washed with $H_2O$ (5 ml) and EtOAc (5 ml).
[§]DIH prepared as described in experimental section.

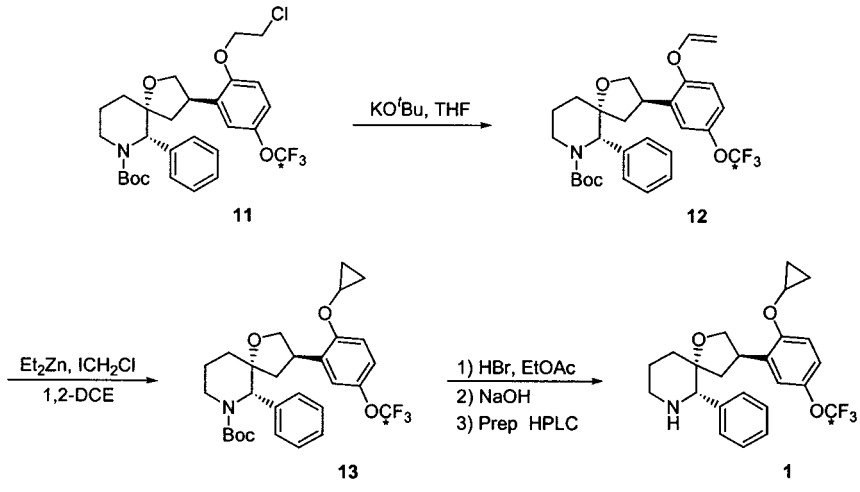



**Scheme 3.**

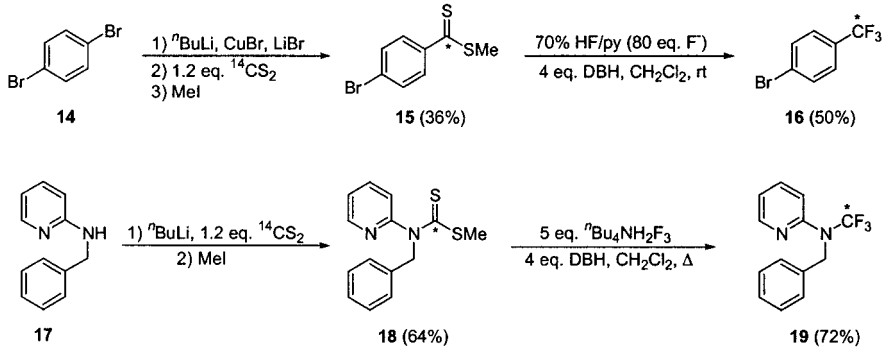
Compound **7**, a product of incomplete substitution, appears to support the mechanism of stepwise C–S bond replacement proposed by Kuroboshi.[12] This material was converted to **3** by subjecting it to similar reaction conditions giving an additional 3.2 mCi (49%) of [$^{14}$C]aryl iodide **3**. In our hands, use of DBH in the oxidative desulfurization–fluorination of **5** generally gave $<5\%$ of each of the corresponding [$^{14}$C]bromo analogs of **3** and **7**.

Having obtained **3**, in-house procedures for the preparation of **1** were followed.[3,4] This entailed the reductive Heck coupling of **3** (20.3 mCi) with spiroalkene **2**, to give the desired benzyl-protected phenol **9** (78% by radioactive HPLC) with 90% diastereomeric excess, as well as the reduced aryl iodide **8** (20%) (Scheme 3). The reaction mixture was purified on silica gel and by preparative HPLC to yield 12.9 mCi (67%) of **9**. Deprotection of **9** with Pearlman's catalyst/$H_2$ gave 10.0 mCi of




**Scheme 4.**




**Scheme 5.**

[$^{14}$C]phenol **10**, which was alkylated with chloroethyl tosylate yielding 11.3 mCi (93%) of [$^{14}$C]alkyl chloride **11**.

Dehydrohalogenation of **11** with potassium *t*-butoxide gave 11.1 mCi (98%) of [$^{14}$C]vinyl ether **12**. Cyclopropanation of **12** with $Zn(CH_2Cl)_2$,[17] formed *in situ*, gave 8.1 mCi (73%) of [$^{14}$C]cyclopropyl ether **13** after prep. HPLC purification (Scheme 4). Deprotection of **13** with HBr in EtOAc gave crude **1**, which was purified by prep. HPLC to yield 4 mCi (59 mCi/mmol) of tracer.

The application of related desulfurization–fluorination procedures[18,19] to the labeling of other types of trifluoromethyl groups was illustrated by the preparation of [$^{14}$C]aryl trifluoromethyl **16** and [$^{14}$C]trifluoromethylamine **19** (Scheme 5). Aryl dithiocarboxylate **15** was prepared from $^{14}CS_2$,[20] and converted to **16** in moderate yield using

HF/py and DBH.[18] Dithiocarbamate **18** was prepared in a similar manner, and reacted with $^{n}Bu_4NH_2F_3$ and DBH to give the first instance of a C-14 labeled trifluoromethylamine compound (**19**).[19]

## Conclusion

In conclusion, we have shown that a C-14 label can readily be incorporated into a trifluoromethoxy group, using a two step procedure from $^{14}CS_2$ *via* a [$^{14}$C]xanthate. The application of this methodology to the synthesis of a drug candidate has been demonstrated. This labeling approach has been extended to the synthesis of [$^{14}$C]aryl trifluoromethyl and [$^{14}$C]trifluoromethylamine groups as well. Although Kuroboshi and co-workers[12,18,19] have shown that electron rich aromatic rings may be halogenated under the desulfurization–fluorination conditions, this could facilitate further synthetic elaboration of the trifluoromethylated product. The high occurrence of trifluoromethyl groups in pharmaceutical and agrochemical products, together with their metabolic stability, makes the desulfurization–fluorination approach to $^{14}CF_3$ groups a potentially valuable labeling procedure.

## Experimental

Radioactivity measurements were carried out using a Bioscan Lumi-Scint liquid scintillation counter with Packard Ultima Gold™ scintillant. Analytical HPLC measurements were performed on a system consisting of Shimadzu LC-10ADVP pumps, SPD-10AVP UV detector, CTO-10ASVP column oven, SIL-10ADVP auto-injector, SCL-10AVP system controller and Packard Radiomatic™ 150TR flow monitor controlled by a Compaq computer running Shimadzu Class-VP software. Preparative and semi-preparative HPLC were performed on a system comprising of Rainin Dynamax SD-200 pumps and Shimadzu SPD-10AVP UV detector controlled by a Dell computer running Dynamax PC software.

Mass spectra were recorded on an HP1100 LCMSD instrument in API-ES positive ionization mode.

$^1$H NMR spectra were measured at 400 MHz on a Varian Unity-400 spectrometer. Chemical shifts are reported in ppm ($\delta$) and are referenced to the residual solvent peak (chloroform at 7.26 ppm).

Spiroalkene **2** was obtained from Merck Process Research. All other reagents were obtained from Aldrich Chemical Co. and used as is. Commercial anhydrous $CH_2Cl_2$, DMF and 1,2-DCE were dried over 4 Å molecular sieves before use. All reactions were carried out under a nitrogen atmosphere.

The identities of all intermediates and the final product were established by $^1$H NMR and/or by co-elution on HPLC with authentic standards obtained either in-house or form Aldrich.

### *[dithiocarbonate-$^{14}$C]Methyl 4-benzyloxyphenyl dithiocarbonate (**5**)*

The title compound was prepared by an adaptation of the procedure of Lee *et al.*[13] 4-Benzyloxyphenol **4** (2.235 mmol, 0.447 g), benzene (15 ml), tetrabutylammonium phosphate (250 µl), and 50% aq. NaOH (8 ml) were placed in a 50 ml flask, frozen in liquid $N_2$, and evacuated on a manifold. [$^{14}$C]Carbon disulfide (150.0 mCi, 2.685 mmol) was transferred to the vessel under vacuum. The yellow reaction mixture was allowed to warm to room temp, and MeI (7.23 mmol, 450 µl) was added under $N_2$. The white, biphasic mixture was stirred vigorously for 8 h at room temp, at which stage $<1\%$ of the 4-benzyloxyphenol remained by HPLC (analytical sample blown dry to remove benzene, then taken up in acetonitrile) (Zorbax Rx-C18 column, $4.6 \times 250$ mm, 1 ml/min, 210/254 nm, 70% acetonitrile/0.1%aq. $HClO_4$ isocratic for 20 min, 4-benzyloxyphenol $t_R = 3.5$ min, xanthate $t_R = 12.2$ min, $>99\%$ radiochemical purity). The reaction mixture was diluted with benzene (15 ml) and $H_2O$ (30 ml), and the layers separated. The aqueous layer was extracted with benzene ($3 \times 30$ ml), and the combined organic layers washed with $H_2O$ ($3 \times 15$ ml). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was taken up in benzene (10 ml), counted (65.6 mCi, 43.7% radiochemical yield) and analyzed by HPLC (Zorbax Rx-C18 column, same conditions as above, xanthate $t_R = 12.2$ min, $>99\%$ radiochemical purity). The [$^{14}$C]xanthate **5** solution in benzene was used without purification.

### *1,3-Diiodo-5,5-dimethylhydantoin (**6**)*

The title compound was prepared by adapting the procedure of Orazi *et al.*[16] 5,5-dimethylhydantoin (2.929 g, 22.86 mmol) was dissolved in a solution of NaOH (1.829 g, 45.71 mmol) in $H_2O$(20 ml) cooled in an ice bath. Ice (25 g) was added, and then a solution of ICl (8.164 g,

50.28 mmol) in $CHCl_3$ (25 ml) was added dropwise with vigorous stirring over 20 min at 0 °C. The slurry was stirred for a further 15 min at 0 °C, then quickly filtered, rinsing thoroughly with ice-cold $H_2O$ (200 ml) and anhydrous EtOAc (100 ml). The pale yellow solid was pumped under vacuum to constant weight (4.158 g, 48%) and stored in the dark under $N_2$.

### *[trifluoromethy1-$^{14}$C]4-Benzyloxy-3-iodophenyl trifluoromethyl ether (**3**)*

The title compound was prepared by adapting the procedure of Kuroboshi *et al.* for the synthesis of the 3-bromo analog of **3**.[12] 70% HF/pyridine solution (106 mmol $F^-$, 2.65 ml) was added dropwise to a mixture of DIH **6** (6.018 mmol, 2.287 g) in $CH_2Cl_2$ (20 ml) cooled to −78 °C over 2 min. The benzene solution of [$^{14}$C]xanthate **5** (61.7 mCi, 1.063 mmol, 9.40 ml) was concentrated *in vacuo* in $CH_2Cl_2$ (10 ml), and the solution added dropwise to the reaction mixture over 5 min. The reaction mixture was warmed to 0 °C, and stirred for 80 min. HPLC analysis at this time showed complete consumption of **5** (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 60% acetonitrile/0.1%aq. $HClO_4$ isocratic for 20 min, linear gradient to 100% acetonitrile over 5 min, 100% acetonitrile isocratic for 15 min, xanthate $t_R = 16.2$ min). The reaction mixture was quenched by the addition of 10% $NaHSO_3$/10% $NaHCO_3$ aq. solution (20 ml). The mixture was diluted with $Et_2O$ (30 ml) and $H_2O$ (30 ml), the layers separated, and the aqueous solution extracted with $Et_2O$ (5 × 15 ml). The combined organic layers were washed with $H_2O$ (3 × 15 ml), separated, dried over $Na_2SO_4$, and filtered. The solution was concentrated to a brown oil which was dissolved in MeCN (20 ml), counted (57.3 mCi), and analyzed by HPLC (ZorbaxRx-C18 column, same conditions as above, aryl iodide $t_R = 17.6$ min, thioether $t_R = 20.4$ min), which revealed a 51% : 14% [$^{14}$C]aryl iodide **3**/[$^{14}$C]thioether **7** product ratio. Other unidentified radioactive impurities observed in the HPLC assay included the following peaks: $t_R = 12.9$ min (7%), $t_R = 19.6$ min (4%), $t_R = 27.5$ min (17%), $t_R = 32.0$ min (5%) as well as a number of peaks of $< 1\%$. The crude mixture was purified by preparative HPLC (Zorbax SB-Phenyl column, 20 × 250 mm, 20 ml/min, 210/254 nm, 52% acetonitrile/0.1%aq. $HClO_4$ isocratic) to yield 17.1 mCi of [$^{14}$C]aryl iodide and 6.5 mCi (11%) of [$^{14}$C]thioether **7**. For **7**: $^1$H NMR $\delta$ 7.68 (d, 1H,

$J = 2.7$ Hz), 7.51–7.33 (m, 5H), 7.16 (dd, 1H, $J = 8.9$, 2.6 Hz), 6.81 (d, 1H, $J = 8.9$ Hz), 5.13 (s, 2H) and 2.38 (s, 3H).

[$^{14}$C]Thioether **7** (6.5 mCi, 0.116 mmol) was converted to the desired [$^{14}$C]aryl iodide **3** by reaction with DIH (0.232 mmol, 88.2 mg) and 70% HF/pyridine (0.116 mmol, 0.29 ml) in $CH_2Cl_2$ (5 ml) using the conditions described above. The crude reaction mixture was purified by preparative HPLC (Zorbax SB-Phenyl column, same method as above) to give 3.2 mCi of [$^{14}$C]aryl iodide. The purified batches of **3** were combined, concentrated, and taken up in toluene to yield 20.3 mCi (33%) of [$^{14}$C]aryl iodide **3** at 92.2% radiochemical purity. $^1$H NMR $\delta$ 7.70 (d, 1H, $J = 2.5$ Hz), 7.51–7.34 (m, 5H), 7.17 (dd, 1H, $J = 9.0$, 2.2 Hz), 6.83 (d, 1H, $J = 9.0$ Hz) and 5.15 (s, 2H).

### *[trifluoromethyl-$^{14}$C][3R,5R,6S]-7-$^t$Butyloxycarbonyl-3-(2-benzyloxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-azaspiro[4.5]decane (**9**)*

The above toluene solution of [$^{14}$C]aryl iodide **3** (19.2 mCi, 0.343 mmol, 18.9 ml) was transferred to a 4 ml reaction vial. The toluene was evaporated in a stream of $N_2$, and the residue taken up in 10% $H_2O$/DMF (780 µl). To the solution were added spiroalkene **2** (0.514 mmol, 167.1 mg), LiCl (1.713 mmol, 72.6 mg), $^n$Bu$_4$NCl (0.171 mmol, 47.6 mg), potassium formate (0.514 mmol, 43.2 mg) and $Pd_2(dba)_3$ (0.017 mmol, 15.7 mg), stirring the reaction mixture at 30 °C. After 86 h, HPLC analysis showed complete consumption of **3** (Phenomenex Customsil ODS-4 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 70% acetonitrile/$H_2O$ to 95% acetonitrile/$H_2O$ linear gradient over 40 min, reduced aryl iodide **8** $t_R = 14.7$ min, aryl iodide **3** $t_R = 20.8$ min, benzyl-protected phenol **9** $t_R = 37.2$ min, 3-epimer of **9** $t_R = 37.8$ min). The reaction mixture was diluted with $H_2O$ (2 ml) and extracted with EtOAc (5 × 2 ml). The combined organic layers were washed with $H_2O$ (2 × 2 ml), dried over $Na_2SO_4$ and concentrated. The brown residue was purified by silica gel chromatography (eluted with 5% EtOAc/hexanes) and preparative HPLC (Zorbax Rx-C18 column, 20 × 250 mm, 20 ml/min, 210/254 nm, 74% acetonitrile/0.1%aq. $HClO_4$ isocratic), then taken up in MeOH (10 ml) to give 12.9 mCi (67%) of benzyl-protected phenol **9** at 95.0% radiochemical purity by HPLC (Phenomenex Customsil ODS-4 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 70% acetonitrile/$H_2O$ to 95% acetonitrile/$H_2O$ linear gradient over 40 min, **9** $t_R = 37.2$ min). The identity of **9** was established by co-elution

with an authentic sample of unlabeled material obtained from Merck Process Research.

*[trifluoromethyl-$^{14}$C][3R,5R,6S]-7-$^{t}$Butyloxycarbonyl-3-(2-hydroxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-azaspiro[4.5]decane (**10**)*

To the above MeOH solution of [$^{14}$C]benzyl-protected phenol **9** (12.9 mCi, 0.222 mmol, 10.0 ml) were added $Et_3N$ (0.417 mmol, 58 µl) and Pd $(OH)_2$ (29 mg), and the mixture stirred at room temp under an atmosphere of $H_2$ (1 atm). After 4 h 40 min of reaction, HPLC analysis (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 80% acetonitrile/0.1% aq. $HClO_4$ isocratic for 20 min, 80% acetonitrile/0.1% aq. $HClO_4$ to 100% acetonitrile over 5 min, benzyl-protected phenol $t_R = 24.0$ min, phenol $t_R = 7.3$ min) showed complete consumption of starting material. The reaction mixture was filtered through a Celite pad and was washed with MeOH, to give 12.2 mCi (95%) of [$^{14}$C]phenol **10** at 92% radiochemical purity by HPLC. The identity of **10** was established by co-elution with an authentic sample of unlabeled material obtained from Merck Process Research.

*[trifluoromethyl-$^{14}$C][3R,5R,6S]-7-$^{t}$Butyloxycarbonyl-3-[2-(2-chlorethoxy)-5-trifluoromethoxyphenyl]-6-phenyl-1-oxa-7-azaspiro[4.5]decane (**11**)*

The MeOH solution of [$^{14}$C]phenol **10** (12.2 mCi, 0.210 mmol) was concentrated *in vacuo*, and the clear residue taken up in DMF (5 ml). Chloroethyl tosylate (0.424 mmol, 77 µl) and cesium carbonate (0.435 mmol, 142.0 mg) were added to the solution, which was then stirred at 50 °C for 7 h. HPLC analysis at this stage indicated that the reaction was complete (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 80% acetonitrile/0.1% aq. $HClO_4$ isocratic for 20 min, phenol **10** $t_R = 7.3$ min, alkyl chloride **11** $t_R = 14.8$ min). The reaction mixture was cooled to 5 °C, diluted with EtOAc (10 ml) and cold $H_2O$ (5 ml) and the layers separated. The aqueous layer was extracted with EtOAc (6 × 10 ml), and the combined organic layers washed with water (2 × 10 ml), dried over $Na_2SO_4$, and filtered to provide 11.3 mCi (93%) of [$^{14}$C]alkyl chloride **11** at 93% radiochemical purity by HPLC. The identity of **11** was established by co-elution with an authentic sample of unlabeled material obtained from Merck Process Research.

*[trifluoromethyl-$^{14}$C][3R,5R,6S]-7-$^{t}$Butyloxycarbonyl-3-(2-vinyloxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-azaspiro[4.5]decane (**12**)*

The above EtOAc solution of [$^{14}$C]alkyl chloride **11** (11.3 mCi, 0.195 mmol) was concentrated *in vacuo*, and the clear oil taken up in THF (15 ml). The solution was cooled 5 °C, and KO$^{t}$Bu (0.774 mmol, 86.8 mg) was added in a single portion. The reaction mixture was stirred at 5–8 °C for 15 min, and then at room temp for 2 h, at which time reaction was deemed to be complete by HPLC analysis (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 80% acetonitrile/0.1% aq. $HClO_4$ isocratic for 20 min, alkyl chloride **11** $t_R = 14.8$ min, vinyl ether **12** $t_R = 18.1$ min). The reaction mixture was then cooled in an ice bath, and $H_2O$ (20 ml) was added. The THF was removed in vacuo, and the remaining aqueous solution extracted with EtOAc (3 × 15 ml). The combined organic layers were washed with 1 M $NH_4Cl$ (30 ml) and $H_2O$ (2 × 20 ml), then dried over $MgSO_4$, filtered, concentrated, and taken up in toluene to provide 11.1 mCi (98%) of [$^{14}$C]vinyl ehter **12** at 93.7% radiochemical purity by HPLC. The identity of **12** was established by co-elution with an authentic sample of unlabled material obtained from Merck Process Research.

*[trifluoromethyl-$^{14}$C][3R,5R,6S]-7-$^{t}$Butyloxycarbonyl-3-(2-cyclopropyloxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-azaspiro[4.5]decane benzenesulfonate (**13**)*

$Et_2Zn$ (1 M in hexanes, 1.0 mmol, 1.0 ml) was added dropwise over 10 min to 1,2-DCE (2 ml) cooled to −28 °C. The toluene solution of [$^{14}$C]vinyl ether **12** (11.1 mCi, 0.191 mmol) prepared as described above was concentrated in vacuo in a separate flask, and the clear oil taken up in 1,2-DCE (5 ml). This solution was added dropwise to the $Et_2Zn$ solution over 5 min, maintaining a temperature of −24 to −18 °C. Chloroiodomethane (1.922 mmol, 140 µl) was added dropwise over 5 min, and the reaction mixture stirred at −16 to −7 °C for 8 h. HPLC analysis at this stage showed complete consumption of [$^{14}$C]vinyl ether (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 83% acetonitrile/0.1% aq. $HClO_4$ isocratic for 20 min, vinyl ether **12** $t_R = 13.8$ min, cyclopropyl ether **13** $t_R = 15.5$ min). The reaction was diluted with EtOAc (5 ml) at −12 °C, followed by 2M $NH_4Cl$ (5 ml) and $H_2O$ (10 ml). The layers were separated, and the aqueous extracted with EtOAc (5 × 7 ml). The combined organic layers were washed with 4% aq. $NaHCO_3$ (2 × 5 ml) and $H_2O$ (4 × 5 ml), then concentrated *in vacuo*,

and purified by preparative HPLC (Zorbax Rx-C18 column, 20 × 250 mm, 20 ml/min, 210/254 nm, 72% acetonitrile/$H_2O$ isocratic), to give 8.1 mCi (73%) of **13** at 94.9% radiochemical purity by HPLC (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 80% acetonitrile/0.1% aq. $HClO_4$ isocratic for 30 min, cyclopropyl ether $t_R = 20.7$ min). The identity of **13** was established by co-elution with an authentic sample of unlabeled material obtained from Merck Process Research.

### *[trifluoromethyl-$^{14}$C][3R,5R,6S]-3-(2-Cyclopropyloxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-azaspiro[4.5]decane benzenesulfonate (**1**)*

[$^{14}$C]Cyclopropyl ether **13** (8.1 mCi, 0.140 mmol) was taken up in EtOAc (4 ml), cooled to 0 °C, and HBr (7.072 mmol, 800 µl) was added. The reaction mixture was warmed to room temp with stirring. After 5 h, reaction was deemed to be complete by HPLC (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 80% acetonitrile/0.1% aq. $HClO_4$ isocratic for 30 min, **1** $t_R = 2.8$ min. cyclopropyl ether **13** $t_R = 20.7$ min). The reaction was cooled in an ice-bath, diluted with EtOAc (15 ml) and basified to pH 11 by the dropwise addition of 2.5 M NaOH. After further dilution with $H_2O$ (10 ml), the layers were separated, and the aqueous extracted with EtOAc (3 × 5 ml). The combined organic layers were washed with brine (2 × 10 ml) and $H_2O$ (3 × 10 ml), then concentrated *in vacuo*. The residue was purified by semi-prep HPLC (Phenomenex Luna C8 column, 9 × 250 mm, 5 ml/min, 210/254 nm, 40% acetonitrile/0.1% aq. $HClO_4$ isocratic) to yield 4.0 mCi of [$^{14}$C]**1** at 98.9% radiochemical purity (Phenomenex Luna C8 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 45% acetonitrile/0.15% aq. $HClO_4$ isocratic for 40 min, **1** $t_R = 28.1$ min). $^1$H NMR $\delta$ 8.94 (d, 1 H, $J = 11.5$ Hz), 8.34–8.29 (m, 1H), 7.56–7.53 (m, 1H), 7.45 (d, 2H, $J = 7.5$ Hz), 7.36–7.31 (m, 2H), 7.26–7.20 (m, 4H), 7.03 (d, 1H, $J = 8.9$ Hz), 6.96 (d, 1H, $J = 8.9$, 1.9 Hz), 6.90 (d, 1H, $J = 2.6$ Hz), 4.08 (d, 1H, $J = 10.2$ Hz), 3.86–3.82 (m, 1H), 3.57–3.51 (m, 2H), 3.17 (d, 1H, $J = 11.2$ Hz), 2.99–2.89 (m, 1H), 2.30–2.20 (m, 1H), 2.14–2.04 (m, 2H), 1.92–1.88 (m, 2H), 1.70–1.59 (m, 3H), 0.75–0.67 (m, 2H) and 0.59–0.49 (m, 2H).

### *[trifluoromethyl-$^{14}$C]1-Bromo-4-trifluoromethylbenzene (**16**)*

The [$^{14}$C]methyl 1-bromo-4-dithiocarboxybenzene intermediate (**15**) was prepared by modification of the procedure of Verkruijsse and

Brandsma.[20] In a flame-dried 15 ml 2-neck flask attached to a gas transfer manifold, 1.0 M *n*-BuLi in hexane (0.39 mmol, 390 µl) was added to anhyd. THF (250 µl) at −20 °C under $N_2$ atmosphere. The solution was cooled to −80 °C, and 1,4-dibromobenzene (0.372 mmol, 87.8 mg, 47.6 µl) was added dropwise over 10 min. After stirring for 10 min at −80 °C, the reaction mixture was warmed to −65 °C, and a solution of CuBr (0.074 mmol, 10.6 mg) and anhyd. LiBr (0.149 mmol, 12.9 mg) in THF (170 µl) was added dropwise over 5 min, before stirred at −65 °C for 15 min. The mixture was then frozen in liquid $N_2$, and $^{14}CS_2$ being (25 mCi, 0.446 mmol) transferred to the reaction vessel. The reaction was warmed to −40 °C for 30 min, and MeI (0.6 mmol, 85.2, mg, 37 µl) was added over 5 min. The reaction mixture was allowed to warm to rt, then quenched with 5% aq. KCN (10 ml). $Et_2O$ (20 ml) was added, the layers separated, the aqueous extracted with $Et_2O$ (3 × 10 ml). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to give 10.5 mCi of a red–brown oil with 85% radiochemical purity containing 8.9 mCi (36%) of **15** (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 50% acetonitrile/0.1% aq. $HClO_4$ linear gradient to 100% MeCN over 20 min, **15** $t_R$ = 20.4 min). Found: *m/z* 249.0. Calculated for **15**: 248.92.

The title compound was prepared using the procedure of Furuta *et al.*[18] A portion of the unpurified material (3 mCi, 0.054 mmol) was taken up in anhyd. $CH_2Cl_2$ (1.0 ml), cooled to 0 °C, and 70% HF/pyr (4.32 mmol of $F^-$, 108 µl) was added. Dibromohydantoin (0.216 mmol, 61.8 mg) was added in one portion, and the reaction mixture was stirred at room temperature for 1 h, before diluting with 10 : 1 hexane/$Et_2O$. The material was passed through a silica gel plug, eluting with 10 : 1 hexane/$Et_2O$. The eluent was washed with a 5% aq. $NaHCO_3$/$NaHSO_3$ solution, then dried over $Na_2SO_4$, filtered and concentrated to give a pale brown oil (1.95 mCi) with 70% radiochemical purity containing 1.27 mCi of **16** (50%), which was co-eluted with an authentic sample of 1-bromo-4-trifluoromethylbenzene purchased from Aldrich (Zorbax Rx-C18 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 50% acetonitrile/0.1% aq. $HClO_4$ linear gradient to 100% MeCN over 20 min, **16** $t_R$ = 14.8 min).

### *[trifluoromethyl-$^{14}$C]N-Benzyl-N-(2-pyridyl)trifluoromethylamine (**19**).[19]*

The [$^{14}$C]methyl *N*-benzyl-*N*-(2-pyridy)dithiocarbamate (**18**) intermediate was prepared by adapting the procedure of Kanie *et al.*[19] To a

solution of *N*-(2-pyridyl)benzylamine (0.353 mmol, 65.1 mg) in anhyd. THF (5 ml) was added dropwise at −15 °C, 1.6 M *n*-Buli in hexane (0.424 mmol, 265 µl). After stirring the orange–brown reaction mixture at −15 to −5 °C for 1 h, the reaction vessel was placed on a gas transfer manifold, frozen in liquid $N_2$, and $^{14}CS_2$ (25 mCi, 0.446 mmol) transferred. The reaction was stirred at room temperature overnight, then cooled to 0 °C and MeI (0.706 mmol, 100.2 mg, 44 µl) added dropwise over 5 min. The reaction was stirred at room temperature for 6 h, then quenched by the addition of sat. aq. $NaHCO_3$ (5 ml), and diluted with $CH_2Cl_2$ (10 ml). The layers were separated, and the aqueous layer extracted with $CH_2Cl_2$ (3 × 10 ml). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 17.2 mCi of a pale brown oil with 93% radiochemical purity containing 16.0 mCi (64%) of **18** (Zorbax Rx-C8 column, 4.6 × 250 mm, 1 ml/min, 210/254 nm, 5% acetonitrile/0.1% aq. $HClO_4$ linear gradient to 100% MeCN over 30 min, **18** $t_R = 25.1$ min). $^1$H NMR $\delta$ 7.52 (d, 2H $J = 7.9$ Hz) and 7.64 (d, 2H $J = 7.9$ Hz). Found: $m/z$ 277.0. Calculated for **18**: 277.06.

The title compound was prepared using the procedure of Kanie *et al.*[19] To a suspension of tetrabutylammonium dihydrogentrifluoride (0.146 mmol, 85.2 µl of 1,2-DCE solution) and dibromohydantoin (0.117 mmol, 33.3 mg) in anhyd. $CH_2Cl_2$ (1.0 ml) was added dropwise a solution of **18** (0.029 mmol, 1.72 mCi) in toluene (0.5 ml) at 0 °C. The reaction was stirred at 0 °C for 4 h then poured into pH 10 NaOH/$NaHCO_3$ buffer (10 ml). The mixture was extracted with $Et_2O$ (3 × 5 ml), and the combined organic layers dried over $MgSO_4$, filtered and concentrated to give a pale brown oil (1.29 mCi) with 90% radiochemical purity containing 1.16 mCi (72%) of **19** (Zorbax XDB-C8 column), 3.5 × 150 mm, 0.75 ml/min, 220/254 nm, 5% acetonitrile/pH 3.5 ammonium formate buffer linear gradient to 95% MeCN over 12 min, **19** $t_R = 11.0$ min). $^1$H NMR $\delta$ 8.35 (ddd, 1H, $J = 1.0, 2.0, 5.0$ Hz), 7.60 (ddd, 1H, $J = 2.1, 6.9, 7.0$ Hz), 7.34–7.18 (m, 5H), 7.10–6.98 (m, 1H), 6.99 (ddd, 1H, $J = 0.8, 4.9, 6.8$ Hz) and 5.01 (q, 2H, $J = 2.2$ Hz). Found: $m/z$ 255.2. Calculated for **19**: 255.09.

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