Use of Dibutyl[^{14}C]formamide as a Formylating Reagent in the *Vilsmeier–Haack* Reaction and Synthesis of a ^{14}C-Labeled Novel Phosphodiesterase-4 (PDE-4) Inhibitor

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A simple, high-yielding synthesis of dibutyl[^{14}C]formamide ([^{14}C]DBF; **1**) from $^{14}CO_2$ was developed (*Scheme 1*): reaction of $LiBEt_3H$ and $^{14}CO_2$ followed by aqueous workup gave $H^{14}CO_2H$ in high yield. Conversion of the [^{14}C]formic acid to **1** was effected by a standard carbodiimide coupling procedure. The utility of **1** as an alternative to dimethyl[^{14}C]formamide ([^{14}C]DMF) in alkylation reactions and in the [^{14}C]*Vilsmeier–Haack* reaction was demonstrated for several substrates (*Table 2*). A ^{14}C-labeled phosphodiesterase-4 (PDE-4) inhibitor, [^{14}C]-**2**, was synthesized by application of this technology (*Scheme 2*).

Introduction. – Dimethylformamide (DMF) is a reagent of great utility in organic synthesis and is often utilized as an electrophile in alkylations or *Vilsmeier–Haack* reactions to synthesize aldehydes (for recent reviews, see [1]). Its role as a C_1-synthon makes dimethyl[^{14}C]formamide ([^{14}C]DMF) a useful radiolabeling reagent, but due to the high cost of commercial [^{14}C]DMF and the cumbersome purifications described in literature preparations [2], it has been infrequently used in radiolabeled syntheses. The synthesis of a more lipophilic [^{14}C]DMF equivalent might allow for simplified handling as extractions with H_2O would not be precluded. Furthermore, there is ample literature precedent for expecting a DMF equivalent such as dibutyl[^{14}C]formamide ([^{14}C]DBF; **1**) to react similarly to DMF in *Vilsmeier–Haack* reactions and alkylations [1]. Based on this analogy, we developed a short, high-yielding synthesis of [^{14}C]DBF as an alternative to [^{14}C]DMF. We have also demonstrated the utility of this reagent in the radiochemical synthesis of a novel ^{14}C-labeled phosphodiesterase-4 (PDE-4) tracer, [^{14}C]-**2**.

Results and Discussion. – 1. *Dibutyl[^{14}C]formamide* ([^{14}C]DBF; **1**). The reported syntheses of [^{14}C]DMF entail the high-temperature reaction of dimethylamine and [^{14}C]formic acid [2a] or activation of the [^{14}C]formic acid as a mixed anhydride and subsequent reaction with Me_2NH [2b]. In these preparations, the purification of the product is achieved by distillation [2c]. While these are viable, high-yielding synthetic procedures for large-scale preparation, they are inefficient on a small scale. We therefore investigated a standard amide-bond-forming reaction to couple the dialkyl-

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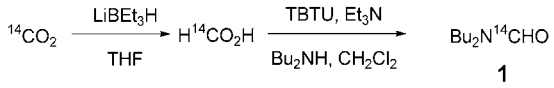
amine and [^{14}C]formic acid with the expectation that a standard extractive workup would remove the bulk of the impurities leaving the dialkyl[^{14}C]formamide in the organic layer[2]).

Reaction of $^{14}CO_2$ with $LiBEt_3H$ in THF gave [^{14}C]formic acid in 80% isolated yield after acidification with aqueous HCl solution followed by extraction with CH_2Cl_2 (*Scheme 1*). Coupling of the acid with dibutylamine in presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) or 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) gave dibutyl[^{14}C]formamide (**1**) in 90% yield and high radiochemical purity (95–99%) after flash chromatography (silica gel). The compound was stable to long term storage in CH_2Cl_2, toluene, and MeOH[3]).

Scheme 1. *Conversion of $^{14}CO_2$ to $Bu_2N^{14}CHO$*



The alkylation of dibutyl[^{14}C]formamide (**1**) with several different nucleophiles was studied (*Table 1*). The reactions were conducted with 1 equiv. of **1** and 1–2 equiv. of alkylating reagent at $-78°$. Yields were typically high and resulted in no major radiochemical by-products.

The utility of dibutyl[^{14}C]formamide (**1**) as a substrate in the *Vilsmeier–Haack* reaction was also probed. Formamide **1** was treated with either phosphorous oxychloride (= phosphoric trichloride) or diphosphoryl chloride [4] to give a *Vilsmeier–Haack* reagent which was coupled with a variety of aromatic substrates. The yields for the coupling correlate with the electronic nature of the arene, with only activated aromatic substrates producing good yields (*Table 2*). This is consistent with the general trend of the *Vilsmeier–Haack* reactions, *i.e.*, the higher the electron density of the substrate, the better the yields for the product. As reported previously by *Heaney* and co-workers [4], the use of diphosphoryl chloride gave higher and more reproducible yields than $POCl_3$, which is at least partially due to the added stability of the *Vilsmeier–Haack* reagent formed from $Cl_2PO_2POCl_2$ over the adduct with $POCl_3$.

2. *^{14}C-Labeled Phosphodiesterase-4* (PDE-4) *Inhibitor* via *[^{14}C]DBF*. In an effort to develop new therapeutic agents for the treatment of asthma, *Merck* has been engaged in the study of phosphodiesterase-4 (PDE-4) inhibitors. PDE-4 is a high-affinity cAMP-selective isozyme, and is found in almost all cell types that have been implicated in asthma pathogenesis [5]. Candidate **2** was identified as a potent, selective PDE-4 inhibitor [6]. To perform preliminary drug metabolism and distribution studies, a ^{14}C-labeled tracer was required.

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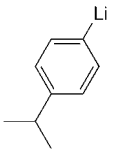
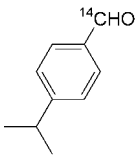
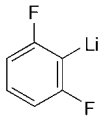
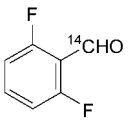
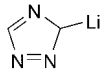
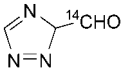
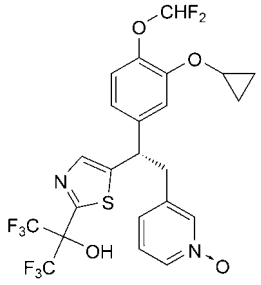
[2]) If the target of synthesis was dibutyl[^{14}C]formamide rather than [^{14}C]DMF, an extractive workup would also be possible for this synthetic approach potentially eliminating the need for the distillation. For a preliminary communation on dibutyl[^{14}C]formamide, see [3]. Portions of this work were presented at the 2004 Fall meeting of the USA Northeast Chapter International Isotope Society, King of Prussia, Pennsylvania, USA, October 28–29, 2004.

[3]) Dibutyl[^{14}C]formamide was stored at $-30°$ with no change in the HPLC trace over a 3-month period.

Table 1. *Synthesis of ^{14}C-Labeled Aldehydes* via *Alkylation of $Bu_2N^{14}CHO$*

Substrate	Product	Yield[a])
PhMgBr	Ph^{14}CHO	60%
		75%
		60%
		60%

[a]) Isolated radiochemical yield based on $Bu_2N^{14}CHO$.



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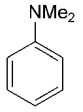
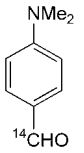
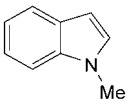
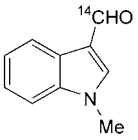
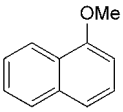
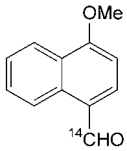
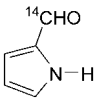
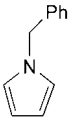
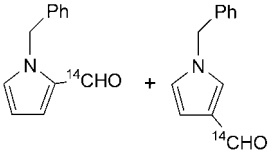
Friesen and co-workers have reported the synthesis of **2** from DMF [7]. We reasoned that replacement of DMF with [^{14}C]DBF would allow preparation of ^{14}C-labeled **2** *via* the same route (*Scheme 2*). *Vilsmeier–Haack* reaction of **1** with the dianion generated from **3** gave a ^{14}C-labeled hydroxybenzaldehyde **4** in 78% yield. Alkylation of **4** with sodium chlorodifluoroacetate in the presence of K_2CO_3 was readily accomplished. Reaction of **5** with the anion generated from thiazole **6** led to a racemic mixture of alcohol **7** in 87% yield. We could convert racemic **7** to **10**, but we felt that we would obtain a better yield of the desired (*S*)-isomer **10** by conducting oxidation of **7** to the corresponding ketone followed by asymmetric reduction as described by *Frey* and co-workers [7d]. Oxidation of **7** to **8** with MnO_2 was achieved in 85% yield. Asymmetric reduction of **8** with freshly prepared (+)-(*R*)-BINAL (= lithium {(*R*)-[1,1′-binaphthalene]-2,2′-diolato}ethoxyhydroaluminate) resulted in

Table 2. *Synthesis of ^{14}C-Labeled Aldehydes* via Vilsmeier–Haack *Reaction*

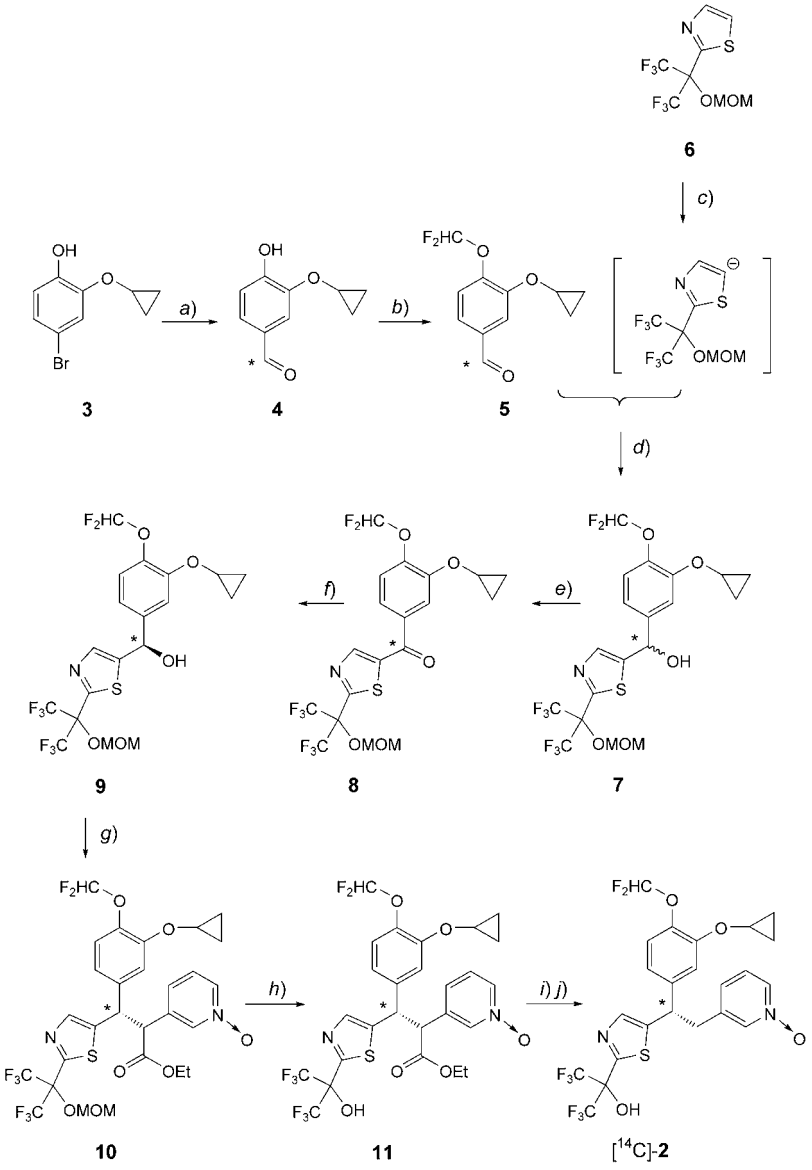
Substrate	Product	Catalyst	Yield[a])
		$POCl_3$	80%
		$POCl_3$	48%
		$Cl_2PO_2POCl_2$ $Cl_2PO_2POCl_2$	78% 82%
		$Cl_2PO_2POCl_2$	74%
		$Cl_2PO_2POCl_2$	83% (85 : 15)

[a]) Isolated radiochemical yield based on $Bu_2N^{14}CHO$.

enantiomerically enriched **9** (enantiomer ratio (*R*)/(*S*) 85 : 15). This enantiomer ratio was kept unchanged throughout the subsequent reactions. Tosylation of **9** followed by displacement with ethyl pyridine-3-acetate 1-oxide gave **10**, in which the chiral center was inverted. Removal of the methoxymethyl (MOM) protecting group in **10** yielded **11**, and hydrolysis of the ethyl ester in **11** tandem with decarboxylation provided [^{14}C]-**2**. Purification of the final tracer was effected by prep. reversed-phase HPLC followed by a prep. chiral LC separation to furnish [^{14}C]-**2** (1.6 mCi) with 99.6% radiochemical purity and 99.5% ee.

Conclusion. – We developed a simple and convenient synthesis of dibutyl[^{14}C]formamide (**1**) from $^{14}CO_2$ and showed that **1** is a good replacement for [^{14}C]DMF as a formylating reagent in ^{14}C-label synthesis. The utility of **1** was demonstrated in the preparation of a novel ^{14}C-labeled PDE-4-inhibitor tracer.

Scheme 2. *Synthesis of [^{14}C]-***2**



a) 1. BuLi (1.0 equiv.), THF, −40°, 0.5 h; 2. *s*-BuLi (1.2 equiv.), THF, *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA), −30°, 0.5 h; 3. **1**, $POCl_3$, THF, 0°, 1 h; 78%. *b*) ClF_2CCO_2Na, K_2CO_3, DMF, H_2O, 100°, 2 h; 95%. *c*) BuLi, ^{t}BuOMe, −40°, 1 h. *d*) **5**, ^{t}BuOMe, −40° to −10°, 1 h; 87% for 2 steps. *e*) MnO_2, ^{t}BuOMe, 60°, 2 h; 85%. *f*) (+)-(*R*)-BINAL, THF, TMEDA, −50°, 1 h; 65%. *g*) 1. BuLi, Ph_3CH, THF, −78°, 10 min; 2. Ts_2O, THF, −78°, 0.5 h; 3. ethyl pyridine-3-acetate 1-oxide, lithium hexamethyldisilazanide (LiHMDS), THF, 3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one (DMPU), −35°, 1 h; then this enolate was added to the tosylate soln. at −78°, and stirred at −78° for 20 h. *h*) Conc. HCl soln., MeOH, 60°, 2 h. *i*) LiOH, H_2O, r.t., 1.5 h. *j*) PhCl, 135°, 8 h; 40% for 3 steps.

Experimental Part

General. Anh. solvents were obtained from *Aldrich* and were dried over 4-Å molecular sieves for at least 24 h prior to use. FC = flash chromatography. Anal. HPLC: *Shimadzu* HPLC system with *LC-10ATVP* pumps, *SPD-10AVP* UV detector, *CTO-10ASVP* column oven heated to 40°, a *SCL-10A* controller, and a *Packard-Radiomatic™-150TR* flow monitor; product identification by HPLC comparison with unlabeled material by using either *Method A* (40 → 80% MeCN/0.1% aq. CF_3COOH soln. over 30 min), *Method B* (10 → 60% MeCN/0.1% aq. CF_3COOH soln. over 30 min), or *Method C* (40 → 100% MeCN/0.1% aq. CF_3COOH soln. over 30 min), all reversed-phase analyses were conducted on a *Zorbax-SB-C-8* column heated to 40° and were concluded with a 10 min wash with 100% MeCN; the chiral assay was performed by using *Method D* (*ChiralPak-AD* column (4.6 × 250 mm), flow rate 1.0 ml/min, 2% EtOH/hexane). ^{1}H-NMR Spectra: *Varian-U-400* spectrometer.

[^{14}C]Formic Acid. A flask containing 1M $LiBEt_3H$ (7 ml) in THF (7 mmol) was cooled in liq. N_2 and evacuated to 0.01 Torr. Then $^{14}CO_2$ (250 mCi, 53 mCi/mmol, 4.72 mmol; *NEN*) was transferred *via* standard vacuum techniques. The mixture was warmed to r.t. and stirred for 3 h. The flask was purged with N_2 for 10 min, and then 6M HCl (2 ml) was added which resulted in extensive bubbling. The THF was removed by passing a N_2 stream over the soln., and the aq. soln. was extracted with Et_2O (5 × 20 ml). The Et_2O soln. was dried ($MgSO_4$) to give 204 mCi (82%) of [^{14}C]formic acid.

Dibutyl[^{14}C]formamide (**1**; [^{14}C]DBF): *Procedure A with EDC as the Coupling Agent.* A soln. of [^{14}C]formic acid (106 mCi, 2.0 mmol, 53 mCi/mmol) in Et_2O was concentrated to near dryness under a stream of N_2, and the residual Et_2O was removed by chasing with CH_2Cl_2 (2 × 10 ml). To the oil was added CH_2Cl_2 (5 ml), *N*,*N*-dimethylpyridin-4-amine (DMAP; 228 mg, 1.87 mmol), and Et_3N (526 mg, 5.2 mmol). The resulting mixture was stirred for 1 h. A soln. of EDC (1.4 g, 7.30 mmol) and 1-hydroxy-1*H*-benzotriazole (HOBt; 1.3 g, 7.3 mmol) in CH_2Cl_2 (5 ml) was added, followed by addition of Bu_2NH (0.5 ml). The soln. was stirred for 12 h at r.t. The reaction was halted by addition of sat. $NaHCO_3$ soln. (5 ml). The org. layer was washed with 1M HCl (3 × 5 ml), $NaHCO_3$ soln. (5 ml), and sat. NaCl soln. (5 ml). The org. layer was counted at 92 mCi (90%), and the radiochemical purity was assessed by HPLC (*Method A*) at 95%.

[^{14}C]DBF (**1**): *Procedure B with TBTU as the Coupling Agent.* A soln. of 100 mCi of [^{14}C]formic acid (2.0 mmol, 56 mCi/mmol) in Et_2O was concentrated to near dryness under a stream of N_2, and the residual Et_2O was removed by chasing with CH_2Cl_2 (2 × 10 ml). To the oil was added CH_2Cl_2 (5 ml), DMAP (228 mg, 1.87 mmol), and Et_3N (526 mg, 5.2 mmol). The resulting mixture was stirred for 1 h. A soln. of 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU; 1.5 g, 7.30 mmol) in CH_2Cl_2 (5 ml) was added, followed by addition of Bu_2NH (0.5 ml). The soln. was stirred for 1 h at r.t., and then worked up as described in *Procedure A*. The org. layer was counted at 95 mCi (95%), and the radiochemical purity was assessed by HPLC (*Method A*) at 99%.

General Procedure for the Vilsmeier–Haack *Reaction: 1-Methyl-1*H*-indole-3-[^{14}C]carboxaldehyde.* A soln. of **1** (18 mCi, 0.34 mmol, 53 mCi/mmol) in toluene (1 ml) was stirred as diphosphoryl chloride (75 µl, 0.54 mmol) was added, and the resulting soln. was stirred for 30 min. A soln. of 1-methyl-1*H*-indole (52 mg, 0.40 mmol) in toluene (0.1 ml) was added, and the resulting soln. was stirred for 3 h after which HPLC (*Method A*) indicated the reaction to be complete; therefore, aq. NaOH soln. (2 ml) was added, and the biphasic soln. was stirred for 2 h. The aq. soln. was extracted with AcOEt (3 × 3 ml). The combined org. phase counted at 18 mCi (88% radiochemical purity by HPLC (*Method A*). Purification by FC (silica gel, 2% MeOH/CH_2Cl_2) gave 14 mCi (78%) of 1-methyl-1*H*-indole-3-[^{14}C]carboxaldehyde. The compound was characterized by HPLC (*Method B*).

General Procedure for Alkylation of Dibutyl[^{14}C]formamide (**1**) *with (4-Isopropylphenyl)lithium: 4-Isopropyl[^{14}C]benzaldehyde.* A soln. of 1-iodo-4-isopropylbenzene (840 µl, 4.8 mmol) in THF (3.4 ml) at −78° was stirred as 2.5M BuLi (2.9 ml, 7.2 mmol) was added *via* syringe over 5 min. After stirring for 40 min, a soln. of **1** (140 mCi 58 mCi/mmol, 2.4 mmol) in toluene (6 ml) was added, and the mixture was stirred for 1 h after which HPLC (*Method C*) showed no remaining **1**; therefore, H_2O (10 ml) was added. The soln. was extracted with Et_2O (30 ml) and the org. layer concentrated to *ca.* 3 ml. Purification by FC (silica gel, 8% Et_2O/hexane) gave 4-isopropylbenz[^{14}C]aldehyde (105 mCi, 75%); 99.7% radiochemical purity by HPLC (*Method C*).

3-(Cyclopropyloxy)-4-hydroxybenz[^{14}C]aldehyde (**4**). A soln. of 4-bromo-(2-cyclopropyloxy)phenol [7] (458 mg, 2.0 mmol) in THF (10 ml) under N_2 was cooled to −78° with stirring, and 1.4M MeLi in Et_2O (1.4 ml, 2.0 mmol) was added at such a rate that the internal temp. did not exceed −30°. The mixture was then stirred at −40° for 0.5 h, cooled to −78°, and charged with 1.3M *s*-BuLi in cyclohexane (2 ml, 2.6 mmol) at −78°. After 0.5 h, a soln. of freshly prepared **1** (78 mCi) and diphosphoryl chloride (75 µl, 0.54 mmol) in THF (3 ml) and

cyclohexane (1 ml) was added, and the resulting mixture was warmed to 0°. After 1 h, toluene (10 ml) and 2M aq. HCl (10 ml) were added. The aq. layer was extracted with toluene (5 ml × 2), the combined org. layer evaporated, and the residue purified by FC (silica gel, hexane/AcOEt 70:30): **4** (62 mCi, 79%; 53 mCi/mmol); radiochemical purity 99% (*Method B*). ^{1}H-NMR ($CDCl_3$): 0.85 (*m*, 2H); 0.90 (*m*, 2 H); 3.90 (*m*, 1 H); 6.03 (*s*, 1 H); 7.04 (*d*, *J* = 8.1, 1 H); 7.45 (*dd*, *J* = 1.9, 8.1, 1 H); 7.73 (*d*, *J* = 1.9, 1 H); 9.85 (*s*, 1 H). MS: 181.2 ([*M* + H]$^+$).

3-(Cyclopropyloxy)-4-(difluoromethoxy)benz[^{14}C]aldehyde (**5**). Under N_2, sodium chlorodifluoroacetate (213 mg, 1.4 mmol), K_2CO_3 (290 mg, 2.1 mmol), and **1** (20 mCi 53 mCi/mmol) in DMF (1.5 ml) and H_2O (0.2 ml) were mixed under stirring, degassed with N_2 for 5 min, and then stirred at 100° for 2 h. After cooling to r.t., the mixture was purified by FC (silica gel, CH_2Cl_2): **5** (19 mCi, 95%; 53 mCi/mmol); radiochemical purity 98% (*Method B*). ^{1}H-NMR ($CDCl_3$): 0.77 (*m*, 2 H); 0.82 (*m*, 2 H); 3.81 (*m*, 1 H); 6.59 (*t*, *J* = 7.2, 1 H); 7.22 (*d*, *J* = 8.2, 1 H); 7.41 (*dd*, *J* = 1.9, 8.2, 1 H); 7.77 (*d*, *J* = 1.9, 1 H); 9.88 (*s*, 1 H). MS: 230.2 ([*M* + H]$^+$).

(αRS)-α-[3-(Cyclopropyloxy)-4-(difluoromethoxy)phenyl]-2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]thiazol-5-[^{14}C]methanol (**7**). Under N_2, a soln. of 2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]thiazole [7] (**6**; 550 mg, 18.6 mmol), ^{t}BuOMe (60 ml), and toluene (10 ml) was cooled to −78°, and 1.6M BuLi in hexane (12 ml, 19 mmol) was added. The mixture was stirred at −40° for 1 h, then a soln. of **5** in toluene (2 ml) was introduced. After stirring at −40° for an additional hour, the mixture was warmed to −10°. Brine (5 ml) was added; the mixture was concentrated and purified by FC (silica gel, hexane/AcOEt 70:30): **7** (61 mCi, 89%; 53 mCi/mmol); radiochemical purity 96% (*Method B*). ^{1}H-NMR ($CDCl_3$): 0.80 (*m*, 2 H); 0.81 (*m*, 2 H); 3.52 (*s*, 3 H); 3.79 (*m*, 1 H); 5.06 (*s*, 2 H); 6.09 (*s*, 1 H); 6.52 (*t*, *J* = 7.9, 1 H); 7.00 (*dd*, *J* = 1.9, 8.3, 1 H); 7.17 (*d*, *J* = 8.3, 1 H); 7.40 (*d*, *J* = 1.9, 1 H); 7.68 (*s*, 1 H). MS: 526.1 ([*M* + H]$^+$).

[3-(Cyclopropyloxy)-4-(difluoromethoxy)phenyl)][2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]thiazol-5-yl][^{14}C]methanone (**8**). Under N_2, MnO_2 (162 mg, 1.9 mmol) and **7** (20 mCi, 0.38 mmol; 53 mCi/mmol) in ^{t}BuOMe (10 ml) were stirred at 60° for 2 h. After cooling to r.t., the mixture was purified by FC (silica gel, hexane/AcOEt 70:30): **8** (17 mCi, 85%; 53 mCi/mmol); radiochemical purity 94% (*Method C*). ^{1}H-NMR ($CDCl_3$): 0.88 (*m*, 2 H); 0.90 (*m*, 2 H); 3.59 (*s*, 3 H); 3.90 (*m*, 1 H); 5.17 (*s*, 2 H); 6.65 (*t*, *J* = 7.1, 1 H); 7.30 (*d*, *J* = 8.2, 1 H); 7.54 (*dd*, *J* = 2.1, 8.2, 1 H); 7.87 (*d*, *J* = 2.1, 1 H); 8.36 (*s*, 1 H). MS: 524.2 ([*M* + H]$^+$).

(αR)-α-[3-(Cyclopropyloxy)-4-(difluoromethoxy)phenyl]-2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]thiazol-5-[^{14}C]methanol (**9**). Under N_2, 5.68M EtOH in THF (0.50 ml in 1.62 ml) was added dropwise within 15 min to 1.0M $LiAlH_4$ in THF (8.2 g). Then, a soln. of (+)-(*R*)-[1,1′-binaphthalene]-2,2′-diol (=(+)-(*R*)-Binol) in THF (2.63 g in 7.3 ml) was added within 40 min. Over the time, the suspension turned into a soln., and the final temp. was kept at 60°. *Caution:* on addition of (+)-(*R*)-Binol, an exothermic reaction takes place. After stirring at 60° for 0.5 h, neat TMEDA (1.39 ml) was added quickly to the slurry. The mixture was stirred for 15 min at 60° before it was allowed to cool to r.t. This slurry of (+)-(*R*)-BINAL was stirred under a positive N_2 pressure, and was cooled to −78°. Ketone **7** (17 mCi, 0.3 mmol) in THF (4 ml) was then added *via* a syringe and a needle. The mixture was stirred at −50° for 1 h and then quenched with sat. NH_4Cl soln. (4 ml) at −50°. The mixture was filtered through a pad of *Celite* and purified by FC (silica gel, hexane/AcOEt 70:30): **9** (11 mCi, 65%; 53 mCi/mmol); radiochemical purity 99% (*Method C*); ratio (*R*)/(*S*) 85:15 (*Method D*). ^{1}H-NMR ($CDCl_3$): 0.80 (*m*, 2 H); 0.81 (*m*, 2 H); 3.52 (*s*, 3 H); 3.79 (*m*, 1 H); 5.06 (*s*, 2 H); 6.09 (*s*, 1 H); 6.52 (*t*, *J* = 7.9, 1 H); 7.00 (*dd*, *J* = 1.9, 8.3, 1 H); 7.17 (*d*, *J* = 8.3, 1 H); 7.40 (*d*, *J* = 1.9, 1 H); 7.68 (*s*, 1 H). MS: 526.1 ([*M* + H]$^+$).

α-{(1S)-[3-(Cyclopropyloxy)-4-(difluoromethoxy)phenyl][2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]thiazol-5-yl][^{14}C]methyl}pyridine-3-acetic Acid Ethyl Ester 1-Oxide (**10**). At −78°, 1.0M LiHMDS in THF (1.8 ml, 1.8 mmol) was added to a soln. of ethyl pyridine-3-acetate 1-oxide (364 mg, 2 mmol) in THF (2.5 ml) and DMPU (1 ml) at −78°. The mixture was then stirred at −35° for 1 h to form a lithium enolate slurry. In a separated flask, **9** (10 mCi, 0.17 mmol) in THF (3 ml) was stirred at −78°, while a drop of 1% Ph_3CH soln. in THF was added followed by 1.6M BuLi in hexane (0.2 ml, 0.32 mmol). After stirring at −78° for 10 min, a soln. of Ts_2O (130 mg, 0.4 mmol) in THF (1 ml) was introduced. After stirring at −78° for 0.5 h, the previously prepared lithium enolate slurry was transferred *via* cannula to the cold (−78°) tosylate soln. The resulting soln. was kept in a −78° freezer for 20 h. Then 1M aq. HCl was injected into the cold (−78°) mixture followed by ^{t}BuOMe. The final pH was *ca.* 6. The aq. layer was extracted with ^{t}BuOMe (5 × 10 ml), the combined org. layer evaporated, and the residue purified by FC (silica gel, MeOH/AcOEt 10:90): **10** (4.4 mCi, 44%; 53 mCi/mmol); radiochemical purity 97% (*Method C*). ^{1}H-NMR ($CDCl_3$): 0.78 (*m*, 1 H); 0.84 (*m*, 1 H); 0.99 (*t*, *J* = 7.1, 3 H); 3.50 (*s*, 3 H); 3.82 (*m*, 1 H); 4.15 (*d*, *J* = 12.0, 1 H); 4.90 (*d*, *J* = 12.0, 1 H); 5.03 (*s*, 2 H); 6.41 (*t*, *J* = 7.6, 1 H); 6.69 (*dd*, *J* = 2.0, 8.1, 1 H); 6.98 (*d*, *J* = 8.3, 1 H); 7.01 (*d*, *J* = 2.4, 1 H); 7.16 (*d*, *J* = 8.0, 1 H); 8.04 (*m*, 1 H); 8.11 (*m*, 1 H); 8.23 (*s*, 1 H). MS: 181.2 ([*M* + H]$^+$).

5-[(1S)-1-[3-(Cyclopropyloxy)-4-(difluoromethoxy)phenyl]-2-(1-oxidopyridin-3-yl)[1-^{14}C]ethyl]-α,α-bis-(trifluoromethyl)thiazol-2-methanol ([^{14}C]-**2**). A soln. of MOM ester **11** (4 mCi, 0.075 mmol) in MeOH (2 ml) and 36% HCl soln. (0.1 ml, 1 mmol) was stirred at 60° for 2 h. After cooling to r.t., a soln. of LiOH (100 mg, 2.4 mmol) in H_2O (0.5 ml) was introduced, and the soln. was stirred at r.t. for 1.5 h. Aq. 2.0M HCl was used to adjust the pH to 2, and the mixture was evaporated. Chlorobenzene (2 ml) was added and the soln. was stirred at 135° for 8 h. The mixture was purified by reversed-phase HPLC (*Zorbax-RX-C-18* prep. column 25 × 250, MeCN/H_2O/CF_3COOH 35 : 65 : 0.1) and chiral LC separation (*ChiralPak-AD* semi-prep. column 25 × 250, EtOH/hexane 2 : 98): [^{14}C]-**2** (1.6 mCi, 40%; 53 mCi/mmol); 99.6% radiochemical purity (*Method C*) and 99.5% ee (*Method D*). ^{1}H-NMR ($CDCl_3$): 0.66 (*m*, 1 H); 0.76 (*m*, 2 H); 0.79 (*m*, 2 H); 3.30 (*m*, 1 H); 3.44 (*m*, 1 H); 3.67 (*m*, 1 H); 4.45 (*t*, *J* = 7.8, 1 H); 6.49 (*t*, *J* = 7.7, 1 H); 6.78 (*dd*, *J* = 2.1, 8.2, 1 H); 6.91 (*d*, *J* = 7.8, 1 H); 7.05 (*d*, *J* = 2.1, 1 H); 7.11 (*d*, *J* = 8.2, 1 H); 7.17 (*t*, *J* = 7.8, 1 H); 7.65 (*s*, 1 H); 8.11 (*d*, *J* = 7.5, 1 H); 8.12 (*s*, 1 H). MS: 573.1 ($[M+H]^+$).

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