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Functionalization through Lithiation of (*S*)-*N*-(1-Phenylpropyl)-2-phenylquinoline-4-carboxamide. Application to the Labeling with Carbon-11 of NK-3 Receptor Antagonist SB 222200

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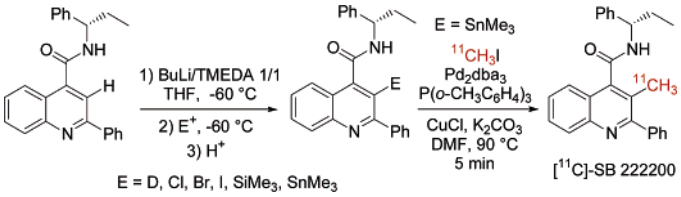
Received November 6, 2006



Lithiation of (*S*)-*N*-(1-phenylpropyl)-2-phenylquinoline-4-carboxamide with the complex *n*-BuLi/TMEDA (1/1 molar ratio) in THF at −60 °C for 5 h occurred selectively at the position 3 of the quinoline ring. This selectivity was shown by the absence of racemization of the stereogenic center and the formation of the corresponding functionalized quinolines in 59−74% yield by subsequent reaction with an electrophile at −60 °C for 1 h. The 3-trimethylstannyl derivative was subjected to a Stille reaction using methyl, phenyl, or thienyliodide to afford the alkyl or aryl quinolines in moderate to good yields. This methodology was successfully applied to the radiosynthesis of [^{11}C]SB 222200 using methyl iodide labeled with carbon-11 (β^+ emitter, $t_{1/2}$ = 20.4 min) for the in vivo study of NK-3 receptor by positron emission tomography (48−58% radiochemical yields from [^{11}C]CH_3I, decay corrected, 45 min total synthesis time).

Introduction

The human seven-transmembrane G protein-coupled NK-3 receptor mediates the pharmacological actions of neurokinin B (NKB), a small peptide endogenous neurotransmitter of the mammalian tachykinin family characterized by a predominant expression in the brain.[1] Numerous data suggest its involvement in the modulation of central monoaminergic system,[2] and recent reports have established the role of the NKB/NK-3 receptor system in a range of central nervous system (CNS) disorders such as anxiety, depression, psychosis, schizophrenia, and Parkinson's disease.[3] These properties make the NK-3 receptor a potential target for in vivo imaging studies by positron emission tomography (PET) or single photon emission computed tomography (SPECT). PET and SPECT can advantageously play a key role in various areas of clinical diagnosis and also in drug discovery. On the basis of the interactions of a biological target with an appropriate radioligand, these noninvasive techniques permit the visualization of the brain receptors during both physiological and pathophysiological conditions. To our knowledge, no PET and SPECT radioligand for the NK-3 receptor has been reported so far.

2-Phenylquinolines bearing the (*S*)-*N*-(1-phenylpropyl)carboxamide function in position 4, such as SB 223412 (or

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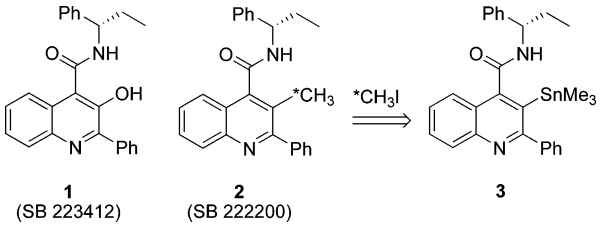
10.1021/jo062285p CCC: $37.00
Published on Web 02/24/2007

SCHEME 1. NK-3 Receptor Antagonists 1 and 2 and Strategy to Label 2 with Carbon-11 (*C = ^{12}C or ^{11}C)



1 (SB 223412) **2** (SB 222200) **3**

Talnetant **1**, hNK-3-CHO binding K_i = 1.0 nM), represent a class of highly potent antagonists of the NK-3 receptor.[4] Clinical trials revealed that Talnetant **1** had an antipsychotic efficacy with an excellent tolerability and a beneficial impact on cognitive deficit in schizophrenia.[5] With the aim of developing radioligands for PET and SPECT studies, we previously synthesized fluorinated and iodinated quinolinecarboxamides that retained the affinity of Talnetant.[6] The labeling with fluorine-18[7] (β^+ emitter, $t_{1/2}$ = 109.7 min) or iodine-123[8] (γ emitter, $t_{1/2}$ = 13.2 h) of these compounds is now underway for evaluation as NK-3 radioligands.

In the 2-phenylquinoline-4-carboxamide series, SB 222200 **2** had also to be considered as a ligand suitable for a radiolabeling (Scheme 1). Indeed, its pharmacological profile demonstrated high affinity (slightly lower than that of Talnetant **1**, hNK-3-CHO binding K_i = 4.2 nM), selectivity toward the other subtypes (K_i hNK-1/K_i hNK-3 > 10^5; K_i hNK-2/K_i hNK-3 > 250), reversible binding, and central nervous system penetration (Talnetant being only moderately CNS penetrant).[4b,e−g] From a radiochemical point of view, the presence of a methyl group onto the quinoline ring allowed us to envisage a labeling with carbon-11 (β^+ emitter, $t_{1/2}$ = 20.4 min) using a Stille coupling reaction (Scheme 1).

Preparations of ^{11}C-labeled compounds are always a challenge, requiring synthetic procedures taking into account the radioactivity, the short half-life of the radioisotope, and the use of sub-micromolar quantities of the labeled reactant. The synthesis time is a crucial parameter, and the reactions have to be rapid, efficient, selective, and preferably without any intermediate purification. Moreover, carbon-11 is available from the cyclotron only in forms of $[^{11}C]CO_2$ and $[^{11}C]CH_4$ then giving access to a limited number of labeled precursors (e.g., $[^{11}C]$HCN, $[^{11}C]$CO, $[^{11}C]COCl_2$, $[^{11}C]CH_3I$). The radiolabeling strategy based on the Stille reaction was attractive for several reasons: (i) the pallado-catalyzed cross-coupling reaction usually proceeds under conditions compatible with a broad range of functional groups;[9] (ii) it used $[^{11}C]$-methyl iodide as radiolabeled precursor synthetically well-established in all PET centers; (iii) it has been previously proved to be compatible with carbon-11 chemistry and used successfully for the synthesis of several PET radiotracers;[10,11] and (iv) the resulting $Csp^2-{}^{11}Csp^3$ bond would be stable in vivo. Due to the high reactivity of the trimethylstannyl derivatives compared to that of the tributylstannyl analogues, we undertook to work with the tin precursor **3**, although a competitive transfer of an unlabeled group leading to a reduced specific radioactivity could not be excluded.[10c]

The synthesis of quinoline **3** was not straightforward due to the limited reported methods giving direct access to 2-phenylquinoline-4-carboxylic derivatives functionalized at the position 3. Quinoline-4-carboxylic acids bearing a phenyl group at position 2 were usually prepared by Pfitzinger[4b,e,12] or Doebner[13] reactions. Recently, we developed a one-step synthesis of 2-phenylquinoline-4-carboxylates and carboxamides from arylimines and acrylates or acrylamides.[14] This former, as well as the Doebner reaction corresponding to a three-component reaction between pyruvic acid, benzaldehyde, and an aniline, was restricted to 3-unsubstituted heterocycles. The Pfitzinger reaction involving an isatin and an aryl methyl ketone in the

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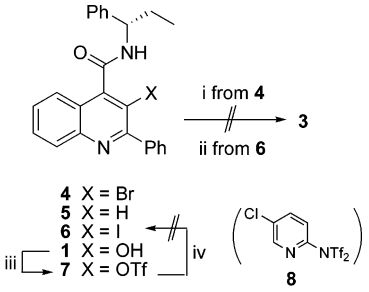
SCHEME 2. Attempts to Synthesize the Tin Precursor 3 by Palladium-Mediated Cross-Coupling between Hexamethylditin and Quinolines 4, 6, and 7[a]



[a] Reagents and conditions: (i) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, dioxane, reflux, 24−72 h; (ii) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, LiCl, THF or dioxane, reflux, 24−96 h; (iii) **8**, Et_3N, CH_2Cl_2, rt for 30 min then reflux for 2 h (98%); (iv) KI or NaI or CsI, CH_2Cl_2 or acetone or dioxane or DMF, reflux, 3−96 h.

presence of potassium hydroxide allowed the synthesis of 2-phenylquinoline-4-carboxylic acids bearing in position 3 a non-base-sensitive substituent such as a fluorine atom, an alkoxy or an amino group. 3-Chloro- and 3-bromoquinoline-4-carboxylic acids could not be obtained by this way using the corresponding α-haloacetophenone.[4b,15] Here we report our effort to design a concise and general synthesis of 2-phenylquinoline-4-carboxamides functionalized at position 3 including the preparation of tin compound **3** and the successful application to the labeling with carbon-11 of SB 222200 **2**.

Results and Discussion

Initially, we focused on the preparation of the tin precursor **3** from the 3-bromoquinoline **4** (Scheme 2). Indeed, the cross-coupling of halogenated heterocycles with hexamethylditin under catalysis by palladium complexes constitutes an attractive route for the synthesis of trimethyltin derivatives in terms of efficiency and mild experimental conditions.[16] The previously described preparation of 3-bromoquinoline **4** used a three-step synthesis (Pfitzinger then Sandmeyer reactions, and finally amidation with (*S*)-1-phenylpropylamine) starting from isatin and aminoacetophenone.[4e,15] In our hands, this sequence afforded the expected quinoline **4** in less than 10% yield, much lower than that claimed by the authors (25% yield). We noticed that both Pfitzinger and Sandmeyer reactions gave modest yields (40 and 43% yield, respectively). 3-Bromoquinoline **4** was involved in a the palladium-promoted reaction with hexamethylditin. After heating in dioxane for 3 days, the starting bromoquinoline **4** was recovered in 60% yield besides the reduced analogue **5** (11% yield) and SB 222200 **2** (25% yield). No tin product **3** was detected. These results revealed a low reactivity of the bromoquinoline **4** and the occurrence of side reactions[17] as the cleavage of the Sn−C bond from hexamethylditin in the transmetalation step and the dehalogenation.

Then we planned to use the iodoquinoline **6** as precursor of the quinoline **3**. To our knowledge, iodoquinoline **6** had not been prepared before, so we subjected 3-aminoquinoline carboxylic acid to a Sandmeyer reaction using cuprous or potassium[18] iodide. Unfortunately, all the attempts failed, and 3-iodoquinoline carboxylic acid was never detected in the crude product (data not presented).

With Talnetant[4e] **1** in hand, we next thought to use it as starting material for the synthesis of the tin precursor **3**. The strategy involved the conversion of the alcohol **1** into the triflate **7**, followed by a pallado-catalyzed cross-coupling reaction using hexamethylditin (Scheme 2).[19] The triflate **7** was obtained in a nearly quantitative yield (98%) from Talnetant **1** and triflimide **8**.[20] The treatment of triflate **7** with hexamethylditin in THF at reflux up to 4 days did not lead to the desired tin product **3**. Talnetant **1** was recovered as the main product (81% yield) with significant amounts of SB 222200 **2** (14%). The triflate **7** was also found to be totally unreactive toward iodide salts[21] for conversion into the iodoquinoline **6**.

Finally, we turned to lithiation as a promising alternative. Indeed, the directed orthometalation (DoM) is an efficient method for functionalizing (hetero)aromatic structures due to the high reactivity of the lithiated species toward electrophile reagents.[22] Surprisingly, this strategy has been poorly explored in the quinoline-4-carboxylic series. To our knowledge, the silylation of *N*,*N*-diethylquinoline-4-carboxamide[23] and the deuteration of quinoline-4-carboxylic acid[24] were the sole examples reported so far.[25] With (*S*)-*N*-(1-phenylpropyl)-2-phenylquinoline-4-carboxamide **5** being readily prepared,[4e] we envisaged the deprotonation at the position 3 activated by the carboxamide function in position 4. Such a deprotonation was not common as (i) the position 3 was sterically hindered, (ii)

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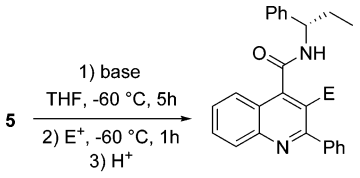
TABLE 1. Functionalization of 5 through Lithiation[a]



3, **4**, **6**, **9-11**

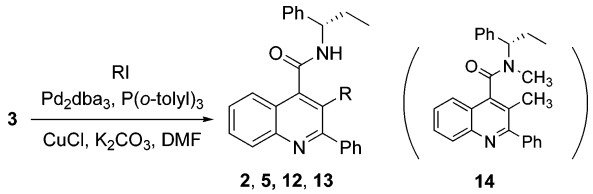
entry	base	equiv	electrophile	product	E	yield[d] (%)	$[\alpha]_D$[e]
1	LDA	10	CD_3OD[b]	**9**	D		
2	LTMP	10	CD_3OD[b]	**9**	D		
3	*t*-BuLi	10	CD_3OD[b]	**9**	D		
4	*n*-BuLi	10	CD_3OD[b]	**9**	D	34	
5	*n*-BuLi/TMEDA (1/1)	10	CD_3OD[b]	**9**	D	74	
6	*n*-BuLi/TMEDA (1/1)	4	CD_3OD[b]	**9**	D		
7	*n*-BuLi/TMEDA (1/1)	6	CD_3OD[b]	**9**	D		
8	*n*-BuLi/TMEDA (1/1)	10	I_2[c]	**6**	I	59	−47.8
9	*n*-BuLi/TMEDA (1/1)	10	CBr_4[c]	**4**	Br	63	−41.2[f]
10	*n*-BuLi/TMEDA (1/1)	10	C_2Cl_6[c]	**10**	Cl	69	−40.4[g]
11	*n*-BuLi/TMEDA (1/1)	10	$ClSnMe_3$[c]	**3**	$SnMe_3$	71	−17.3
12	*n*-BuLi/TMEDA (1/1)	10	$ClSiMe_3$[c]	**11**	$SiMe_3$	70	−18.4

[a] With 1 equiv of **5**. [b] With 350 equiv. [c] With 11−17 equiv. [d] Isolated yield. [e] $c = 0.5$, MeOH, 20 °C. [f] Lit.[4e] $[\alpha]_D = -41.4$ ($c = 0.5$, MeOH). [g] Lit.[4e] $[\alpha]_D = -40.5$ ($c = 0.5$, MeOH).

aromatic *N*-benzylcarboxamides were known to undergo lithiation α to nitrogen,[26] and (iii) the acidic benzylic proton beared the asymmetric center. However, our[6a] and other[27] previous works demonstrated that the *N*-(1-phenylpropyl) and (1-phenylethyl)carboxamide functions were not affected in the presence of an excess of LTMP (lithium 2,2,6,6-tetramethylpiperidine) or *n*-BuLi/TMEDA (*n*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethyldiamino-1,2-ethane), respectively.

Lithiation of quinoline **5** was first studied using deuterium as electrophile under several conditions of base (lithium amides or alkyllithium), solvent, temperature, and time. Deuteration was easily monitored by ^{1}H NMR showing (or not) an attenuation for the signal of the proton in position 3 characterized by a singlet at 7.84 ppm. Only significant results corresponding to lithiation for 5 h at −60 °C are reported in Table 1. With lithium amides (LTMP or LDA), even taken in large excess (10 equiv), no incorporation of deuterium has been detected (entries 1 and 2). A similar observation has been made with *t*-BuLi (entry 3). With *n*-BuLi, deuterated product **9** was obtained in moderate yield (entry 4). A significant increase in yield has been found by using a *n*-BuLi/TMEDA complex (1/1 molar ratio) (entry 5). Incorporation of deuterium at the benzylic position was never detected (the integration of the quartet at 5.24 ppm assigned to the benzylic proton remained unchanged). All attempts to use lower the amounts of base failed (entries 6 and 7). Thus, the conditions we selected for lithiation of quinoline **5** were as follows: *n*-BuLi/TMEDA (10 equiv) in THF at −60 °C for 5 h.

TABLE 2. Stille Reaction from 3[a]



2, **5**, **12**, **13** **14**

entry	R	RI equiv	*T* (° C)	time	product	yield (%)[b]	byproducts (yield %)[b]
1	*p*-tolyl	1.5	90	24 h	**12**	70	**5** (20)
2	2-thienyl	1.5	90	24 h	**13**	68	**5** (19)
3	CH_3	1.5	90	24 h	**2**	32	**5** (33) + **14** (20)
4	CH_3	1.0	90	24 h	**2**	43	**5** (51)
5	CH_3	1.0	90	6 h	**2**	39	**5** (30) + **3** (15)
6	CH_3	1.0	60	6 h	**2**	39[c]	**5** (28) + **3** (12)
7	CH_3	1.0	60	5 min	**2**	25	**5** (5) + **3** (56)

[a] With 1 equiv of **3**. [b] Isolated yield. [c] $[\alpha]_D = -34.5$ ($c = 0.8$, MeOH), lit.[4b,e] $[\alpha]_D = -36.0$ ($c = 1$, MeOH).

Functionalization of **5** was then studied with other electrophiles (iodine, carbon tetrabromide, hexachloroethane, chlorotrimethylsilane, and chlorotrimethylstannane) under the above conditions. Halogenoquinolines **4**, **6**, and **10** were prepared in yields ranging from 59 to 69% (entries 8−10). Silyl and stannyl derivatives **11** and **3** were obtained in 70−71% yields (entries 11 and 12). It is noteworthy that the optical rotations of the bromo and chloro compounds **4** and **10** were identical to that reported for these compounds prepared by the Sandmeyer reaction.[4e] These results revealed that the synthetic sequence did not lead to racemization of the stereogenic center despite the drastic lithiation conditions used.

For comparison with bromoquinoline **4**, iodoquinoline **6** was involved in the palladium-catalyzed reaction with hexamethylditin under the conditions given in Scheme 2. Once again, no tin product **3** was obtained. The starting iodoquinoline (50%) was recovered in a mixture with quinoline **5** (20%) and SB 222200 **2** (22%).

The reactivity of 3-trimethylstannylquinoline **3** was studied in the Stille reaction using *p*-tolyl, 2-thienyl, and methyl iodides (Table 2). The conditions used [Pd_2dba_3, P(*o*-tolyl)$_3$, CuCl, K_2CO_3 in DMF] were taken from those having proven reliable in radioactive chemistry.[10c] The yields of the expected compounds depended strongly on the aryl or alkyl iodide used. Reactions carried out for 24 h at 90 °C starting from *p*-tolyl or 2-thienyl iodides (1.5 equiv) led to the corresponding 3-arylquinolines **12** and **13** in about 70% yield. The quinoline **5** was isolated as the sole byproduct in 20% yield in both cases (entries 1 and 2). Under the same conditions, SB 222200 **2** was obtained using methyl iodide (1.5 equiv) in 32% yield (entry 3). In addition to the reduced product **5** formed in 35% yield, the quinoline **14** resulting from the N-methylation of SB 222200 **2** was isolated in 20% yield. The formation of **14** was avoided by decreasing the amount of methyl iodide from 1.5 to 1 equiv (entry 4). However, the yield in SB 222200 **2** was not higher than 43%, and the quinoline **5** was found as the major product (51%). By decreasing the reaction time (24 to 6 h) and eventually the temperature (90 to 60 °C), no improvement in SB 222200 **2** yield was observed (entries 5 and 6). The formation of the quinoline **5** was reduced (28−30% yields), but significant amounts of the starting trimethylstannylquinoline **3** were recovered (12−15%). As the reaction time in carbon-11 chemistry had to be minutes scale due to the short half-life of the radioisotope ($t_{1/2} = 20.4$ min), the formation of SB 222200

(25) For the synthesis of quinoline-4-carboxylic acids by introduction of the carboxylic function through lithiation, see: (a) Riego, E.; Bayo, N.; Cuevas, C.; Albericio, F.; Alvarez, M. *Tetrahedron* **2005**, *61*, 1407−1411. (b) Ondi, L.; Volle, J.-N.; Schlosser, M. *Tetrahedron* **2005**, *61*, 717−725. (c) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1999**, *55*, 12149−12156.

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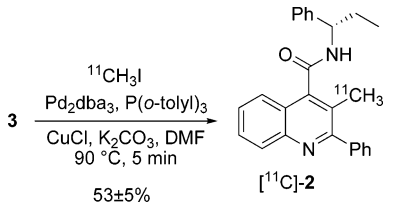
SCHEME 3. Synthesis of [^{11}C]-SB 222200 [^{11}C]-2[a]



[a] Radiochemical yield decay corrected, calculated from $^{11}CH_3I$ after HPLC purification (mean value of 10 runs).

2 was examined after 5 min of coupling reaction. Interestingly, SB 222200 **2** was obtained in 25% yield under these conditions (entry 7). The major product recovered was the starting material (56%), the quinoline **5** being isolated in only traces amount. These observations were promising for the Stille reaction in radioactive chemistry using methyl iodide labeled with carbon-11. The optical value found for SB 222200 **2** obtained in the Stille coupling was in good agreement with that reported for SB 222200 prepared by Pfitzinger from isatin and propiophenone.[4b,e] This result confirmed the absence of racemization during the overall synthesis.

The radioactive Stille reaction using [^{11}C]methyl iodide was studied according to the procedure previously developed[10c] (Scheme 3). A 5 min coupling reaction time was chosen. No formation of [^{11}C]-SB 222200 [^{11}C]-**2** was observed when the coupling was carried out at 60 °C. At 90 °C, [^{11}C]-SB 222200 [^{11}C]-**2** was obtained in radiochemical yields ranging from 48 to 58% (calculated from $^{11}CH_3I$ as limiting reagent, and decay corrected from the end of bombardment EOB, >10 runs). The overall synthesis of [^{11}C]-SB 222200 [^{11}C]-**2** was achieved within 40 min total time including HPLC purification.

In conclusion, the direct orthometalation using *n*-BuLi/TMEDA (1/1 molar ratio) was shown to be the tailor-made reaction for the synthesis of 3-functionalized analogues **3**, **4**, **6**, and **9**−**11** of the quinoline **5** without any racemization of the stereogenic center. The Stille coupling of 3-trimethylstannylquinoline **3** with methyl iodide labeled with carbon-11 constituted an efficient route to [^{11}C]-SB222200 [^{11}C]-**2**. Formulation and production of highly radioactive [^{11}C]-SB222200 [^{11}C]-**2** are now underway in the view of its evaluation as a radiotracer of NK-3 receptor for PET imaging studies.

Experimental Section

Functionalization of (*S*)-*N*-(1-Phenylpropyl)-2-phenylquinoline-4-carboxamide 5 through Lithiation: Representative Procedure. TMEDA (1.74 g, 15 mmol) was added dropwise at −20 °C to *n*-butyllithium (15 mmol) in hexanes and THF (20 mL). After cooling to −60 °C, quinoline **5** (0.549 g, 1.5 mmol) in THF (40 mL) was added to the reaction mixture. The final solution was stirred for 5 h at −60 °C, and the electrophile (16.5−25.5 mmol) in THF (20 mL) was added. Stirring was continued for 1 h, and saturated NH_4Cl (0.5 mL) was added. The mixture was warmed to room temperature, diluted in AcOEt, dried over $MgSO_4$, filtered off, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel.

Stille Reaction from 3-Trimethylstannylquinoline 3: Representative Procedure. A mixture of trimethylstannylquinoline **3** (0.170 g, 320 μmol), P(*o*-$CH_3C_6H_4)_3$ (34.7 mg, 114 μmol), CuCl (51.3 mg, 518 μmol), K_2CO_3 (72 mg, 518 μmol), aryl (353 μmol) or alkyl iodide (320 μmol), and $Pd_2(dba)_3$ (26.1 mg, 28.5 μmol) in DMF (25 mL) was stirred for 6 h at 90 °C. After concentration under vacuum, the crude residue was purified by chromatography on silica gel.

Radiosynthesis of [^{11}C]-SB 222200 [^{11}C]-2. [^{11}C]Iodomethane[28] (148−222 MBq, 4−6 mCi)[29] synthesized from cyclotron[30] produced [^{11}C]CO_2 was distilled into a vial (1 mL) previously purged with nitrogen and containing Pd_2dba_3 (1.38 mg, 1.5 μmol), P(*o*-$CH_3C_6H_4)_3$ (1.84 mg, 6.0 μmol), and DMF (100 μL). After stirring for 3 min, the radioactivity was counted and the mixture was transferred into a second vial preheated at 90 °C for 3 min and containing quinoline **3** (2 mg, 3.7 μmol), CuCl (0.60 mg, 6.0 μmol), K_2CO_3 (0.84 mg, 6.0 μmol), and DMF (100 μL). The resulting mixture was heated under stirring at 90 °C for 5 min then filtered (Rotilabo Spritzenfilter 13 mm). The radioactivity of the filtrate was measured. The filtrate was analyzed by radioTLC (R_f = 0.85 assigned to [^{11}C]-**2**) and was injected onto semipreparative HPLC (μPorasil Waters column, 9.4 × 205 mm, mobile phase pentane/ethyl acetate 85/15, flow rate 3.5 mL·min^{-1}, λ = 254 nm). The fraction containing the radioactive product [^{11}C]-**2** was collected at 15.2 min (t_R = 8 min for the tin precursor **3**). The solvents were evaporated, and the radioactivity was counted. [^{11}C]-**2** was obtained in 53 ± 5% radiochemical yield (decay corrected and calculated from [^{11}C]iodomethane, >10 runs) with a radiochemical purity up to 98% assessed by radioTLC analysis. Batches of 19−32 MBq (0.5−0.8 mCi) were obtained in about 40 min from EOB (end of bombardment, carried out for 2 min at 2 μA).

Acknowledgment. The authors thank the "PUNCH-Orga" network (Pôle Universitaire Normand de Chimie Organique) for a grant to I.B., the "Ministère de la Recherche et des Nouvelles Technologies", CNRS (Centre National de la Recherche Scientifique), CEA (Commissariat à l'Energie Atomique), the "Région Basse-Normandie", and the European Union (FEDER funding) for financial support.

Supporting Information Available: Detailed experimental procedures for the preparation of compounds **3**, **4**, **6**, **7**, and **9**−**13**, the radiosynthesis of [^{11}C]-SB 222200 [^{11}C]-**2**, product characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062285P

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(29) Curie (Ci) and Becquerel (Bq) radioactivity units (1 mCi = 10^{-3} Ci = 37 MBq = 37.10^6 Bq). Only Bq is the SI unit (1 Bq = 1 desintegration/s).

(30) IBA Cyclone 18/9.