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Rapid Methylation for the Synthesis of a ^{11}C-Labeled Tolylisocarbacyclin Imaging the IP_2 Receptor in a Living Human Brain

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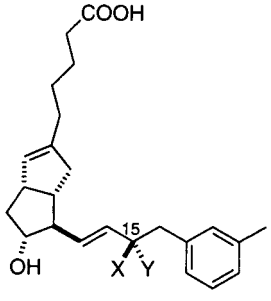
Abstract—A rapid method for Pd-promoted cross-coupling of methyl iodide and tributyltin derivatives of tolylisocarbacyclins was developed with the objective of applying to the PET study on the IP_2 receptor in a living human brain. The high efficiency is obtainable for both of the one-pot operation using a large excess of CuCl and the stepwise operation consisting of the initial preparation of a methylpalladium complex followed by mixing with the remaining requisite materials for the cross-coupling. The latter protocol allowed for the highly reproducible synthesis of an actual PET tracer with total radioactivity of several GBq. Several stannanes could be employed as precursors of PET tracers in this rapid cross-coupling reaction.

Introduction

The role of prostaglandins (PGs) in brain function has attracted intense attention in recent years, because the neuroscience is expected to represent a leading criterion in the area of PG life science in the next decades.[1] Accordingly, the development of PG molecular probes, which serve specifically for brain research, has become increasingly important. In this context, we recently developed some novel PG probes **1**–**3**.[1,2] 15*R*-TIC **1** and 15-deoxy-TIC **3** bind selectively to a PGI_2 receptor (IP_2) in the central nervous system (CNS),[2a,b] while 15*S*-TIC **2** shows a dual binding affinity for both of the IP_1 (a peripheral nervous system (PNS)-type PGI_2 receptor) and IP_2.[2a] Thus, the 15*R* and 15-deoxy derivatives **1** and **3**, and the 15*S* compound **2** will serve as good ligands for the CNS-specific and PNS-type PGI_2 receptor in the brain, respectively. Furthermore, the specific location of the IP_2 receptor was visualized by an in vitro autoradiography of rat brain slices using the tritium-labeled ligand [^{3}H]-**4**[3] and also by an in vivo positron emission tomography (PET) of a rhesus monkey[1,4] using the ^{11}C-labeled ligand [^{11}C]-**5**[5]. In the latter challenging studies, the newly devised rapid methylation reaction[6] played a crucial role to realize the synthesis of a PET tracer, 15*R*-[^{11}C]TIC methyl ester [^{11}C]-**6**. However, there remains a room for further improvement to satisfy the applicable level required for a living human brain whose volume is ca. 10 times larger than that of monkey. This paper describes an advanced rapid Stille methylation[7] using a model nonradiolabeled system and the synthesis of stannyl precursor **7** and related compounds, which represent key intermediates for the real PET study. The facile ^{13}C-incorporation into TICs is also described.



1, X = OH, Y = H: 15*R*-TIC
2, X = H, Y = OH: 15*S*-TIC
3, X = H, Y = H: 15-deoxy-TIC
[^{3}H]-**4**, X = OH, Y = ^{3}H: tritium-labeled 15*R*-TIC

Keywords: labeling; palladium and compounds; prostacyclins; tin and compounds.
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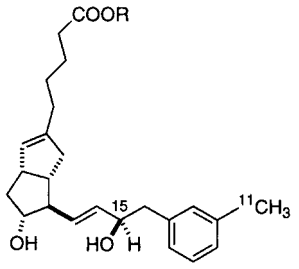
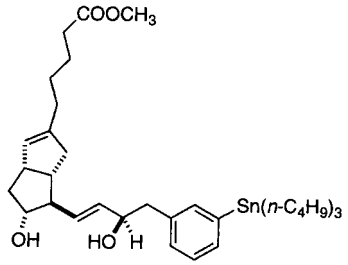
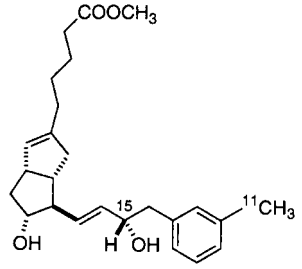


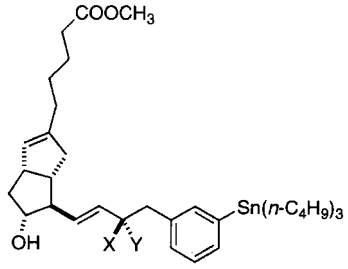
[^{11}C]-**5**, R = H: 15*R*-[^{11}C]TIC
[^{11}C]-**6**, R = CH_3: 15*R*-[^{11}C]TIC methyl ester



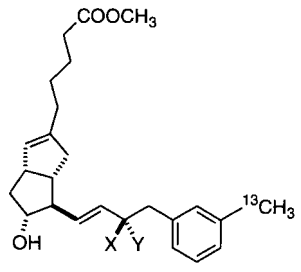
7



[^{11}C]-**8**: 15*S*-[^{11}C]TIC methyl ester



9, X = H, Y = OH
10, X = H, Y = H

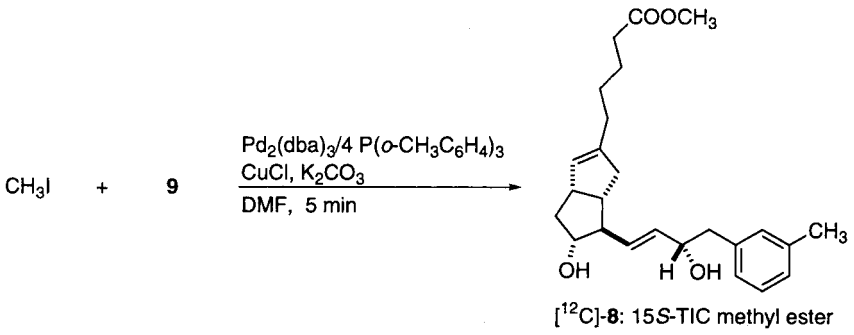


[^{13}C]-**6**, X = OH, Y = H
[^{13}C]-**8**, X = H, Y = OH
[^{13}C]-**11**, X = H, Y = H

Rapid Methylation for the Synthesis of a ^{11}C-Labeled Tolylisocarbacyclin

Conventional organic synthesis appreciates high productivity and selectivity. The criteria of synthetic efficiency in an in vivo PET study using ^{11}C as a positron nuclide are different. The investigation needs the rapid chemical reaction for the incorporation of ^{11}C into bioactive organic compounds, because of the time-limitation of the short-lived positron emitter (half-life 20.3 min).[8] Furthermore, the reaction uses a very small amount of a ^{11}C source, requiring special operational condition.[8] The synthesis of [^{11}C]TIC methyl esters, [^{11}C]-**6** and [^{11}C]-**8**, was previously accomplished based on our modified Stille reaction.[5] The reaction was promoted with a Pd(0) complex generated in situ from $Pd_2(dba)_3$ (dba=dibenzylideneacetone) and P(*o*-$CH_3C_6H_4)_3$ (1:4) in the absence of Cu(I) salt and K_2CO_3 at 130°C for 7 min in DMF to give the desired compounds in 33–45% yield[4] and with the total amount of radioactivity of 150–250 MBq. The resulting [^{11}C]-labeled compound [^{11}C]-**6** was subjected to intravenous administration to achieve the clear imaging of the IP_2 receptor in a living monkey brain.[1,9] In order to realize the imaging of the receptor in a human brain, however, 15*R*-[^{11}C]TIC methyl ester [^{11}C]-**6** with a total radioactivity even higher than several GBq is required. This strict requirement prompted us to further pursue a rapid, more efficient Stille methylation. For the synthesis of the actual TIC structure systems, we intended to apply our previously optimized methylation of tributylphenylstannane for a model reaction, which is characterized by the use of $Pd_2(dba)_3$ and P(*o*-$CH_3C_6H_4)_3$ (1:4) together with a Cu(I) salt and K_2CO_3 at 60°C.[6]

In the search for optimized conditions of a rapid Stille methylation, the 15*S* stannane **9** was selected as a standard tin substrate because of the structural resemblance to the more valuable 15*R* precursor **7** (Scheme 1). The previous coupling reaction between tributylphenylstannane and methyl iodide was conducted with a ratio of 40:1.[6] However, tributyltin derivatives of tolylisocarbacyclins are precious compounds, therefore the coupling reaction was performed for 5 min using 5 equiv. of **9** relative to methyl iodide (Scheme 1). The reaction product was purified by silica gel column chromatography, and the yields of the 15*S*-TIC methyl ester [^{12}C]-**8** were determined by HPLC using its authentic sample and anisole as an internal standard. The results are summarized in Table 1. Unexpectedly, the simple application of the same ratio between methyl iodide and metallic reagents as optimized for the model methylation of tributylphenylstannane in the one-pot operation[6] (method A) was not successful (entries 1 and 2 in Table 1). Such a discrepancy between a functionalized substrate and a simple nonpolar model compound is often observed. Reaction with modulating the ratio of metallic reagents to the tin substrate **9** was revealed that the addition of excess CuCl markedly increased the yield up to 93% (entries 3–5). We then attempted immediately to apply this method to the synthesis of the PET tracer [^{11}C]-**6** using $^{11}CH_3I$[10] and stannane **7**. However, the reaction using the above conditions lacked reproducibility for some unknown reasons. During the investigation to overcome this difficulty in harmony with the actual PET tracer synthesis, we obtained significant information from a negative



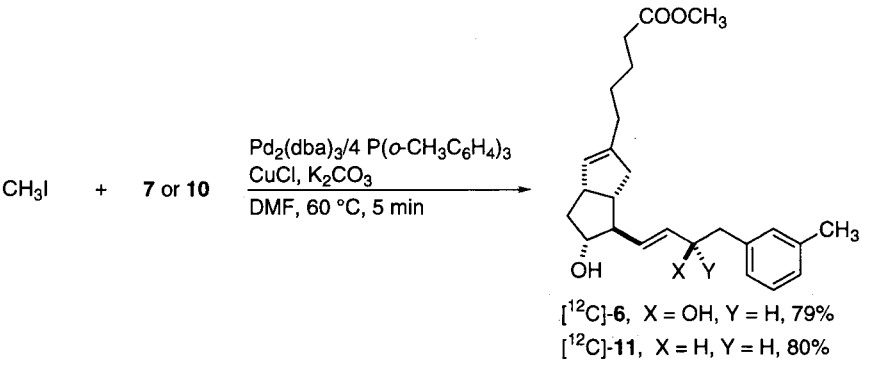
Scheme 1. Rapid cross-coupling reaction of methyl iodide and stannane **9** to [^{12}C]-**8**. (1:5 mol ratio)

experiment on the model system[6] that use of CuI in place of CuCl severely retarded the methylation of tributylphenylstannane. In order to minimize this inhibitory effect of CuI which is also produced in the actual reaction system, we changed the one-pot operation (method A) (entry 5 in Table 1) to a stepwise procedure (method B) (entry 9 in Table 1). The stepwise procedure consists of independent syntheses of a methylpalladium complex and a phenyl–copper complex at low temperatures, followed by the mixing of these species in one portion at a higher temperature. Thus, a solution of $Pd_2(dba)_3$ and P(*o*-$CH_3C_6H_4)_3$ in DMF was prepared in a dry Schlenk tube under argon atmosphere at room temperature. In another dry Schlenk tube, a solution of stannane **9**, CuCl, and K_2CO_3 in DMF was prepared under argon at room temperature. Methyl iodide was added to the solution in the first Schlenk tube and, after the color of the solution had changed to pale orange, the resulting solution containing a methylpalladium compound was transferred to the solution in the second Schlenk tube containing a phenylcopper species, after which the mixture was heated to 60°C for 5 min. This stepwise procedure gave the desired methylated derivative [^{12}C]-**8** in 74% yield using 8 equiv. of CuCl (entry 9 in Table 1). The use of higher temperatures and larger excesses of CuCl (22 equiv.) results in negative effects (entries 10 and 11 in Table 1). The methylation of the stannyl precursors **7** and **10**, by the same procedure as that in entry 9 proceeded well in 5 min, giving 15*R*-TIC methyl ester [^{12}C]-**6** and 15-deoxy-TIC methyl ester [^{12}C]-**11**[2b] in 79 and 80% yield, respectively (Scheme 2).[11] Notably, this stepwise procedure was very efficient for the actual PET tracer synthesis, giving [^{11}C]-**6** with the total radioactivity of several giga-Becquerel with a high reproducibility.[12] The PET tracer synthesis is conducted at an extremely low concentration of a positron source and therefore, the reaction is substantially slow. Under such conditions, the influence of undesired secondary reactions becomes inevitably large. The use of a trapping substrate in a large excess at high temperature accelerates the reaction to compensate such disadvantages to some extent, as usually seen in a PET study.[8] The stepwise procedure (method B) elaborated in this study will therefore provide an expedient way to overcome a problem encountered in complicated organometallic

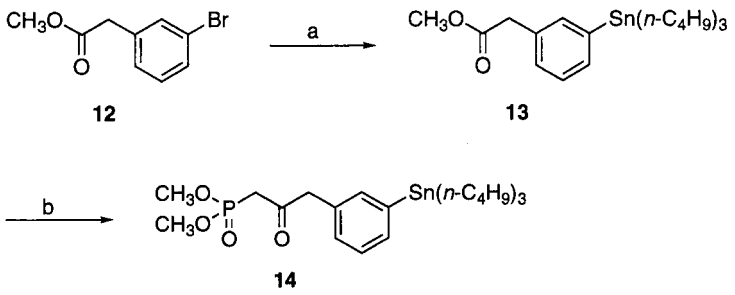
Table 1. Rapid cross-coupling of methyl iodide and stannane **9** to [^{12}C]-**8**

Entry	CH_3I:**9**:Pd:Cu[a] (molar ratio)	Operation protocol[b]	*T* (°C)	15*S*-TIC methyl ester [^{12}C]-**8** yield (%)[c]
1	1:5:1:2	A	60	0
2	1:5:2:2	A	60	0
3	1:5:2:8	A	60	25
4	1:5:2:8	A	100	23
5	1:5:2:22	A	60	93
6	1:1:2:8	B	60	8
7	1:5:2:2	B	60	10
8	1:5:2:4	B	60	55
9	1:5:2:8	B	60	74
10	1:5:2:8	B	100	24
11	1:5:2:22	B	60	66

[a] Pd=a Pd(0) complex generated in situ from $Pd_2(dba)_3$ and P(*o*-$CH_3C_6H_4)_3$ (1:4). Cu=CuCl.
[b] Method A: one-pot operation. Method B: stepwise procedure (see text).
[c] Yield based on methyl iodide and determined by HPLC analysis.



Scheme 2. Rapid cross-coupling of methyl iodide and stannane **7** or **10** by the stepwise procedure. [CH_3I:tin substrate (**7** or **10**)=1:5 mol ratio. Yield was based on methyl iodide.]



Scheme 3. Synthesis of the phosphonate **14**: (a) $[(n\text{-}C_4H_9)_3Sn]_2$, $Pd(PPh_3)_4$, 1,4-dioxane, 90°C, 24 h, 52%; (b) $(CH_3O)_2P(O)CH_3$, $n\text{-}C_4H_9Li$, THF, −78°C, 54%.

reactions conducted by a one-pot operation at an extremely low concentration.

Thus, we devised a rapid, high-yield methylation method which is applicable to the synthesis of a PET tracer with a sufficient total radioactivity for in vivo imaging of the IP_2 receptor in a human brain.[13]

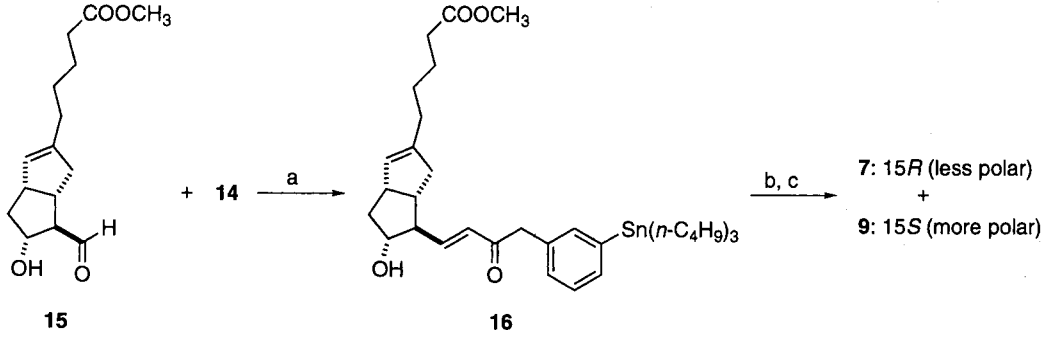
Synthesis of ^{13}C-Labeled Tolylisocarbacyclins

^{13}C is a stable isotope and ^{14}C has a long half-life and, therefore, the coupling does not require the reaction-accelerating additives such as a Cu(I) salt and K_2CO_3. Thus, the coupling between [^{13}C]methyl iodide and a stoichiometric amount of the stannane **7**, **9**, or **10**, is performed in the presence of the Pd(0) complex generated in situ from $Pd_2(dba)_3$ and $P(o\text{-}CH_3C_6H_4)_3$ (1:4) at 50°C for 15 h, giving the corresponding [^{13}C]tolylisocarbacyclin methyl esters [^{13}C]-**6**, [^{13}C]-**8**, and [^{13}C]-**11**, in 78, 82, and 83% yield, respectively. These isotope-labeled TIC derivatives can be used for a study on biometabolism of TICs.

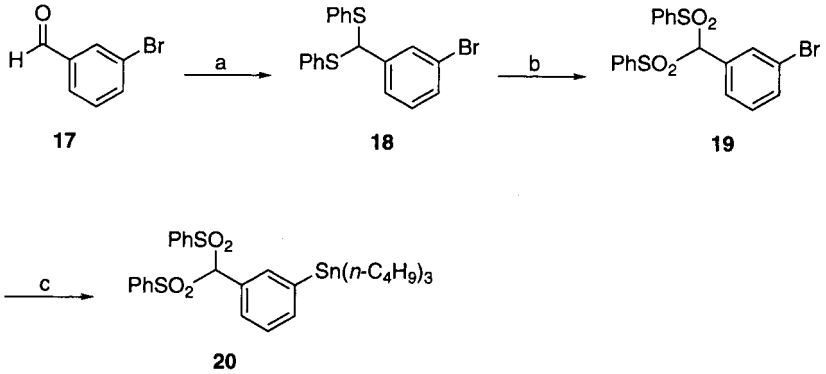
Synthesis of Stannyl Precursors 7, 9, and 10

Synthesis of the phosphonate 14 (Scheme 3)

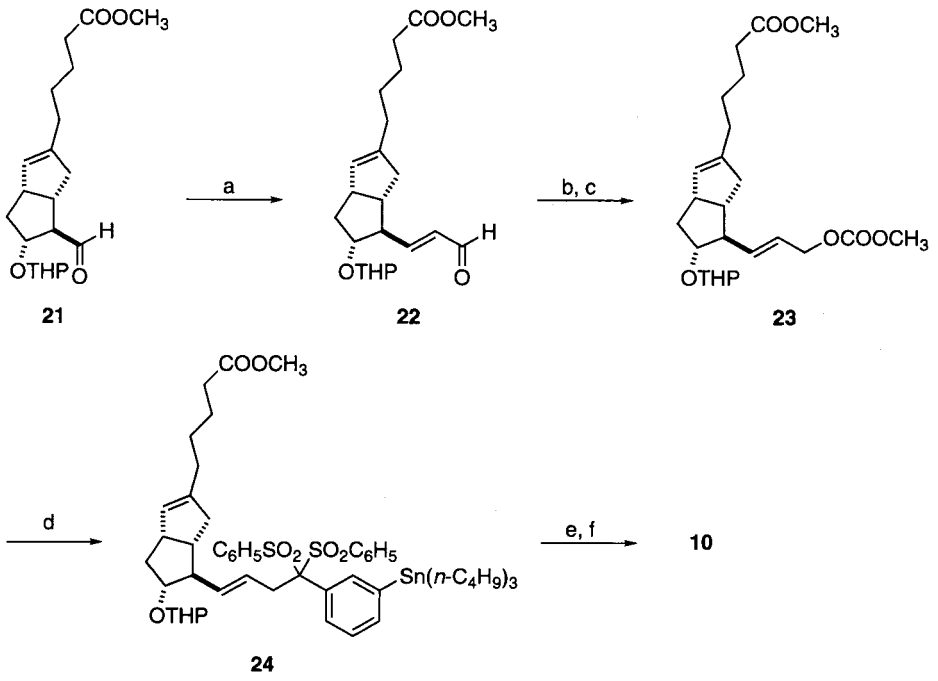
The cross-coupling of methyl 3-bromophenylacetate **12** with hexa-*n*-butylditin in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0)[14] gave the tri-*n*-butyltin-substituted derivative **13** in 52% yield. The resulting methyl ester **13** was condensed with the anion of dimethyl methylphosphonate to afford the β-ketophosphonate **14**, a Horner–Emmons reagent, in 54% yield.



Scheme 4. Synthesis of (15*R*)-16-[3-(tri-*n*-butylstannyl)phenyl]-17,18,19,20-tetranorisocarbacyclin methyl ester **7** and its 15-epimer **9**: (a) NaH, DME, 91%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH, 87%; (c) separation of the C(15) epimers.



Scheme 5. Synthesis of the sulfone **20**: (a) PhSH, $(CH_3)_3SiCl$, $CHCl_3$, 99%; (b) 30% H_2O_2, CH_3COOH, $(CH_3CO)_2O$, 70%; (c) $[(n\text{-}C_4H_9)_3Sn]_2$, $Pd(PPh_3)_4$, 1,4-dioxane, 90°C, 17 h, 44%.



Scheme 6. Synthesis of 15-deoxy-16-[3-(tri-*n*-butylstannyl)phenyl]-17,18,19,20-tetranorisocarbacyclin methyl ester **10**: (a) $(C_6H_5)_3PCHCHO$, benzene, reflux, 66%; (b) $NaBH_4$, CH_3OH; (c) $ClCOOCH_3$, 4-(dimethylamino)pyridine, CH_2Cl_2, 91% (2 steps); (d) $Pd_2(dba)_3{\cdot}CHCl_3$, dppe, 3-[(*n*-$C_4H_9)_3Sn]C_6H_4CH(SO_2C_6H_5)_2$ (**20**), THF, 60°C, 98%; (e) Mg, CH_3OH; (f) pyridinium *p*-toluenesulfonate, CH_3OH, 69% (2 steps).

Synthesis of 7 and 9 (Scheme 4)

The Horner–Emmons reaction of the aldehyde **15**[15] and the phosphonate **14** gave the enone **16** in 91% yield. The chemoselective 1,2-reduction of the C(15) keto group with $NaBH_4$ in the presence of cerium(III) chloride[16] gave a 1:1 mixture of the stereoisomeric diol **7** (less polar), and **9** (more polar) in 87% yield, accompanied by a small amount of the destannylated compound. The C(15) stereoisomers were separated by conventional silica gel column chromatography.

Reaction of methyl iodide and a stannyl precursor **9** was accomplished by the stoichiometric use of the Pd(0) complex generated in situ from $Pd_2(dba)_3$ and P(*o*-$CH_3C_6H_4)_3$ (1:4) in DMF, giving [^{12}C]-**8** in 73% yield, identical with an authentic sample. The alcohol **9** has the *S* configuration at the C(15) stereocenter, while **7** possesses the *R* configuration.

Synthesis of the sulfone 20 (Scheme 5)

Reaction of 3-bromobenzaldehyde **17** with benzenthiol in the presence of chlorotrimethylsilane afforded the dithioacetal **18** in 99% yield. Oxidation of **18** with hydrogen peroxide under acidic conditions gave the sulfone **19** in 70% yield. Condensation of **19** with hexa-*n*-butylditin in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) gave the stannane **20** in 44% yield.[14]

Synthesis of 10 (Scheme 6)

The Wittig reaction of the aldehyde **21**[15] with (formylmethylene)triphenylphosphorane gave (*E*)-α,β-unsaturated aldehyde **22** in 66% yield.[17] Carbonyl reduction of **22** using $NaBH_4$, followed by methoxycarbonylation of the alcohol with $ClCOOCH_3$ gave the allyl carbonate **23** in 91% overall yield. The cross-coupling reaction between **23** and the sulfone **20** with $Pd_2(dba)_3{\cdot}CHCl_3$/1,2-bis(diphenylphosphino)ethane (1:3)[18] gave the sulfone **24** in 98% yield. Reductive removal of the $C_6H_5SO_2$ group in **24** with Mg metal in CH_3OH and subsequent removal of the tetrahydropyranyl group gave the stannane **10** in 69% overall yield, leaving the tri-*n*-butyltin substituent intact.

Conclusions

We developed a rapid procedure for the Stille methylation of arylstannanes **7**, **9**, or **10** by a novel stepwise procedure using a Pd(0) complex generated from $Pd_2(dba)_3$ and P(*o*-$CH_3C_6H_4)_3$ (1:4) in the presence of CuCl and K_2CO_3. This protocol is useful for the synthesis of ^{11}C-incorporated TIC derivatives with the high radioactivity sufficient for the imaging of a living human brain. The stable $^{13}CH_3$ group is readily incorporated into a TIC derivative conveniently by the Pd(0)-mediated reaction using $^{13}CH_3I$ without a Cu(I) salt.

Experimental

General

^{1}H NMR spectra were recorded on a JEOL GSX-270 (270 MHz), JMN-GX-500 (500 MHz), or JNM-A600 (600 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity

(s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), integration, coupling constants, and assignment. ^{13}C NMR spectra were recorded on a JEOL GSX-270 (270 MHz), JMN-GX-500 (500 MHz), or JNM-A600 (600 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 77.0 ppm). High-resolution mass spectra were recorded on a JEOL JMS-700 instrument. Infrared (IR) spectra was recorded on a Perkin–Elmer PARAGON 1000 spectrometer. HPLC analysis was performed using a JASCO PU-980 pump, a JASCO UV-970 UV detector, a JASCO DG-980-50 degasser, and a JASCO CO-965 column oven. The analytical column was a Wakopak Wakosil 5C18-200T (250×4.6 mm). The apparatus (test tubes, flasks, and Schlenk tubes) used for all air and/or moisture sensitive reactions were evacuated by heating with a heat gun under high vacuum and then filled with dry argon before use. Solvents and solutions were transferred by syringe-septum and cannula techniques. Tetrahydrofuran (THF), dimethoxyethane (DME), and 1,4-dioxane were used after fresh distillation over sodium-benzophenone ketyl under argon. *N*,*N*-dimethylformamide (DMF), dichloromethane, and chloroform were used after distillation over CaH_2 under argon. Methanol was used after distillation over activated Mg under argon. Tetrakis(triphenylphosphine)palladium(0) (Aldrich), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (Kanto Chemicals), tris(dibenzylideneacetone)-dipalladium(0) (Aldrich), hexa-*n*-butylditin (Merck), tri-*o*-tolylphosphine (Aldrich), copper(I) chloride (WAKO), potassium carbonate (WAKO), [^{13}C]methyl iodide (ISOTEC), (formylmethylene)triphenylphosphorane (Aldrich), Methyl chloroformate (Tokyo Kasei), 1,2-bis(diphenylphosphino)ethane (Kanto Chemicals), *n*-butyllithium (1.6 M in hexane), sodium hydride (60% oil dispersion), sodium borohydride, 4-(dimethylamino)pyridine, cerium-(III) chloride heptahydrate, benzenethiol, 30% aqueous H_2O_2, magnesium turnings, and pyridinium *p*-toluenesulfonate (all from Nacalai) were commercial grade. Chlorotrimethylsilane (Tokyo Kasei) and dimethyl methylphosphonate (Tokyo Kasei) were used after distillation. The molarity of a solution of *n*-butyllithium in hexane was determined by titration. Methyl iodide was distilled over P_4O_{10} prior to use. Methyl 3-bromophenylacetate **12** was prepared by methyl esterification of commercially available 3-bromophenylacetic acid (Tokyo Kasei). R_f values on TLC were recorded on precoated silica gel (Merck Kieselgel 60 F_{254} plates). Column chromatography was conducted using Kanto Chemical silica gel 60 (spherical), 40–50 μm and Kanto Chemical silica gel 60N (spherical, neutral), 40–50 μm. Literature procedures were used to prepare the aldehyde intermediates, **15** and **21**.[15a]

Product analysis

(15*R*)-16-*m*-Tolyl-17,18,19,20-tetranorisocarbacyclin methyl ester [^{12}C]-**6**: mobile phase CH_3OH–H_2O (65/35 v/v), flow rate 1.0 mL min^{-1}, detection 254 nm, column temperature 40°C, retention time 28.4–28.6 min; (15*S*)-16-*m*-tolyl-17,18,19,20-tetranorisocarbacyclin methyl ester [^{12}C]-**8**: mobile phase CH_3OH-H_2O (68/32 v/v), flow rate 1.0 mL min^{-1}, detection 254 nm, column temperature 40°C, retention time 29.8–30.2 min; 15-deoxy-16-*m*-tolyl-17,18,19,20-tetranorisocarbacyclin methyl ester [^{12}C]-**11**: mobile phase CH_3OH-H_2O (83/17 v/v), flow rate 1.0 mL min^{-1}, detection 246 nm, column temperature 40°C, retention time 14.7–14.9 min.

Reaction of methyl iodide and stannane 9 leading to [^{12}C]-8 (entry 5 in Table 1, Method A: one-pot operation). In a dry Schlenk tube (10 mL), tris(dibenzylideneacetone)dipalladium(0) (1.2 mg, 1.3 μmol), tri-*o*-tolylphosphine (1.6 mg, 5.2 μmol), copper(I) chloride (2.6 mg, 26.2 μmol), and potassium carbonate (3.6 mg, 26.0 μmol) were placed under argon. After addition of DMF (0.4 mL), the mixture was stirred for 5 min at room temperature followed by successive additions of solutions of **9** (4.4 mg, 6.5 μmol) in DMF (0.4 mL) and methyl iodide in DMF (0.2 M, 6 μL, 1.2 μmol). The resulting mixture was stirred under argon at 60°C for 5 min, and rapidly cooled (ice bath). The reaction mixture was filtered and concentrated under reduced pressure by azeotropic removal of DMF with toluene. The residue was purified by chromatography on silica gel (0.77 g) using 2:1, 1:1, and 2:3 mixtures of hexane and ethyl acetate as eluents. The products were analyzed by HPLC with anisole as an internal standard. Yield of 15*S*-TIC methyl ester [^{12}C]-**8**: 93%. The product was identified by HPLC with an added authentic reference compound.

Reaction of methyl iodide and stannane 7 leading to [^{12}C]-6.[11] Reaction was conducted using **7** (4.4 mg, 6.5 μmol) by the same procedure as described above. The residue was purified by chromatography on silica gel (0.77 g) using 4:1, 5:2, and 3:2 mixtures of hexane and ethyl acetate as eluents. The products were analyzed by HPLC with anisole as an internal standard. Yield of 15*R*-TIC methyl ester [^{12}C]-**6**: 82%.

Reaction of methyl iodide and stannane 10 leading to [^{12}C]-11.[11] Reaction was conducted using **10** (4.0 mg, 6.1 μmol) by the same procedure as described above. Chromatography of the product on silica gel (0.5 g) using a 12:1 mixture of hexane and ethyl acetate as an eluent gave a yellow oil. The oil was further purified by chromatography on silica gel (0.6 g) using a 15:1 mixture of hexane and ethyl acetate as an eluent. HPLC analysis with anisole as an internal standard showed the yield of 15-deoxy-TIC methyl ester [^{12}C]-**11** to be 92%.

Reaction of methyl iodide and stannane 9 leading to [^{12}C]-8 (entry 9 in Table 1, Method B: stepwise procedure). In a dry Schlenk tube A (10 mL), a solution of tris(dibenzylideneacetone)dipalladium(0) (1.0 mg, 1.1 μmol) and tri-*o*-tolylphosphine (1.3 mg, 4.4 μmol) in DMF (250 μL) was placed under argon. While in another dry Schlenk tube B (10 mL), a solution of **9** (4.2 mg, 6.2 μmol), copper(I) chloride (1.0 mg, 10 μmol), and potassium carbonate (1.4 mg, 10 μmol) in DMF (250 μL) was placed under argon. After addition of a solution of methyl iodide in DMF (0.2 M, 6 μL, 1.2 μmol) to the solution of the Schlenk tube A, the mixture was stirred for 3 min at room temperature and the color of the solution changed to pale orange. This solution was transferred to the Schlenk tube B washing the inside of the Schlenk tube A with DMF

(100 μL) and then the mixture was heated at 60°C for 5 min. The reaction mixture was filtered and concentrated under reduced pressure by azeotropic removal of DMF with toluene. The residue was purified by chromatography on silica gel (0.77 g) using 2:1, 1:1, and 2:3 mixtures of hexane and ethyl acetate as eluents. The yield of 15*S*-TIC methyl ester [^{12}C]-**8** was determined by HPLC with anisole as an internal standard to be 74%. The product was identified by HPLC by co-injection with the authentic reference compound.

Reaction of methyl iodide and stannane 7 leading to [^{12}C]-6. Reaction was conducted using **7** (4.2 mg, 6.2 μmol) by the same procedure as described above. The product was purified by chromatography on silica gel (0.77 g) using 4:1, 5:2, and 3:2 mixtures of hexane and ethyl acetate as eluents, and analyzed by HPLC using anisole as an internal standard. Yield of 15*R*-TIC methyl ester [^{12}C]-**6**: 79%.

Reaction of methyl iodide and stannane 10 leading to [^{12}C]-11. Reaction was conducted using **10** (4.1 mg, 6.2 μmol) by the same procedure as described above. The product was purified by chromatography on silica gel (0.77 g) using 15:1 and 12:1 mixtures of hexane and ethyl acetate as eluents, and analyzed by HPLC using anisole as an internal standard. Yield of 15-deoxy-TIC methyl ester [^{12}C]-**11**: 80%.

Cross-coupling reaction of [^{13}C]methyl iodide and 7 leading to [^{13}C]-6. In a dry Schlenk tube (10 mL), tris(dibenzylideneacetone)dipalladium(0) (4.4 mg, 4.8 μmol) and tri-*o*-tolylphosphine (5.8 mg, 19.2 μmol) were placed under argon. After addition of DMF (1.5 mL), the mixture was stirred for 5 min at room temperature and then a solution of [^{13}C]methyl iodide in DMF (0.8 M, 10 μL, 8 μmol) was added. The mixture was further stirred for 3 min at room temperature followed by successive addition of a solution of a tributyltin derivative **7** (5.0 mg, 7.42 μmol) in DMF (1.5 mL). The resulting mixture was stirred under argon at 50°C for 15 h. The whole mixture was filtered and concentrated under reduced pressure by azeotropic removal of DMF with toluene. The residue was subjected to silica gel column chromatography (1.3 g) using 5:2 and 1:1 mixtures of hexane and ethyl acetate as eluents to give a slightly yellow oil. Further purification by silica gel column chromatography (0.7 g) using 2:1 and 1:1 mixtures of hexane and ethyl acetate as eluents gave [^{13}C]-**6** (2.3 mg, 5.76 μmol, 78% yield) as a colorless oil. TLC R_f 0.50 (1:4 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.2–1.7 (m, 7, 2 CH_2, CH, and 2 OH), 1.8–2.1 (m, 4, 2 CH_2), 2.2–2.5 (m, 5, 2 CH_2 and CH), 2.33 (d, 3, $^1J_{C\text{-}H}$=126.4 Hz, $^{13}CH_3$), 2.79 (dd, 1, *J*=6.4 and 13.2 Hz, benzylic C*H*H), 2.85 (dd, 1, *J*=7.4 and 13.2 Hz, benzylic C*H*H), 2.9–3.1 (br, 1, allylic CH in ring), 3.6–3.7 (m, 1, CHO), 3.67 (s, 3, OCH_3), 4.35 (q, 1, *J*=6.5 Hz, CHO), 5.28 (s, 1, vinylic in ring), 5.45 (dd, 1, *J*=8.6 and 15.4 Hz, vinylic in chain), 5.61 (dd, 1, *J*=6.6 and 15.4 Hz, vinylic in chain), 6.95–7.10 (m, 3, aromatic), 7.20 (t, 1, *J*=7.4 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 24.7, 27.2, 30.6, 33.9, 39.4, 39.8, 44.1, 44.3, 45.7, 51.4, 58.2, 73.6, 77.1, 126.6, 127.3 (*J*=2.8 Hz), 128.3, 128.4, 130.4 (*J*=3.8 Hz), 133.0, 134.3, 137.8 (*J*=3.6 Hz), 138.1 (*J*=44.0 Hz), 141.5, 174.1; HRMS (FAB, NBA/NaI), *m/z* calcd for $C_{24}{}^{13}CH_{34}O_4Na$ (M^++Na) 422.2388, found 422.2380.

Cross-coupling reaction of [^{13}C]methyl iodide and 9 leading to [^{13}C]-8. Reaction was conducted using tris(dibenzylideneacetone)dipalladium(0) (5.0 mg, 5.5 μmol), tri-*o*-tolylphosphine (6.7 mg, 22 μmol), [^{13}C]methyl iodide in DMF (0.8 M, 11.5 μL, 9.2 μmol), and **9** (5.6 mg, 8.3 μmol) by the same procedure as that described for the synthesis of [^{13}C]-**6**. The residue was subjected to silica gel column chromatography (1.3 g) using 2:1, 1:1, and 2:3 mixtures of hexane and ethyl acetate as eluents to give a slightly yellow oil. Further purification by silica gel column chromatography (0.7 g) using 2:1, 1:1, and 2:3 mixtures of hexane and ethyl acetate as eluents gave [^{13}C]-**8** (2.7 mg, 6.78 μmol, 82% yield) as a colorless oil. TLC R_f 0.41 (1:4 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20–1.85 (m, 7, 2 CH_2, CH, and 2 OH), 1.85–2.10 (m, 4, 2 CH_2), 2.2–2.5 (m, 5, 2 CH_2 and CH), 2.33 (d, 3, $^1J_{C\text{-}H}$=126.5 Hz, $^{13}CH_3$), 2.77 (dd, 1, *J*=7.8 and 13.2 Hz, benzylic C*H*H), 2.85 (dd, 1, *J*=5.4 and 13.2 Hz, benzylic C*H*H), 2.95–3.05 (br, 1, allylic CH in ring), 3.6–3.8 (m, 1, CHO), 3.67 (s, 3, OCH_3), 4.34 (q, 1, *J*=6.3 Hz, CHO), 5.28 (s, 1, vinylic in ring), 5.49 (dd, 1, *J*=8.3 and 15.4 Hz, vinylic in chain), 5.63 (dd, 1, *J*=6.3 and 15.4 Hz, vinylic in chain), 6.95–7.10 (m, 3, aromatic), 7.19 (t, 1, *J*=7.4 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 24.7, 27.2, 30.6, 33.9, 39.5, 39.7, 44.0, 44.3, 45.6, 51.5, 58.2, 73.3, 77.2, 126.6, 127.3 (*J*=2.8 Hz), 128.31, 128.34, 130.4 (*J*=3.6 Hz), 132.7, 134.2, 137.6 (*J*=3.6 Hz), 138.0 (*J*=44.0 Hz), 141.4, 174.1; HRMS (FAB, NBA/NaI), *m/z* calcd for $C_{24}{}^{13}CH_{34}O_4Na$ (M^++Na) 422.2388, found 422.2385.

Cross-coupling reaction of [^{13}C]methyl iodide and 10 leading to [^{13}C]-11. Reaction was conducted using tris(dibenzylideneacetone)dipalladium(0) (5.4 mg, 5.9 μmol), tri-*o*-tolylphosphine (7.2 mg, 23.6 μmol), [^{13}C]methyl iodide in DMF (0.8 M, 12.5 μL, 10 μmol), and **10** (5.8 mg, 8.8 μmol) by the same procedure as that described for the synthesis of [^{13}C]-**6**. The residue was subjected to silica gel column chromatography (1.3 g) using 15:1, 10:1, and 7:1 mixtures of hexane and ethyl acetate as eluents to give a slightly yellow oil. Further purification by silica gel column chromatography (0.7 g) using 15:1 and 7:1 mixtures of hexane and ethyl acetate as eluents gave [^{13}C]-**11** (2.8 mg, 7.31 μmol, 83% yield) as a colorless oil. TLC R_f 0.44 (2:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15–2.10 (m, 10, 4 CH_2, CH, and OH), 2.15–2.50 (m, 7, 3 CH_2 and CH), 2.32 (d, 3, $^1J_{C\text{-}H}$=126.0 Hz, $^{13}CH_3$), 2.60–2.75 (m, 2, benzylic CH_2), 2.90–3.05 (m, 1, allylic CH in ring), 3.6–3.7 (m, 1, CHO), 3.67 (s, 3, OCH_3), 5.23 (dd, 1, *J*=8.8 and 15.2 Hz, vinylic in chain), 5.27 (d, 1, *J*=1.0 Hz, vinylic in ring), 5.53 (dt, 1, *J*=6.8 and 15.2 Hz, vinylic in chain), 6.95–7.05 (m, 3, aromatic), 7.17 (t, 1, *J*=7.6 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 24.7, 27.2, 30.6, 33.9, 34.5, 35.8, 39.3, 39.7, 44.3, 45.6, 51.5, 58.7, 77.1, 125.6, 126.5 (*J*=3.6 Hz), 128.1 (*J*=3.4 Hz), 128.3, 129.4 (*J*=3.8 Hz), 132.08, 132.13, 137.8 (*J*=44.0 Hz), 141.4, 141.3 (*J*=3.4 Hz), 174.1; HRMS (FAB, NBA/NaI), *m/z* calcd for $C_{24}{}^{13}CH_{34}O_3Na$ (M^++Na) 406.2439, found 406.2436.

Methyl 3-(tri-*n*-butylstannyl)phenylacetate 13. In a dry

Schlenk tube (20 mL), tetrakis(triphenylphosphine)palladium(0) (11.5 mg, 9.95 μmol) was placed under argon. After addition of solutions of **12** (223 mg, 0.974 mmol) in 1,4-dioxane (3 mL) and hexa-*n*-butylditin (1.81 g, 3.13 mmol) in 1,4-dioxane (4 mL), the mixture was stirred for 24 h at 90°C. The reaction mixture was cooled to room temperature. After addition of a 20% aqueous KF solution (5 mL), the resulting mixture was filtered. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (5 mL×3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (20 g) using hexane, followed by a 50:1 mixture of hexane and ethyl acetate as an eluent to give **13** (224.6 mg, 0.510 mmol, 52% yield). TLC R_f 0.74 (10:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 1743, 1585; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, 9, J=7.3 Hz, 3 CH_3), 1.05 (m, 6, 3 CH_2), 1.35 (m, 6, 3 CH_2), 1.55 (m, 6, 3 CH_2), 3.59 (s, 2, CH_2), 3.66 (s, 3, OCH_3), 7.2–7.4 (m, 4, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.6, 13.7, 27.4, 29.1, 41.4, 51.9, 128.1, 128.6, 128.7, 128.9, 135.2, 137.2, 142.4; HRMS (FAB, NBA/NaI), *m/z* calcd for $C_{21}H_{36}O_2SnNa$ (M^++Na) 463.1635, found 463.1618.

1-(Dimethoxyphosphory)-3-[3-(tri-*n*-butylstannyl)phenyl]-2-propanone 14. In a dry Schlenk tube (20 mL), a solution of dimethyl methylphosphonate (296 mg, 2.4 mmol) in THF (8 mL) was placed under argon at −78°C. After addition of a solution of *n*-butyllithium in hexane (1.56 M, 1.54 mL, 2.4 mmol) over 10 min at −78°C, the mixture was stirred for 30 min at −78°C to give a white suspension. This mixture was transferred to a round-bottomed flask (50 mL) containing a solution of **13** (528 mg, 1.2 mmol) in THF (5 mL) kept at −78°C over 10 min. The resulting mixture was further stirred at −78°C for 1 h, and poured into a saturated NH_4Cl aqueous solution (10 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (25 g) using 3:1 and 1:2 mixtures of hexane and ethyl acetate as eluents to give **14** (348 mg, 0.65 mmol, 54% yield). TLC R_f 0.34 (1:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 1719, 1633, 1586, 1258; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, 9, J=7.3 Hz, 3 CH_3), 1.05 (m, 6, 3 CH_2), 1.32 (m, 6, 3 CH_2), 1.53 (m, 6, 3 CH_2), 3.10 (d, 2, J_{P-H}=22.5 Hz, CH_2), 3.78 (d, 6, J_{P-H}=11.3 Hz, 2 OCH_3), 3.86 (s, 2, CH_2), 7.1–7.4 (m, 4, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.5, 13.6, 27.3, 29.0, 40.0 (J=128.3 Hz), 51.1, 53.0 (J=6.4 Hz), 128.2, 129.2, 132.7, 135.4, 137.4, 142.9, 199.5 (J=5.5 Hz); HRMS (FAB, NBA/NaI), *m/z* calcd $C_{23}H_{41}O_4PSnNa$ (M^++Na) 555.1667, found 555.1660.

15-Dehydro-16-[3-(tri-*n*-butylstannyl)phenyl]-17,18,19,20-tetranorisocarbacyclin methyl ester 16. In a dry round-bottomed flask (10 mL), a solution of **14** (98 mg, 184 μmol) in DME (2 mL) was placed at 0°C under argon. After addition of NaH (60% oil dispersion, 7.2 mg, 180 μmol), the mixture was stirred for 5 min at 0°C to give a white clear solution. A solution of the aldehyde **15** (24 mg, 90 μmol) in DME (1 mL) was added at 0°C over 5 min and then the mixture was stirred for 5 min at 0°C, followed by addition of a saturated NH_4Cl aqueous solution (1 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (13 g) using a 5:1 mixture of hexane and ethyl acetate as an eluent to give **16** (55 mg, 81.9 μmol, 91% yield). TLC R_f 0.34 (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 3428, 1739, 1689, 1624, 1585; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 9, J=7.4 Hz, 3 CH_3), 0.9–1.0 (m, 6, 3 CH_2), 1.2–1.7 (m, 18, 8 CH_2, CH, and OH), 1.85–2.2 (m, 4, 2 CH_2), 2.25–2.5 (m, 5, 2 CH_2 and CH), 3.0–3.1 (br, 1, allylic CH), 3.65 (s, 3, OCH_3), 3.81 (s, 2, CH_2), 3.8–3.9 (m, 1, CHO), 5.28 (s, 1, vinylic in ring), 6.24 (d, 1, J=15.8 Hz, vinylic in chain), 6.81 (dd, 1, J=8.4 and 15.8 Hz, vinylic in chain), 7.1–7.4 (m, 4, aromatic); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 9.6, 13.8, 24.7, 27.2, 27.4, 29.2, 30.6, 33.9, 40.0, 40.2, 44.4, 46.1, 48.2, 51.6, 58.2, 77.3, 128.2, 129.2, 130.2, 133.9, 135.1, 137.6, 141.6, 142.7, 148.6, 174.2, 197.5; HRMS (FAB, NBA/NaI), *m/z* calcd for $C_{36}H_{56}O_4SnNa$ (M^++Na) 695.3098, found 695.3072.

(15*R*)-16-[3-(Tri-*n*-butylstannyl)phenyl]-17,18,19,20-tetranorisocarbacyclin methyl ester 7 and its 15-epimer 9. In a test tube (10 mL), a solution of **16** (30 mg, 44 μmol) in CH_3OH (1.2 mL) was placed at −20°C. Cerium(III) chloride heptahydrate (16 mg, 43 μmol) was added and the mixture was stirred for a few minutes at −20°C, followed by successive addition of $NaBH_4$ (2.5 mg, 66 μmol). The mixture was stirred for 30 min at −20°C. A saturated NH_4Cl aqueous solution (1 mL) was added to the reaction mixture and the organic layer was separated. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude mixture of the C(15)-epimers, **7** and **9**, which was subjected to silica gel column chromatography (8 g) using 8:3 and 2:3 mixtures of hexane and ethyl acetate as eluents to give stereochemically pure **7** (13.2 mg, 19.6 μmol, 44% yield) and **9** (12.7 mg, 18.9 μmol, 43% yield) as the less and more polar materials, respectively. **7**: TLC R_f 0.41 (1:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 3410, 1740, 1584; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.89 (t, 9, J=7.4 Hz, 3 CH_3), 0.9–1.0 (m, 6, 3 CH_2), 1.2–1.7 (m, 19, 8 CH_2, CH, and 2 OH), 1.8–2.1 (m, 4, 2 CH_2), 2.2–2.5 (m, 5, 2 CH_2 and CH), 2.7–2.9 (m, 2, benzylic CH_2), 2.9–3.1 (m, 1, allylic CH), 3.5–3.8 (m, 1, CHO), 3.67 (s, 3, OCH_3), 4.3–4.4 (m, 1, CHO), 5.28 (s, 1, vinylic in ring), 5.47 (dd, 1, J=8.4 and 15.3 Hz, vinylic in chain), 5.63 (dd, 1, J=6.4 and 15.3 Hz, vinylic in chain), 7.1–7.4 (m, 4, aromatic); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 9.6, 13.8, 24.8, 27.3, 27.4, 29.2, 30.6, 34.0, 39.4, 39.9, 44.35, 44.40, 45.7, 51.6, 58.3, 73.8, 77.3, 128.0, 128.3, 129.3, 133.0, 134.3, 134.8, 137.4, 137.6, 141.5, 142.6, 174.2; HRMS (FAB, NBA/NaI), *m/z* calcd for $C_{36}H_{58}O_4SnNa$ (M^++Na) 697.3263, found 697.3232. **9**: TLC R_f 0.31 (1:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 3369, 1741, 1458; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.89 (t, 9, J=7.4 Hz, 3 CH_3), 1.0–1.1 (m, 6, 3 CH_2), 1.2–1.7 (m, 19, 8 CH_2, CH, and 2 OH), 1.8–2.1 (m, 4, 2 CH_2), 2.2–2.5 (m, 5, 2 CH_2 and CH), 2.7–2.9 (m, 2, benzylic CH_2), 2.9–3.1 (m, 1, allylic CH), 3.6–3.8 (m, 1, CHO), 3.67 (s, 3, OCH_3), 4.3–4.4 (m, 1, CHO), 5.28 (s, 1, vinylic in ring), 5.52 (dd, 1,

J=7.9 and 15.3 Hz, vinylic in chain), 5.65 (dd, 1, J=5.4 and 15.3 Hz, vinylic in chain), 7.1–7.4 (m, 4, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.6, 13.7, 24.7, 27.2, 27.4, 29.1, 30.6, 33.9, 39.6, 39.8, 44.29, 44.32, 45.7, 51.5, 58.2, 73.4, 77.2, 127.9, 128.3, 129.3, 132.9, 134.1, 134.7, 137.2, 137.6, 141.4, 142.4, 174.2; HRMS (FAB, NBA/NaI), m/z calcd for $C_{36}H_{58}O_4SnNa$ (M^++Na) 697.3263, found 697.3259.

Determination of the C(15) stereochemistry of 9. In a dry Schlenk tube (10 mL), tris(dibenzylideneacetone)dipalladium(0) (4.4 mg, 4.8 μmol) and tri-*o*-tolylphosphine (5.8 mg, 19.2 μmol) were placed under argon. After addition of DMF (1.5 mL), the mixture was stirred for 5 min at room temperature and then a solution of methyl iodide in DMF (0.8 M, 10 μL, 8 μmol) was added. The mixture was further stirred for 3 min at room temperature followed by successive addition of a solution of the tributyltin derivative **9** (5.1 mg, 7.6 μmol) in DMF (1.5 mL). The resulting mixture was stirred under argon at 50°C for 15 h. The mixture was filtered and concentrated under reduced pressure by azeotropic removal of DMF with toluene. The residue was subjected to silica gel column chromatography (1.3 g) using successively 2:1, 1:1, and 2:3 mixtures of hexane and ethyl acetate as eluents to give a slightly yellow oil. Further purification by silica gel column chromatography (0.7 g) using successively 2:1, 1:1, and 2:3 mixtures of hexane and ethyl acetate as eluents gave [^{12}C]-**8** (2.2 mg, 5.5 μmol, 73% yield) as a colorless oil. TLC R_f 0.40 (1:4 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.2–1.8 (m, 7, 2 CH_2, CH, and 2 OH), 1.85–2.10 (m, 4, 2 CH_2), 2.2–2.5 (m, 8, CH_3, 2 CH_2, and CH), 2.77 (dd, 1, J=7.4 and 13.2 Hz, benzylic C*H*H), 2.85 (dd, 1, J=5.4 and 13.2 Hz, benzylic C*H*H), 2.95–3.05 (br, 1, allylic CH in ring), 3.6–3.8 (m, 1, CHO), 3.67 (s, 3, OCH_3), 4.34 (q, 1, J=6.4 Hz, CHO), 5.28 (d, 1, J=1.0 Hz, vinylic in ring), 5.49 (dd, 1, J=8.3 and 15.3 Hz, vinylic in chain), 5.63 (dd, 1, J=6.2 and 15.3 Hz, vinylic in chain), 6.95–7.10 (m, 3, aromatic), 7.19 (t, 1, J=7.6 Hz, aromatic); HRMS (FAB, NBA/NaI), m/z calcd for $C_{25}H_{34}O_4Na$ (M^++Na) 421.2355, found 421.2355. The R_f value, ^{1}H NMR, and HRMS (FAB) of the product were identical with these of authentic 15*S*-TIC methyl ester [^{12}C]-**8**.

3-[Bis(phenylthio)methyl]bromobenzene 18. In a round-bottomed flask (500 mL), a solution of benzenethiol (7.55 g, 83.2 mmol) in $CHCl_3$ (50 mL) was placed at room temperature followed by successive addition of solutions of 3-bromobenzaldehyde **17** (5.91 g, 32.0 mmol) in $CHCl_3$ (50 mL) and chlorotrimethylsilane (9.4 g, 86.5 mmol) in $CHCl_3$ (10 mL). The resulting mixture was stirred for 12 h at room temperature. The reaction mixture was poured into a saturated $NaHCO_3$ aqueous solution (100 mL). The organic layer was separated and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (200 g) using hexane, followed by 10:1, 7:1, and 5:1 mixtures of hexane and ethyl acetate as eluents to give **18** (12.27 mg, 31.6 mmol, 99% yield). TLC R_f 0.38 (10:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 1583, 1474, 1070; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.33 (s, 1, benzylic CH), 7.0–7.5 (m, 14, aromatic); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 59.9, 122.3, 126.5, 128.1, 128.9, 129.9, 130.9, 131.0, 132.8, 133.8, 141.9; HRMS (FAB, NBA/NaI), m/z calcd for $C_{19}H_{15}{}^{79}BrS_2Na$ (M^++Na) 408.9696, found 408.9699; m/z calcd for $C_{19}H_{15}{}^{81}BrS_2Na$ (M^++Na) 410.9676, found 410.9687.

3-[Bis(phenylsulfonyl)methyl]bromobenzene 19. In a round-bottomed flask (500 mL), a mixture of an aqueous H_2O_2 solution (30%, 35 mL), acetic acid (32 mL), and acetic anhydride (17 mL) were placed. This mixture was heated to 70°C and stirred for 5 min. After addition of a solution of **18** (4.0 g, 10.3 mmol) in acetic acid (20 mL), the resulting mixture was heated to reflux for 12 h. The reaction mixture was cooled to room temperature and poured into H_2O to give a white precipitate. This precipitate was washed with hexane and cold acetone, and dried under vacuum to give **19** (3.26 g, 7.24 mmol, 70% yield). TLC R_f 0.54 (1:1 hexane/ethyl acetate); IR (KBr, cm^{-1}) 1584, 1447, 1335, 1163; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.36 (s 1, benzylic CH), 7.0–7.9 (m, 14, aromatic); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 87.8, 122.5, 127.8, 129.0, 129.8, 130.1, 133.5, 134.8, 137.5; HRMS (FAB, NBA/NaI), m/z calcd for $C_{19}H_{15}O_4{}^{79}BrS_2Na$ (M^++Na) 472.9493, found 472.9491; m/z calcd for $C_{19}H_{15}O_4{}^{81}BrS_2Na$ (M^++Na) 474.9473, found 474.9479.

1-(Tri-*n*-butylstannyl)-3-[bis(phenylsulfonyl)methyl]-benzene 20. In a dry Schlenk tube (20 mL), **19** (330 mg, 730 μmol) and tetrakis(triphenylphosphine)palladium(0) (46 mg, 40 μmol) were placed under argon. After addition of 1,4-dioxane (5 mL), the mixture was stirred for 5 min at room temperature. A solution of hexa-*n*-butylditin (1.28 g, 2.2 mmol) in 1,4-dioxane (2 mL) was added and the mixture was stirred for 17 h at 90°C. The reaction mixture was cooled to room temperature, washed with a 20% aqueous KF solution (5 mL), and filtered. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (60 g) using 10:1 and 5:1 mixtures of hexane and ethyl acetate as eluents to give **20** (211.5 mg, 320 μmol, 44% yield). TLC R_f 0.48 (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 1449, 1336, 1163, 1079; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 9, J=7.3 Hz, 3 CH_3), 9.0–1.0 (m, 6, 3 CH_2), 1.2–1.7 (m, 12, 6 CH_2), 5.39 (s, 1, benzylic CH), 7.0–7.8 (m, 14, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.6, 13.6, 27.3, 28.9, 88.8, 125.2, 128.0, 128.7, 129.7, 134.3, 138.1, 138.4, 142.9; HRMS (FAB, NBA/NaI), m/z calcd for $C_{31}H_{42}O_4S_2SnNa$ (M^++Na) 685.1448, found 685.1447.

Methyl 5-[(1*S*,5*S*,6*R*,7*R*)-6-(2-formylvinyl)-7-tetrahydropyran-2-yloxybicyclo[3.3.0]oct-2-ene-3yl]pentanoate 22. In a round-bottomed flask (30 mL), a solution of **21** (203.8 mg, 0.58 mmol) in benzene (7.0 mL) was placed at room temperature. After addition of (formylmethylene)triphenylphosphorane (206.9 mg, 0.68 mmol), the reaction mixture was heated to reflux for 36 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was subjected to silica gel column

chromatography (100 g) using a 10:1 mixture of hexane and ethyl acetate as an eluent to give **22** (144.5 mg, 0.38 mmol, 66% yield). TLC R_f 0.49 (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 1733, 1691; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.4–1.8 (m, 13, 6 CH_2 and CH), 1.9–2.6 (m, 7, 3 CH_2 and CH), 2.95–3.15 (br, 1, allylic CH in ring), 3.4–4.1 (m, 3, CH_2O and CHO), 3.67 (s, 3, OCH_3), 4.55–4.7 (m, 1, CHO), 5.30 (s, 1, vinylic in ring), 6.21 (dt, 1, J=7.9 and 15.8 Hz, vinylic in chain), 6.86 (dt, 1, J=7.4 and 15.8 Hz, vinylic in chain), 9.53 and 9.54 (each d, 1, J=7.5 Hz, C(O)H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.3, 19.5, 24.7, 25.4, 25.5, 27.2, 30.6, 30.7, 30.9, 34.0, 36.8, 39.2, 39.7, 39.8, 43.7, 45.9, 46.0, 51.6, 53.4, 56.2, 62.2, 62.6, 79.4, 82.8, 96.7, 99.5, 128.1, 128.2, 133.2, 133.3, 141.2, 141.3, 159.7, 160.1, 174.2, 194.0, 194.2; HRMS (FAB, NBA/NaI), m/z calcd for $C_{22}H_{32}O_5Na$ (M^++Na) 399.2148, found 399.2162.

Methyl 5-[(1*S*,5*S*,6*R*,7*R*)-6-(3-methoxycarbonyloxy-1-propenyl)-7-tetrahydropyran-2-yloxybicyclo[3.3.0]oct-2-ene-3yl]pentanoate 23. In a round-bottomed flask (10 mL), a solution of **22** (15.2 mg, 40.4 μmol) in methanol (2.0 mL) was placed at 0°C. After addition of $NaBH_4$ (2 mg, 53 μmol), the mixture was stirred for 10 min at 0°C. The reaction mixture was poured into a saturated NH_4Cl aqueous solution (2 mL). Ethyl acetate (2 mL) was added and the organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (2.0 mL) at 0°C and then 4-(dimethylamino)pyridine (10 mg, 82 μmol) and methyl chloroformate (5 μL, 65 μmol) were added. The mixture was stirred for 8 h at room temperature. The reaction mixture was poured into a saturated NH_4Cl aqueous solution (2 mL). Ethyl acetate (2 mL) was added and the organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (2 g) using a 5:1 mixture of hexane and ethyl acetate as an eluent to give **23** (16.0 mg, 36.7 μmol, 91% yield). TLC R_f 0.47 (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 1746; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.4–1.8 (m, 13, 6 CH_2 and CH), 1.9–2.5 (m, 7, 3 CH_2 and CH), 2.9–3.05 (br, 1, allylic CH in ring), 3.4–3.9 (m, 3, CH_2O and CHO), 3.67 (s, 3, OCH_3), 3.77 and 3.78 (s each, 3, OCH_3), 4.5–4.7 (m, 1, CHO), 5.26 (s, 1, vinylic in ring), 5.6–5.9 (m, 2, vinylic in chain); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.0, 20.1, 24.8, 25.5, 25.6, 27.3, 30.6, 30.7, 30.9, 34.0, 36.4, 38.8, 39.7, 39.8, 43.5, 43.6, 45.5, 45.7, 51.5, 53.4, 54.7, 54.8, 54.9, 55.8, 61.5, 62.6, 68.6, 68.7, 78.9, 82.8, 95.9, 99.6, 124.2, 124.3, 128.2, 128.3, 138.3, 138.4, 141.2, 141.4, 155.7, 174.2; HRMS (FAB, NBA/NaI), m/z calcd for $C_{24}H_{36}O_7Na$ (M^++Na) 459.2359, found 459.2353.

16-[Bis(phenylsulfonyl)]-15-deoxy-11-*O*-tetrahydropynan-2-yl-16-[3-(tri-*n*-butylstannyl)phenyl]-17,18,19,20-tetranorisocarbacyclin methyl ester 24. In a dry Schlenk tube (10 mL), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (3.1 mg, 3 μmol) and 1,2-bis(diphenylphosphino)ethane (3.6 mg, 9 μmol) were placed under argon. After addition of THF (1.5 mL), the mixture was stirred for 5 min at room temperature. Then solutions of carbonate **23** (16.5 mg, 37.8 μmol) in THF (1.5 mL) and disulfone **20** (28 mg, 42 μmol) in THF (1.5 mL) were successively added. The resulting mixture was stirred for 26 h at 60°C. The reaction mixture was filtered and concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (3.0 g) using a 12:1 mixture of hexane and ethyl acetate as an eluent to give **24** (37.8 mg, 37.0 μmol, 98% yield). TLC R_f 0.58 (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 1739, 1448, 1143, 1077; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 9, J=7.3 Hz, 3 CH_3), 0.9–1.1 (m, 6, 3 CH_2), 1.1–1.9 (m, 25, 12 CH_2 and CH), 1.9–2.4 (m, 7, 3 CH_2 and CH), 2.9–3.1 (br, 1, allylic CH in ring), 3.3–4.0 (m, 5, CH_2O, CHO, and allylic CH_2 in chain), 3.64 (s, 3, OCH_3), 4.5–4.7 (m, 1, CHO), 5.24 (m, 1, vinylic in ring), 5.3–5.7 (m, 2, vinylic in chain), 7.2–7.9 (m, 14, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.6, 9.7, 13.67, 13.69, 14.2, 19.57, 19.64, 24.7, 25.5, 25.6, 27.1, 27.19, 27.20, 27.3, 27.4, 27.6, 28.97, 29.02, 29.1, 30.5, 30.7, 31.0, 31.2, 33.9, 36.2, 39.0, 39.90, 39.95, 43.6, 43.7, 45.5, 45.6, 51.4, 55.2, 55.7, 60.4, 62.3, 62.4, 78.8, 83.1, 93.7, 93.8, 96.3, 99.5, 122.4, 122.6, 127.35, 127.44, 127.84, 127.87, 127.93, 128.0, 128.2, 128.7, 129.7, 131.75, 131.76, 131.78, 131.9, 134.12, 134.14, 134.2, 134.3, 136.89, 136.93, 137.0, 137.8, 141.1, 141.3, 141.8, 141.9, 174.1; HRMS (FAB, NBA/NaI), m/z calcd for $C_{53}H_{74}O_8S_2{}^{120}SnNa$ (M^++Na) 1045.3755, found 1045.3729.

15-Deoxy-16-[3-(tri-*n*-butylstannyl)phenyl]-17,18,19,20-tetranorisocarbacyclin methyl ester 10. In a round-bottomed flask (10 mL), a solution of **24** (7.5 mg, 7.3 μmol) in dry methanol (0.5 mL) was placed at room temperature. After addition of activated Mg (14 mg, 576 μmol), the mixture was stirred for 2 h at room temperature. A saturated NH_4Cl aqueous solution (1 mL) and ether (2 mL) were added to the reaction mixture. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (4.8 mg) was dissolved in methanol (0.5 mL) at room temperature. After addition of pyridinium *p*-toluenesulfonate (5 mg, 19 μmol), the reaction mixture was stirred for 4 h at room temperature. After addition of a distilled water (0.5 mL) and ether (1 mL), the organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel column chromatography (0.5 g) using a 12:1 mixture of hexane and ethyl acetate as an eluent gave **10** (3.3 mg, 5.0 μmol, 69% yield). TLC R_f 0.54 (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 2925, 1742, 1459; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 9, J=7.3 Hz, 3 CH_3), 1.0–1.1 (m, 6, 3 CH_2), 1.2–2.1 (m, 22, 10 CH_2, CH, and OH), 2.2–2.5 (m, 7, 3 CH_2 and CH), 2.6–2.8 (m, 2, benzylic CH_2), 2.9–3.0 (m, 1, allylic CH in ring), 3.6–3.7 (m, 1, CHO), 3.67 (s, 3, OCH_3), 5.265 (dd, 1, J=8.7 and 15.2 Hz, vinylic in chain), 5.272 (s, 1, vinylic in ring), 5.56 (dt, 1, J=6.9 and 15.2 Hz, vinylic in chain), 7.0–7.1 (d, 1, J=7.3 Hz, aromatic), 7.2–7.4 (dd, 3, J=6.8 and 7.3 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.5, 13.7, 24.7, 27.2, 27.4, 29.1, 30.6, 33.9, 34.6, 36.0, 39.3, 39.7, 44.3, 45.6, 51.5, 58.6, 77.1, 127.7, 128.26, 128.29, 132.0, 132.1, 133.9,

136.5, 141.2, 141.4, 141.9, 174.1; HRMS (FAB, NBA/NaI), *m/z* calcd for $C_{36}H_{58}O_3{}^{120}SnNa$ (M^++Na) 681.3314, found 681.3307.

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