SYNTHESIS OF IODINATED AND RADIOIODINATED (*E*)-N-(3-IODOPROP-2-ENYL)-2β-CARBOMETHOXY-3β-(3', 4'-DICHLOROPHENYL) NORTROPANE (β-CDIT): A LIGAND FOR THE DOPAMINE TRANSPORTER.

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SUMMARY

The synthesis of (*E*)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(3', 4'-dichlorophenyl) nortropane (β-CDIT) and its radioiodinated analogues is described. Three different synthetic methods are reported for the preparation of (*E*)-N-[3-(tributylstannyl)-2-enyl]-2β-carbomethoxy-3β-(3', 4'-dichlorophenyl) nortropane, which was iododestannylated for the preparation of the corresponding iodinated derivative. We also report the radiolabelling of β-CDIT with ^{125}I or ^{123}I that could be used for *in vitro* and *in vivo* exploration of the dopamine transporter.

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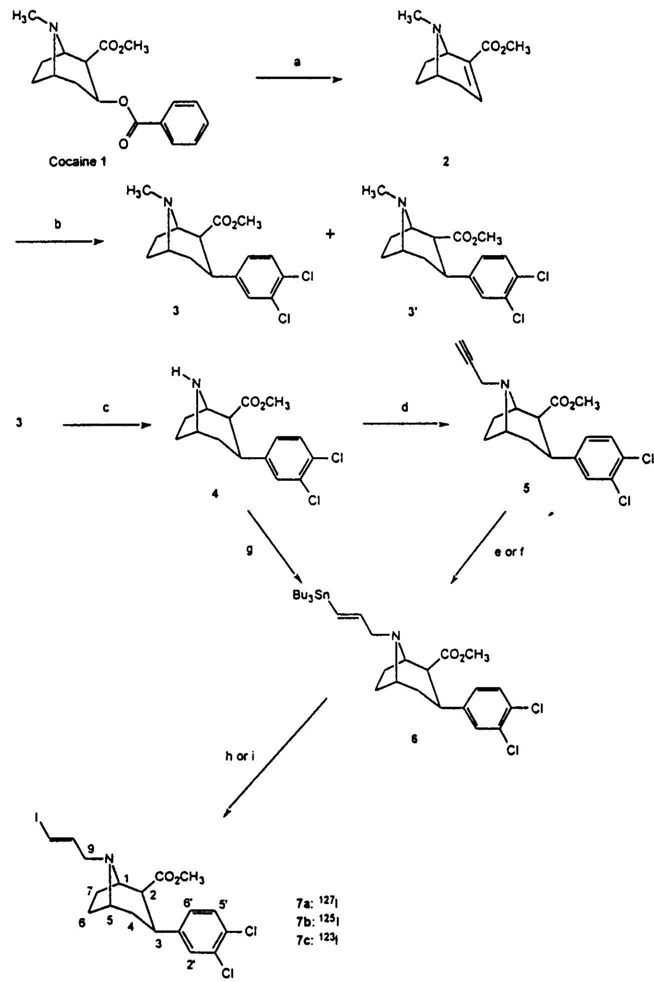
INTRODUCTION

The use of human brain exploration by Single Photon Emission Tomography (SPET) has greatly increased within the last years due to the successful development of new ligands labelled with single photon emitting radionuclides (e.g. iodine-123). In particular, radioiodinated ligands with high affinity and specificity for the dopamine reuptake site are of great interest for better understanding of the physiological and pathophysiological processes of central dopaminergic neurotransmission. Moreover, the availability of these new SPECT tracers should allow diagnosis and treatment evaluation of neurological and neuropsychiatric disorders such as Parkinson's disease (1), Alzheimer's disease (2) and schizophrenia (3) in atraumatic conditions. Several radiochemical probes with a modified cocaine structure have been reported for the characterization of the cocaine binding site on the dopamine transporter (4-10). For example (*E*)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(4'-chlorophenyl) nortropane (IPT) is a specific *in vivo* dopamine reuptake agent (6). However this tropane derivative exhibits high serotonin transporter affinity *in vitro* leading to discrepancies in *in vivo* results (10). Based on these results, we conceived a new iodinated ligand, (*E*)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(3', 4'-dichlorophenyl) nortropane (β-CDIT), and demonstrated its potential use as a specific dopamine transporter reuptake agent (11). In addition, preliminary SPECT imaging on non-human primates has revealed that ß-CDIT should be a potential ligand for SPECT exploration of the dopamine transporter (12). We report here the full synthesis of β-CDIT starting from (-) cocaine. We also describe the preparation of the tributyltin precursor by three different methods. It was iododestannylated with 127, 125 or 123 iodine to obtain the corresponding iodinated and radioiodinated derivatives used for *in vitro* and *in vivo* characterization of the dopamine transporter site (11,12).

RESULTS AND DISCUSSION

β-CDIT 7a and its radioiodinated analogues [^{125}I] β-CDIT 7b and [^{123}I] β-CDIT (**7c**) were synthesized from natural (-) cocaine 1 as described in Scheme 1. The starting material (ecgonidine alkyl ester) was prepared by hydrolysis of (-) cocaine 1. The resulting compound was then reacted with phosphorous oxychloride and was treated with the corresponding alcohol according to 13. Ecgonidine methyl ester 2 was obtained by this method using methanol as the alkylating agent. The Michael addition of 3, 4-dichlorophenyl magnesium bromide to α, β-ethylenic ester 2, at -40°C in diethylether, followed by a quenching procedure with trifluoroacetic acid at -78°C, gave a mixture of 2α- and 2β-carbomethoxy-3β-(3', 4'-dichlorophenyl) tropanes 3 and 3' respectively. These reactions were first reported by Clarke *et al.* (13) and were improved by Carroll *et al* (14). Compound 3 was then separated from its epimer 3' by flash chromatography and characterized by ^{1}H NMR at 200 MHz. For compound 3 the axial hydrogen H-4β, observed at 2.36 ppm, was deshielded by the axial methylester function in the 2β position. By comparison, the equatorial hydrogen H-4α, further away from the ester function, displayed a signal between 1.44 and 1.68 ppm which overlapped with the resonance signals of hydrogens H-6α and H-7α. The axial hydrogen H-4β exhibited a characteristic triplet of doublets due to coupling with the equatorial hydrogen H-5 for the doublet ($^3J_{4\beta,5}$= 2.9 Hz), and with the equatorial hydrogen H-4α and the axial hydrogen H-3 for the triplet ($^2J_{4\alpha,4\beta}$= $^3J_{3,4\beta}$= 12.0 Hz). The singlets of the methyl groups were observed at 2.14 ppm for the N-methyl substituent and at 3.45 ppm for the methylester function. The product (**3**) possessed the same absolute configuration as natural (-) cocaine. N-demethylation of the compound (**3**) was accomplished by conversion to its carbamate using 2,2,2-trichloroethyl chloroformate followed by zinc-acetic acid reduction to supply compound 4 according to the general procedure previously described by Clarke et al (13). Three methods were developed from nortropane 4 for the preparation of the tributyltin precursor 6. For methods e and f, N-(prop-2-ynyl)-2β-carbomethoxy-3β-(3', 4'-dichlorophenyl) nortropane 5 was first synthesized by N-alkylation of the nortropane derivative 4 with propargyl bromide. Hydrostannylation of the alkynyl derivative 5 with tributyltin hydride in the presence of AIBN as catalyst in toluene, yielded a 3/1 mixture of *E*-isomer 6 and *Z*-isomer 6' N-(3-tributylstannyl-2-enyl)-2β-carbomethoxy-3β-(3', 4'-dichlorophenyl) nortropane (route e). The *E*-tributyltin isomer 6 was isolated from this mixture by flash chromatography using petroleum ether (40-65°C) / ethyl acetate: 90/10 v/v (49% yield). The same results were reported in the literature (6) for the hydrostannylation of N-(prop-2-ynyl)-2β-carbomethoxy-3β-(4'-chlorophenyl) nortropane. Another method for the preparation of the *E*-tributyltin precursor 6 from the N-prop-2-ynylnortropane derivative 5 consists of addition of Lipshutz reagent n-$Bu_3SnCuBu(CN)Li_2$ to the triple bond at -78°C (15). Using this method, a 13% yield of the pure *E*-tributyltin derivative 6 was obtained after purification by flash chromatography, as described above. In order to improve the yield of the tin precursor 6 a third method was checked consisting of a reaction of (*E*)-3-(tributylstannyl)prop-2-enyl chloride with nortropane 4, according to a similar method described by Goodman *et al.* (6). By method g, a 50% yield of the *E*-tributyltin precursor 6 was obtained. Characterization of the *E*-tributylstannylpropenyl nortropane derivative 6 by ^1H NMR at 200 MHz confirmed the expected structure. In particular, hydrogens H-9 and H-9' of the CH_2 in the N-propenyl chain did not have the same chemical shift (δ_9=3.06 ppm, $\delta_{9'}$ is localized in the range 2.72-2.93 ppm). This magnetic difference was attributed to the steric hindrance of the N-stannylpropenyl group. The olefinic hydrogens displayed a high resolution ABXX' structure in the range 5.68-6.01 ppm with a trans coupling constant ^3J= 19.1 Hz. Iododestannylation of the tributyltin precursor 6 yielded 77% β-CDIT 7a.

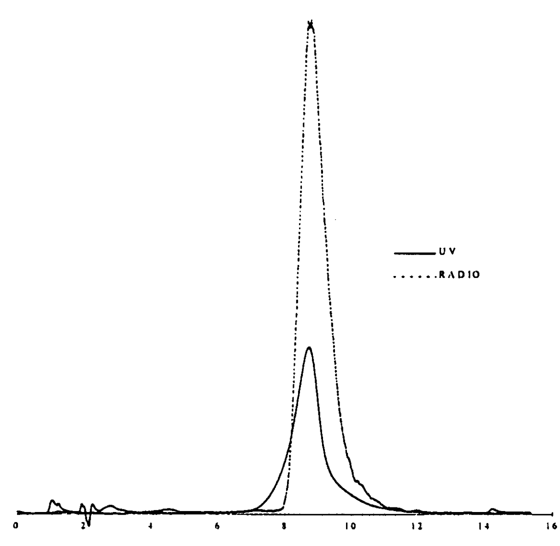
Scheme 1: Synthesis of (*E*)-N-(3-iodoprop-2-enyl)-2ß-carbomethoxy-3ß-(3',4'-dichlorophenyl) nortropane 7a and its radioiodinated analogues [^{125,123}I] ß-CDIT 7b, 7c from cocaine.



a)1) 0.75N HCl, 3h, reflux; 2) $POCl_3$, overnight, reflux; 3) MeOH, 4 days, r.t.: 74%. b)1) 3,4-$Cl_2C_6H_3MgBr$, Et_2O, 3h, -40°C; 2) F_3CCO_2H, 1h, -78°C; 3) HCl, 0°C, isomer 3 : 44%. c)1) Cl_3CCH_2OCOCl, 75min, 120°C; 2) Zn, AcOH, overnight, r.t.: 87%. d)1) $HC{\equiv}CCH_2Br$, KI, EtOH, overnight, reflux; 2) $NaHCO_3$: 76%. e)$HSnBu_3$, AIBN, toluene, overnight, reflux : 49%. f)1) $Bu_3SnCu(Bu)CNLi_2$, THF, 10min, -90°C; 2) NH_4Cl : 13%. g)1) *E*-$Bu_3SnCH{=}CHCH_2Cl$, KI, EtOH, overnight, reflux; 2) $NaHCO_3$: 50%. e) I_2, $CHCl_3$: 77%. f)1) [^{125}I] NaI or [^{123}I] NaI, H_2O_2, EtOH, HCl, 20min, r.t.; 2) $Na_2S_2O_5$; 3) $NaHCO_3$: >60%.

This compound retained the absolute configuration of (-) cocaine at C-2 and C-3. Characterization by ^1H NMR allowed assignment of the triplet of the doublet at 2.48 ppm of the hydrogen H-4β ($^3J_{4\beta,5}$=2.9 Hz, $^2J_{4\alpha,4\beta}$=$^3J_{3,4\beta}$= 12.4 Hz), the singlet at 3.45 ppm of the 2β-methylester function, the doublet at 6.13 ppm of the olefinic hydrogen H-11 and the doublet of triplets at 6.41 ppm of the olefinic hydrogen H-10 in trans position to each other ($^3J_{10,11}$= 14.5 Hz) due to retention of the olefinic configuration during the iodine-metal exchange. The radioiodinated compounds [^{125}I] β-CDIT **<u>7b</u>** and [^{123}I] β-CDIT **<u>7c</u>** were prepared by iododestannylation of the stannyl derivative <u>6</u> using radiolabelled sodium iodide [^{125}I] or [^{123}I] respectively and 3% w/v hydrogen peroxide as oxidizing agent at room temperature according to a general radiolabelling method (6).The radioiodinated products [^{125}I] β-CDIT **<u>7b</u>** or [^{123}I] β-CDIT **<u>7c</u>** were isolated by HPLC on a RP18 column using methanol / water / triethylamine (75/25/0.2) as eluent and compared to their corresponding unlabelled analogues **<u>7a</u>** by HPLC with simultaneous UV and radioactivity detection as presented in Figure 1. It was shown to be

Figure 1 : HPLC analysis by coinjection of iodinated **<u>7a</u>** and [^{125}I] radioiodinated **<u>7b</u>** β-CDIT into a RP18 column using MeOH / H_2O / Et_3N : 75 / 25 / 0.2 as eluent.



the expected product on the basis of the elution profile. Radiolabelling yield after HPLC purification was > 60%.

This paper describes the synthesis of iodinated and radioiodinated ß-CDIT. These compounds were obtained by iododestannylation of the corresponding tributyltin precursor which was prepared by three different methods. ß-CDIT labelled with 125 or 123 iodine was obtained with good radiochemical yields (>60%) with a radiochemical purity >95% and specific radioactivity of 2200 Ci / mmol for [^{125}I] ß-CDIT. [^{125}I] ß-CDIT was used for *in vitro* and *in vivo* characterization in rats (11) and [^{123}I] ß-CDIT was used for *in vivo* examination of the dopamine transporter site in monkeys (12).

EXPERIMENTAL PART

Cocaine hydrochloride was purchased from Coopération Pharmaceutique Française; *n*-butyllithium 1.6M solution in hexane, propargyl alcohol, tributyltin hydride, 2,2,2-trichloroethylchloroformate, trifluoroacetic acid and zinc from Aldrich; triphenylphosphine from Acros; 1-bromo-3,4-dichlorobenzene from Lancaster; α,α'-azoisobutyronitrile (AIBN) from Merck; copper (I) cyanide, iodine, magnesium, phosphorus oxychloride, potassium iodide, triethylamine from Prolabo; [^{125}I] NaI from Amersham (in NaOH 0.1N solution, specific activity = 2200 Ci/mmol) and [^{123}I] NaI from Cis Bio International (in NaOH 0.1N solution, specific activity > 5000 Ci/mmol). All reagents were used without purification and solvents were usually distilled and dried. Thin layer chromatography analyses were conducted using silica gel 60F254 TLC plates (Merck) and compounds were revealed by UV detection or iodine chamber. Flash chromatography was used for routine purification of reaction products using silica gel 230-400 Mesh (Merck) ASTM. HPLC was performed on a Beckman 331 isocratic liquid chromatograph fitted with UV at 254 nm and a radioactivity detector, using a reverse phase 10RP18 column (25 cm × 4.6 mm) from Chrompack. NMR spectra were recorded on a Brüker Avance DPX 200 spectrometer (at 200 MHz for ^{1}H and 50 MHz for ^{13}C) using $CDCl_3$ as solvent. Chemical shifts were expressed in ppm relative to tetramethylsilane as internal standard. Mass spectra were obtained on a CG-MS Hewlett Packard 5989A spectrometer (electronic impact at 70 eV). The purity of the synthesized compounds was verified by gas chromatography (CG, HP 5890A, II) coupled with a mass spectrometer. A 25 m × 0.2 mm fused silica capillary column OVI (HP1) (Hewlett Packard) was directly inserted into the ion source of the HP quadrupole mass spectrometer through a heated (250°C) interface box. Helium was used as carrier gas with a flow rate through the column of 0.7 mL / min. The temperature remained at 70°C for 1 min and was then programmed up to 300°C at 10°C / min. The experimental time was 1 hour. The temperature of the ion source was 200°C. For target compound **7a**, elemental analyses were within ± 0.4% of the theoretical values and were determined in the Laboratory of the Service Central d'Analyses du CNRS (Vernaison, France).

Ecgonidine methyl ester **2**:

Ecgonidine methyl ester was prepared according to the method described in the literature (13, 16). Cocaine hydrochloride **1** (20 g, 58 mmol) was refluxed with 0.75 N HCl solution (200 mL) for 3 hours. The reaction was cooled to room temperature and extracted with Et_2O (2 × 30 mL) in order to remove the benzoic acid obtained as by-product. The aqueous solution was evaporated to dryness and refluxed overnight with $POCl_3$ (40 mL). Excess $POCl_3$ was removed by distillation *in vacuo*. The residue was treated with MeOH (400 mL) and stirred at room temperature for one week. The methanolic solution was evaporated, brought to basic pH with a solution of K_2CO_3 10% (100 mL), extracted with Et_2O (4 × 25 mL), washed with brine, dried with Na_2SO_4 and the solvent was evaporated. Distillation of the residue (45-47°C/ 0.2 torr) yielded 72% pure product **2** (7.4 g, 41 mmol).

^1H NMR ($CDCl_3$): δ = 1.26-1.32 (m, 1H, H-6α); 1.55-1.66 (m, 2H, H-4α, H-7α); 1.90-1.95 (m, 2H, H-6β, H-7β); 2.11 (s, 3H, NCH_3); 2.35-2.44 (m, 1H, H-4β); 3.01 (m, 1H, H-5); 3.49 (s, 3H, OCH_3); 3.55 (m, 1H, H-1); 6.58 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$): δ = 30.2 (C-6), 31.7

(C-7), 34.5 (C-4), 36.4 (NCH_3), 51.6 (OCH_3), 57.0 (C-5), 58.6 (C-1), 134.1 (C-2), 135.9 (C-3), 166.5 (CO_2).

2β-Carbomethoxy-3β-(3',4'-dichlorophenyl) tropane 3:

According to a previously reported method (13), compound 3 was prepared from ecgonidine methyl ester 2 and 3,4-dichlorophenylmagnesium bromide in dry Et_2O. The Grignard reagent was prepared from Mg (1.2 g, 50 mmol), 1-bromo-3,4-dichlorobenzene (11.3 g, 50 mmol) in Et_2O (40 mL). Compound 2 (1.5 g, 8.3 mmol) in dry Et_2O (25 mL) was added dropwise to a vigorously stirred solution of 3,4-dichlorophenylmagnesium bromide under dry N_2 at -40°C and stirring was continued at -40°C for 3 hours. The solution was further cooled to -78°C and treated with 5.8 mL of trifluoroacetic acid dissolved in 25 mL of dry Et_2O and stirred for one hour. The mixture was brought to 0°C and diluted with water (40 mL). The aqueous phase was separated and acidified with a concentrated HCl solution (17 mL) and the organic layer was separated. The aqueous layer was treated with a solution of concentrated NH_4OH (90 mL) to basic pH at 0°C and extracted with Et_2O (3 × 30 mL). This solution was dried and evaporated to yield a residue which was purified by flash chromatography (Et_2O/Et_3N: 9/1 v/v). A yield of 44% of the product 3 was obtained (1.1 g).

^1H NMR ($CDCl_3$): δ = 1.44-1.68 (m, 3H, H-4α, H-6α, H-7α); 1.94-2.22 (m, 2H, H-6β, H-7β); 2.14 (s, 3H, NCH_3); 2.36 (td, 1H, $^3J_{4\beta,5}$ = 2.9 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ =12.0 Hz, H-4β); 2.78-2.91 (m, 2H, H-2, H-3); 3.27 (m, 1H, H-5); 3.45 (s, 3H, OCH_3); 3.49 (m, 1H, H-1); 7.02 (dd, 1H, $^3J_{5',6'}$ = 8.4 Hz, $^4J_{2',6'}$ = 2.0 Hz, H-6'); 7.23 (2d, 2H, $^3J_{5',6'}$ = 8.4 Hz, $^4J_{2',6'}$ = 2.0 Hz, H-2', H-5'). ^{13}C NMR ($CDCl_3$): δ = 25.6 (C-6), 26.2 (C-7), 33.6 (C-3), 34.3 (C-4), 42.3 (NCH_3), 51.7 (OCH_3), 52.9 (C-2), 62.5 (C-5), 65.6 (C-1), 127.2 (C-6'), 129.8 (C-2'), 130.0 (C-4'), 130.2 (C-5'), 132.2 (C-3'), 144.1 (C-1'), 172.2 (CO_2). MS (EI): m/z = 331 (1%, $C_{16}H_{19}{}^{37}Cl_2NO_2^+$), 329 (6%, $C_{16}H_{19}{}^{37}Cl^{35}ClNO_2^+$), 327 (9%, $C_{16}H_{19}{}^{35}Cl_2NO_2^+$), 300 (1%, $C_{15}H_{16}{}^{37}Cl_2NO^+$), 298 (2%, $C_{15}H_{16}{}^{37}Cl^{35}ClNO^+$), 296 (2%, $C_{15}H_{16}{}^{35}Cl_2NO^+$), 270 (3%, $C_{14}H_{16}{}^{37}Cl^{35}ClN^+$), 268 (4%, $C_{14}H_{16}{}^{35}Cl_2N^+$), 242 (1%, $C_{12}H_{12}{}^{37}Cl^{35}ClN^+$), 240 (3%, $C_{12}H_{12}{}^{35}Cl_2N^+$), 155 (5%, $C_8H_{13}NO_2^+$), 154 (1%, $C_8H_{12}NO_2^+$), 97 (34%, $C_6H_{11}N^+$), 96 (43%, $C_6H_{10}N^+$), 83 (100%, $C_5H_9N^+$), 82 (94%, $C_5H_8N^+$), 59 (2%, $CO_2CH_3^+$).

2β-Carbomethoxy-3β-(3',4'-dichlorophenyl) nortropane 4:

According to reported procedures (13, 17), the tropane derivative 3 (656 mg, 2 mmol) was treated with 2,2,2-trichloroethyl chloroformate (1.2 mL, 11 mmol). The mixture was heated at 120°C for 75 min under nitrogen atmosphere. After cooling, the excess of reagent was distilled *in vacuo* (60-62°C / 15 torr) yielding the crude carbamate which was dissolved in 95% acetic acid (15 mL) containing freshly activated zinc dust (1.6 mg, 24.4 mmol) and stirred at room temperature for 24h. The solution was filtered with celite, treated with a 10% NaOH solution and extracted with $CHCl_3$ to yield the crude product which was purified by flash chromatography using Et_2O / Et_3N: 9/1 as eluent. The pure product 4 (526 mg, 84%) was a waxy substance.

^{1}H NMR ($CDCl_3$): δ = 1.53-1.73 (m, 3H, H-4α, H-6α, H-7α); 1.93-2.07 (m, 2H, H-6β, H-7β); 2.29 (td, 1H, $^3J_{4\beta,5}$ = 2.8 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ =12.8 Hz, H-4β); 2.77 (dd, 1H, $^3J_{1,2}$ = 1.6 Hz, $^3J_{2,3}$ = 5.9 Hz, H-2); 3.14 (dt, 1H, $^3J_{2,3}$ = $^3J_{3,4\alpha}$ = 5.9 Hz, $^3J_{3,4\beta}$ = 12.8 Hz, H-3); 3.37 (s, 3H, OCH_3); 3.66 (m, 2H, H-1, H-5); 6.56 (bs, 1H, NH); 6.97 (dd, 1H, $^3J_{5',6'}$ = 8.2 Hz, $^4J_{2',6'}$ = 2.0 Hz, H-6'); 7.11 (d, 1H, $^4J_{2',6'}$ = 2.0 Hz, H-2'); 7.18 (d, 1H, $^3J_{5',6'}$ = 8.2 Hz, H-5'). ^{13}C NMR ($CDCl_3$): δ = 26.3 (C-6), 27.6 (C-7), 32.1 (C-4), 34.9 (C-3), 49.6 (C-2), 52.5 (OCH_3), 54.5 (C-5), 56.1 (C-1), 127.2 (C-6'), 129.8 (C-2'), 130.8 (C-5'), 131.6 (C-4'), 132.9 (C-3'), 140.7 (C-1'), 173.3 (CO_2).

N-(prop-2-ynyl)-2β-carbomethoxy-3β-(3',4'-dichlorophenyl) nortropane 5:

A solution of propargyl bromide 80% in toluene (75 mL, 673 μmol) was added to a solution of the nortropane derivative 4 (163.6 mg, 60 μmol) in absolute EtOH containing a catalytic amount of potassium iodide. The mixture was refluxed overnight and the solvent evaporated under reduced pressure. Water (20 mL) was added to the residue and the mixture was brought to basic pH with $NaHCO_3$, extracted with Et_2O, dried over Na_2SO_4 and the solvent was evaporated. After flash chromatography (Et_2O / Et_3N: 95/5) the pure compound **5** was isolated as a waxy substance (140 mg, 78%)

^{1}H NMR ($CDCl_3$): δ = 1.52-1.80 (m, 3H, H-4α, H-6α, H-7α); 1.89-2.30 (m, 2H, H-6β, H-7β); 2.09 (t, 1H, $^4J_{9,11}$ = 2.4 Hz, H-11); 2.49 (td, 1H, $^3J_{4\beta,5}$ = 2.5 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ =12.0 Hz, H-4β); 2.78-2.94 (m, 2H, H-2, H-3); 3.04 (AA'X, 2H, $^2J_{9,9'}$ = 16.2 Hz, $^4J_{9,11}$ = 2.5 Hz, H-9, H-9'); 3.44 (m, 1H, H-5); 3.47 (s, 3H, OCH_3); 3.90 (m, 1H, H-1); 7.03 (dd, 1H, $^3J_{5',6'}$ = 8.3 Hz, $^4J_{2',6'}$ = 2.0 Hz, H-6'); 7.25 (2d, 2H, $^4J_{2',6'}$ = 2.0 Hz, $^3J_{5',6'}$ = 8.3 Hz, H-2', H-5').

(E)-3-tributylstannylprop-2-en-1-ol:

This compound was prepared according to the procedure described in the literature (18). Propargyl alcohol (8.5 mL, 146 mmol) was heated to 100°C overnight with $HSnBu_3$ (52 mL, 187 mmol) and a catalytic amount of AIBN. Flash chromatography with petroleum ether (40-60°C) / EtOAc: 9/1 v/v yielded pure (*E*)-3-tributylstannylprop-2-en-1-ol as a colourless oil (39.6 g, 78%).

^{1}H NMR ($CDCl_3$): δ = 0.87 [t, 15H, ^{3}J = 8.6 Hz, $3CH_3$, $(-CH_2)_3Sn$]; 1.27-1.68 (m, 12H, 3 CH_2CH_2); 2.46 (t, 1H, ^{3}J = 5.6 Hz, OH); 4.16 (dd, 2H, ^{3}J = 5.6 Hz, ^{3}J = 3.0 Hz, CH_2C=); 6.08-6.29 (ABX_2, 2H, $^3J_{AB}$ = 19.0 Hz, $^3J_{BX}$ = 3.0 Hz, CH=CH).

(E)-3-tributylstannylprop-2-enyl chloride:

This compound was prepared according to the procedure described in the literature (6). (*E*)-3-tributylstannylprop-2-en-1-ol (813 mg, 2.34 mmol) was dissolved in CCl_4 (4.5 mL) containing triphenylphosphine (750 mg, 2.86 mmol) and the reaction mixture was heated at 60°C in a sealed vial for 48 h. CCl_4 was evaporated and the product was purified by flash chromatography using petroleum ether (40-60°C) / Et_3N: 98/2 v/v yielded pure (*E*)-3-tributylstannylprop-2-enyl chloride (599 mg, 70%) as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 0.95 [t, 15H, $3CH_3$, $(-CH_2)_3Sn$]; 1.29-1.71 (m, 12H, 3 CH_2CH_2); 4.10

(dd, 2H, ^3J = 6.0 Hz, ^4J = 1.0 Hz, $ClCH_2C$=); 6.10 (dt, 1H, ^3J = 18.7 Hz, ^3J = 6.0 Hz, CH=); 6.35 (dt, 1H, ^3J = 18.7 Hz, ^4J = 1.0 Hz, SnCH=).

(E)-N-(3-tributylstannylprop-2-enyl)-2β-carbomethoxy-3β-(3',4'-dichlorophenyl) nortropane 6:

Method e: [as described in the literature (6)]: The N-propargylnortropane derivative 5 (100 mg, 286 mmol) was dissolved in toluene (1.5 mL) containing 97% $HSnBu_3$ (168 mg, 560 μmol) and AIBN (14 mg). The reaction mixture was heated at 90°C for 5 hours, blanketed under dry nitrogen atmosphere. The solvent was then removed *in vacuo* and the residue purified by flash chromatography using Et_2O / Et_3N: 9 / 1 v/v as eluent. Purification of the (*E*)-tin isomer 6 was then performed on preparative silica gel TLC 60F254 Merck using petroleum ether (40-65°C) / EtOAc: 9 / 1 v/v as eluent. Rf 5 = 0.10, Rf *E*-isomer 6 = 0.25, Rf *Z*-isomer 6' = 0.55. The *E*-isomer 6 (86.2 mg, 49%) was obtained as a colourless oil.

Method f: [as described in the literature (15)]: Lipshutz reagent was prepared from a suspension of CuCN (66 mg, 737 μmol) in tetrahydrofuran (2mL) which was cooled to -90°C, blanketed under nitrogen atmosphere. Then 1.6M *n*-BuLi solution in hexanes (1 mL, 1.6 mmol) was added dropwise to form the complex $nBu_2Cu(CN)Li_2$. The mixture was allowed to stand for 15 min at -90°C to yield a colourless solution. Tri-*n*-butyltin hydride (430 μL, 1.6 mmol) was added dropwise with a syringe. Stirring was continued for 10 min at the same temperature until the solution yellowed and H_2 gas was liberated. N-propargylnortropane derivative 5 (212 mg, 607 μmol) was added neat. The reaction mixture was stirred for 10 min at -90°C and quenched with a solution of NH_4Cl 1M (10 mL). Extraction with Et_2O (3 × 20 mL) was followed by drying the organic phase over Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by flash chromatography using petroleum ether (40-65°C) / AcOEt: 9 / 1 v/v as eluent. (*E*)-N-tributylstannylprop-2-enylnortropane derivative 6 (51 mg, 13%) was separated from its gem isomer.

Method g: (*E*)-3-tributylstannylprop-2-enyl chloride (110 mg, 301 µmol) was added to a solution of nortropane derivative 4 (95 mg, 304 µmol) in absolute EtOH (3 mL) containing a catalytic amount of KI (5 mg, 30 µmol). The reaction mixture was refluxed overnight. The solvent was evaporated under *vacuum* and the residue was treated with H_2O (15 mL) and then brought to alkaline pH with a 5% $NaHCO_3$ solution. The aqueous phase was extracted with Et_2O (3 × 10 mL). Combined organic layers were dried over Na_2SO_4. After removing the solvent, the product was purified by flash chromatography using petroleum ether / EtOAc: 9 / 1 as eluent. *E*-isomer 6 (96 mg, 50%) was obtained as a colourless oil.

^{1}H NMR *E*-isomer 6 ($CDCl_3$): δ= 0.82 (t, 9H, ^3J= 7.0 Hz, $3CH_3$); 1.10-1.62 [m, 21H, (-$CH_2CH_2CH_2)_3Sn$, H-4α, H-6α, H-7α]; 1.98 (m, 2H, H-6ß, H-7ß); 2.48 (td, 1H, $^3J_{4\beta,5}$= 2.9Hz, $^2J_{4\alpha,4\beta}$= $^3J_{3,4\beta}$= 12.4Hz, H-4ß); 2.72-2.93 (m, 3H, H-2, H-3, H-9'); 3.06 (dd, 1H, $^2J_{9,9'}$= 13.5Hz, $^3J_{9,10}$= 3.7Hz, H-9); 3.35 (m, 1H, H-5); 3.45 (s, 3H, OCH_3); 3.64 (m, 1H, H-1); 5.68-6.01 (ABXX', 2H, $^3J_{10,11}$= 19.1Hz, $^3J_{9',10}$= 5.9Hz, $^3J_{9,10}$= 3.7Hz, CH=CH); 7.05 (dd, 1H, $^3J_{5',6'}$= 8.3Hz, $^4J_{2',6'}$= 2.0Hz, H-6'); 7.25 (d, 1H, $^3J_{5',6'}$= 8.3Hz, H-5'); 7.26 (d, 1H, $^4J_{2',6'}$= 2.0Hz, H-2').

^{1}H NMR *Z*-isomer (6) ($CDCl_3$): δ= 0.83 (t, 9H, ^3J= 7.1 Hz, $3CH_3$); 1.19-2.10 [m, 23H, (-$CH_2CH_2CH_2)_3Sn$, H-4α, H-6α, H-6ß, H-7α, H-7ß]; 2.47 (td, 1H, $^3J_{4\beta,5}$= 3.0Hz, $^2J_{4\alpha,4\beta}$= $^3J_{3,4\beta}$= 12.2Hz, H-4ß); 2.66-2.93 (m, 4H, H-2, H-3, H-9, H-9'); 3.35 (m, 1H, H-5); 3.45 (s, 3H, OCH_3); 3.64 (m, 1H, H-1); 5.86 (d, 1H, $^3J_{10,11}$= 12.7Hz, H-11); 6.35 (ddd, 1H, $^3J_{10,11}$= 12.7Hz, $^3J_{9,10}$= 7.0Hz, $^3J_{9',10}$= 4.6Hz, H-10); 7.04 (dd, 1H, $^3J_{5',6'}$= 8.3Hz, $^4J_{2',6'}$= 2.0Hz, H-6'); 7.23 (m, 2H, H-2', H-5').

(E)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(3',4'-dichlorophenyl) nortropane **7a**:

A solution of the *E*-tin precursor 6 (200 mg, 310 µmol) in $CHCl_3$ (2 mL) was cooled to 0-5°C. A 0.1 N iodine solution in $CHCl_3$ was then added dropwise to the stirred mixture until a coloured solution was obtained. The organic phase was washed with brine (2 × 1 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product purified by flash chromatography using Et_2O / Et_3N (95 / 5 v / v) as eluent. TLC analyses were carried out with

Et_2O / Et_3N (95 / 5), Rf 7a= 0.98. The *E*-iodinatednortropane derivative 7a (77 mg, 52%) was obtained as an oil. Anal. ($C_{18}H_{20}Cl_2INO_2$) calc.: C, 45.0, H, 4.2, N, 2.9. Found: C, 44.6, H, 4.1, N, 2.5%.

^{1}H NMR ($CDCl_3$): δ= 1.52-1.72 (m, 3H, H-4α, H-6α, H-7α); 1.83-2.02 (m, 2H, H-6ß, H-7ß); 2.46 (td, 1H, $^3J_{4ß,5}$= 2.8Hz, $^2J_{4\alpha,4ß}$= $^3J_{3,4ß}$= 12.0Hz, H-4ß); 2.68-2.92 (m, 4H, H-2, H-3, NCH_2-); 3.33 (m, 1H, H-5); 3.49 (s, 3H, OCH_3); 3.61 (m, 1H, H-1); 6.13 (d, 1H, $^3J_{10,11}$= 14.5Hz, H-11); 6.41 (dt, 1H, $^3J_{9,10}$= 6.6Hz, $^3J_{10,11}$= 14.5Hz, H-10); 7.03 (dd, 1H, $^3J_{5',6'}$= 8.3Hz, $^4J_{2',6'}$= 2.1Hz, H-6'); 7.25 (d, 1H, $^4J_{2',6'}$= 2.1Hz, H-2'); 7.26 (d, 1H, $^3J_{5',6'}$= 8.3Hz, H-5'). ^{13}C NMR: δ= 26.2 (C-6), 26.4 (C-7), 34.0 (C-3), 34.2 (C-4), 51.8 (OCH_3), 52.7 (C-2), 58.3 (C-9), 61.5 (C-5), 62.7 (C-1), 77.6 (C-11), 126.7 (C-6'), 129.4 (C-2'), 129.6 (C-4'), 129.7 (C-5'), 131.7 (C-3'), 143.2 (C-1'), 143.8 (C-10), 171.3 (CO_2). MS (EI): m/z = 481 (9%, $C_{18}H_{20}{}^{35}Cl^{37}ClINO_2^+$); 479 (10%, $C_{18}H_{20}{}^{35}Cl_2INO_2^+$); 450 (2%, $C_{17}H_{17}{}^{35}Cl^{37}ClINO^+$); 448 (3%, $C_{17}H_{17}{}^{35}Cl_2INO^+$); 422 (3%, $C_{16}H_{17}{}^{35}Cl^{37}ClIN^+$); 420 (7%, $C_{16}H_{17}{}^{35}Cl_2IN^+$); 356 (7%, $C_{18}H_{20}{}^{37}Cl_2NO_2^+$); 354 (38%, $C_{18}H_{20}{}^{35}Cl^{37}ClNO_2^+$); 352 (60%, $C_{18}H_{20}{}^{35}Cl_2NO_2^+$); 324 (3%, $C_{17}H_{16}{}^{37}Cl_2NO^+$); 322 (9%, $C_{17}H_{16}{}^{37}Cl^{35}ClNO^+$); 320 (16%, $C_{17}H_{16}{}^{35}Cl_2NO^+$); 316 (2%, $C_{15}H_{16}{}^{37}Cl_2NO_2^+$); 314 (4%, $C_{15}H_{16}{}^{37}Cl^{35}ClNO_2^+$); 312 (6%, $C_{15}H_{16}{}^{35}Cl_2NO_2^+$); 307 (3%, $C_{10}H_{14}INO_2^+$); 296 (1%, $C_{16}H_{16}{}^{37}Cl_2N^+$); 294 (7%, $C_{16}H_{16}{}^{37}Cl^{35}ClN^+$); 292 (10%, $C_{16}H_{16}{}^{35}Cl_2N^+$); 249 (4%, $C_8H_{12}IN^+$); 248 (20%, $C_8H_{11}IN^+$); 235 (54%, $C_7H_{10}IN^+$); 234 (54%, $C_7H_9IN^+$); 180 (24%, $C_{10}H_{14}NO_2^+$); 167 (94%, $C_3H_4I^+$); 68 (100%, $C_4H_6N^+$).

(E)-N-(3-[$^{125/123}$-I]iodoprop-2-enyl)-2ß-carbomethoxy-3ß-(3',4'-dichlorophenyl)nortropanes 7b and 7c:

According to a radiolabelling method (6), [^{125}I] ß-CDIT 7b and [^{123}I] ß-CDIT 7c were prepared in a vial containing the stannyl precursor 6 (50 μg), EtOH (50 μL), 0.1N HCl aqueous solution (50 μL), [^{125}I] NaI (1 mCi) or [^{123}I] NaI (2 mCi) and 3% w/v H_2O_2 (50 μL). After 20 min at room temperature, the reaction was stopped with 15M $Na_2S_2O_5$ aqueous solution (100 μL), brought to basic pH with 5% $NaHCO_3$ and extracted with AcOEt (3 × 1 mL). After separation the organic layer was evaporated under a nitrogen stream. Isolation of the radiolabelled compounds **7b** and **7c** was performed by HPLC on a RP18 column using MeOH / H_2O / Et_3N: 75 / 25 / 0.2 v/v/v as mobile phase (flow rate= 1 mL / min). To be injected, the residue was dissolved in the mobile phase (100 μL). The fraction eluted at the retention time of 12 min for the radioiodinated derivatives **7b** and **7c** was collected, introduced into a C18 SepPak cartridge and eluted with EtOH (2 × 1 mL). The solvent was evaporated under a nitrogen stream. The radiolabelled ligand **7b** or **7c** was obtained with a radiochemical purity > 95%, and 60% radiochemical yield.

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