Asymmetric synthesis of (2S)-and (2R)-4-(3-t-butylamino-2-hydroxypropoxy)-benzimidazol-2-[^{11}C]-one ((S)-and (R)-[^{11}C]-CGP 12177) from optically active precursors

Akli HAMMADI, Christian CROUZEL

Service Hospitalier Frédéric Joliot, D.R.I.P.P., C.E.A.
91406 Orsay FRANCE

SUMMARY

Enantiomers of CGP 12177 ((2S)-and (2R)-4-(3-t-butylamino-2-hydroxypropoxy)-benzimidazol-2-one), a potent adrenergic β-receptor antagonist were synthesized and labelled with ^{11}C for Positron Emission Tomography studies of β-receptors in heart. The synthesis was accomplished from (2S)-and (2R)-3-tosyloxy-1,2-propanediol acetonide. Enantiomeric excess was greather than 95% for each of the prepared enantiomers. (S)- and (R)-[^{11}C]-CGP 12177 were obtained with a specific radioactivity of 29.6-44.4 GBq/μmol.

KEY WORDS : asymmetric synthesis, CGP 12177 enantiomers, ^{11}C, PET, β-receptor.

INTRODUCTION

CGP 12177 (4-(3-t-butylamino-2-hydroxypropoxy)-benzimidazol-2-one) has been shown to be a β-selective adrenergic antagonist of the aryloxypropanolamine type[1]. Several β-blockers in this class are used to study physiological processes in the mammalian heart[2]. Five antagonists, propanolol, practolol, pindolol, atenolol and CGP 12177[3] have been labelled with carbon-11 for Positron Emission Tomography[4] (PET) studies. From this approach, it was observed that [^{11}C]-pindolol and [^{11}C]-CGP 12177 have in common a high affinity and a low lipophilicity. [^{11}C]-CGP 12177 presents the geatest advantages[5]. Nowadays, racemate is used to study physiological processes of the heart in vivo under normal or pathological conditions[6]. The stereochemistry of this tracer molecule is now the aspect that has to be considered. In vitro studies with (S)-and (R)-[^{3}H]-CGP 12177 have shown that β-adrenergic blocking activity resides in the (S)-isomer[7]. For these reasons the carbon-11 labelled (S)-CGP 12177 is desired for PET studies of β-

0362–4803/91/060681–10$05.00

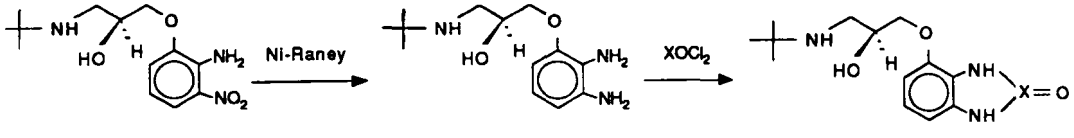
Received 14 January, 1991
Revised 1 February, 1991

adrenergic receptors. In the present work, (R)-and (S)-CGP 12177 were synthesized and radiolabeled for this purpose.

RESULTS AND DISCUSSION

Synthesis of (2S)-and (2R)-1-(2-amino-3-nitrophenoxy)-3-(t-butylamino)-2-propanol.

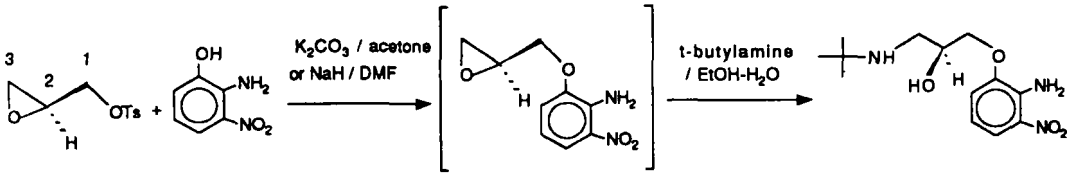
(2S)-1-(2-amino-3-nitrophenoxy)-3-(t-butylamino)-2-propanol [(2S)-4] is a possible precursor for the synthesis of (S)-CGP 12177 [(2S)-1] and radiosynthesis of carbon-11 labelled (S)-CGP 12177 [(2S)-2] as shown in Scheme 1.



(2S)-4 (2S)-3 (2S)-1 X = C
(2S)-2 X = ^{11}C

Scheme 1

In initial efforts to synthesize (2R)-and(2S)-4, we attempted to utilize the enantiomeric glycidyl tosylates (6) previously used by Sharpless in the synthesis of other β-adrenergic blockers[8]. Unfortunaly, we obtained (2S)-4 in the range of 65-84% ee[9] (Scheme 2).



(2S)-6 7 (2S)-5 (2S)-4

Scheme 2

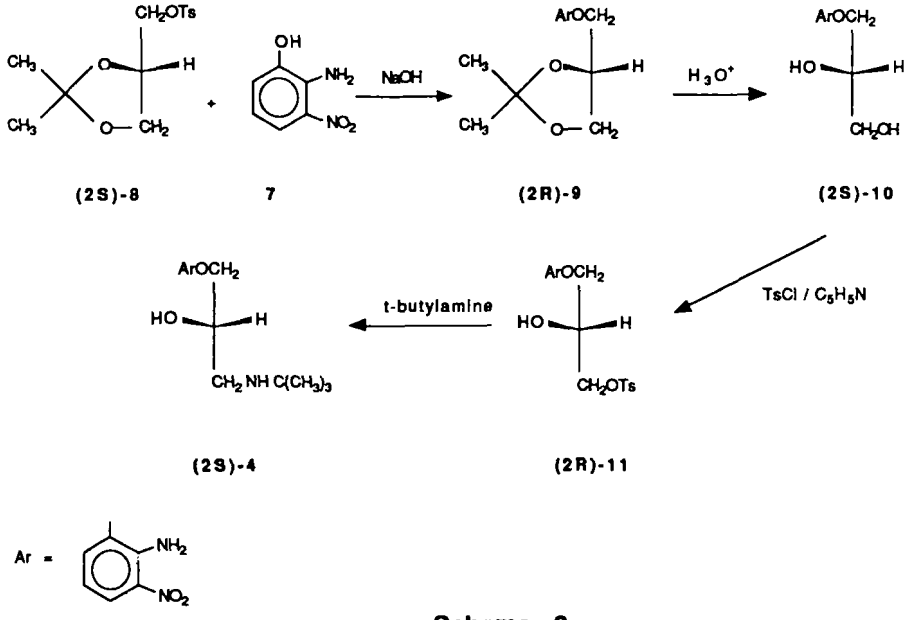
Reaction of (2S)-glycidyl tosylate [(2S)-6)] with sodium 2-amino-3-nitrophenoxide in DMF, followed by addition of t-butylamine gave the expected aryloxypropanolamine [(2S)-4] with 84% ee, indicating a selectivity of 96:4 in favor of direct sulfonate displacement (Table 1).The results obtained under refluxing acetone-K_2CO_3 conditions exhibited a C-1 : C-3 ratio of only 85:15 (63% ee).

Table 1. Asymmetric synthesis of **4** from chiral **6**

entry	6 (no of equiv)	% ee [6]	condn,[a] time (h)	(2S)-4 yield[b] %	(2S)-4 $[\alpha]_D$ in methanol	(2S)-4 % ee	(2S)-4 selectivity[e] C-1 : C-3
1	(2S)-6(2)	91	A, 18	66	+ 14.5 (c= 1)	65[c,d]	86 : 14
2	(2S)-6(1)	91	A, 18	60	+ 14.1 (c= 1)	63[d]	85 : 15
3	(2S)-6(1)	91	B, 12	70	+ 18.9 (c= 1)	84[d]	96 : 4

a) Reaction conditions of glycidyl tosylate with 2-amino-3-nitrophenol : A, K_2CO_3-refluxing acetone; B, NaH-DMF. b) Isolated yield of (2S)-4 (referred to glycidyl tosylate) after purification. c) Determined by ^{1}H NMR of (2S)-5 using Eu(hfc)$_3$ as chiral shift reagent. d) Determined from optical rotation (ref. to $[\alpha]_D$ max. value[9]). e) Regioselectivity (a : b) was calculated according to the formula : a = 1/2 (%ee [6] + %ee [4]) / %ee [6] ; b = 1- a.

We had previously noted that individual enantiomers of the 3-aryloxy-1-amino-2-propanol nucleus can readily be prepared from optically active glycerol derivatives[10]. In order to obtain the key intermediates **(2R)-and (2S)-4** having high optical purity in good yield, efforts were then directed to the use of enantiomers of 3-tosyloxy-1,2-propanediol acetonide **[8]** (Scheme 3).



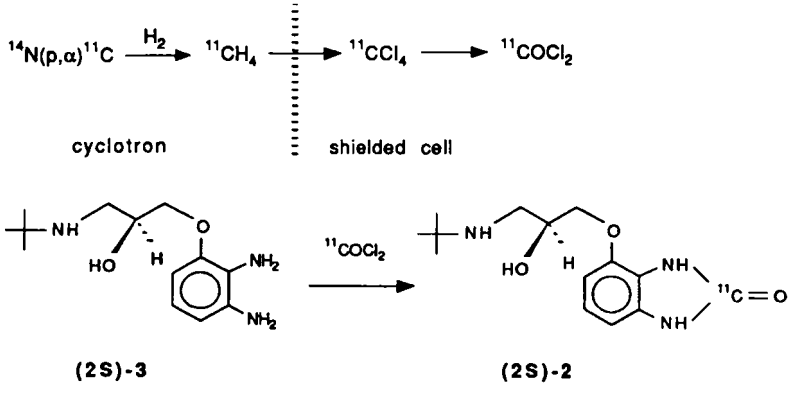
Scheme 3

Reaction of 2-amino-3-nitrophenol [7] with sodium hydroxide in EtOH-H_2O, followed by addition of (2S)-3-tosyloxy-1,2-propanediol acetonide [**(2S)-8**] gave (2R)-3-(2-amino-3-nitrophenoxy)-1,2-propanediol acetonide [**(2R)-9**]. The crude intermediate **(2R)-9** was readily hydrolyzed into the corresponding diol **(2S)-10** in 70% yield after crystallisation from **(2S)-8**. Treatment of the diol **(2S)-10** with 1.1 equiv of p-toluenesulfonyl chloride led to **(2R)-11** in 90% yield after chromatographic purification. Monotosylate **(2R)-11** was then treated with an excess of t-butylamine to give the aryloxypropanolamine **(2S)-4** ($[\alpha]_D$ = +21.4° (c= 0.7, CH_3OH)) in 85% yield after chromatographic purification (54% overall yield from **(2S)-8**). The optical purity was estimated to be 95% ee judging from the reported value[9]. This compound is easily recrystallized to an enantiomeric purity of > 99% and stable to handling at room temperature.

Synthesis of (S)-CGP 12177 [(2S)-1] and carbon-11 labelled (S)-CGP 12177 [(2S)-2].

Reduction of **(2S)-4** using Raney nickel gave (2S)-1-(2,3-diaminophenoxy)-3-(t-butylamino)-2-propanol [**(2S)-3**] in 98% yield (scheme 1). This diamino **(2S)-3** was then treated with phosgene in toluene to afford the hydrochloride of (2S)-CGP 12177 [**(2S)-1**], in an overall yield of 43% from **(2S)-8**. (R)-CGP 12177 was thereby obtained in an analogous fashion starting with **(2R)-8**. The compounds have been fully characterized by ^{1}H-NMR, mass spectrometry, centesimal analysis, HPLC (RP-18 column).

(S)-CGP 12177 was labelled with carbon-11 by reaction of carbon-11 phosgene[11] on the diamino precursor **(2S)-3** as shown in Scheme 4.



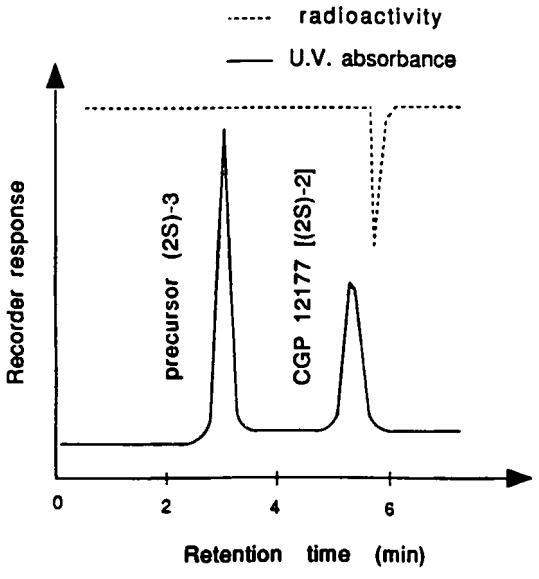
(2S)-3 (2S)-2

Scheme 4

The radiosynthesis was carried out semi automatically in a well shielded cell. The time for the synthesis and the purification (Scheme 5) of carbon-11 labelled (2S)-CGP 12177 after the end of the bombardment was 30 min. We

obtained 100-200 mCi (3.7-7.4 GBq) of radiochemically (> 99%) and chemically pure **(2S)-2** with a specific activity of 800-1200 mCi/μmol (29.6-44.4 GBq/μmol). The labelled compound **(2S)-2** was characterized by HPLC coinjection with **(2S)-1**.

Scheme 5 : Separation of (S)-[^{11}C]-CGP 12177 **[(2S)-2]** by HPLC



HPLC analysis was done on a RP-18 column using physiological saline solution-ethanol (7:1) containing phosphate buffer (pH 2.3) at 2mM as an elution solution. The flow was 4 ml/min and a uv detector at 254 nm was used. The radioactivity was detected by an ionisation chamber.

In conclusion, both enantiomers of CGP 12177 have been synthesized in six steps from 3-tosyloxy-1,2-propanediol acetonide with an overall yield of 43%. PET studies of β-adrenergic receptors using carbon-11 labelled (S)-CGP 12177 are now under investigation in our laboratories.

EXPERIMENTAL

Melting points are uncorrected . ^{1}H-NMR spectra were recorded on a Brucker AM 250 (250 MHz) and a Bruker 200 (200 MHz) with tetramethylsilane as internal standard. Mass spectra were obtained using a Nermag R 10-10 instrument at 70eV. Optical rotations were measured in a 1 ml cell at 20°C (± 2°C) using a Perkin-Elmer Polarimeter 241. Microanalyses were performed by the Service de Microanalyse du CNRS, Gif sur Yvette. Analytical thin layer chromatography was performed on Merck Kieselgel 60 F_{254}. Silica gel 60 (230-400 mesh) was used for column chromatography. Solvents were distilled before use and, if necessary, dried following literature methods.

(2S)-1-(2-amino-3-nitrophenoxy)-3-(t-butylamino)-2-propanol [(2S)-4] from (2S)-glycidyl tosylate [(2S)-6].

Procedure A.

(2S)-glycidyl tosylate (91% ee, from Aldrich Chemical Co., 456 mg, 2.0 mmol) was added to a solution of 2-amino-3-nitrophenol [7] (323 mg, 2.1 mmol) and K_2CO_3 (290 mg, 2.1 mmol) in acetone. The reaction mixture was heated at reflux with stirring for 18h. The solvent was then evaporated. The residue was partitioned between CH_2Cl_2 (100 ml) and H_2O (20 ml). The organic layer was dried over magnesium sulfate, evaporation of CH_2Cl_2 afforded a red oil (360 mg) which was determined by NMR to be 83% product **[(2S)-5]**.
[(2S)-5]; ^{1}H-NMR ($CDCl_3$) δ 2.80 (1H, dd, 2.5, 5Hz), 2.95 (1H, t, 5Hz), 3.35-3.45 (1H, m), 3.95 (1H, dd, 5, 11.5Hz), 4.35 (1H, dd, 2.5, 11.5Hz), 6.30-6.40 (2H, m), 6.50 (1H, t, 8.5Hz), 6.90 (1H, d, 8.5Hz), 7.70 (1H, d, 8.5Hz).

The crude epoxy ether **(2S)-5**, 360 mg (representing 294 mg, 1.4 mmol), and t-butylamine (1.0 g, 13.7 mmol) in 20 ml of 90% ethanol were stirred for 18h at room temperature. Evaporation of the solvent afforded an oil which was dissolved in 25 ml of 1N HCl. The aqueous acidic solution was washed with ether (3 x 20 ml), made alkaline with 1N NaOH, and extracted with CH_2Cl_2 (3 x 50 ml). These organic layers were dried over $MgSO_4$ and concentrated to give a red oil. Purification by flash chromatography (elution with ethyl acetate-methanol-triethylamine, 90-10-1.5) afforded 340 mg (60%) of **(2S)-4** as a red oil, which solidified under high vacuum (m.p. 60-61°C).
$[\alpha]_D$ = +14.1 (c 1.0, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ 1.10 (9H, s), 2.30-2.45 (2H, m), 2.70 (1H, dd, 7, 12Hz), 2.90 (1H, dd, 4, 12Hz), 4.00 (3H, m), 6.30-6.40 (2H, m), 6.50 (1H, t, 8Hz), 6.95 (1H, d, 8Hz), 7.75 (1H, d, 8Hz). Found: C 55,02%; H 7.82%; N 13.47%. $C_{13}H_{21}N_3O_4$ requires : C 55.12%; H 7.42%; N 14.84%. Mass spectrum, m/z (relative intensity): 283 (3.8 M^+); 268 (10.5); 193 (7.7); 153 (7.6); 112 (13.5); 107 (10.5); 86 (58.2); 71 (22.1); 57 (22.6); 41 (25.2); 30 (100).

Procedure B.

2-amino-3-nitrophenol [7] (308 mg, 2 mmol) in DMF (2 ml, stored over 3-Å sieves) was added to a suspension of sodium hydride (oil free, 48 mg, 2 mmol) in DMF at room temperature under a nitrogen atmosphere. After 15-30 min, a solution of (2S)-glycidyl tosylate (91% ee, 456 mg, 2 mmol) in DMF (2 ml) was added, and the mixture was stirred overnight at 25°C under nitrogen. t-butylamine (1.825 g, 25 mmol) and water (0.2 ml, 11 mmol) were then added and the reaction was heated to reflux. After 6h the reaction mixture was cooled and quenched into 30 ml of distilled water. The solution was then extracted three times with 200 ml of methylene chloride. The combined organic phases back-extracted twice with 50 ml of 1N HCl. The acid layers were rendered alkaline with sodium carbonate and extracted twice with 150 ml of methylene chloride. The organic layers were washed with 10 ml of water, dried over magnesium sulfate, and evaporated. Purification of the resulting oil by flash chromatography afforded 0.396 g (70%) of **(2S)-4** as red crystals (m.p. 60-62°C).
$[\alpha]_D$ = + 18.9 (c 1.0, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ 1.05 (9H, s), 2.30-2.40 (2H, m),

2.70 (1H, dd, 7, 12Hz), 2.85 (1H, dd, 4, 12Hz), 4.05 (3H, m), 6.30-6.45 (2H, m), 6.55 (1H, t, 8Hz), 7.00 (1H, d, 8Hz), 7.75 (1H, d, 8Hz).

(2R)-3-(2-amino-3-nitrophenoxy)-1,2-propanediol acetonide [(2R)-9].

A solution of NaOH (0.32 g, 8 mmol) and 2-amino-3-nitrophenol [7] (1.23 g, 8 mmol) in 15 ml of 90% ethanol was added to 2 g (7 mmol) of (2S)-3-tosyloxy-1,2-propanediol acetonide [**(2S)-8**] (95% ee, from Aldrich Chemical Co.) and the mixture was refluxed for 24h. The cooled reaction mixture was evaporated and the oily residue was partitioned between methylene chloride (100 ml) and water (50 ml). The aqueous layer was discarded and the organic layer was dried ($MgSO_4$) and evaporated affording 1.8 g of a red oil, which was determined by NMR to be 80% product [**(2R)-9**]. Integration of the area of protons of the tosyl group was used as a measure of remaining starting material.
[**(2R)-9**]; ^{1}H-NMR ($CDCl_3$) δ 1.40 (3H, s), 1.45 (3H, s), 3.90-4.20 (4H, m), 4.30 (1H, m), 6.30-6.40 (2H, m), 6.45 (1H, t, 8Hz), 6.75 (1H, d, 8Hz), 7.60 (1H, d, 8Hz).

(2S)-(+)-3-(2-amino-3-nitrophenoxy)-1,2-propanediol [(2S)-10].

The crude acetonide [**(2R)-9**], 1.8 g (representing 1.5 g, 5.6 mmol), was dissolved in a mixture of ethanol (15 ml) and 1N HCl (2.5 ml) and stirred for 6h at room temperature. The reaction mixture was then neutralized with Na_2CO_3. Evaporation of the solvent and purification by flash chromatography (elution with ethyl acetate) afforded 1.13 g (88%) of **(2S)-10** as a yellow oil. Crystallization from ethyl acetate-cyclohexane gave the diol **(2S)-10** as a yellow solid (m.p. 138-139°C).
$[\alpha]_D$ = + 30. 7 (c 0.8, CH_3OH); ^{1}H-NMR (CD_3OD) δ 3.70 (2H, m), 4.05 (3H, m), 6.50 (1H, t, 8Hz), 6.80 (1H, d, 8Hz), 7.65 (1H, d, 8Hz). Mass spectrum (DCI/NH_3), m/z (relative intensity) : 246 (20); 229 (100 MH^+).

(2R)-(+)-3-(2-amino-3-nitrophenoxy)-1-(p-toluenesulfoxy)-2-propanol [(2R)-11].

p-toluenesulfonyl chloride (1.05 g, 5.5 mmol) in 3 ml of anhydrous methylene chloride was added slowly to a solution of diol **(2S)-10** (1.13 g, 5.0 mmol) in 4 ml of anhydrous pyridine at 0°C. After the mixture was stirred overnight at room temperature, the resulting solution was then diluted with methylene chloride (100 ml), washed with 1N HCl (10 ml) and then with water (10 ml), dried ($MgSO_4$) and evaporated. Purification by flash chromatography (ethyl acetate) afforded 1.7 g (90%) of **(2R)-11** as a red oil.
$[\alpha]_D$ = + 2.3 (c 2, CH_3OH) ; ^{1}H-NMR ($CDCl_3$) δ 2.35 (3H, s), 3.20 (1H, m), 4.00 (2H, m), 4.20 (3H, m), 6.25-6.35 (2H, m), 6.50 (1H, t, 8Hz), 6.75 (1H, d, 8Hz), 7.20 (2H, d, 9Hz), 7.60 (1H, d, 8Hz), 7.65 (2H, d, 9Hz).

(2S)-(+)-1-(2-amino-3-nitrophenoxy)-3-(t-butylamino)-2-propanol [(2S)-4].

A mixture of the tosylate **(2R)-11** (1.70 g, 4.5 mmol) and t-butylamine (3.29 g, 45 mmol) was heated at reflux in acetonitrile (40 ml) for 6h. The solvent was evaporated and the residue was dissolved in methylene chloride (120 ml) and water (30 ml). The phases are separated, the aqueous phase extracted with methylene chloride, the organic phases washed with brine, dried over $MgSO_4$ and the solvent evaporated. Purification by flash chromatography afforded **(2S)-4** (1.08 g, 85%) as the last fraction. The red oil was stored overnight at 0°C. After drying (P_2O_5-vacuum), a red solid, m.p. 61-62°C, was obtained.

$[\alpha]_D$ = + 21.4 (c 0.7, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ 1.10 (9H, s), 2.30-2.40 (2H, m), 2.70 (1H, dd, 6.5, 12Hz), 2.95 (1H, dd, 4, 12Hz), 4.00 (3H, m), 6.35-6.45 (2H, m), 6.50 (1H, t, 8Hz), 6.95 (1H, d, 8Hz), 7.75 (1H, d, 8Hz). Mass spectrum, m/z (relative intensity) : 283 (3.5 M^+); 268 (10.5); 193 (7.5); 153 (7.5); 112 (13.5); 107 (10.1); 86 (58.1); 71 (22.2); 57 (22.5); 41 (25.1); 30 (100).

(2S)-(+)-1-(2,3-diaminophenoxy)-3-(t-butylamino)-2-propanol [(2S)-3].

Raney nickel (230 mg) was suspended in EtOH (8ml). After 15 minutes stirring at 65°C, **(2S)-4** (1.0 g, 3.5 mmol) in THF (17 ml) and hydrazine hydrate (1.7 ml) in EtOH (17 ml) were added simultanely and the reaction was stirred at 65-70°C for 2h. The solution was then filtered and the solvent evaporated under vacuum to give an oil (860 mg). The residue was diluted in ether, activated carbon was added and the mixture was stirring for 30 min, filtered and then concentrated. Crystallization from petroleum ether give the desired product **(2S)-3** (800 mg, 90%) as a grey solid (m.p. 74-76°C).

$[\alpha]_D$ = + 6.9 (c 1.0, CH_3OH); ^{1}H-NMR (CD_3OD) δ 1.40 (9H, s), 3.1 (1H, m), 3.30 (1H, m), 4.05 (2H, m), 4.30 (1H, m), 6.60 (2H, d, 8Hz), 6.85 (1H, t, 8Hz). Mass spectrum (DCI/NH_3), m/z (relative intensity) : 254 (100 MH^+).

(2S)-(-)-4-(3-t-butylamino-2-hydroxypropoxy)-benzimidazol-2-one [(2S)-1].

Compound **(2S)-3** (800 mg, 3.16 mmol) was suspended in anhydrous ether (200 ml). Then 2.5 ml of phosgene 20% in toluene (from Fluka Chemical Co.) were slowly added at 20°C. The mixture turned immediately violet and a precipitate is formed. After 20 min the solvent was evaporated under vacuum to give a white solid. Crystallisation from methanol-ether afforded 1.17 g (95%) of (S)-CGP 12177 hydrochloride as a white solid (m.p. 246-249°C).

$[\alpha]_D$ = - 10.8 (c 0.8, CH_3OH); ^{1}H-NMR (CD_3OD) δ 1.30 (9H, s), 3.05 (1H, m), 3.20 (1H, m), 4.05 (2H, m), 4.15 (1H, m), 6.60 (2H, d, 8Hz), 6.90 (1H, t, 8Hz). Mass spectrum (DCI/NH_3), m/z (relative intensity) : 280 (100 MH^+).

(S)-[^{11}C]-CGP 12177 [(2S)-2].

The operations were all carried out by remote control in closed shielded cell. [^{11}C]-$COCl_2$ was prepared according to the procedure described in reference 11.

The labelled phosgene [^{11}C]-$COCl_2$ was transferred under a helium stream to a tube containing **(2S)-3** (0.8 µmol) in 40 µl of methylene chloride and 100 µl of toluene. The solvent was then evaporated (bath temperature was 130°C) and the reaction mixture was cooled in a water bath. The radioactive residue was dissolved in 1ml of a mixture of a physiological saline solution-ethanol (7:1) containing phosphate buffer (pH 2.3) at 2 mM (used as chromatography eluent) and injected in the HPLC chromatographic system : RP-18 column (length: 30.5 cm, internal diameter 7 mm), flow rate of 4 ml/min. The products were separated and the retention times were 2.5 min for the precursor **(2S)-3** and 5.0 min for (S)-[^{11}C]-CGP 12177. The radioactive fraction, containing the labelled product, was collected, and the ethanol was evaporated under a nitrogen stream. The solution was then sterilized by passage through a Millipore filter and introduced into a seringue. Starting with about 1 Ci (37 GBq) of $^{11}CH_4$,100-200 mCi (3.7-7.4 GBq) of (S)-[^{11}C]-CGP 12177 were obtained 30 min after the end of bombardment with a specific radioactivity of 800-1200 mCi/µmol (29.6-44.4 GBq/µmol).

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