Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Synthesis of stereoisomers of 6β- and 7β-(benzylthio)-3-(*p*-tolyl) tropane-2-carboxylic acid methyl ester

Fadi Masri[a]; Françoise Riche[a]; Andre Durif[a]; Christian Philouze[a]; Yannick Vallée[a]
[a] Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité, UMR CNRS/UJF 5616, Institut de Chimie Moléculaire de Grenoble, FR-2607, Université Joseph Fourier Grenoble I, Grenoble Cedex 9, France

To cite this Article Masri, Fadi , Riche, Françoise , Durif, Andre , Philouze, Christian and Vallée, Yannick(2004) 'Synthesis of stereoisomers of 6β- and 7β-(benzylthio)-3-(*p*-tolyl) tropane-2-carboxylic acid methyl ester', Journal of Sulfur Chemistry, 25: 4, 259 — 268
To link to this Article: DOI: 10.1080/17415990412331282459
URL: http://dx.doi.org/10.1080/17415990412331282459

J. Sulfur Chemistry
Vol. 25, No. 4, August 2004, 259–268

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Synthesis of stereoisomers of 6β- and 7β-(benzylthio)-3-(*p*-tolyl) tropane-2-carboxylic acid methyl ester

FADI MASRI, FRANÇOISE RICHE*, ANDRE DURIF, CHRISTIAN PHILOUZE and YANNICK VALLÉE

Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité,
UMR CNRS/UJF 5616, Institut de Chimie Moléculaire de Grenoble, FR-2607,
Université Joseph Fourier Grenoble I, 301 rue de la chimie, BP 53,
38041 Grenoble Cedex 9, France

(*Received 25 May 2004; In final form 25 June 2004*)

To develop new ^{99m}Tc-labelled agents to evaluate dopamine transporters (DAT) involved in Parkinson' s disease, by *in vivo* SPECT imaging, we have synthesized six new sulfur-containing ligands with the tropane skeleton. We have introduced the complexing sulfur atom far from the three sites of recognition by DAT of these tropane derivatives. The 6β-substituted tropinone has been obtained by a double Mannich condensation followed by the introduction of the moieties for molecular interactions at the binding site on C2 and C3, leading to the six stereoisomers.

Keywords: Cocaine analogues; Tropanes; Dopamine transporter

1. Introduction

Neurological disorders such as Parkinson's disease are associated with a significant decrease in dopamine transporters (DAT) located presynaptically on dopamine neurons [1, 2]. The first symptoms following degeneration appear when half of these neurons are affected. Hence, the measurement of their depletion through radioactive labelling of the dopamine transporter followed by imaging would be a good way to diagnose the disorder at an early stage and monitor the progression of these diseases after treatment.

Among molecules that bind and/or are specific to the DAT, cocaine and other tropane derivatives have been widely studied. They were labelled either with β^+-emitters (^{18}F, ^{11}C)

* Corresponding author. E-mail: francoise.riche@ujf-grenoble.fr

J. Sulfur Chemistry
ISSN 1741-5993 print; ISSN 1741-6000 online © 2004 Taylor & Francis Ltd
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990412331282459

[3, 4] used for PET (positron emission tomography) or γ-emitters (^{123}I, ^{99m}Tc) [5–7] used for SPECT (single photon emission computed tomography). Examples are given in figure 1.

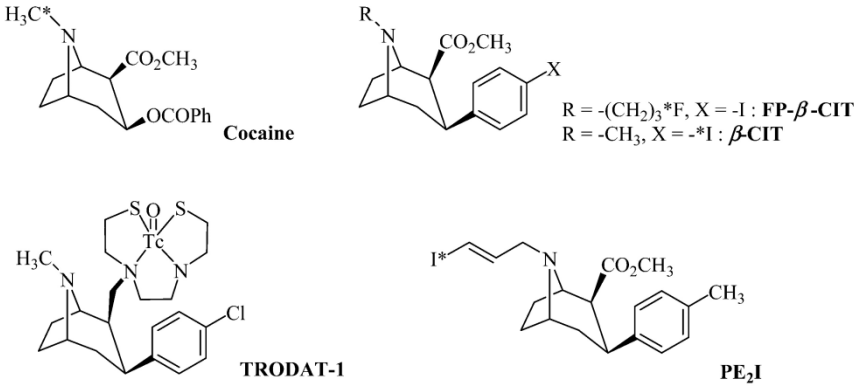
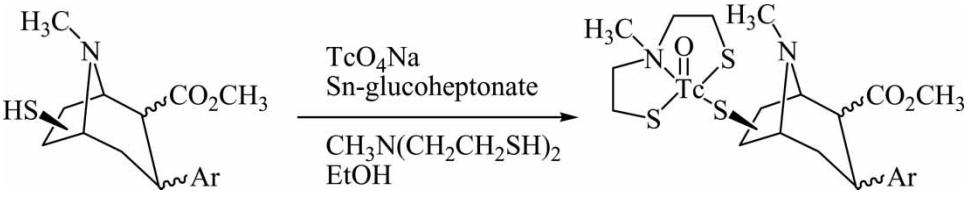


Figure 1. Labelled tropane derivatives used for DAT imaging.

None of these compounds are sufficiently active for DAT imaging. SAR data suggest that it is important for recognition that compounds bear a methyl group on the nitrogen, an ester on the C2 position (β) and an aromatic group on the C3 position (β) of the tropane ring. Affinity for the DAT is better if the aromatic is a tolyl group [8].

We propose a new approach to labelling tropane analogues with technetium 99m ($T_{1/2}$ = 6.02 h, γ-emission, 140 keV); Tc99m is the most widely used radionuclide in diagnostic nuclear medicine (over 85% of routine nuclear medicine procedures currently performed use radiopharmaceuticals based on Tc99m, which is readily produced by a Mo99/Tc99m generator). The metal is introduced far from the three sites of recognition, on the two-carbon bridge of the tropane ring, *via* a sulfur atom, following the '3+1' strategy [9] as shown in scheme 1.



SCHEME 1

We chose to keep a methyl group on the nitrogen and a methyl ester on C2 in reference to cocaine and to introduce a tolyl group on C3 in reference to the good affinity of PE_2I for the DAT. We report here the synthesis of six new racemic thiols, in protected forms to avoid eventual dimerisation by oxidation. Deprotection has been performed on one of these compounds. Target molecules are shown in figure 2.

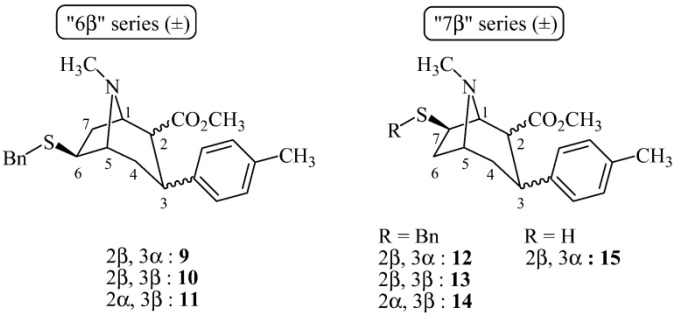
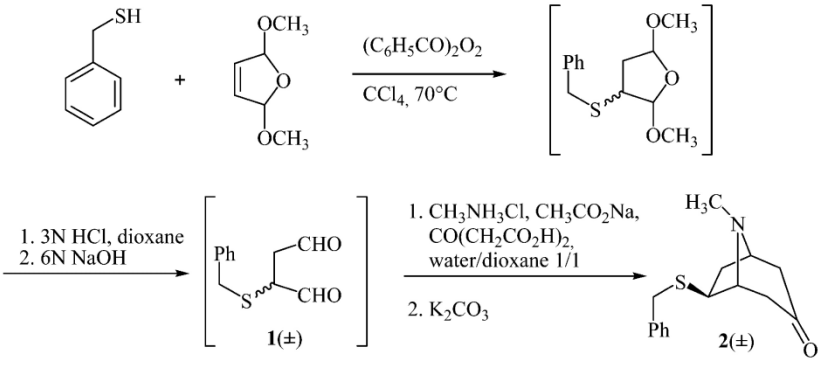


Figure 2. Target molecules.

2. Results and discussion

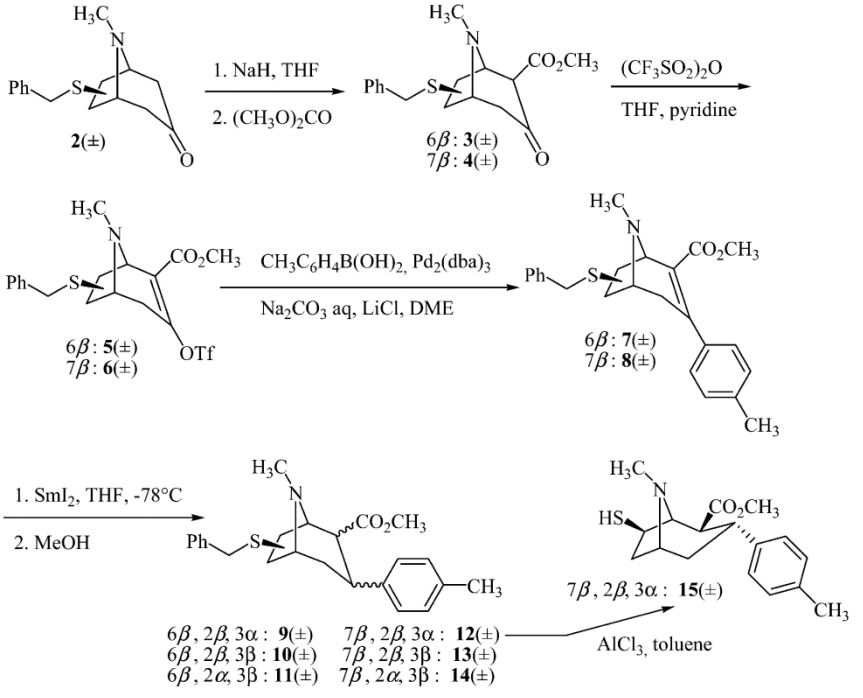
The introduction of a substituent on the two-carbon bridge involves the total synthesis of the ring. The key step is based upon a double Mannich-type condensation reaction between methylamine, acetonedicarboxylic acid and 2-benzylsulfanylsuccinaldehyde **1** (scheme 2).



SCHEME 2

The dialdehyde **1** was obtained by free radical addition of benzylmercaptan to 2,5-dimethoxydihydrofuran in CCl_4 at 70°C with benzoyl peroxide as initiator. After evaporation of the solvent, the crude product was stirred for a few hours in a 2M HCl-dioxane mixture and then neutralized by the addition of 6M NaOH to give **1**. This compound is unstable and only NMR analysis could be carried out to characterize it. The dialdehyde was then added to a solution of acetonedicarboxylic acid, methylamine hydrochloride and sodium acetate according to Zhao [10] but in a mixture of water and dioxane for better solubility. Decarboxylation was carried out by addition of potassium carbonate and compound **2** was isolated after chromatography as an oil in 10% yield (over three steps). NMR analysis showed that only the *exo* product was obtained.

Tropinone **2** was then used for the synthesis of all six stereoisomers (scheme 3). After deprotonation with NaH in THF, the resulting enolate was reacted with dimethyl carbonate to give in 66% yield the methoxycarbonylated derivatives **3** and **4** (11:9). A small quantity of the two isomers was separated by preparative HPLC and characterized by NMR but the subsequent two steps were carried out on the mixture.



SCHEME 3

Ketones **3** + **4** were converted into their enol triflates **5** + **6** (85% yield) by reaction with trifluoromethanesulfonic anhydride in pyridine. Compounds **5** + **6** were then coupled with *p*-tolylboronic acid in 1,2-dimethoxyethane (DME) in the presence of sodium carbonate, lithium chloride and tris(dibenzylideneacetone)dipalladium(0) according to the Suzuki protocol [11] to provide the alkenes **7** and **8** in 75% yield. At this stage, the isomers **7** and **8** could be separated by liquid chromatography and their structures assigned by X-rays analysis. Figures 3 and 4 show ORTEP views of **7** and **8**, respectively.

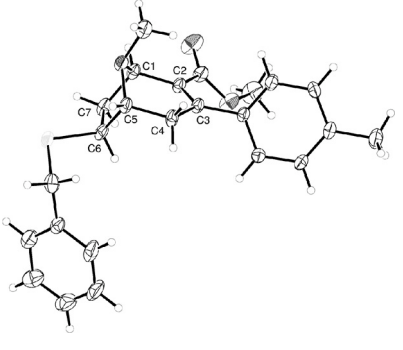


Figure 3. ORTEP view of compound **7**.

Reduction of **7** with samarium diiodide in THF at −78°C followed by quenching with methanol gave the saturated tropane derivatives **9** (2β,3α; 38%), **10** (2β,3β; 28%), and **11** (2α,3β; 7%). Reduction of **8** under the same conditions provided compounds **12** (2β,3α; 35%), **13** (2β,3β; 30%) and **14** (2α ,3β; 10%). All configurations were assigned after NMR studies,

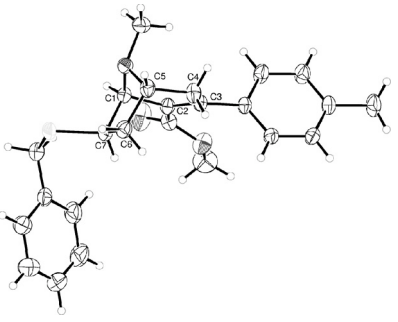


Figure 4. ORTEP view of compound **8**.

including ^{1}H, ^{13}C, COSY and GHMQC. Finally, **15** was obtained in 53% yield by treatment with $AlCl_3$ in toluene [12], demonstrating that the deprotection of the benzyl sulfides is possible.

In conclusion, we have synthesized six new compounds bearing a sulfur atom on the two-carbon bridge of the functionalized tropane. Labelling of these compounds with the '3+1' strategy, after deprotection of the thiol function, is in progress.

3. Experimental

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in oven-dried or flame-dried glassware equipped with a magnetic stir bar. Toluene was freshly distilled over sodium. All reagents were purchased from either Aldrich or Fluka chemical companies and used without purification. Reactions were monitored by thin-layer chromatography (TLC) using commercial aluminium-backed silica gel plates (Merck, Kieselgel 60 F_{254}). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with either a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v). Column chromatography to purify the products was performed using Macherey Nagel Silica Gel 60 (230–400 mesh). Melting points were determined with a Büchi B-545 apparatus. Infrared (IR) spectra were obtained either as neat films, or as a thin film of a dichloromethane or ether solution of the compound on sodium chloride discs. All IR spectra were recorded on a Nicolet Impact-400 Fourier transform infrared spectrometer and the data are reported in reciprocal centimeters (cm^{-1}). ^{1}H (300 MHz), and ^{13}C (75 MHz) NMR spectra were run using $CDCl_3$ as the solvent. Mass spectra were recorded on a ThermoFinnigan PolarisQ ion-trap spectrometer using DCI (ammonia-isobutane 63:37). Elemental analyses were performed at the Service Central d' Analyse du CNRS, Vernaison, France.

3.1 *2-Benzylthiosuccinaldehyde-1 and 6β-benzylsulfanyl-8-methyl-8-azabicyclo[3.2.1]octane-3-one (±)-2*

To a solution of 2,5-dimethoxy-2,5-dihydrofuran (17.1 g, 0.13 mol) in CCl_4 (100 mL), benzylmercaptan (24.5 g, 0.19 mol) and benzoyl peroxide (6.3 g, 0.02 mol) were added. The solution was then stirred under reflux for 12 h. After washing with water, the solvent was evaporated and crude 3-benzylsulfanyl-2,5-dimethoxytetrahydrofuran was dissolved in a mixture of 2M HCl (100 mL) and dioxane (50 mL) and stirred for 4 h at room temperature. After addition of 6M aqueous NaOH until neutralization, and extraction with $CHCl_3$, compound **1** was isolated and used without further purification. It was added to a solution of methylamine chlorhydrate (18 g, 0.26 mol), 3-oxopentanedicarboxylic acid (38 g, 0.26 mol) and sodium acetate (38 g, 0.26 mol) in a water-dioxane (200 mL, v/v) mixture. Decarboxylation was achieved by addition of potassium carbonate (100 g). After extraction with chloroform,

compound **2** was purified by liquid chromatography on silica gel (cyclohexane-ethyl acetate 5:1) to give **2** as a red oil (3.4 g, 13.02 mmol, 10% over three steps).

1: ^{1}H NMR δ (ppm): 2.72 (dd, 1H, S−CH−C$\underline{H}_2$−CHO, $^2J_{H-C-H} = 18.5$ Hz, $^3J_{CH_2-CHS} = 2.7$ Hz), 3.06 (dd, 1H, S−CH−C$\underline{H}_2$−CHO, $^2J_{H-C-H} = 18.5$ Hz, $^3J_{CH_2-CHS} = 8.4$ Hz), 3.63–3.73 (m, 3H, Ph−C$\underline{H}_2$−S−C$\underline{H}$−CH$_2$−CHO), 7.28–7.33 (m, 5H, CH$_{Ar}$), 9.32 (s, 1H, CHO), 9.69 (s, 1H, CHO); ^{13}C NMR δ (ppm): 35.3 (Ph−$\underline{C}$H$_2$−S−CH−CH$_2$−CHO), 42.7 (S−CH−$\underline{C}$H$_2$−CHO), 46.6 (S−$\underline{C}$H−CH$_2$−CHO), 128.0, 129.2 and 129.5 (CH$_{Ar}$), 137.0 (C$_{qAr}$), 192.4 (CHO), 198.4 (CHO).

2: IR (neat) ν(cm^{-1}): 2940, 1705, 1490, 1450, 1410, 1345, 1215; ^{1}H NMR δ (ppm): 1.97–2.13 (m, 4H, H$_{7\alpha}$, H$_{7\beta}$, H$_{4\alpha}$, H$_{2\alpha}$), 2.6–2.67 (m, 2H, H$_{4\beta}$, H$_{2\beta}$), 2.62 (s, 3H, N−CH$_3$), 2.86 (dd, 1H, H$_6$, $^3J_{6-7\alpha} = 8.6$ Hz, $^3J_{6-7\beta} = 5.7$ Hz), 3.25–3.30 (m, 1H, H$_5$), 3.51–3.55 (m, 1H, H$_1$), 3.74 (s, 2H, S−CH$_2$), 7.24–7.28 (m, 5H, CH$_{Ar}$); ^{13}C NMR δ (ppm): 37.0 (N−CH$_3$), 38.0 (S−CH$_2$), 38.6 (C$_7$), 45.0 (C$_2$), 45.6 (C$_4$), 46.4 (C$_6$), 60.8 (C$_1$), 67.3 (C$_5$), 127.6 and 129.0 and 129.1(CH$_{Ar}$), 138.5 (C$_{qAr}$), 208.4 (C$_3$); m/z 262 [M + H$^+$]; Calcd. (%) for C$_{15}$H$_{19}$NOS: C, 68.93; H, 7.33; N: 5.36. Found: C, 68.69; H, 7.37; N, 5.20.

3.2 *Synthesis of 6β- and 7β-benzylthio-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl esters (±)-3 and -4*

To a dispersion of sodium hydride (60% in mineral oil, 0.42 g, 17.5 mmol) in THF (50 mL) were added the compound **2** (1.3 g, 4.98 mmol) and dimethyl carbonate (0.675 g, 7.5 mmol). The resulting mixture was heated at reflux overnight. After returning to room temperature, the solvent was evaporated, the residue taken up in chloroform and washed with water. The chloroform was then dried over sodium sulfate and evaporated. Compounds **3** and **4** were purified (but not separated) by liquid chromatography (silica gel, cyclohexane-ethyl acetate, 9:2 to 2:1), as a red oil (1.05 g, 3.28 mmol, 66%). Small quantities of **3** and **4** were separated by HPLC [Nucleosil 100–7 C18, eluent MeOH−H$_2$O−THF (50:40:10)+0.1% Et$_3$N]. IR mixture **3** + **4** (neat) ν(cm^{-1}): 3600–2700, 2940, 1740, 1655. Calcd (%) for C$_{17}$H$_{21}$NO$_3$S (mixture of **3** and **4**): C, 63.92; H, 6.63; N, 4.39. Found: C, 64.12; H, 6.81; N, 4.52.

3: (36%) ^{1}H NMR δ (ppm): 1.7 (d, 1H, H$_{4\alpha}$, $^2J_{4\alpha-4\beta} = 18.5$ Hz), 1.95 (pseudo q, 1H, H$_{7\alpha}$, $^2J_{7\alpha-7\beta} = 12$ Hz, $^3J_{7\alpha-6} = 6$ Hz, $^3J_{7\alpha-1} = 6$ Hz), 2.2 (dd , 1H , H$_{7\beta}$, $^2J_{7\beta-7\alpha} = 12$ Hz, $^3J_{7\beta-6} = 8.5$ Hz), 2.37 (s, 3H, N−CH$_3$), 2.65 (dd, 1H, H$_{4\beta}$, $^2J_{4\beta-4\alpha} = 18.5$ Hz, $^3J_{4\beta-5} = 5$ Hz), 2.8 (dd, 1H, H$_6$, $^3J_{6-7\beta} = 8.3$ Hz, $^3J_{6-7\alpha} = 6.5$ Hz), 3.1 (broad d, 1H, H$_5$, $^3J_{5-4\beta} = 5$ Hz), 3.70 (s, 2H, S−CH$_2$), 3.75 (s, 3H, O−CH$_3$), 3.8 (m, 1H, H$_1$), 7.2–7.5 (m, 5H, CH$_{Ar}$), 11.71 (broad s, 1H, O−H); ^{13}C NMR δ (ppm): 32.5 (C$_4$), 35.9 (N−CH$_3$), 37.9 (S−CH$_2$), 43.9 (C$_7$), 47.2 (C$_6$) 51.2 (O−CH$_3$), 57.6 (C$_1$), 64.8 (C$_5$), 101.4 (C$_2$), 127.5, 129.1 and 129.2 (CH$_{Ar}$), 138.7 (C$_{qAr}$), 169 and 171.7 (CO$_2$, C$_3$); m/z 320 [M + H$^+$].

4: (30%) ^{1}H NMR δ (ppm): 1.78 (d, 1H, H$_{4\alpha}$, $^2J_{4\alpha-4\beta} = 18.9$ Hz), 1.93–1.98 (m, 2H, H$_{6\alpha}$, H$_{6\beta}$), 2.41 (s, 3H, N−CH$_3$), 2.66–2.72 (m, 1H, H$_{4\beta}$), 3.07 (dd, 1H, H$_7$, $^3J_{7-6\beta} = 8.0$ Hz, $^3J_{7-6\alpha} = 4.3$ Hz), 3.40–3.42 (m, 1H, H$_5$), 3.71–3.74 (m, 1H, H$_1$), 3.77 (s, 2H, S−CH$_2$), 3.81 (s, 3H, O−CH$_3$), 7.29–7.33(m, 5H, CH$_{Ar}$), 11.74 (sl, 1H, O−H); ^{13}C NMR δ (ppm): 31.2 (C$_4$), 34.8 (N−CH$_3$), 37.8 (S−CH$_2$), 39.4 (C$_6$), 51.1 (C$_7$), 51.9 (O−CH$_3$), 56.7 (C$_5$), 63(C$_1$), 100.1 (C$_2$), 127.3 and 128.8 and 129.1 (CH$_{Ar}$), 139.1 (C$_{qAr}$), 170.4 and 171.7 (C$_3$, CO), m/z 320 [M + H$^+$].

3.3 *Synthesis of 6β- and 7β-benzylthio-3-trifluoromethanesulfonyloxo-8-methyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl esters (±)-5 and -6*

To a solution of **3** + **4** (0.3 g, 1.13 mmol) in THF (5 mL) at 0°C, were added pyridine (0.8 mL, 9.4 mmol) and trifluoromethanesulfonic anhydride (0.2 mL, 1.13 mmol). The mixture was stirred at 0°C for 20 min and 24 h at room temperature. Brine was added (20 mL) and the crude product extracted with diethyl ether (3 × 30 mL). The organic extracts were combined, dried over sodium sulfate and the solvent removed. The resultant residue was purified by

liquid chromatography (silica gel, cyclohexane-ethyl acetate, 5:2) and compounds **5** + **6** were obtained as a yellow oil (360 mg, 0.8 mmol, 85%). A small quantity of **5** was obtained from **3** following the same procedure.

IR **5** + **6** (neat) $\nu(cm^{-1})$: 1720, 1665, 1500, 1445, 1290, 1230, 1140, 1075, 830, 710; m/z 452 $[M + H^+]$.

5: ^{1}H NMR δ (ppm): 1.8 (d, 1H, $H_{4\alpha}$, $^2J_{4\alpha-4\beta} = 18.5$ Hz), 2.04 (ddd, 1H, $H_{7\alpha}$, $^2J_{7\alpha-7\beta} = 12.9$ Hz, $^3J_{7\alpha-6} = 6.8$ Hz, $^3J_{7\alpha-1} = 6.05$ Hz), 2.37–2.44 (m, 1H, $H_{7\beta}$), 2.43 (s, 3H, N−CH_3), 2.73 (dd, 1H, $H_{4\beta}$, $^2J_{4\beta-4\alpha} = 18.5$ Hz, $^3J_{4\beta-5} = 4.9$ Hz), 2.84 (dd, 1H, H_6, $^3J_{6-7\beta} = 8.5$ Hz, $^3J_{6-7\alpha} = 6.8$ Hz), 3.2 (d, 1H, H_5, $^3J_{5-4\beta} = 4.9$ Hz), 3.77 (s, 2H, S−CH_2), 3.79 (s, 3H, O−CH_3), 4.0 (d, 1H, H_1, $^3J_{1-7\alpha} = 6.05$ Hz), 7.28–7.32 (m, 5H, CH_{Ar}); ^{13}C NMR δ (ppm): 31.7 (C_4), 34.9 (N−CH_3), 37.5 (S−CH_2), 43.4 (C_7), 46.7 (C_6), 52.3 (O−CH_3), 60.4 (C_1), 64.9 (C_5), 112.2 and 116.5 and 120.7 and 125 (CF_3), 124.6 (C_2), 127.4 and 128.7 and 128.8 (CH_{Ar}), 137.9 (C_{qAr}), 147.9 (C_3), 163.4 (CO). Because of the stability of triflate, elemental analysis could not be achieved.

6: Spectroscopic data was obtained by comparison of compound **5** with the mixture of **5** + **6**. ^{1}H NMR δ (ppm): 1.86 (d, 1H, $H_{4\alpha}$, $^2J_{4\alpha-4\beta} = 18.8$ Hz), 1.9–2.02 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.41 (s, 3H, N−CH_3), 2.68 (dd, 1H, $H_{4\beta}$, $^2J_{4\beta-4\alpha} = 18.8$ Hz, $^3J_{4\beta-5} = 5.3$ Hz), 3.21 (dd, 1H, H_7, $^3J_{7-6\beta} = 8.5$ Hz, $^3J_{7-6\alpha} = 4.1$ Hz), 3.41 (dd, 1H, H_5, $^3J_{5-6\beta} = 5.5$ Hz, $^3J_{5-4\beta} = 5.3$ Hz), 3.74 (s, 2H, S−CH_2), 3.82 (s, 3H, O−CH_3), 3.95 (s, 1H, H_1), 7.21–7.33 (m, 5H, CH_{Ar}); ^{13}C NMR δ: 31.1 (C_4), 34.3 (N−CH_3), 37.6 (S−CH_2), 39.6 (C_6), 51.0 (C_7), 52.5 (O−CH_3), 57.2 (C_5), 66.2 (C_1), 112.2 and 116.5 and 120.7 and 125.0 (CF_3), 123.7 (C_2), 127.2 and 128.7 and 129.1 (CH_{Ar}), 138.7 (C_{qAr}), 149.6 (C_3), 164.0 (CO); m/z 452 $[M + H^+]$.

3.4 *Synthesis of 6β-benzylthio-8-methyl-3-p-tolyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (±)-7 and of 7β-benzylsulfanyl-8-methyl-3-p-tolyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (±)-8*

To a solution of **5** and **6** (1.6 g, 3.55 mmol) in dimethoxyethane, was added *p*-tolylboronic acid (0.72 g, 5.27 mmol), lithium chloride (0.32 g, 7.53 mmol), tris(benzylideneacetone)dipalladium(0) (0.18 g, 0.20 mmol) and aqueous sodium carbonate (2M, 3.7 mL). The mixture was heated at reflux for 8 h. After filtration and washing with diethyl ether, the mixture of solvents was washed with aqueous ammonia 22%, then brine. The solvents were subsequently combined, dried over sodium sulfate and removed. The resultant residue (1.05 g, 2.67 mmol, 75%) was purified by liquid chromatography (silica gel, cyclohexane-ethyl acetate-triethylamine, 8:3.5:0.1). Compounds **7** and **8** were recrystallized from ethanol-cyclohexane (99:1) to give white crystals of **7** and orange crystals of **8**. IR **7** + **8** (neat)) $\nu(cm^{-1})$: 2790, 1705, 1510, 1430, 1355, 1270, 1230, 725.

7: mp: 142–143°C, ^{1}H NMR δ (ppm): 1.8 (d, 1H, $H_{4\alpha}$, $^2J_{4\alpha-4\beta} = 18.9$ Hz), 2.01 (ddd, 1H, $H_{7\alpha}$, $^2J_{7\alpha-7\beta} = 12.5$ Hz, $^3J_{7\alpha-6} = 6.42$ Hz, $^3J_{7\alpha-1} = 6.0$ Hz), 2.3–2.42 (m, 1H, $H_{7\beta}$), 2.33 (s, 3H, Ar−CH_3), 2.45 (s, 3H, N−CH_3), 2.63 (dd, 1H, $H_{4\beta}$, $^2J_{4\beta-4\alpha} = 18.9$ Hz, $^3J_{4\beta-5} = 4.9$ Hz), 2.93 (dd, 1H, H_6, $^3J_{6-7\beta} = 8.3$ Hz, $^3J_{6-7\alpha} = 6.4$ Hz), 3.16 (d, 1H, H_5, $^3J_{5-4\beta} = 4.9$ Hz), 3.47 (s, 2H, S−CH_2), 3.78 (s, 3H, O−CH_3), 3.86 (d, 1H, H_1, $^3J_{1-7\alpha} = 6.0$ Hz), 6.94 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 7.9$ Hz), 7.1 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 7.9$ Hz), 7.22–7.3 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm): 21.6 (Ar−CH_3), 35.6 (C_4), 35.7 (N−CH_3), 38 (S−CH_2), 43.7 (C_7), 47.8 (C_6), 51.7 (O−CH_3), 60.9 (C_1), 64.8 (C_5), 127.0 and 127.4 and 128.9 and 129.2 and 129.3 (CH_{Ar}), 129.8 (C_2), 137.8 and 138.0 and 138.8 (C_{qAr}), 143.2 (C_3), 168.8 (CO); m/z 394 $[M + H^+]$.

8: mp: 112°C, ^{1}H NMR δ (ppm): 1.92 (d, 1H, $H_{4\alpha}$, $^2J_{4\alpha-4\beta} = 19.0$ Hz), 1.91–2.00 (m, 1H, $H_{6\beta}$), 2.07 (dd, 1H, $H_{6\alpha}$, $^2J_{6\alpha-6\beta} = 13.4$ Hz, $^3J_{6\alpha-7} = 8.7$ Hz), 2.34 (s, 3H, Ar−CH_3), 2.5 (s, 3H, N−CH_3), 2.67 (ddd, 1H, $H_{4\beta}$, $^2J_{4\beta-4\alpha} = 19.0$ Hz, $^3J_{4\beta-5} = 4.7$ Hz, $^4J_{4\beta-6\alpha} = 1.2$ Hz), 3.26 (dd, 1H, H_7, $^3J_{7-6\alpha} = 8.7$ Hz, $^3J_{7-6\beta} = 3.8$ Hz), 3.38 (dd, 1H, H_5, $^3J_{5-6\beta} = 6.6$ Hz, $^3J_{5-4\beta} = 4.6$ Hz), 3.51 (s, 3H, O−CH_3), 3.82 (s, 2H, S−CH_2), 3.88 (s, 1H, H_1), 6.98

(d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 8.2$ Hz), 7.1 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 7.9$ Hz), 7.2–7.27 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm): 21.2 (Ar$-CH_3$), 34.3 (C_4), 34.6 (N$-CH_3$), 37.6 (S$-CH_2$), 39.6 (C_6), 50.4 (C_7), 51.3 (O$-CH_3$), 56.5 (C_5), 65.8 (C_1), 126.6 and 126.8 (CH_{Ar}), 127.9 (C_2), 128.4 and 128.8 and 128.9 (CH_{Ar}), 137.6 and 137.7 and 138.7 (C_{qAr}), 144.6 (C_3), 168.4 (CO); *m/z* 394 [M + H$^+$].

3.5 *Synthesis of 6β-benzylthio-8-methyl-3α-p-tolyl-8-azabicyclo[3.2.1]octane-2β-carboxylic acid methyl ester (±)-9, 6β-benzylthio-8-methyl-3β-p-tolyl-8-azabicyclo[3.2.1] octane-2β-carboxylic acid methyl ester (±)-10 and 6β-benzylthio-8-methyl-3β-p-tolyl-8-azabicyclo[3.2.1]octane-2α-carboxylic acid methyl ester (±)-11*

To a solution of **7** (400 mg, 1.01 mmol) in THF (5 mL), was added samarium (800 mg, 5.08 mmol), then diiodoethane (1.4 g, 4.96 mmol) in THF (5 mL), slowly. After stirring for 30 min. at −78°C, anhydrous methanol (15 mL) was introduced and the mixture was allowed to reach room temperature and then stirred for two hours. Glacial acetic acid (5 mL) and water (5 mL) were then added and the mixture was basified with aqueous ammonia (22%). The three resultant products were extracted with diethyl ether (3 × 20 mL), the organic layer was dried over sodium sulfate and evaporated. Each compound was separated on silica gel (cyclohexane-ethyl acetate, 8:1). Yield **9** + **10** + **11** : 290 mg (0.73 mmol, 73%). IR **9** + **10** + **11**(neat) ν(cm^{-1}): 2950, 1730, 1520, 1450, 1240, 1170, 815, 710. Calcd (%) for $C_{24}H_{29}NO_2S$ (mixture of **9** + **10** + **11**): C, 72.87; H, 7.39; N; 3.54. Found: C, 73.05; H, 7.60; N, 3.65.

9: 150 mg (0.38 mmol, 38%); ^{1}H NMR δ (ppm): 1.39 (ddd, 1H, $H_{4\beta}$, $^2J_{4\beta-4\alpha} = 13.4$ Hz, $^3J_{4\beta-3} = 9.1$ Hz, $^3J_{4\beta-5} = 1.0$ Hz), 2.06–2.10 (m, 2H, $H_{7\alpha}$, $H_{7\beta}$), 2.28 (s, 3H, Ar$-CH_3$), 2.35–2.42 (m, 2H, $H_{4\alpha}$), 2.44 (dd, 1H, H_2, $^3J_{2-3} = 9.6$ Hz, $^3J_{2-1} = 2.1$ Hz, 2.52 (s, 3H, N$-CH_3$), 2.88 (t, 1H, H_6, $^3J_{6-7\alpha} = {}^3J_{6-7\beta} = 7.4$ Hz), 3.15 (broad d, 1H, H_5, $^3J_{5-4\alpha} = 8.1$ Hz), 3.3 (q, 1H, H_3, $^3J_{obs} = 17.8$ Hz and 8.9 Hz), 3.48–3.51 (m, 1H, H_1), 3.54 (s, 3H, O$-CH_3$), 3.76 (s, 2H, S$-CH_2$), 6.98 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 8.2$ Hz), 7.03 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 8.3$ Hz), 7.23–7.27 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm): 21.3 (Ar$-CH_3$), 36.0 (C_3), 38.6 (S$-CH_2$), 39.2 (C_4), 39.3 (C_7), 42.1 (N$-CH_3$), 48.8 (C_6), 52.1 (O$-CH_3$), 54.5 (C_2), 64.4 (C_1), 67.3 (C_5), 127.4, 127.7 and 128.9 and 129.2 and 129.4 (CH_{Ar}), 136.1 and 138.8 and 140.9 (C_{qAr}), 175.3 (CO); *m /z* 396 [M + H$^+$].

10: 110 mg (0.28 mmol, 28%); ^{1}H NMR δ (ppm): 1.6–1.66 (m, 1H, $H_{4\alpha}$), 2.2–2.25 (m, 2H, $H_{7\alpha}$, $H_{7\beta}$), 2.27 (s, 3H, Ar$-CH_3$), 2.46–2.55 (m, 1H, $H_{4\beta}$), 2.51 (s, 3H, N$-CH_3$), 2.78–2.83 (m, 2H, H_2, H_3), 3.06 (dd, 1H, H_6, $^3J_{6-7\beta} = 7.7$ Hz, $^3J_{6-7\alpha} = 6.4$ Hz), 3.32 (sl, 1H, H_5), 3.45 (s, 3H, O$-CH_3$), 3.68 (m, 1H, H_1), 3.78 (s, 2H, S$-CH_2$), 7.06 (s, 4H, $C_6\underline{H}_4CH_3$), 7.20–7.26 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm): 21.3 (Ar$-CH_3$), 34.2 (C_4), 34.3 (C_3), 37.2 (C_7), 38.9 (S$-CH_2$), 43.5 (N$-CH_3$), 45.9 (C_6), 51.5 (O$-CH_3$), 52.3 (C_2), 66.7 (C_1), 69.6 (C_5), 127.4 and 127.5 and 129.0 and 129.1 and 129.2 (CH_{Ar}), 135.8 and 138.7 and 139.8 (C_{qAr}), 172.2 (CO); *m /z* 396 [M + H$^+$].

11: 30 mg (0.07 mmol, 7%). ^{1}H NMR δ (ppm): 1.9 (ddd, 1H, $H_{4\alpha}$, $^2J_{4\alpha-4\beta} = 13.7$ Hz, $^3J_{4\alpha-3} = 4.8$ Hz, $^3J_{4\alpha-5} = 2.3$ Hz), 2.29 (s, 3H, Ar$-CH_3$), 2.31–2.41 (m, 3H, $H_{7\alpha}$, $H_{4\beta}$, $H_{7\beta}$), 2.53 (s, 3H, N$-CH_3$), 2.77 (dd, 1H, H_6, $^3J_{6-7\beta} = 8.3$ Hz, $^3J_{6-7\alpha} = 6.5$ Hz), 3.05–3.07 (m, 1H, H_5), 3.33–3.41 (m, 1H, H_2), 3.44 (s, 3H, O$-CH_3$), 3.5–3.55 (m, 1H, H_3), 3.6–3.64 (m, 1H, H_1), 3.62 (s, 2H, S$-CH_2$), 7.0 (s, 4H, $C_6\underline{H}_4CH_3$), 7.04–7.31 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm): 20.9 (Ar$-CH_3$), 34.8 (C_3), 35.1 (C_7), 36.1 (C_4), 38.1 (S$-CH_2$), 40.3 (N$-CH_3$), 45.7 (C_6), 46.9 (C_2), 51.2 (O$-CH_3$), 61.8 (C_1), 67.4 (C_5), 126.7 and 127.1 and 128.4 and 128.7 and 128.8 (CH_{Ar}), 135 and 138.6 and 140.4 (C_{qAr}), 174.2 (CO); *m /z* 396 [M + H$^+$].

3.6 *Synthesis of 7β-benzylthio-8-methyl-3α-p-tolyl-8-azabicyclo[3.2.1]octane-2β-carboxylic acid methyl ester (±)-12, 7β-benzylthio-8-methyl-3β-p-tolyl-8-azabicyclo[3.2.1]octane-2β-carboxylic acid methyl ester (±)-13 and 7β-benzylthio-8-methyl-3β-p-tolyl-8-azabicyclo[3.2.1]octane-2α -carboxylic acid methyl ester (±)-14*

Compounds **12**–**14** were obtained from **8** according to the same procedure as for **9**–**11**. Yield **12** + **13** + **14**: 150 mg (0.38 mmol, 74%). IR **12** + **13** + **14** (neat) ν (cm^{-1}): 2950, 1730, 1520, 1450, 1240, 1170, 815, 710. Calcd (%) for $C_{24}H_{29}NO_2S$ (mixture of **12**–**14**): C, 72.87; H, 7.39; N, 3.54. Found: C, 72.65; H, 7.62; N, 3.50.

12: 150 mg (0.38 mmol, 38%). ^{1}H NMR δ (ppm): 1.35 (ddd, 1H, $H_{4\beta}$, $^2J_{4\beta-4\alpha} = 14.2$ Hz, $^3J_{4\beta-3} = 9.9$ Hz, $^3J_{4\beta-5} = 2.1$ Hz), 1.93–2.03 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.29–2.32 (m,1H, $H_{4\alpha}$), 2.31 (s, 3H, Ar−CH_3), 2.51 (dd, 1H, H_2, $^3J_{2-3} = 8.2$ Hz, $^3J_{2-1} = 1.0$ Hz), 2.53 (s, 3H, N−CH_3), 2.93 (t, 1H, H_7, $^3J_{7-6\alpha} = {}^3J_{7-6\beta} = 7.6$ Hz), 3.33 (q, 1H, H_3, $^3J_{obs} = 18.1$ Hz et 8.1 Hz), 3.35–3.43 (m, 1H, H_5), 3.44 (m, 1H, H_1), 3.64 (s, 3H, O−CH_3), 3.78 (s, 2H, S−CH_2), 6.98 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 8.3$ Hz), 7.04 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 8.1$ Hz), 7.24–7.31 (m, 5H, $C_6\underline{H}_5$); ^{13}C NMR δ (ppm): 21.4 (Ar−CH_3), 35.6 (C_3), 36.6 (C_4), 38.4 (S−CH_2), 38.5 (C_6), 42.2 (N−CH_3), 47.9 (C_7), 52.3 (O−CH_3), 56.0 (C_2), 60.9 (C_5), 70.8(C_1), 127.4 and 127.7 and 128.9 and 129.3 and 129.5 (CH_{Ar}), 136.0 and 138.7 and 141.4 (C_{qAr}), 174.8 (CO); m/z 396 [M + H^+].

13: 60 mg (0.15 mmol, 30%); ^{1}H NMR δ (ppm): 1.56–1.62 (m, 1H, $H_{4\alpha}$), 2.07 (dd, 1H, $H_{6\alpha}$, $^2J_{6\alpha-6\beta} = 13.8$ Hz, $^2J_{6\alpha-7} = 8.5$ Hz), 2.17 (dd, 1H, $H_{6\beta}$, $^2J_{6\beta-6\alpha} = 13.8$ Hz, $^2J_{6\beta-7} = 6.1$ Hz), 2.27 (s, 3H, Ar−CH_3), 2.5 (s, 3H, N−CH_3), 2.5–2.55 (m, 1H, $H_{4\beta}$), 2.77–2.8 (m, 2H, H_2, H_3), 3.12 (dd, 1H, H_7, $^3J_{7-6\alpha} = 8.5$ Hz, $^3J_{7-6\beta} = 5.9$ Hz), 3.47 (sl, 4H, H_5, O−CH_3), 3.55 (s, 1H, H_1), 3.86 (s, 2H, S−CH_2), 7.04 (s, 4H, $C_6\underline{H}_4CH_3$), 7.25–7.37 (m, 5H, $C_6\underline{H}_5$); ^{13}C NMR δ (ppm): 21.3 (Ar−CH_3), 33.4 (C_4), 34.4 (C_3), 36.5 (C_6), 38.7 (S−CH_2), 43.4 (N−CH_3), 45.8 (C_7), 51.5 (O−CH_3), 52.7 (C_2), 63.8 (C_5), 72.2 (C_1), 127.4 and 127.5 and 129.0 and 129.1 and 129.4 (CH_{Ar}), 135.7 and 138.6 and 139.8 (C_{qAr}), 171.7 (CO); m/z 396 [M + H^+].

14: 20 mg (0.05 mmol, 10%). ^{1}H NMR δ (ppm): 1.83–1.93 (m, 3H, $H_{4\alpha}$, $H_{6\alpha}$, $H_{6\beta}$), 2.27 (s, 3H, Ar−CH_3), 2.36–2.44 (m, 1H, $H_{4\beta}$), 2.57 (s, 3H, N−CH_3), 3.28–3.3 (m, 1H, H_5), 3.41 (s, 3H, O−CH_3), 3.44–3.52 (m, 2H, H_2, H_1), 3.54–3.61 (m, 2H, H_3, H_7), 3.86 (AB, 2H, S−CH_2, $\delta_A = 3.91$ ppm, $\delta_B = 3.81$ ppm, $J_{AB} = 13.3$ Hz), 6.97 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 8.2$ Hz), 7.02 (d, 2H, $C_6\underline{H}_4CH_3$, $^3J = 8.3$ Hz), 7.23–7.27 (m, 5H, $C_6\underline{H}_5$); ^{13}C NMR δ (ppm): 21.0 (Ar−CH_3), 32.9 (C_4), 35.2 (C_3), 37.9 (C_6, S−CH_2), 39.5 (N−CH_3), 43.2 (C_7), 46.9 (C_2), 51.2 (O−CH_3), 60.0 (C_5), 68.4 (C_1), 126.8 and 127.5 and 128.5 and 128.8 and 129.0 (CH_{Ar}), 135.3 and 139.0 and 140.2 (C_{qAr}), 173.9 (CO); MS: 396 [M + H^+].

3.7 *Synthesis of 7β-mercapto-8-methyl-3α-p-tolyl-8-azabicyclo[3.2.1]octane-2β-carboxylic acid methyl ester (±)-15*

To a solution of **12** (23 mg, 58.15 μmol) in toluene (5 mL) was added 5 equiv. of $AlCl_3$ (38 mg, 290 μmol). After agitation for 3 h at room temperature, water (5 mL) and aqueous ammonia (22%) were added at 0°C. The so-obtained crude product was extracted with dichloromethane (3 × 10 mL), and the organic layer was dried over sodium sulfate and evaporated. Compound **15** was purified on silica gel (pentane-ethyl acetate: 7:3) to give **15** as a yellow oil.

15: 9 mg (29.5 μmol, 51%); ^{1}H NMR δ (ppm): 1.43 (ddd, 1H, $H_{4\beta}$, $^2J_{4\beta-4\alpha} = 14.1$ Hz, $^3J_{4\beta-3} = 9.7$ Hz, $^3J_{4\beta-5} = 2.0$ Hz), 2.13–2.17 (m, 2H, $H_{6\alpha}$, $H_{6\beta}$), 2.29–2.35 (m, 1H, $H_{4\alpha}$), 2.29 (s, 3H, Ar−CH_3), 2.61 (s, 3H, N−CH_3), 2.66 (d, 1H, H_2, $^3J_{2-3} = 8.6$ *Hz*), 3.22–3.29 (m, 1H, H_7), 3.36 (q, 1H, H_3, $^3J_{obs} = 17.6$ and 8.3 Hz), 3.43–3.48 (m, 2H, H_1, H_5), 3.63 (s, 3H, O−CH_3), 7.08 (s, 4H, CH_{Ar}). ^{13}C NMR δ (ppm): 20.9 (Ar−CH_3), 35.4 and 35.7 and 41.6 and 41.8 and 41.9 (C_3 and C_4 and C_6 and C_7 and N−CH_3), 51.9 (O−CH_3), 55.6 (C_2), 60.8 (C_5), 73.8 (C_1), 127.3, 129.2 (CH_{Ar}), 135.8, 141.0 (C_{qAr}), 174.4 (CO); m/z 306 [M + H^+].

Acknowledgments

This work was supported in part by funding of CIS biointernational, Schering S.A., Radiochemical Development II, B.P.32, 91192 Gif-sur-Yvette, France.

References

[1] Morgan, G. F. and Nowotnik, D. P., 1999, *Drug News Perspec.*, **12**, 137.
[2] Neumeyer, J. L., Wang, S., Gao, Y., Milius, R. A., Kula, N. S., Campbell, A., Baldessarini, R. J., Zea-Ponce, Y., Baldwin, R. M. and Innis, R. B., 1994, *J. Med. Chem.*, **37**, 1558.
[3] Fowler, J. S., Volkow, N. D., Wolf, A. P., Dewey, S. L., Schlyer, D. J., MacGregor, R. R., Hitzemann, R., Logan, J., Bendriem, B., Gadley, S. J. and Christman, D., 1989, *Synapse*, **4**, 371.
[4] Chaly, T., Dhawan, V., Kazumata, K., Antonini, A., Dahl, J. P., Matacchieri, R., Margouleff, C., Belakhlef, A., Wang, S., Tamagnan, G., Neumeyer, J. L. and Eidelberg, D., 1996, *Nucl. Med. Biol.*, **33**, 999.
[5] Neumeyer, J. L., Wang, S., Milius, R. A., Baldwin, R. M., Zea-Ponce, Y., Hoffer, P. B., Sybirska, E. H., Al-Tikriti, M. S., Laruelle, M. and Innis, R. B., 1991, *J. Med. Chem.*, **34**, 3144.
[6] Emond, P., Garreau, L., Chalon, S., Boazi, M., Caillet, M., Bricard, J., Frangin, Y., Mauclaire, L., Besnard, J. C. and Guilloteau, D., 1997, *J. Med. Chem.*, **40**, 1366.
[7] Kung, M. P., Sevenson, D. A., Plössl, K., Meegalla, S. K., Beckwith, A., Essman, W. D., Mu, M., Lucki, I. and Kung, H. F., 1997, *Eur. J. Nucl. Med.*, **24**, 372.
[8] Singh, S., 2000, *Chem. Rev.*, **100**, 925.
[9] Meegalla, S., Plössl, K., Kung, M.-P., Stevenson, D. A., Liable-Sands, L. M., Rheingold, A. L. and Kung, H. F., 1995, *J. Am. Chem. Soc.*, **117**, 11037.
[10] Zhao, L., Johnson, K. M., Zhang, M., Flippen-Anderson, J. and Kozikowski, A. P., 2000, *J. Med. Chem.*, **43**, 3283.
[11] Oh-e, T., Miyaura, N. and Suzuki, A., 1993, *J. Org. Chem.*, **58**, 2201.
[12] Arnoldi, A., Bonsignori, A., Melloni, P., Merlini, L., Quadri, M. L., Rossi, A. C. and Valsecchi, M., 1990, *J. Med. Chem.*, **33**, 2865.