SYNTHESIS OF S-[^{3}H]-DO-710, A BENZAMIDE LIGAND OF THE D_2-DOPAMINE RECEPTOR AND OF S-[^{3}H]-AZIDOSULPRIDE, ITS PHOTOACTIVABLE ANALOG.

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SUMMARY

The preparation of the tritium labelled benzamides, S-[^{3}H]-DO-710 and S-[^{3}H]-azidosulpride is reported. The synthesis involves enantioselective preparation of the pyrrolidinyl moiety, reductive tritiation of an allylic precursor and conversion of an amino, to an azido function.

Both labelled ligands are D_2-dopaminergic antagonists, useful in binding experiments and to achieve covalent bonds after light exposure at the receptor site level.

Key words : DO-710, Azidosulpride, Benzamides, D_2-dopaminergic antagonists

INTRODUCTION

The central dopamine D_1 and D_2 receptors are relatively well defined pharmacological entities (1). However, extensive studies with various antagonists have shown some discrepancies for the D_2 receptors,

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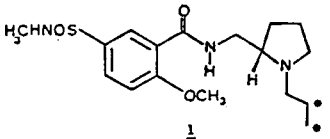
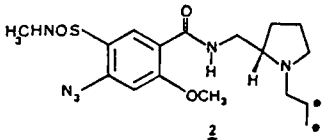
specially in tentatives to correlate in vitro with behavioural datas (2). According to these results some questions are arising about the homogeneity of the D_2 receptors. At present, it is not clear if there are two subtypes for the D_2 receptor or two distinct D_2 and D_4 receptors (3). Selective ligands may contribute to a better identification of these entities.

Among the usual neuroleptics, sulpiride-like compounds represent promising tools for such studies (4). Taking advantage of the polyfunctionnal nature of sulpiride, we performed various chemical modifications on this compound in order to select new ligand candidates for radiolabelling (5). This paper describes the synthesis of a novel radiolabelled ligand 1 and its photoactivable analog 2. The biochemical results obtained with these compounds are published elsewhere (6,7).



1
S-[^{3}H]-DO-710



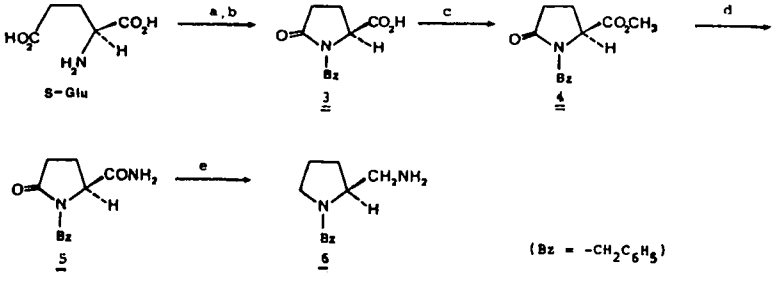
2
S-[^{3}H]-Azidosulpride

We have shown earlier that N-methylation of the sulfamoyl group and replacement of the ethyl by a n-propyl group on the pyrrolidine nitrogen of sulpiride increased both in vitro and in vivo activities (4,5,7). Hence, the tritiated compounds 1 and 2 were readily available from their N-allyl precursors via catalytic tritiation. Furthermore, it is well known that only the S isomers of benzamides contribute significantly to their biological activity (8). Therefore, we decided to prepare the optically active pyrrolidinyl moiety, the usual amidification step yielding the benzamide enantiomers (see below).

RESULTS AND DISCUSSION

The S(-)-2-aminomethylpyrrolidine 6 was prepared starting from S-glutamic acid, with conservation of the absolute configuration of the asymetric carbon through the chemical transformations.

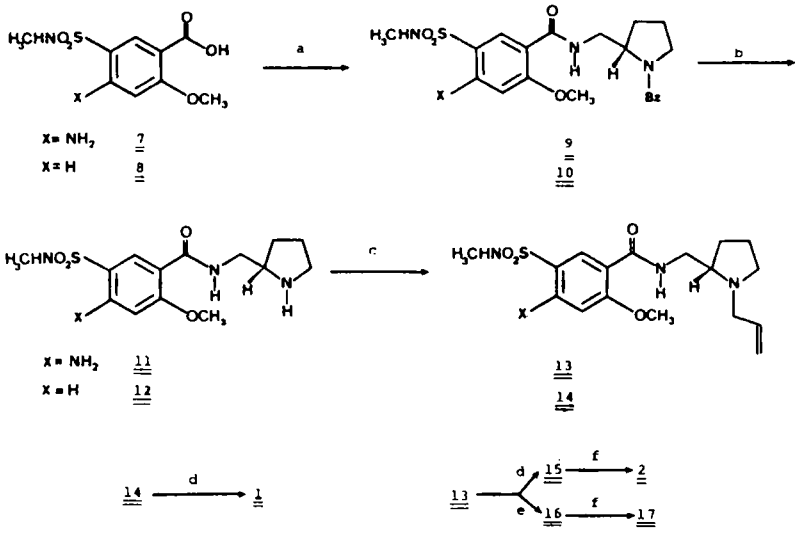
Catalytic reductive amination of S-glutamic acid in the presence of benzaldehyde and palladium black followed by cyclisation in aqueous medium, provided the S-(-)-pyrroglutamic acid 3 (9). This acid was esterified with diazomethane in ethyl ether to yield the methyl ester 4 which was converted to its amide 5 with methanolic ammonia. Lithium aluminium hydride reduction of the two amide functions of 5 yielded 2-aminomethyl-N-benzyl pyrrolidine 6 with a satisfying overall yield. To ascertain that no racemisation occured during these steps, all reactions were performed with R and S glutamic acid. The datas for the non natural isomer are not shown (Scheme 1).



a : C_6H_5CHO, H_2-Pd/C 10% ; b: H^+, Δ ; c: CH_2N_2 ; d: MeOH, NH_3 ; e: $LiAlH_4$, THF.

Scheme I .

Condensation of the benzoic acids 7 (10) and 8 (11) with the amine 6 using the mixed anhydride method, afforded the amides 9 and 10. Hydrogenolytic cleavage of the benzyl groups led to the adducts 11 and 12 wich were alkylated to 13 and 14 with allyl bromide under basic conditions. Catalytic tritiation of the double bonds of 13 and 14 gave rise to the radiolabelled compounds 1 and 15 (12). Using a Sandmeyer reaction, compound 15 was converted in the labelled azidobenzamide 2. The HPLC recordings for the reaction mixture showed a complete conversion of compound 15 to azido 2 (Fig. 1). Purification of compound 2 was achieved by HPLC (see experimental part). The structure of 2 was clearly assigned by IR and MS datas performed on the non radiolabelled analog 17 obtained from coumpound 16 (13) (Scheme 2).



Scheme II.

The biological assays performed with S-[^{3}H]-DO-710 and S-[^{3}H]-azidosulpride have demonstrated several advantages over already existing radiolabelled dopamine antagonists particularly in binding experiments. Compounds 1 and 2 show high selectivity for the dopamine D_2-receptor and low non-specific fixation.

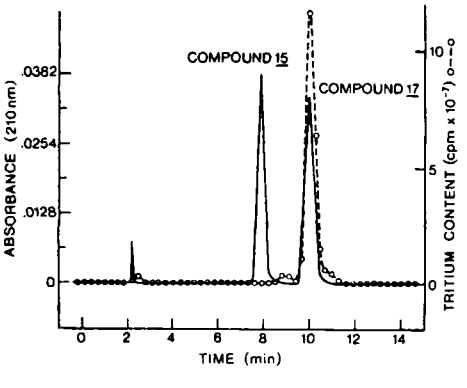


Figure 1 : Purification by HPLC of [^{3}H]-azidosulpride 2.

The mixture obtained after diazotation and azidation of the amino precursor (compound 15) was injected in a μBondapak C_{18} column (250x4.6 mm) in acetonitrile and 10 mM ammonium acetate (pH 4.2)(25:75) at a flow rate of 1 ml/min. 0.3 min fractions were collected and assayed for tritium content (o-o-o). In a similar experiment, a mixture of azidosulpride and its amino precursor (compounds 15 and 17, 20 nmol. each) was injected and absorbance at 210 nm was recorded (——).

This last feature allowed a precise autoradiographic mapping of the dopaminergic areas present in the rat brain. Photoactivation of S-[^{3}H]-azidosulpride allows covalent linking to the receptor protein. The low rate of non-specific incorporation observed with this compound can probably be accounted to the fact that, in contrast to [^{125}I]-N_3-NAPS, another recently described photoactivable ligand (14), the azido function is located at proximity of the chemical functions involved in the drug-receptor interaction.A similar finding was observed with [^{125}I]-azidoclebopride (15). An illustration of the usefulness of S-[^{3}H]-azidosulpride was the characterization of D_2 receptors in the striatum, the anterior pituitary and the olfactory bulb of the rat (7).

EXPERIMENTAL PART

Material and procedures

Melting points were taken on a Kofler hot stage. ^{1}H-NMR spectra were performed on a WP-80 MHz instrument using tetramethylsilane as internal standard. NMR datas are reported for free bases. IR spectra were obtained with a PYE-UNICAM SP3-300S apparatus. The optical rotations were taken on a polarimeter PERKIN-ELMER 241 MC. Compounds were analysed for C, H, N and gave results within ±0.4 % of the theoretical values.

S-N-Benzyl-5-oxo-2-pyrrolidine carboxylic acid 3

Benzaldehyde (16.8 ml, 0.245 mol), dissolved in methanol (160 ml), was added dropwise to an ice-cooled solution of L-glutamic acid (30 g, 0.204 mol) in a sodium hydroxyde solution (1M, 410 ml). After stirring for 12 h, the mixture was hydrogenated (3 g of Pd/C, 10 % ; 3.5 atm) for 24 h. After filtration of the catalyst, the remaining solution was concentrated in vacuo to remove most of the methanol. Adjusting the aqueous solution carefully to pH 3.5 (4 M, aqueous HCl) yielded a white solid (N-benzyl glutamic acid). This solid was taken up in water (500 ml), the mixture was adjusted at pH 2.5 (4 M, aqueous HCl)

and heated at reflux during 12 h. The chilled aqueous solution was extracted with ethyl acetate (2 x 300 ml), the organic layer was washed (satured brine), dried (Na_2SO_4) and evaporated in vacuo to yield an oil, identified as acid 3, which crystallized in hexane : m.p. 94°C (hexane/ethyl acetate) (13.4 g ; 36 %) (Found : C, 65.49 ; H, 5.94 ; N, 6.53. $C_{12}H_{13}NO_2$ requires : C,65.74 ; H,5.97 ; N,6.39 %). $\delta(CDCl_3)$ 9.80(1H, s, COOH) ; 7.25(5H, br s, Ar H), 5.15(1H, d, J 16 Hz, CH_AH_B-Ar), 4.25-3.85(2H, m, CHCOOH, CH_AH_B-Ar) ; 3.75-2.10(4H, m, pyrrolidinyl H) ; $[\alpha]_{546}^{20}$ + 54.9° (c 2, MeOH).

S-N-Benzyl-5-oxo-2-pyrrolidine-carboxymethyl ester 4

An etheral solution of diazomethane (prepared from nitrosomethylurea (12 g) and potassium hydroxyde (50 % aqueous solution, 60 ml)) was added fractionwise to an ice-cooled solution of compound 3 (6 g, 0.027 mol) in dry ether (150 ml), until the coloration remained yellow. The solvent was concentrated in vacuo to yield an oil identified as ester 4 (6 g, 95 %), b.p. 151°C/0.4 mm, $\delta(CDCl_3)$ 7.5-7.25(5H, m, ArH), 5.05(1H, d, J 14 Hz, CH_AH_B-Ar), 4.25-3.90(2H, m, CHCOOMe, CH_AH_B-Ar), 3.6(3H, s, $COOCH_3$), 2.90-2.05(4H, m, pyrrolidinyl H).

S-N-Benzyl-5-oxo-2-pyrrolidine carboxamide 5

The methyl ester 4 (9.5 g, 0.04 mol) was dissolved in methanol (500 ml) saturated with gazeous ammonia. The mixture was left for 24 h at room temperature. Evaporation in vacuo of the solvent gave the amide 5 as needles (8.07 g, 90 %), m.p. 180°C (hexane/ethyl acetate). $\delta(CDCl_3)$, 7.50-7.25(5H, m, ArH), 4.90(1H, d, J 15 Hz, CH_AH_B-Ar), 4.1-3.3(4H, m, $CHCONH_2$, CH_AH_B-Ar), 2.85-2.05(4H, m, pyrrolidinyl H), $[\alpha]_{546}^{20}$ + 140° (c 2, MeOH).

S-2-Aminomethyl-N-benzyl-pyrrolidine 6

The amide compound 5 (3.3 g, 0.015 mol) was added portionwise to a slurry of lithium-aluminium hydride (LAH) (3.5 g, 0.09 mol) in

tetrahydrofuran (300 ml, sodium dry). After complete addition, the mixture was chilled and the excess of LAH was destroyed caustiously (6.7 ml of H_2O in 50 ml of THF). The inorganic material was filtered off and carefully washed with ethyl ether. After evaporation in vacuo of the combined organic layers, the oily residue was distilled using a short-path column, to yield the amine 6 (2.4 g, 84 %), b.p. 90°C/0.2 mm, δ($CDCl_3$) 7.45-7.15(5H, m, ArH), 3.90(1H, d, J 14 Hz, CH_AH_B), 3.25 (1H, d, J 14.5 Hz, CH_AH_B, 3.05-1.15(10H, pyrrolidinyl H, CH_2NH_2 and CH_2NH_2 exch. with D_2O), $[\alpha]_{546}^{20}$ - 130° (c 1, MeOH).

S-4-Amino-N-[(1-benzyl-2-pyrrolidinyl)-methyl]-2-methoxy-5-N'-(methylsulfamoyl)-benzamide, hydrochloride 9

Compound 7 (5.2 g, 0.02 mol) was dissolved in acetone (15 ml). Triethylamine (2.42 g, 0.024 mol) was added followed by a portionwise addition of ethyl chloroformate (2.28 g, 0.021 mol) at -15°C. After 15 min compound 6 (3.99 g, 0.021 mol) in acetone (15 ml) was slowly added to the mixture. After 2 h at room temperature the solvent was evaporated in vacuo and the residue taken up in H_2O (100 ml). Extraction with ethyl acetate (2 x 75 ml) and aqueous acid base work up (3 M, HCl ; 10 % aq. K_2CO_3) gave after evaporation in vacuo an oily residue, which after careful acidification (pH 3 ; 3N HCl) yielded the benzamide 9 as hydrochloride (5.33 g, 62 %) m.p. 187°C (from water)(Found C, 52.83 ; H, 6.32 ; N, 11.39. $C_{12}H_{29}N_4O_4SCl$ requires C, 52.77 ; H, 6.32 ; N, 11.72), R_F (Et_2O/MeOH/Triethylamine : 18/1/1) 0.40, δ(DMSO) 8.4-7.2(9H, m, ArH, SO_2NH CO-NH), 6.7(2H, m, NH_2), 4.0(3H, OCH_3), 3.6(2H, m, CH_2-Ar), 3.4(5H, m, CH_2NH, pyrrolidinyl H), 2.4(3H, m, CH_3NH), 2.3-1.8(4H, m, pyrrolidinyl H). $[\alpha]_{546}^{20}$ - 30° (c 2, MeOH).

S-N-[(1-benzyl-2-pyrrolidinyl)-methyl]-2-methoxy-5-N'-(methylsulfamoyl)-benzamide, hydrochloride 10

The same procedure was followed as for the preparation of compound 9, starting from the acid 8 (11) and amine 6. Yield 66 %, m.p.

172°C (from IPrOH/Et_2O)(Found C, 54.79 ; H, 6.32 ; N, 8.86 $C_{21}H_{28}N_3O_4SCl$ requires C, 54.47 ; H, 6.31 ; N, 9.07), R_F (MeOH/NH_4OH : 95/5), 0.65, δ(DMSO) 8.15-7.25(10H, m, ArH, SO_2NH, CONH), 4.1(3H, s, OCH_3), 3.7(2H, m, CH_2-Ar), 3.3(5H, m, $CONHCH_2$, pyrrolidinyl H), 2.55(3H, m, CH_3NH) 2.95-1.95(4H, m, pyrrolidinyl H), $[\alpha]_{546}^{20}$ -2.60° (c 2, MeOH).

S-4-Amino-2-methoxy-5-N'-(methylsulfamoyl)-N[(2-pyrrolidinyl)-methyl] benzamide, hydrochloride 11

A solution of compound 9 (0.8 g, 1.88 mmol) in methanol (50 ml) and acetic acid (5 ml) was hydrogenated in a Parr bottle with 10 % Pd/C (0.2 g) at 60 psi for 7 h. Filtration and evaporation gave 11 (10.6 g, 85 %). m.p. 212°C (from ethyl ether/isopropanol), R_F (MeOH/NH_4 : 99/1) 0.10, δ(DMSO) 9.3 (1H, br s, CONH), 8.9(1H, m, SO_2NH), 8.3-7.15(2H, m, ArH), 6.60(2H, m, NH_2), 4.15(1H, m, NH), 3.95(3H, s, OCH_3), 3.7-2.6(5H, m, CONH-CH_2, pyrr H), 2.35(3H, m, CH_3NH), 2.2-1.6(4H, m, pyrrolidinyl H), $[\alpha]_{546}^{20}$ + 11° (c 2, MeOH).

S-2-Methoxy-5-N'-(methylsulfamoyl)-N[(2-pyrrolidinyl)-methyl]-benzamide, hydrochloride 12

The same procedure was followed as for the preparation of compound 11. Yield 50 %, m.p. 200°C (isopropanol) R_F(MeOH/NH_4OH : 95/5) 0.25, δ(DMSO) 9.4-9.2(1H, m, CONH), 8.9-8.6(1H, m, SO_2NH), 8.3-7.15(3H, m, ArH), 4.15(1H, m, NH), 3.95(3H, s, OCH_3), 3.7-2.6(5H, m, $CONHCH_2$, pyrrolidinyl H), 2.35(3H, m, CH_3NH), 2.2-1.6(4H, m, pyrrolidinyl H).

S-N-[(1-Allyl-2-pyrrolidinyl)-methyl]-4-amino-2-methoxy-5-N'-(methylsulfamoyl)-benzamide 13

To a solution of 11 (0.60 g, 1.58 mmol) in absolute methanol (30 ml) was added sodium carbonate (0.375 g, 3.16 mmol), potassium iodide (0.2 g, 1.58 mmol) and allyl bromide (0.23 g, 1.89 mmol). The mixture

was refluxed under argon and then concentrated in vacuo. Water was added and the extraction performed with dichloromethane. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give 13 (0.49 g, 82 %), m.p. 150°C (from Et_2O/isoPrOH) (found : C, 50.87 ; H, 6.75 ; N,13.69. $C_{17}H_{26}N_4O_4S$ requires C, 50.98 ; H, 7.05 ; N, 13.69), R_F (MeOH/NH_4OH : 24/1) 0.75, δ($CDCl_3$) 8.9-7.2(4H, m, ArH, SO_2NH, CONH), 6.60 (2H, m, NH_2), 5.8-5.3(3H, m, CH_2-CH=CH_2), 4.1(3H, s, OCH_3), 3.80-3.10 (7H, m), 2.4(3H, m, CH_3NH), 2.2-1.9(4H, m, pyrrolidinyl H), $[\alpha]_{546}^{20}$ - 56.1° (c 2, MeOH).

S-N[(1-Allyl-2-pyrrolidinyl)-methyl]-2-methoxy-5-N'-(methylsulfamoyl)-benzamide, hydrochloride 14

The same procedure was followed as for the preparation of compound 13. Yield 55 %, m.p. 162°C (from isopropanol/Et_2O), R_F (MeOH) 0.45, δ(DMSO) 9.2-8.9(2H, m, CONH, $NHSO_2$), 8.2-7.3(3H, m, ArH), 6.1-5.2(3H, m, CH_2=CH-), 4.1(3H, s, OCH_3), 3.9-3.3(1H, m, $CONHCH_2$, N-CH_2-CH=, pyrrolidinyl H), 2.5(3H, m, CH_3NH), 2.4-1.9(4H, m, pyrrolidinyl H), $[\alpha]_{546}^{20}$ - 8.1° (c 2, MeOH).

S-2-Methoxy-5-N'-(methylsulfamoyl)-N-[(1-^{3}H-2',3'-propyl)-2-pyrrolidinyl)-methyl]-benzamide, hydrochloride 1

Compound 14 (2.15 mg, 5.03 μmol) was dissolved in pure methanol (1 ml) and the solution was frozen (liquide nitrogen). The catalyst was dispersed on the surface and the flask was connected to an automatic gaz manifold. When the vacuum reached 10^{-4} Torr, tritium gaz (70-80 Curies) was introduced and compressed to obtain a pressure of 1.4 Bar. The mixture was stirred at room temperature for 3 h. Palladium oxide was removed by filtration over Millex FG and labile tritium was removed in vacuo with pure methanol (120 ml).

TLC analysis of the reaction (SiO_2: MeOH/NH_4OH : 99/1) reveals a major peak commigrating with the non radioactive compound. Using a preparative TLC, 1 was purified (SiO_2 : MeOH/NH_4OH : 99/1). Quantitative and

comparative estimation (U.V. spectra) indicates a specific radioactivity around 50 Ci/mmol). After several mounths of storage in liquid nitrogen, S-[^{3}H]-DO-710 retained both its chemical and biological properties.

S-4-Amino-2-methoxy-5-N'-(methylsulfamoyl)-N-[(1-(^{3}H-2',3'-propyl)-2-pyrrolidinyl)-methyl]-benzamide 15

Exactly the same procedure was followed as for the preparation of compound 1. The labelled compound was purified by TLC (SiO_2 : MeOH/NH_4OH : 99/1, R_F 0.40) and stored in MeOH in liquid nitrogen. The specific radioactivity was around 38 Ci/mmol.

S-4-Amino-2-methoxy-5-N'-(methylsulfamoyl)-N-[(1-propyl-2-pyrrolidinyl)-methyl]-benzamide 16

A solution of compound 13 (100 mg, 0.26 mmol) in methanol (30 ml) was hydrogenated in a Parr bottle with 10 % Pd/C (0.03 g) at 60 psi for 10 h. Filtration and evaporation of the solvent gave 16 (90 mg, 90 %). m.p. 138°C (from isopropanol) (Found : C, 53.07 ; H, 7.33 ; N, 14.52. $C_{17}H_{28}N_4O_4S$ requires C, 53.10 ; H, 7.34 ; N, 14.57), R_F ($MeOH/NH_4OH$: 95/5) 0.68, δ(DMSO) 8.9-7.2(4H, m, Ar<u>H</u>, -N<u>H</u>SO_2, -CON<u>H</u>), 6.4(2H, m, NH_2), 4.1(3H, s, OCH_3), 3.8-2.9(7H, m, CONHC<u>H</u>$_2$, -C<u>H</u>$_2$-CH_2CH_3, pyrrolidinyl <u>H</u>), 2.45(3H, m, C<u>H</u>$_3$NH), 2.2-1.5(6H, m, CH_2-C<u>H</u>$_2$-CH_3, pyrrolidinyl <u>H</u>), 1.1(3H, t, <u>J</u> 8 Hz, CH_2-CH_2-C<u>H</u>$_3$).

S-4-Azido-2-methoxy-5-N'-(methylsulfamoyl)-N-[(1-propyl-2-pyrrolidinyl)methyl]-benzamide 17

To a solution of 16 (50 mg, 0.12 mmol) in 3N HCl (5 ml) was added at 0°C, sodium nitrite (16 mg, 0.24 mmol) dissolved in H_2O (1 ml). The mixture was stirred at 0°C for 1 h. Sodium azide (17 mg, 0.258 mmol) in water (1 ml) was then added. After stirring (1 h at 0°C) aqueous ammonia was added until pH became alcaline. The mixture was then concentrated <u>in vacuo</u> and the residue taken up with water and dichlorometha-

ne. The organic extract was washed (saturated brine), dried (Na_2SO_4) and concentrated to yield 17 (30 mg, 62 %) m.p. 174°C, R_F (MeOH/NH_4OH : 99/1) 0.60 ν_{max} ($CHCl_3$) 2130 (N_3), m/z 410 (20 %, M^+).

S-4-Azido-2-methoxy-5-N'-(methylsulfamoyl)-N-[(1(^{3}H-2',3'-propyl)-2-pyrrolidinyl) methyl]-benzamide 2

A solution of compound 15 (1 mCi, 26 nmol) was evaporated in vacuo to dryness and dissolved in 20 µl 6N acetic acid. Sodium nitrite (720 nmol in 1 µl H_2O) was added. After 30 min at room temperature, sodium azide (770 nmol in 1 µl H_2O) was added. The reaction was stopped by addition of 8 µl concentrated ammonia. Compound 2 was purified by HPLC using a µBondapak C_{18} column. The peak of radioactivity is coeluted with compound 17 in 10.0 min, whereas compound 15 is eluted in 7.9 min (Fig. 1).

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