The synthesis of [^{14}C]-3S,4R-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine hydrochloride (BRL 29060A), and mechanistic studies using carbon-13 labelling

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SUMMARY

Paroxetine, BRL 29060A 1 has been labelled with both carbon-14 and carbon-13. Hydroxymethylation of 4-(4-fluorophenyl)-1-methyl-1,2,5,6-tetrahydropyridine, using [^{14}C]formaldehyde, produced an enantiomeric mixture of products which was taken without separation through a multistage sequence. Resolution of the mixture of stereoisomers at the penultimate step gave [^{14}C]BRL 29060A with the required configuration. The overall radiochemical yield was 8%. At some stage in this process, as shown by C-13 labelling studies, scrambling of the label took place to give BRL 29060A with the majority of the label in the C-2 position of the piperidine ring and the remainder at the expected 7-methylene position. Further investigations of this route using carbon-13 as the label are described. When sesamol, (3,4-methylenedioxyphenol) was reacted with the O-benzene sulphonate of (±)-*cis*-4-(4-fluorophenyl)-3-(hydroxy[^{13}C]methyl)-l-methylpiperidine, an inversion of configuration resulted via the previously described 1-aza[3.1.1]bicycloheptane ring system. It is also shown that the corresponding (±)-*trans*-substituted piperidine, under similar conditions, does not undergo this inversion.

Key Words: 3,4-Disubstituted piperidine, Paroxetine, anti-depressant, carbon-14 and carbon-13 label scrambling, l-aza[3.1.1]bicycloheptane.

DISCUSSION

4-(4-Fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine can exist in four different stereoisomeric forms. The (-)-*trans* isomer 1, having the configuration 3S,4R, has proved to be a potent anti-depressant drug Paroxetine (BRL 29060A) (1).

As part of the Safety Evaluation of Paroxetine, carbon-14 labelled Paroxetine ([^{14}C]BRL 29060A) was synthesised for use in drug metabolism studies. The synthetic route to [^{14}C]BRL 29060A is shown in scheme 1.

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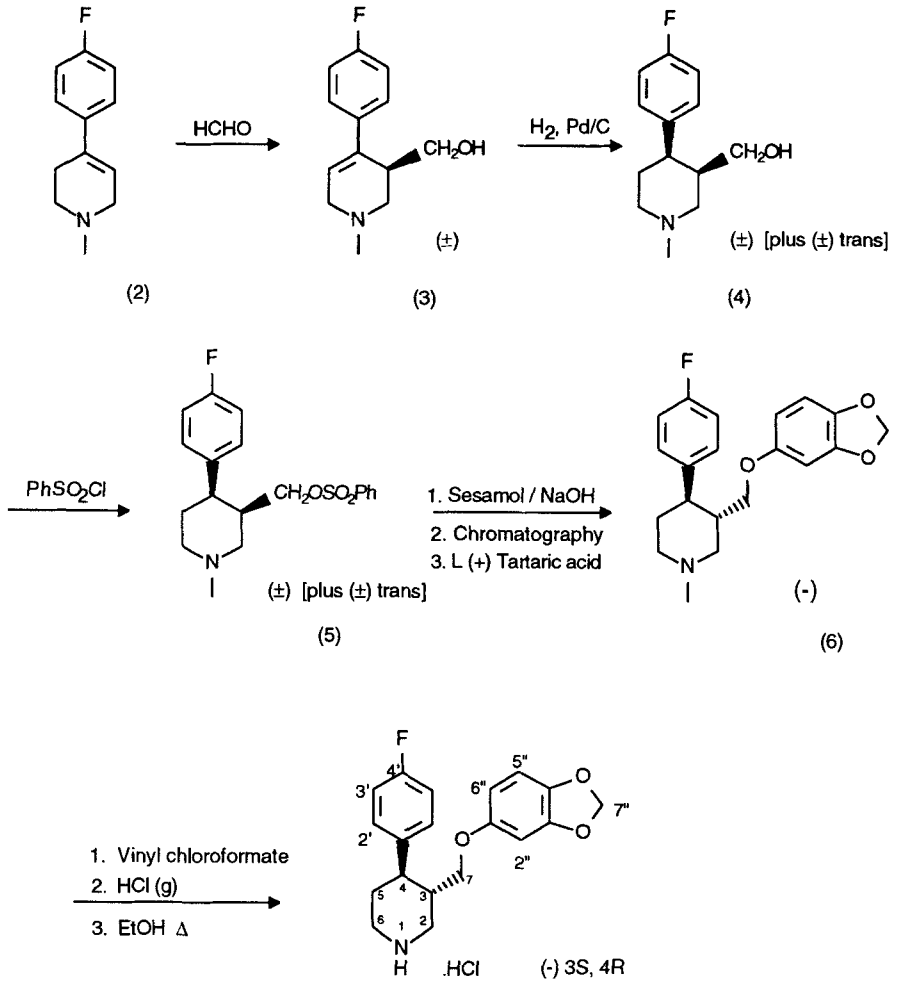
SCHEME 1



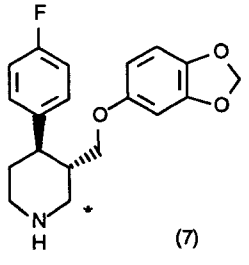
PAROXETINE (BRL 29060A) (1)

This route allowed the use of the commercially available carbon-14 formaldehyde as the radiolabelled precursor. However, 4-(4-fluorophenyl)-1-methyl-1,2,5,6-tetrahydropyridine (2) is a suspected neurotoxin and whilst this can be handled safely on a milligram laboratory scale the handling problems on a large scale preclude its use as a route for the commercial production of Paroxetine.

Prins hydroxymethylation of the tetrahydropyridine 2 with carbon-14 labelled formaldehyde gave 3 (only one enantiomer shown) as a mixture of enantiomers. Hydrogenation of 3 over palladium on charcoal to give the piperidine 4 was performed

without prior separation of the enantiomers. The resulting mixture of stereoisomers 4 (consisting of the (±) *cis* isomers plus a small quantity of (±) *trans*) was treated, under strongly basic conditions, with benzenesulphonyl chloride to produce the sulphonate ester 5. Treatment with sesamol followed by chromatographic purification gave pure racemic 6. At this stage, the required (-)-*trans* isomer 6 was obtained by isolation as its (+) tartrate salt, the enantiomeric purity of which was assessed by comparison of its optical rotation with that of standard material. Demethylation of the free base 6 using vinyl chloroformate gave BRL 29060A 1. Typically, overall radiochemical yields of around 8% were achieved for the multistep synthesis.

It is known (2) that during the displacement of the cis sulphonate ester 5 by sesamol the resultant ether 6 has the required trans configuration and that the stereocentre at C-3 has been inverted. Previously published work by Christensen et al (3) on the preparation of a similarly substituted piperidine suggested the existence of the bicylic system, 1-aza[3.1.1]bicycloheptane as an intermediate, leading to an inversion of configuration during the reaction of p-methoxyphenol with the benzenesulphonate ester of 3-hydroxymethyl-1-methyl-4-phenylpiperidine. In view of the potential consequence this inversion of stereochemistry at C-3 has on the position of the radiolabel in carbon-14 labelled BRL 29060A, a series of carbon-13 labelled studies were undertaken.



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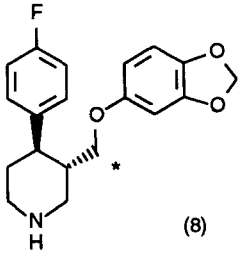


(8)

* Denotes C-13

In order to confirm the position of label in BRL 29060A, the synthesis was carried out as for the carbon-14 synthesis but using [^{13}C] formaldehyde (90 atom %). Analysis of the final product mixture by carbon-13 NMR spectroscopy showed that the major portion of the label was present at the C-2 position of the piperidine ring (7; endo; 47.8ppm). The remaining portion of the label appeared at the 7-methylene position (8; exo; 69.1ppm). Typically, the label ratio was 9:1 (endo:exo). At this point, we decided to examine in more detail the mechanism of this partial scrambling of the label. To this end, further carbon-13 studies were undertaken which involved initial resolution, using (-) and (+)-dibenzoyltartaric acid, of the enantiomers (9 and 10), formed from the

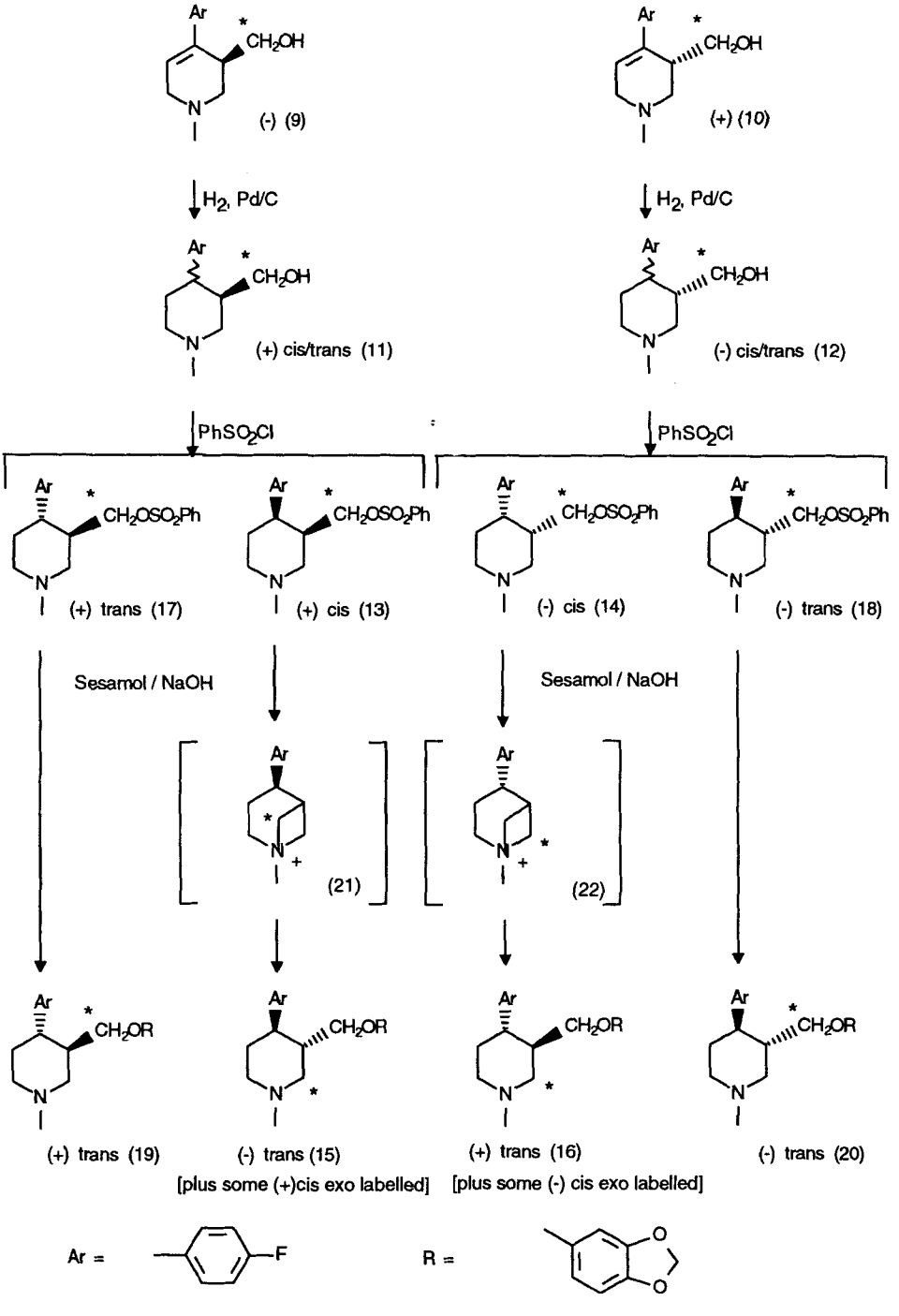
carbon-13 Prins hydroxymethylation reaction (Scheme 2). The pure individual enantiomers were hydrogenated separately in the usual way to give mixtures of (+)-*cis/trans* and (-)-*cis/trans*-products (11 and 12) with typical *cis/trans* ratios of 85:15. It was not found possible to separate the cis and trans components by chromatographic or recrystallisation methods. However, on reacting each stereoisomeric mixture with benzenesulphonyl chloride, the resulting sulphonates could be separated into the *cis*- and *trans*-isomers by column chromatography. Analysis using carbon-13 NMR spectroscopy showed that all the carbon-13 label was located on the exo-methylene carbon atom of each isomer as expected.

When the (+) and (-)-*cis*-benzenesulphonates (13 and 14) were reacted with sesamol, two mixtures, composed mainly of the (-) and (+)-*trans*-N-methyl compounds (15 and 16) with the corresponding (+)- and (-)-*cis*-materials as minor products, were isolated. Separation of the diastereomeric *cis* and *trans* compounds by column chromatography and analysis by carbon-13 NMR spectroscopy showed that the (-) and (+)-*trans*-isomers (15 and 16) were labelled exclusively in the C-2 position of the piperidine ring. The (+) and (-)-*cis*-products, not having undergone any such inversion, were still labelled on the exo-methylene carbon atom. However, reaction of the (+) and (-)-*trans*-benzenesulphonates (17 and 18) with sesamol did not produce any corresponding inversion of configuration. The (+)- and (-)-*trans*-N-methyl compounds (19 and 20) were isolated as the sole products with 100% of the carbon-13 label present at the exo-methylene carbon atom. This inversion of *cis* to *trans* is thought to arise via the cyclic intermediates (21 and 22). These results are similar to those already reported by Christensen et al, as previously mentioned, for another 3,4-disubstituted piperidine ring system. Attack at the least hindered side of the bicyclic intermediate leads to the *trans* configuration. As the *trans* sulphonates 17 and 18 give essentially the pure *trans*-ethers 19 and 20 it is assumed that the bicyclic route is not a significant contributor to the reaction of the *trans* sulphonates, and that a conventional S_N2 displacement is predominant.

In conclusion, it can be said that [^{14}C]BRL 29060A, having the (-) -*trans* configuration, is produced via two distinct pathways. On the one hand, inversion of the (+)-*cis*-sulphonate 13 gives the (-)-*trans*-product 15 with 100% of the label residing in the piperidine ring. However, the (-)-*trans*-product 20 may also arise via the (-)-*trans*-sulphonate 18 without inversion taking place and leaving the label at the exo-methylene position. The (+)-*trans*-products (19 and 16) which are formed respectively from the (+)-*trans*-sulphonate 17 without inversion and from the (-)-*cis*-sulphonate 14

with inversion, along with the small amounts of (+) and (-)-*cis*-materials, are all removed during the chromatographic purification and resolution (with tartaric acid) of the N-methyl product mixture. The final labelled BRL 29060A therefore arises from the

SCHEME 2



mixture of the N-methyl compounds, (-)-*trans*-piperidine labelled compound 15 and (-)-*trans* exomethylene labelled 20, which afford BRL 29060A labelled with a piperidine to exomethylene label ratio of 9:1.

EXPERIMENTAL

Aqueous solutions of [^{14}C]formaldehyde and [^{13}C]formaldehyde (90 atom %) were purchased from Amersham International plc. 1,2-Dichloromethane was dried by distillation from phosphorus pentoxide. Hydrogen chloride gas was dried by passing through concentrated sulphuric acid. All other solvents and reagents were used without prior treatment. Infrared spectra were run as KBr discs (conc. 200:1) on a Perkin-Elmer 681 infrared spectrophotometer. Proton and carbon-13 nuclear magnetic resonance spectra were run in deuterochloroform, unless otherwise stated, using a Jeol JNM-GX 270 FT NMR spectrometer with tetramethylsilane as internal standard. For clarity, only the assignments corresponding to the piperidine C-5 atom (indicating either *cis* or *trans* isomer) and either the piperidine C-2 atom or the exo-methylene C-7 atom (indicating position of label) are quoted for the C-13 NMR spectra of the carbon-13 labelled materials. High pressure liquid chromatography was carried out on a Waters Associates liquid chromatograph with model 510 pump and 441 UV absorbance detector for radiochemical purity determinations and on an LDC CCM chromatograph with Varian autosampler for chemical purity determinations. Optical rotation determinations were carried out in a 1ml cell on a Perkin-Elmer 241 polarimeter. Specific activities and radiochemical purities (by thin layer chromatography and high pressure liquid chromatography), were assessed by scintillation counting using Packard Tri-carb liquid scintillation spectrometers.

THE SYNTHESIS OF [^{14}C]BRL 29060A

(±)-4-(4-Fluorophenyl)-3-hydroxy[^{14}C]methyl-1-methyl-1,2,3,6-tetra-hydropyridine 3.

To a cooled (0^0) solution of the tetrahydropyridine (2; 408.5mg, 2.14mmol) in concentrated hydrochloric acid (2.5ml) was added [^{14}C]formaldehyde (3.7GBq; 54.3mg, 1.69mmol) in water (ca. 500µl) and washed in with a further quantity of water (2ml). The mixture was heated to reflux and the reaction followed by TLC on Merck silica gel 5735 (cyclohexane/ethyl acetate/triethylamine, 2:2:1, v/v). After 4h, the condenser was washed down with water (3ml) and the mixture heated to reflux for a

further 1h. To the cooled solution was added ethyl acetate, then aqueous 10% sodium hydroxide solution until basic. The layers were separated and the aqueous layer extracted with ethyl acetate and the combined organic phase dried ($MgSO_4$). Removal of the solvent gave crude 3 (447.4mg) which was identical to standard material by TLC on Merck silica gel 5735 in the above solvent system.

(±)*cis/trans*-4-(4-Fluorophenyl)-3-hydroxy[^{14}C]methyl-1-methylpiperidine 4.

The crude tetrahydropyridine (3; 447.4mg, 2.34mmol) was hydrogenated in ethanol (5ml) at atmospheric pressure and room temperature over 5% palladium on charcoal. The reaction was followed by TLC on Merck silica gel 5735 (ethyl acetate/methanol/ammonia (5M), 7:3:1, v/v) to completion. The solution was filtered and the filtrate evaporated to yield crude 4 (400mg) which was identical to standard material by TLC on Merck silica gel 5735 in the above solvent system.

[^{14}C] (±)*cis/trans*-4-(4-Fluorophenyl)-3-hydroxymethyl-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)piperidine.

To a vigorously stirred, cooled (5^0) solution of the alcohol (4; 400mg,2.07mmol) in toluene (3ml) was added aqueous 5M sodium hydroxide solution (2ml) followed by the slow dropwise addition of benezenesulphonyl chloride (345µl, 478.5mg, 2.71mmol). The mixture was stirred at room temperature and the reaction followed by t.l.c on Merck silica gel 5735 (ethyl acetate/methanol/ammonia (5M), 20:3:1, v/v) to completion. The layers were separated and the aqueous phase extracted with toluene. The combined organic phase was dried (Na_2SO_4) then evaporated. The resulting yellow oil 5 was dissolved in toluene (4ml) and treated with a solution of sesamol (356.2mg, 2.58mmol) in 4-methylpentan-2-ol (3ml) followed by aqueous 5M sodium hydroxide solution (2ml). The mixture was heated to 100^0 and the reaction followed by TLC as before. After 8.5h, the cooled layers were separated, the aqueous layer extracted with toluene and the combined organic phase dried (Na_2SO_4). Evaporation gave crude racemic 6 (456.2mg) which was chromatographed on a column of Merck silica gel 7734 (ethyl acetate/methanol/ammonia (5M), 20:3:1, v/v) collecting the fractions containing the product (218.1mg) with the same Rf as for standard material.

[^{14}C](-)-*trans*-4-(4-Fluorophenyl)-l-methyl-3-(3,4-methylenedioxyphenoxymethyl)piperidine 6.

The purified isomeric mixture (218.1mg, 0.636mmol) was suspended in water (3ml)

and diluted with non-radioactive (-)*trans*-4-(4-fluorophenyl)-l-methyl-3-(3,4-methylenedioxyphenoxymethyl)piperidine-(+)-tartrate ($[\alpha]_D$ = -48.74^0; 310.1mg, 0.629mmol). (+)-Tartaric acid (206.4mg, 1.38mmol) was added and the mixture heated until a solution was obtained. On cooling, the crystalline (-)-*trans* -(+)-tartrate salt precipitated. This was collected, washed with water, then recrystallised from hot water (3ml) to give the pure tartrate salt (360.1mg; $[\alpha]_D$ = -48.76^0, c=4.84 in methanol). The free base 6 was isolated from its tartrate salt by slurring in ethyl acetate and basifying with aqueous 10% sodium hydroxide solution. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic phase was dried ($MgSO_4$) and evaporated to give 6 (264.7mg).

Paroxetine, [^{14}C]BRL 29060A 1.

To a stirred mixture of the N-methyl compound (6; 264.7mg, 0.772mmol), powdered anhydrous potassium carbonate (1g, 7.25mmol) and dry 1,2-dichloroethane (5ml) was added vinyl chloroformate (500µl, 5.46mmol). The reaction mixture was heated to reflux and followed by TLC on Merck silica gel 5735 (ethyl acetate/methanol/ammonia (5M), 20:3:1, v/v). After 4h, the solvent was evaporated and the residue partitioned between ethyl acetate and brine. The layers were separated and the aqueous phase extracted with ethyl acetate. The combined organic phase was washed with saturated brine, dried ($MgSO_4$) and evaporated. The residue (307mg) was desiccated *in vacuo* then dissolved in dry 1,2-dichloroethane (5ml) and anhydrous hydrogen chloride passed through the solution for 45 mins. The solvent was evaporated, a small volume of anhydrous 1,2-dichloroethane added and re-evaporated. The resulting foam was desiccated under high vacuum for 3h before dissolving in 100% ethanol (10ml) and heating to reflux for 1.5h. The mixture was evaporated and the residue (264.9mg) was slurried in ethyl acetate and basified with aqueous 10% sodium hydroxide solution. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried ($MgSO_4$) and evaporated. The resulting crude material was chromatographed on a column of Merck silica gel 7734 (ethyl acetate/methanol/ammonia (5M), 20:3:1, v/v). The purified free base was converted to the hydrochloride salt with ethanolic hydrogen chloride. The product was evaporated a number of times from propan-2-ol then recrystallised from hot propan-2-ol. The resulting propanolate was equilibrated in a moist atmosphere to give the required hydrated [^{14}C]BRL 29060A 1 (181.5mg), ^{1}H NMR. ppm (DMSO-d_6) 1.85 (d,5eq.), 2.00 (dd,5ax.), 2.45 (m,3), 2.85 (dd,4), 2.90 (d,2ax.), 3.0 (dd,6ax.), ~3.4 (obscured, 6eq.), 3.45 (d,2eq.), 3.50 (dd,7), 3.60 (dd,7'), 5.95 (s,0-CH_2-0), 6.20 (dd,6"), 6.5 (d,2"),

6.75 (d,5"), 7.20 (dd,3'), 7.25 (dd,2'), and 9.0 (s,br,NH_2). Specific activity 1.65MBq.mg^{-1}. Radiochemical purity by TLC on Merck silica gel 5735 in methanol/water/ammonia (0.88) (20:7:1, v/v) 97.9% and chloroform/methanol/acetic acid (18:2:1, v/v) 98.0% and identical to standard material in both systems; radiochemical purity by h.p.l.c. on a μ-Bondapak-C18 column (Waters Associates) eluted with 0.05M phosphate buffer (pH 3.2)/acetonitrile (65:35, v/v) 97.6%; chemical purity by relative h.p.l.c assay with respect to standard material (conditions as for radiochemical purity) 82.5% as pure free base.

CARBON-13 LABELLED STUDIES.

Resolution of (±)-4-(4-fluorophenyl)-3-hydroxy[^{13}C]methyl-1-methyl-1,2,3,-6-tetrahydropyridine (9 and 10).

The racemic alcohol was prepared from [^{13}C] formaldehyde (2g, 66.7mmol) as described for the carbon-14 synthesis. The product was dissolved in hot methanol (35ml) and added to a stirred solution of (-)-dibenzoyl tartaric acid (30g) in warm methanol (35ml). On cooling, a solid precipitated which was collected and washed with methanol to give an off-white solid (8.5g). This was recrystallised from hot acetone/water (5:1). The purified (-)(-) salt (6.7g) was added to aqueous saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated to give the (-) enantiomer (9) (2.28g), $[\alpha]_D$=-130.79^0 (c=5.0002 in methanol) (c.f. standard material $[\alpha]_D$ = -134.3^0), H^1 NMR ($CDCl_3$ + Eu[TFA-Camph]$_3$) one enantiomer present.

All liquors from the resolution of the (-) enantiomer were combined and evaporated. The residue was dissolved in aqueous saturated sodium bicarbonate solution/dichloromethane. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic phase was dried ($MgSO_4$) and evaporated. Treatment of the residue as above but using (+)-dibenzoyl tartaric acid, recrystallisation and isolation as the free base gave the (+) enantiomer (10) (600mg), $[\alpha]_D$=+126.39^0 (c=4.9996 in methanol) (c.f. standard material $[\alpha]_D$=+130^0); H^1 NMR ($CDCl_3$ + Eu[TFA-Camph]$_3$) one enantiomer present.

(+)-*cis/trans*-4-(4-Fluorophenyl)-1-methyl-3-(phenylsulphonyloxy[^{13}C]-methyl)piperidine (13 and 17).

The (-)-[^{13}C] enantiomer (9; 2.28g, 10.3mmol) was hydrogenated as described for the carbon-14 compound. A portion of the resulting (+)-*cis/trans*-alcohol (11; 1.1g,

4.93mmol) was dissolved in toluene (9ml), cooled in ice and treated with aqueous 5M sodium hydroxide solution (6ml) followed by benzenesulphonyl chloride (1ml, 1.38g, 7.84mmol). The mixture was stirred at room temperature for 16h then diluted with water and extracted with toluene. The combined organic phase was washed with brine and dried ($MgSO_4$). Evaporation gave the crude mixture of sulphonates which was chromatographed on a column of Merck silica gel 7734. Elution with ethyl acetate/methanol (4:1, v/v) gave the (*(+)-cis*-sulphonate (13)(1.16g), ^{13}C NMR ppm 25.8 [piperidine C(5)] and 68.9 (100%, CH_2-0); identical to standard material by TLC on Merck silica gel 5735 in the above solvent system. Elution of the column with ethyl acetate/methanol (2:1, v/v) gave the (+)-*trans*-sulphonate (17) (150mg), ^{13}C NMR ppm 34.3 [d, J_{5-7} = 3Hz, piperidine C(5)] and 71.0 (100%, CH_2-0); identical to standard material by TLC on Merck Silica 5735 in the above solvent system.

(-)-*cis/trans*-4-(4-Fluorophenyl)-1-methyl-3-(phenylsulphonyloxy[^{13}C]-methyl)piperidine (14 and 18).

The (+) [^{13}C] enantiomer (10; 508mg, 2.30mmol) was hydrogenated as described above and the resulting alcohol (12; 480mg, 2.15mmol) converted to the sulphonates. Chromatography as before gave the (-)-*cis*-sulphonate 14 (200mg), ^{13}C NMR ppm 25.6 [piperidine C(5)] and 68.6 (100%, CH_2-0); identical to standard material on Merck silica gel 5735 in ethyl acetate/methanol (4:1, v/v), and the (-)-*trans*-sulphonate 18 (35mg), ^{13}C NMR ppm 33.5 [piperidine C(5)] and 70.5 (100%, CH_2-0); identical to standard material on Merck silica gel 5735 in ethyl acetate/methanol (2:1, v/v).

Reaction of (+)-cis-4-(4-fluorophenyl)-1-methyl-3-(phenylsulphonyloxy-[^{13}C]methyl)piperidine 13 with sesamol.

To a stirred solution of the (+)-*cis*-sulphonate (13; 500mg, 1.38mmol) in toluene (5ml) was added a solution of sesamol (300mg, 2.17mmol) in 4-methylpentan-2-ol (5ml) followed by aqueous sodium hydroxide solution (5M, 15mol, 3ml). The mixture was heated at 100^0 for 6.5h, then cooled and the aqueous layer extracted with toluene. The combined organic phase was washed with brine and dried ($MgSO_4$). Evaporation gave a residue, a portion of which (100mg), was chromatographed on a column of Merck silica gel 7734 in ethyl acetate/methanol/ammonia (5M) (40:3:1, v/v) to give (+)-*cis*-4-(4-fluorophenyl)-1-methyl-3-(3,4-methylenedioxyphenoxy[^{13}C]methyl)piperidine (12mg), ^{13}C NMR ppm 26.2 [piperidine C(5)] and 66.2 (100%, CH_2-0), and (-) -*trans*-4-(4-fluorophenyl)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)[^{13}C]piperidine (15)

(59mg), ^{13}C NMR ppm 34.4 [piperidine C(5)] and 59.6 [100%, piperidine C(2)], and were identical to standard materials by TLC on Merck silica gel 5735 in the above solvent system.

Reaction of (+)-trans-4-(4-fluorophenyl)-1-methyl-3-(phenysulphonyloxy-[^{13}C]methyl)piperidine 17 with sesamol.

A solution of sesamol (100mg, 0.725mmol) in N,N-dimethylformamide (1ml) was added to the (+)*trans*-sulphonate (17; 150mg, 0.413mmol) followed by aqueous 40% sodium hydroxide solution (150µl) and the mixture stirred at room temperature. The reaction was followed to completion by TLC on Merck silica gel 5735 (petroleum ether (60-80°)/ethyl acetate/triethylamine, 2:2:1, v/v) then diluted with aqueous sodium hydroxide and water, and extracted with dichloromethane. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation gave (+)-*trans*-4-(4-fluorophenyl)-1-methyl-3-(3,4-methylenedioxyphenoxy[^{13}C]methyl)piperidine (19) (137mg), ^{13}C NMR 33.1 ppm [d,J_{5-7}=3Hz, piperidine C(5)] and 68.4 (100%, CH_2-0); identical to standard material by TLC on Merck silica gel 5735 in the above solvent system.

Reaction of (-)-cis-4-(4-fluorophenyl)-1-methyl-3-(phenylsulphonyloxy-[^{13}C]methyl)piperidine 14 with sesamol.

The reaction was carried out with 14 (200mg, 0.551mmol) as described for the (+)-*cis*-sulphonate 13 to give (-)-*cis*-4-(4-fluorophenyl)-1-methyl-3-(3,4-methylenedioxyphenoxy[^{13}C]methyl)piperidine (22.7mg), ^{13}C NMR 25.8ppm [d,J_{5-7}=6Hz, piperidine C(5)] and 65.9 (100%, CH_2-0), and (+)-*trans*-4-(4-fluorophenyl)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)[^{13}C]piperidine (16) (73.4mg), ^{13}C NMR 33.9 ppm [piperidine C(5)]; and 59.3 [100%, piperidine C(2)]; and were identical to standard materials by TLC on Merck silica gel 5735 in ethyl acetate/methanol/ammonia (0.88) (40:3:1,v/v).

Reaction of (-)-trans-4-(4-fluorophenyl)-l-methyl-3-(phenylsulphonyloxy-[^{13}C]methyl)piperidine 18 with sesamol.

The reaction was carried out on 18 (35mg, 0.096mmol) as described for the (+)-*trans*-sulphonate 17 to give (-)-*trans*-4-(4-fluorophenyl)-1-methyl-3-(3,4-methylenedioxyphenoxy[^{13}C]methyl)piperidine 20 (14mg), ^{13}C NMR 33.6 ppm [piperidine C(5)] and

69.1 (100%, $\underline{C}H_2$-0); identical to standard material by TLC on Merck silica gel 5735 in cyclohexane/ethyl acetate/triethylamine (2:2:1, v/v).

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