Synthesis of (R)-(+)-1,2,3,6-Tetrahydro-4-[U-^{14}C]phenyl-1-[(3-phenyl-3-cyclohexenyl-1-yl)methyl]pyridine, a Potential Antipsychotic Agent.

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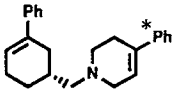
SUMMARY

1,2,3,6-Tetrahydro-4-[U-^{14}C]phenylpyridine (12) was synthesized and coupled to (R)-3-phenyl-3-cyclohexene-1-carboxylic acid to make the titled compound 7 in 21% overall yield. Purification considerations were an important factor in the choice of a reaction sequence to 7, and successful synthesis was facilitated by the superiority of $BF_3.OEt_2$ as dehydrating reagent in this system. This otherwise problematic sequence offers an efficient and simple route to compound 7 (PD 143188).

KEYWORDS: *Antipsychotic, 1,2,3,6-tetrahydro-4-phenylpyridine, phenylmagnesium bromide, Swern's oxidation, (R)-(3-phenyl-3-cyclohexen-1-yl)(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)methanone.*

Introduction

The unlabeled form of (R)-(+)-1,2,3,6-tetrahydro-4-[U-^{14}C]phenyl-1-[(3-phenyl-3-cyclohexenyl-1-yl)methyl]pyridine 7 , a novel dopamine autoreceptor agonist (1), is in development as potential antipsychotic agent . To provide a further insight into the pharmacology of this compound, and learn the details of its metabolism and tissue distribution, a carbon-14 labeled version was requested.



7 **C-14 PD 143188**

We examined all the routes (1) hitherto developed to prepare the compound 7, and we found that the most suitable approach to the synthesis of a radiolabeled analog may be that in which a 3-phenyl-3-cyclohexen-1-yl moiety was prepared from ^{14}C-labelled phenylmagnesium bromide. The **Scheme I** shows the reaction steps in the sequence that are applicable to the preparation of target labeled compound. Using this strategy we could make 5 by the reaction of phenylmagnesium bromide with the ketone 4 . The subsequent dehydration of compound 5 would provide the desired compound 7. This

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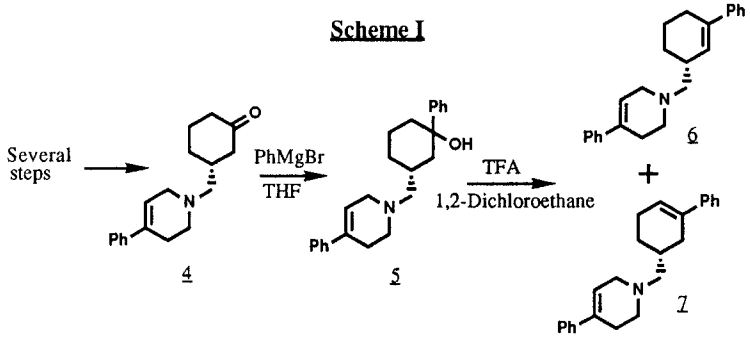
method is attractive because of the relatively few reaction steps involved, but it is not regioselective in the olefin forming dehydration step 5 to 6 and 7. Additionally, it would require a very tedious chromatography to isolate the desired target compound from the mixture. The substantial amount of radioactivity that would be lost as the undesired 6 and a non-recoverable 7 in a single step was a very unattractive feature of this sequence.

Scheme I



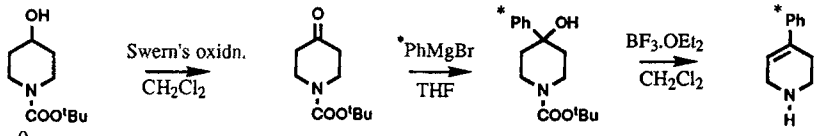
An alternative strategy in which 1,2,3,6-tetrahydro-4-[U-^{14}C]phenylpyridine (12) may be coupled with (R)-3-phenyl-3-cyclohexene-1-carboxylic acid, itself available to us by courtesy of Warner-Lambert Parke-Davis' Psychiatric Disorder Group (2), eliminates these problems. Herein, we report the development of a method to synthesize 1,2,3,6-tetrahydro-4-phenylpyridine, the application of the protocol to the preparation of 12 and the coupling of this labeled intermediate with (R)-3-phenyl-3-cyclohexene-1-carboxylic acid to make the target compound 7.

Results and Discussion

By a preliminary study of the sequence in **Scheme I**, we confirmed the absence of regioselectivity in the olefin forming dehydration step, having obtained a 1:1 mixture of target 7 and its regioisomeric olefin 6 . Further, the best analytical hplc condition we could develop failed to effect a baseline separation of the desired compound 7 from 6. Therefore, the application of this reaction sequence to the synthesis of labeled compound 7 would likely furnish a product of unacceptable quality. As shown in **Scheme II** we sought a solution in an alternative approach that involved 12 as an intermediate and thereby avoided the regioselectivity difficulty. *tert*-Butyl 4-aryl-1,2,3,6-tetrahydropyridine-1-carboxylates which are easily converted to such compounds as 12 are known to be accessible in tolerable yields by Pd^0 catalyzed coupling of the triflate derivative of an N-Boc protected 4-piperidone and aryl boronic acid. This sequence was developed by Wustrow et al (3) in order to

circumvent the problem of poor yields that other workers (4) encountered in the attempted preparation of 1,2,3,6-tetrahydro-4-phenylpyridine from phenyl Grignard reagent and the ketone 10 followed by dehydration.

Scheme II

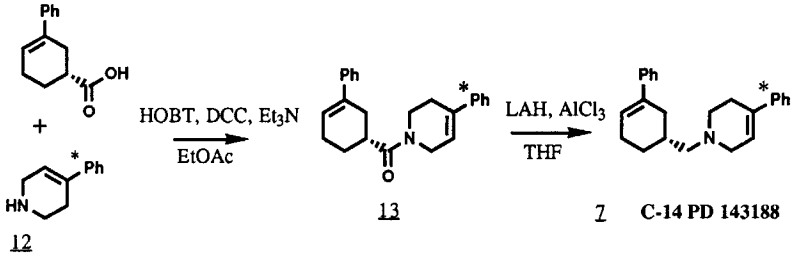


9 10 11 12

We developed a variant of this otherwise problematic reaction sequence, and obtained good yield (82 %) of compound 12. Accordingly, 4-hydroxypiperidine (8) was transformed by a Swern's oxidation of the 1,1-dimethylethyl carboxylate (N-Boc) derivative 9 to the compound 10. [U-^{14}C]Phenylmagnesium bromide generated from bromo[U-^{14}C]benzene by an established method reacted with the compound 10 to make 1,1-dimethylethyl 4-hydroxy-4-[U-^{14}C]phenyl-1-piperidine carboxylate (11). We did not find evidence of a Grignard reaction with the Boc-protecting group under our conditions. Since the low yields in a previous report (4) was in part attributed to such a reaction, the recent report (5) of a mild and selective debenzylation of tertiary amines using α-chloroethyl chloroformate may offer an opportunity for improved reliability of such a sequence. With the benzyl protection potentially removable by other than hydrogenolysis, using such a group eliminates the reaction of Grignard with Boc group (3). The subsequent dehydration of the alcohol 11 to the olefin, a hitherto problematic step, was best achieved with boron trifluoride etherate in methylene chloride at room temperature. This reagent proved to be sufficiently mild, and superior to trifluoroacetic acid (TFA) in effecting elimination and the simultaneous deprotection of Boc group in compound 11 to provide 1,2,3,6-tetrahydro-4-[U-^{14}C]phenylpyridine (12) . Although the dehydration reaction with trifluoroacetic acid was clean, a very low yield (26 %) of compound 12 was obtained. The observed superiority of $BF_3.OEt_2$ as compared to other reagents in dehydrating tertiary alcohol 11 is in agreement with literature report (6). To make (R)-(3-phenyl-3-cyclohexen-1-yl-)(3,6-dihydro-4-[U-^{14}C]phenyl-1(2H)-pyridinyl)methanone (13) as in **Scheme III**, the carboxyl group in (R)-3-phenyl-3-cyclohexene-1-carboxylic acid was activated with 1,3-dicyclohexylcarbodiimide (7) before coupling with 12 . The transformation to compound 7 was accomplished by reduction with $AlCl_3$/LAH in tetrahydrofuran. The simple filtration of the reaction product through a short column of silica gel eluted

with hexane: ethyl acetate followed by one crystallization afforded a radiochemical (98.67 %) and enantiopure (100 %) compound. The results of all spectroscopic analyses of the intermediate compounds were consistent with assigned structures, and were identical with those obtained under similar conditions for the appropriate authentic references.

Scheme III



12 13 7 C-14 PD 143188

Tlc characteristics were also in agreement with reference materials. The labeled compound 7 gave identical spectroscopic results with 'cold' authentic material.

In conclusion, we have developed a reaction sequence providing very high purity grade compound 7. In designing the sequence, we opted to label 1,2,3,6-tetrahydro-4-phenylpyridine so as to eliminate a potential purification difficulty that would result from the generation of regioisomeric olefins in the alternative sequence. Furthermore, by substituting a mild dehydrating reagent, a reportedly problematic sequence was sufficiently improved to be a viable access route to a crucial labeled intermediate 12 which was subsequently coupled with a chiral fragment, followed by reduction to the target compound 7.

Experimental

All reactions were carried out under inert atmosphere. ^{1}H-NMR spectra were recorded with Varian (EM 390) 90 MHz spectrometer, a Gemini 200 MHz or a Varian XL 300 MHz spectrometer. Radiochemical purity of every labeled compound was determined by tlc radiochromatogram with Bioscan 200 imaging scanner. Radiochemical counting was performed on a Parkard 574 liquid scintillation counter using Beckman Ready-Solv MP cocktail. HPLC analyses of final products were performed on a Waters Associates 600E system with on line Applied Biosystems 1000S diode array detector and either an IN/US β-RAM radioactivity detector or Radiomatic series A-200 radioactivity flow detector. Bromo[U-^{14}C]benzene was obtained from American Radiolabeled Chemicals, St Louis, Mo. Column chromatography was carried out on a Merck Kieselgel 60 (230μ).

1,1-Dimethylethyl 4-oxo-1-piperidinecarboxylate (10)

To a stirred solution of oxalyl chloride (15.64 mL, 179.36 mmol) in CH_2Cl_2 (240 mL) at -60 ^oC ($CHCl_3$-dry ice) under argon was added DMSO (31.24 mL, 440.35 mmol) in CH_2Cl_2 (80 mL).

After 2 hr, a solution of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (9) (17.25 g, 85.8 mmol) in CH_2Cl_2 (40 mL) was added dropwise, and the reaction was stirred for a further 15 min. Triethylamine (61.3 mL) was added, and it was stirred for another 5 min at -60°C, after which it was allowed to warm to room temperature in 1.5 hr . The reaction was extracted with chloroform (3 X 200 mL), and the combined organic extract was sequentially washed with 2N NaOH, water, and brine. After the organic solution was dried, the solvent was evaporated and the product was crystallized from hexane to give 10 (10.7 g, 62 %), mp 72 - 74° C. Proton nmr ($CDCl_3$) δ 3.7 (dd 4H, (-CH_2)$_2$NBoc); 2.40 (dd 4H, (-CH_2)$_2$CO); and 1.45 (s, 9H, (-OC(CH_3)$_3$). MS (CI) m/z (rel. inten) 200 (M+ 1, 3.6), 184 (1.8), 172 (5.8), 144 (100), 126 (13.3), 100 (65). IR ($CHCl_3$) 3022, 2980, 2920, 2876, 1691, 1475, 1454, 1425, 1367, 1313, 1275, 1242, 1167, 1126, 987 and 860 cm^{-1}.

1,2,3,6-Tetrahydro-4-[U-^{14}C]phenylpyridine (12)

Bromobenzene (1.613 g, 10.27 mmol, containing 403.46 mg of bromo[U-^{14}C]benzene, sp. act. 347 μCi/mg) was dissolved in anhydrous diethyl ether (12 mL). A 4.0 mL portion of this solution was added to a suspension of magnesium powder (299 mg, 12.327 mmol) in dry ether (20 mL). A crystal of iodine was added, and the reaction was heated to reflux. The remaining bromobenzene solution (8.0 mL) was added dropwise with occassional heating to maintain reflux. The reaction was refluxed for 20 min after the complete addition of the solution of bromobenzene. The reaction mixture was cooled to 0 °C in an ice bath, and a solution of 10 (2.388 g, 12.0 mmol) in dry THF (30 mL) was added. It was stirred at room temperature overnight, poured onto sat'd NH_4Cl solution, and the solution was extracted with ether (3 X 80 mL). The solvent was evaporated to give 11 (3.09 g , 97.9% radiochemical purity). The total crude 11 was dissolved in CH_2Cl_2 (50 mL) and cooled in ice bath. While stirring, $BF_3 \cdot OEt_2$ (3.8 mL, 3 molar equiv.) was added in one portion, and the reaction was stirred overnight at room temperature. The solvent was evaporated on a rotary. The residue was adsorbed onto Celite, and it was applied to a column of silica gel. The column was eluted with CH_2Cl_2: EtOH: NH_4OH (70:30: 5), and the radioactive fractions were combined and concentrated. The solid product was dried under high vaccum to give 12 as a light yellow compound (1.33 g, 82 % yield). Proton nmr ($CDCl_3$) δ 7.35 (m, 5H, aromatic protons); 6.15 (tr, 1H, =C<u>H</u>-); 3.55 (q, 2<u>H</u>, =CHC<u>H</u>$_2$N); 3.33 (tr, 2H, -C<u>H</u>$_2$C<u>H</u>$_2$N); 2..48 (m, 2H, -HNC<u>H</u>$_2$C<u>H</u>$_2$-); 2.04 (brs, 1H, exch. D_2O, N<u>H</u>). The hydrochloride salt gave the following proton nmr result: (D_2O) δ 7.50 (m, 5H, aromatic protons); 6.20 (brs, 1H, =C<u>H</u>-CH$_2$-); 3.90 (brs, 2H, =CHC<u>H</u>$_2$N); 3.55 (tr, 2H, -C<u>H</u>$_2$C<u>H</u>$_2$N-); 2.85 (brs, 2H, -HNC<u>H</u>$_2$-).

(R)-(3-Phenyl-3-cyclohexen-1-yl)(3,6-dihydro-4-[U-^{14}C]phenyl-1(2H)-pyridinyl)methanone (13)

To a stirred solution of 12 (1.33 g, 8.36 mmol), HOBT (1.216 g, 9.0 mmol), and (R)- 3-phenyl-3-cyclohexene-1-carboxylic acid (1.68 g, 8.38 mmol) in dry DMF (20 mL) at 0 °C under argon was

added triethylamine (2.3 mL). After 10 min, DCC (1.86, 9.02 mmol) in ethyl acetate (40 mL) was added dropwise in 30 min. The ice bath was removed after another 10 min, and the reaction was stirred at room temperature overnight. Ethyl acetate was added to the reaction mixture, and the solid precipitate was removed by filtration . The solid was washed with additional volume of ethyl acetate, and it was combined with the above ethyl acetate filtrate. This combined organic solution was sequentially washed with water (3 X 150 mL) and brine, and it was dried. The solvent was evaporated, and the crude product crystallized at refrigeration temperature overnight from hexane-ethyl acetate (40:60). The mother liquor was concentrated and the residue obtained was chromatographed on a silica gel column eluted with hexane:ethyl acetate to give additional material. It was combined with the first crop above, and crystallized from acetone. A further two recrystallizations from CH_2Cl_2 / MeOH gave 13 (1.3 g , 45 %), mp 163 - 164° C. Proton nmr ($CDCl_3$) δ 7.45 - 7.21 (m , 10H, aromatic protons); 6.14 - 6.04 (overlapping brs and d, 2H, vinyl protons); 4.26 (d, 2H, =CHC<u>H</u>$_2$NCO-); 3.91 (m, 1H, -CH_2C<u>H</u>$_2$NCO-); 3.78 (m, 1H, - CH_2C<u>H</u>$_2$NCO-); 2.96 (m, 2H, -C<u>H</u>$_2$$CH_2$NCO-,); 2.63 - 2.35 (m, 5H, -C<u>H</u>$_2$CH=CPh-C<u>H</u>$_2$- and methine proton); and 1.94 - 1.87 (m, 2H, the remaining methylene protons) .

(R)-(+)-1,2,3,6-Tetrahydro-4-[U-^{14}C]phenyl-1-[(3-phenyl-3-cyclohexen-1-yl)methyl]pyridine (7)

To a stirred suspension of LAH (140 mg, 3.84 mmol) in dry THF (20 mL) at 0 °C under argon was added a solution of $AlCl_3$ (170 mg, 1.28 mmol) in dry ether (10 mL). After 45 min, 13 (1.3 g, 3.79 mmol) in dry THF (30 mL) was added dropwise. After the addition was completed, it was stirred for a further 1 hr . Water (5.0 mL) was added cautiously to the reaction mixture followed by 20 % NaOH and solid Na_2SO_4. After standing for 1 hr, it was filtered and concentrated. The residue was chromatographed on silica gel column eluted with 25 % ethyl acetate in hexane, and the fractions were concentrated. The solid was crystallized at refrigeration temperature from ethyl acetate: hexane (70:30) to give labeled PD 143188 (702 mg, 57 % yield, Sp. Act. 36.22 μCi/mg). Tlc on silca gel gave Rf 0.71, 99.73 % RCP; Hplc T_r 3.25 min. gave 99.06 % RCP and 99.49 % CP, on an Alltech Econosil silica column, 5μ, 4.6 mm ID X 250 mm, eluted with 0.01 % TEA and 0.05 % CH_3CN in hexane:ethyl acetate (91:9) and a flow rate of 2.0 mL/min, detection by UV λmax of 260 nm. Chiral hplc on a Daicel Chiracel OD column 4.6 mm ID X 250 mm eluted with 0.1 % TEA and 0.05 % CH_3CN in hexanes:isopropanol (70:30), flow rate at 1.0 mL/min and detection by UV at λmax of 254 nm gave RCP of 98.67 % R-(+), and chemical purity of 100 % R-(+). Proton nmr ($CDCl_3$) δ 7.44 - 7.21 (m, 10 H, aromatic protons); 6.13 (d, 2H, olefinic protons); 3.20 (s, 2H, -C<u>H</u>$_2$N-); 2.78 - 1.92 (m, 12H, methylene and methine protons); and 1.36 (m, 1H, methylene proton).

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