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SYNTHESIS OF TRITIUM AND DEUTERIUM LABELED 8-N-*n*-BUTYL-N-METHYLAMINO-8-(3-HYDROXYPHENYL)-1,4-DIOXASPIRO[4,5]DECANE HYDROCHLORIDE

Richard S. P. Hsi, Richard R.Kurtz and Malcolm W. Moon
Research Laboratories of The Upjohn Company
Kalamazoo, MI 49001 U.S.A.

SUMMARY

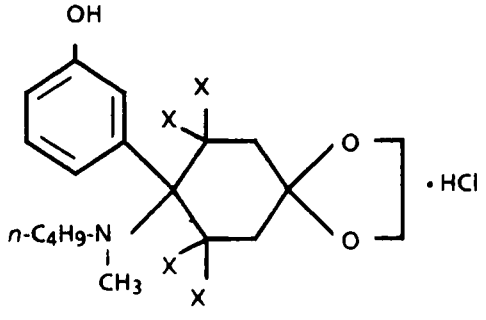
The title compound, a 4-amino-4-arylcyclohexanone derivative with central analgesic activity, was labeled with tritium at the C-7 and C-9 positions. Deuterium labeled intermediates were used as models for developing isotope exchange and synthetic procedures. Deuterium and tritium labeled title compounds were obtained in five steps with overall yields of 18-22% from 1,4-dioxaspiro[4,5]-decan-8-one and 3-bromophenol.

Key Words: Synthesis, isotope exchange, deuterium, tritium, 4-amino-4-arylcyclohexanone, analgesic, 1,4-dioxaspiro[4,5]decan-8-one

INTRODUCTION

The title compound *1c* (1) is a member of a group of 4-amino-4-arylcyclohexanone derivatives which exhibit interesting analgesic activities (1-4). Compound *1c* was selected as a candidate with potential clinical utility, and we undertook the synthesis of a radioactive form of the compound for conducting drug metabolism and disposition studies in test animals.

1 *a*) X = ^{2}H
b) X = ^{3}H
c) X = ^{1}H



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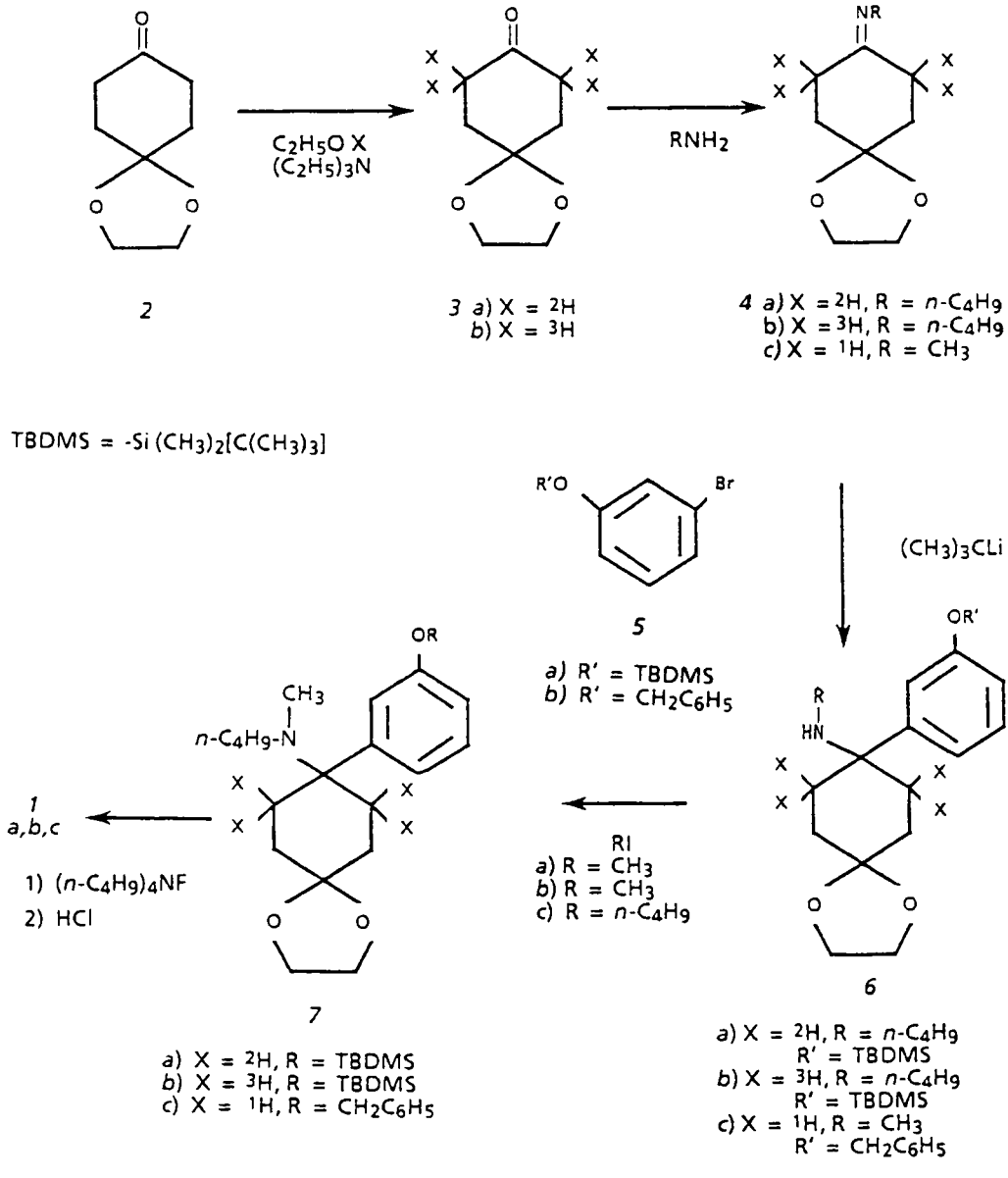
Scheme 1



DISCUSSION AND RESULTS

Compound *1c* was first synthesized from 3-methoxybenzyl alcohol with an overall yield of 5.5% in a lengthy fourteen-step process (1,3) designed to accommodate the preparation of analogs with a wide variety of substituents in the aryl and amino groups. We developed a more efficient four-step route

subsequently for specifically preparing *1c* from 1,4-dioxaspiro[4,5]decan-8-one (2) and this route has been modified to permit synthesis of labeled *1* as shown in Scheme 1. We took advantage of the enolizable protons at the C-7 and C-9 positions of *2*, which could be readily exchanged with tritium from tritiated water. The tritium labels would then be rendered nonexchangeable after removal of the ketone function later in the reaction sequence. Deuterium was used in a model study. The ketone 2 was found to equilibrate rapidly with 95% EtOD in D_2O in the presence of triethylamine at room temperature to afford deuterium labeled ketone *3a*. The same reaction, when carried out in absolute ethanol containing 3% tritiated water, gave tritium labeled ketone *3b*.

For conventional synthesis of unlabeled *1c*, the ketone *2* (1,5) is converted by treatment with a large excess of methylamine to produce the imine *4c*, which undergoes addition of the aryllithium derived from 3-benzyloxyphenyl bromide to afford the amine *6c*, followed by N-alkylation with *n*-butylamine to give the tertiary amine *7c*. The arylation reaction would stabilize the labile labels when deuterated and tritiated ketone *3a* and *3b* are used in the same reaction sequence. However, during the Schiff base formation which would precede arylation, methylamine would function as both a base catalyst and a proton supplier to promote reverse exchange and isotopic dilution. The effect would be amplified when the labeled ketones are subjected to prolonged exposure to a large excess of methylamine, the conditions required for the imine formation to proceed to completion. We found that the isotopic dilution through back exchange could be minimized by reversing the order of introduction of the two N-alkyl groups. Deute ated ketone *3a* was treated with *n*-butylamine in an aprotic solvent, dry benzene, to afford the n-butyl imine *4a*. It was found that a two-fold excess of *n*-butylamine sufficed, and the higher boiling butylamine (in comparison to methylamine) made it possible to carry out the reaction at reflux with simultaneous azeotropic distillation of water formed, thus removing the latter from the reaction mixture and reducing the proton source for back exchange. The loss of deuterium under these conditions, though not totally eliminated, was limited to approximately one-third of what had been incorporated into *3a*.

During the addition of aryllithium to the imine *4c*, the benzyl group was used as a protecting group for the phenol function. The benzyl group was removed by means of catalytic hydrogenolysis at elevated pressures in the final step to regenerate the phenol function in *1c*. In order to avoid such somewhat hazardous conditions during radiosynthesis, we used the *t*-butyldimethylsilyl protecting group, which could be more readily removed under milder conditions. 3-(*t*-Butyldimethylsilyloxy)phenyl bromide (*5a*) was prepared from 3-bromophenol according to known procedures (6) and lithiated with *t*-butyllithium (7). Addition of the aryllithium derived from *5a* to the deuterated imine *4a* gave the deuterated butylamine *6a*.

In a model experiment to study the course of the mono- and dimethylation of the *n*-butylamine *6a*, the benzyloxy analog *8* was treated with an excess of methylamine. Monomethylation was found to proceed much faster than the addition of a second mole of methyl iodide to form the quarternary methiodide *9*. A semilog plot of percentages of remaining starting material against time (Figure 1) showed that the reactions are pseudo-first order and that the reaction half-times for formation of tertiary (*7c*) and quarternary (*9*) amines are 10 minutes and 6.5 hours, respectively. These data indicated that monomethylation could be brought to completion before the formation of appreciable amounts of methiodide. Indeed, when *6a* was allowed to react with a six-fold excess of methyl iodide at room temperature for 1.5 hours, the desired tertiary amine (*7a*) was obtained with negligible dimethylation. Traces of unreacted *6a* were readily removed by column chromatography. Treatment of *7a* with tetrabutylammonium fluoride and anhydrous hydrogen chloride, in that order, removed the silyl blocking group and produced deuterium labeled *1a*. The overall yield was 22.2% based on *3a* used, and two-thirds of the deuterium content of *3a* remained in *1a* as determined with nuclear magnetic resonance spectroscopy and mass spectral analyses. By means of the same route, tritium labeled *1b* was obtained in 18.2% chemical yield from tritium labeled 1,4-dioxaspiro [4,5]decan-8-one (*3b*). The specific activities of *3b* and *1b* were 304.1

mCi/mmol and 234.5 mCi/mmol, respectively. Thus, only 23% of the tritium labels in *3b* was lost during the imine formation.

Figure 1

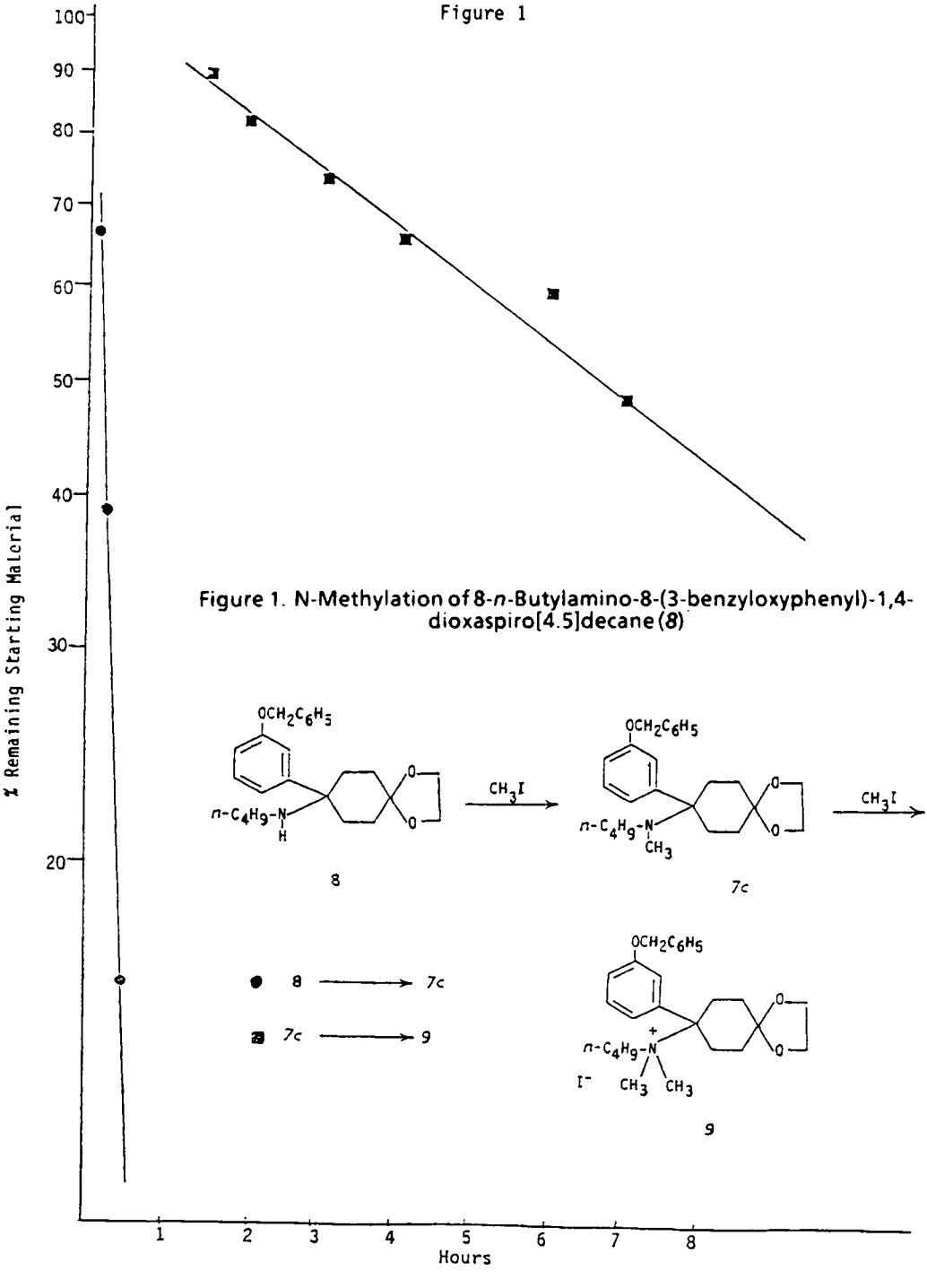


Figure 1. N-Methylation of 8-*n*-Butylamino-8-(3-benzyloxyphenyl)-1,4-dioxaspiro[4.5]decane (*8*)

EXPERIMENTAL SECTION

Radioactivity determinations were carried out with a Packard Tri-Carb Model 2425 liquid scintillation spectrometer by means of the external standard method. Diotol (Burdick & jackson) was used as the scintillation cocktail. Thin layer chromatographic (TLC) analyses were clone on 2.5 cm x 10 cm glass plates precoated with a 250 um layer of Silica Gel GF (Analtech). Developed zones were visualized by means of exposure to iodine vapor. Radioactive zones were detected with a Vanguard Model 880 Autoscanner equipped with a Model 885 Glass Plate Scanner. Ultraviolet spectra were obtained with a Cary Model 15 spectrometer. Mass spectral analyses were carried out with a Varian Model CH-5 spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian A60A or a Varian CFT-20 spectrometer. Melting points were determined with a Thomas-Hoover Unimelt apparatus and were uncorrected.

Deuterium and Tritium Labeled 1,4-Dioxaspiro[4,5]decan-8-one,(*3a* and *3b*)

A solution of 500 mg (3.2 mmol) of the ketoketal *2* and 0.1 ml of anhydrous triethylamine in 3 ml of 95% EtOD in D_2O was kept at room temperature for 16 hours. The solution was concentrated at 32°C and 20 torr. The residue was dissolved in 2 ml of benzene and the solution was again concentrated. This was repeated once more to remove all protic solvents and base, and afford the crystalline *7a* in quantitative yield; TLC (3% v/v MeOH in CH_2Cl_2) showed single component identical to authentic *2*, Rf 0.52; NMR (in $CDCl_3$): a 4.05 (s,4H, $OC\underline{H}_2C\underline{H}_2O$), 2.45 (t,J = 7 Hz, 1.2H, $-C\underline{H}_2-\overset{O}{\overset{\|}{C}}-C\underline{H}_2-$), 2.0 (t collapsing into s, J = 7 Hz, 4H, $-C\underline{H}_2-\overset{O\ O}{\overset{\backslash\ /}{C}}-C\underline{H}_2-$), therefore C-7 and C-9 positions 65% deuterated (theory 80%).

Similarly, 500 mg of *2* was kept in 2.9 ml of absolute ethanol containing 0.1 ml of triethylamine and 0.1 ml of tritiated water (100 Ci)* at room

*The tritium exchange reaction was carried out by Amersham Corp.

temperature for 24 hours to afford 1.75 Ci of *3b*, sp. act. 3.75 mCi/mg. A portion of this material was recrystallized from hexane with non-labeled 2 to afford *3b* of sp. act. 194.2 μCi/mg in 82.5% recovery; TLC (2.5% v/v MeOH in CH_2Cl_2) showed a single radioactive zone with identical Rf as authentic *2*.

Reaction of Amine *8* with Methyl Iodide

A mixture of 0.5 g of *8* (mp 160-164°C) (1.26 mmol), 1.0 g of methyl iodide (7.05 mmol), 1.0 g of anhydrous sodium carbonate, and 5 ml of dimethylformamide was stirred at room temperature. One-half milliliter aliquots were removed from the mixture at selected intervals, purged with nitrogen gas to remove methyl iodide, and partitioned with 25 ml each of benzene and water. The organic phase was washed with water and dried over anhydrous sodium sulfate. This solution was subjected to gas chromatographic (GC) analysis to quantify contents of unreacted *8* and the

Table 1. N-Methylation of Compound *8*.

Time (hr)	Percentage		
	8	*7c*	*9**
0.07	66	33	-
0.25	39	61	-
0.5	16	81	-
0.75	6	94	-
1.5		90	
2.0		82	
3.0	-	74	
4.0	-	66	34
6.0	-	60	40
7.0	-	49	51

*Detected as the pyrolysis product under the GC conditions.

monomethylated *7c*. This sample preparation procedure removed water-soluble *9* in the aqueous phase. To determine total product compositions of longer reaction time samples containing *9*, aliquots of the reaction mixture were purged with nitrogen gas, the residues dissolved in 10 ml of chloroform, and the resulting solutions were directly analyzed by GC.

GC data were obtained on a Hewlett-Packard Model 5840A gas chromatograph with a column (45 cm x 3 mm i.d.) of 3% UCW-982 on 80-100 mesh Chromosorb W, a nitrogen carrier gas (flow rate 50 mL/min), a hydrogen flame ionization detector and an oven temperature of 24°C. Compounds had the following retention times: *6c*, 2.37 min; *8*, 3.54 min; *7c*, 3.96 min, and 8-(3-benzyloxyphenyl)-1,4-dioxaspiro[4,5]dec-7-ene (formed by pyrolysis of *9* under the GC conditions), 1.90 min. Results are shown in Table 1.

Deuterium and Tritium Labeled 8-N-n-Butyl-N-methylamino-8-[3-(t-butyldimethylsilyloxy)phenyl]-1,4-dioxaspiro[4,5]decane (*7a* and *7b*)

a) Imine *4* from Ketoketal *3*

A mixture of 1.472 g of *n*-butylamine (20.12 mmol) and 1.562 g of *7a* (9.75 mmol, 65% deuterated at the C-7 and C-9 positions) in 20 ml of dry benzene was refluxed with stirring under a Dean-Stark water trap for 1.75 hour. Trapped water and distilled benzene were drained from the trap until 18 ml was collected. The remaining mixture was concentrated, first at 32°C and 20 torr, and then at room temperature and 0.2 torr to give the imine *4a* as an oil, which was used without further purification in the next step. Prolonged storage of this material caused severe discoloration of the initially colorless oil.

Similarly,tritium labeled imine *4b* was prepared from 1.562 g of *3b* (10.0 mmol, sp. act. 194.2 μCi/mg). Tritiated *4b* was used without delay in the nextstep.

b) Addition of Aryllithium to *4*

All glassware and syringes used in this reaction were predried at 120°C

and flushed with dry nitrogen gas during cooling, and the reaction was carried out under dry nitrogen gas. To a cold solution (0°C) of 3.59 g of *5a* (12.5 mmol) in 30 ml of dry benzene and 10 ml of hexane in a 100 ml round bottom flask, fitted with nitrogen gas inlet and outlet tubes through a silicon rubber septum, was added 6.6 ml of 1.9M *t*-butyllithium in pentane (12.5 mmol) by means of a syringe. The mixture was stirred at 0°C under dry N_2 for 45 minutes, and a solution of the imine *4a* described above, nominally 9.75 mmol, in 5 ml of hexane was added with a syringe. The ice bath was removed and the mixture was stirred at room temperature for 2 hours. The reaction was quenched by the addition of 25 ml of brine. After 5 minutes of stirring, the two-phased mixture was separated and the aqueous phase was extracted with 25 ml of benzene. The combined organic layers were washed with 25 ml of brine, dried over sodium sulfate, and concentrated at 32°C and 20 torr to give crude *6a* as a pale yellow oil, TLC (10% MeOH in CH_2Cl_2) Rf 0.39. This material was used without purification in the next step.

Tritium labeled *6b* was obtained in a similar manner from *4b* and *5a* and used without delay in the nextstep.

c) N-Methylation

A mixture of the amine 6a from above, nominally 9.75 mmol, 8.68 g of methyl iodide (3.8 ml, 61 mmol), and 4.34 g of anhydrous sodium carbonate (41 mmol) in 20 ml of dry dimethylformamide was stirred at room temperature for 1.5 hour. The almost solidified mixture was diluted with 100 ml of ether, filtered, and the cake was washed with ether. The combined filtrate and washes were concentrated at reduced pressure, and the residue was mixed with 100 ml of water and extracted twice with 100 ml of ether. The combined extracts were washed with 75 ml of brine, dried over sodium sulfate, and concentrated at 32°C and 20 torr to give 3.95 g of a yellow oil. The crude productwas chromatographed on a column of 180 g of silica gel packed in 5% MeOH in CH_2Cl_2. The column was eluted with 15 ml of CH_2Cl_2, 350 ml of 5% MeOH in CH_2Cl_2, and 750 ml of 10% MeOH in CH_2Cl_2. After a

forerun of 350 ml, the eluate was collected in 8 ml fractions at 2.25 minutes per fraction. Fractions 21 through 50 were combined and concentrated to afford 1.37g of *7a* (31.6% yield based on 3a used),TLC (10% MeOH in CH_2Cl_2) Rf 0.44.

Similarly, *6b* was monomethylated to give 3.74 g of crude *7b*, which after chromatographic purification afforded 1.15 g (26.5% yield based on *3b*) of tritium labeled *7b*.

Deuterium and Tritium Labeled 8-N-*n*-Butyl-N-methylamino-8-(3-hydroxyphenyl)-1,4-dioxaspiro[4,5]decane Hydrochloride (*1a* and *1b*)

A mixture of 1.365 g of *7a* (3.15 mmol), 5 ml of dry tetrahydrofuran, and 8.4 ml of 0.75 M solution of tetrabutylammonium fluoride (6.3 mmol) in tetrahydrofuran was stirred at room temperature for 1 hour. Twenty-five ml of brine was added. The mixture was stirred for 5 minutes and extracted twice with 50 ml of ether. The combined extracts were washed with 25 ml of brine, dried over sodium sulfate, and concentrated to give 1.217 g of thick pale yellow syrup. The crude material was dissolved in 25 ml of ether and treated with anhydrous hydrogen chloride in ether. The resulting precipitates were filtered, washed with ether and very briefly air dried. The hygroscopic solids were recrystallized from a mixture of 1.2 ml of methanol and 4.5 ml of ether to afford 771 mg of *1a*, colorless crystals, 22.2% yield based on *3a*; m.p. 205-206.5°C; TLC (10% MeOH in CH_2Cl_2) showed a single component identical to authentic *1*, Rf 0.32. Mass spectral and NMR analyses showed the material was 44% deuterated at the C-7 and C-9 positions. Since the starting material *3a* was 65% deuterated at these positions, approximately one-third of the labels in *3a* was lost during the imine formation.

Similarly, from 1.151 g of *7b*, there was obtained 649 mg of *1b*, 18.2% yield based on *3b*; m.p. 205-206°C; TLC (10% MeOH in CH_2Cl_2) showed a single radioactive component corresponding in Rf to authentic *1c*; sp. act. 65.9 μCi/mg; UV λmax in EtOH 220 nm (ε 6,650), 281 nm (ε 2,700). Anal.-

calculated for $C_{19}H_{30}ClNO_3$ (MW 355.90): C, 64.12; H, 8.50; N, 3.94; Cl, 9.96; found: C, 64.47; H; 8.10; N, 3.65; Cl, 10.10. A comparison of the specific activities of the starting material *3b* (304.1 mCi/mmol) and the product *1b* (234.5 mCi/mmol) indicates that 23% of the tritium labels in *3b* was lost during the imine formation.

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