NOVEL SELECTIVE CATALYTIC REDUCTION WITH TRITIUM: SYNTHESIS OF THE $GABA_A$ RECEPTOR RADIOLIGAND 1-(4-ETHYNYLPHENYL)-4-[2,3-$^3H_2$]PROPYL-2,6,7-TRIOXABICYCLO[2.2.2]OCTANE

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SUMMARY

Protection of the terminal alkyne function in 1-(4-ethynylphenyl)-4-(prop-2-enyl)-2,6,7-trioxabicyclo[2.2.2]octane with a trimethylsilyl group permits the selective catalytic reduction of the olefin moiety with tritium gas to give after deprotection 1-(4-ethynylphenyl)-4-[2,3-$^3H_2$]propyl-2,6,7-trioxabicyclo-[2.2.2]octane. The labeled product at high specific activity is an improved radioligand for the GABA-gated chloride channel of insects and mammals and the intermediate 4-[2,3-$^3H_2$]propyl-1-[4-[(trimethylsilyl)ethynyl]phenyl]-2,6,7-trioxabicyclo[2.2.2]octane is useful for studies on the metabolic activation of this selective proinsecticide.

Key Words: $GABA_A$ receptor radioligand, trioxabicyclooctane insecticide, selective hydrogenation, tritium labeling

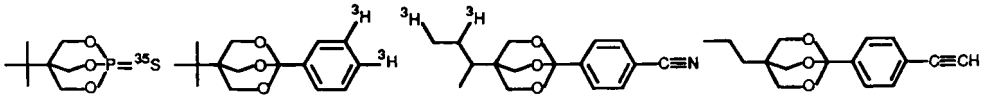
INTRODUCTION

The development of suitable radioligands was a major step in understanding the γ-aminobutyric acid (GABA)-gated chloride channel of the mammalian brain. Recognition of the toxic action of 2,6,7-trioxabicyclo[2.2.2]octanes (TBOs) 1 and 2 as $GABA_A$ receptor antagonists and their radiolabeling[1] helped define the structural and functional relationships of the subunits of the $GABA_A$ receptor,[2] the target of lindane, toxaphene and the chlorinated cyclodiene insecticides.[3] Radioligands 1-3 among others have proved unsatisfactory for the insect receptor probably correlated in part to their low to moderate insecticidal activity.[2b,4] A systematic study of structure-insecticidal activity relationships among the TBOs revealed that the potency of 4 on houseflies exceeded that of 1 and 2 by >700 fold

0362–4803/91/070829–11$05.50

Received 1 March, 1991

and of 3 by 66 fold.[4,5] One requirement of a candidate radioligand for the binding site of an insecticide in insects is high insecticidal activity and another is radiolabeling at high specific activity.



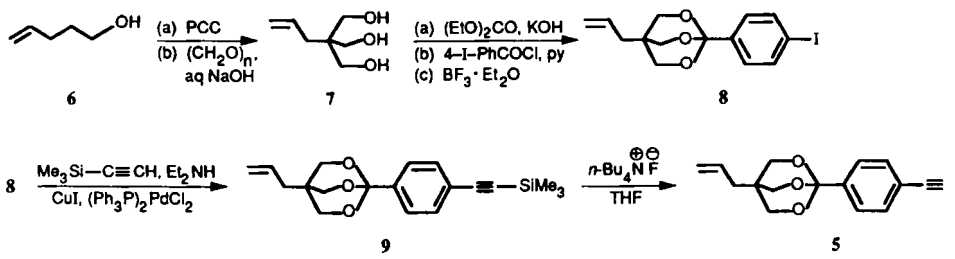
1 2 3 4

TBO 4 satisfies the requirement of high insecticidal potency.[5b] This report describes a novel selective method of catalytic reduction suitable for radiolabeling TBO 4 at high specific activity with $^3H_2$.

RESULTS AND DISCUSSION

The best methods for introducing ^3H into a molecule at the required high specific activity are metal hydride reducing agents (e.g. $NaBT_4$) or catalytic reduction with $^3H_2$ gas.[6] Lack of appropriate functionality in TBO 4 and previously prepared analogues ruled against the use of metal hydride reducing agents. Two possible approaches to radiolabeling TBO 4, each involving catalytic reduction of a suitable precursor with tritium gas, are reductive dehalogenation of a halophenyl derivative and reduction of a 4-propenyl analog. The reductive dehalogenation route was not successful in preliminary studies.* Accordingly 4-(prop-2-enyl)-TBO 5 was prepared as shown in Scheme 1. 4-Penten-1-ol (6) was oxidized with pyridinium chlorochromate[7] to 4-pentenal which upon treatment with formaldehyde underwent

Scheme I



6 7 8 9 5

*Attempts to reductively dechlorinate 4-t-butyl-1-(3,5-dichloro-4-ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octane or its (triisopropylsilyl)ethynyl analog under a variety of conditions always resulted in preferential reduction of the alkyne function.

hydroxymethylation and subsequent crossed Cannizzaro reaction to the triol (7).[8] Reaction with ethyl carbonate followed by pyrolysis afforded the 3-hydroxymethyloxetane[9] which was acylated with 4-iodobenzoyl chloride. Boron trifluoride catalyzed the rearrangement of the resultant oxetane ester to 1-(4-iodophenyl)-TBO 8.[9] This iodophenyl compound underwent palladium-catalysed coupling[10] with (trimethylsilyl)acetylene to form 1-[4-[(trimethylsilyl)ethynyl]phenyl]-TBO 9 which was desilylated[5b] to give 1-(4-ethynylphenyl)-TBO 5.

The introduction of $^3H_2$ into an ethynyl-containing compound such as 5 to give [$^3H_2$]4, via reduction of an olefin function without affecting the ethynyl moiety itself, is a potentially difficult process, and to our knowledge has not been reported. As a model we investigated procedures for selectively reducing the olefin function catalytically with H_2 by a method which would leave the ethynyl group intact. This is essential since the ethynyl group is necessary for high insecticidal activity.

Catalytic reduction of TBO 5 with H_2 under a variety of conditions always resulted in ethynyl reduction prior to olefin reduction. This was not unexpected since it is well known that under competitive conditions an alkyne is reduced preferentially because its higher heat of adsorption enables it to displace an olefin from the catalyst surface.[11] A survey of the literature failed to reveal any method for selective catalytic hydrogenation of alkenes in the presence of alkynes, i.e., a method that would permit reduction with hydrogen of TBO 5 to TBO 4.* The hypothesis was therefore examined that attachment of a suitable bulky substituent to the terminal alkyne function might make the alkyne less reactive to catalytic reduction. Somewhat surprisingly catalytic hydrogenation of the 4-(3,3-dimethylbut-1-ynyl)phenyl-TBO 10 (prepared from TBO 8-Scheme II) over a platinum catalyst in ethyl acetate-triethylamine led to a slow uptake of hydrogen to give

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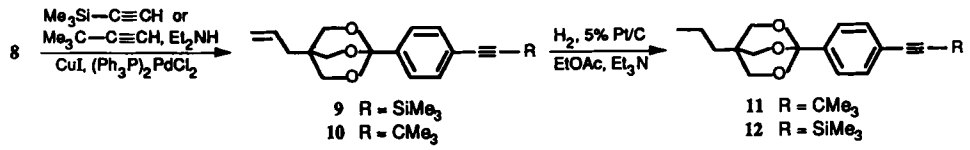
*Selective transformation of a double bond in the presence of a triple bond can be achieved if the triple bond is protected as the (alkyne)dicobalt(hexacarbonyl) complex by reduction with diimide or hydroboration but not by catalytic hydrogenation (for a relevant review, see Ben-Efraim[12]).

Scheme II



9 R = $SiMe_3$
10 R = CMe_3

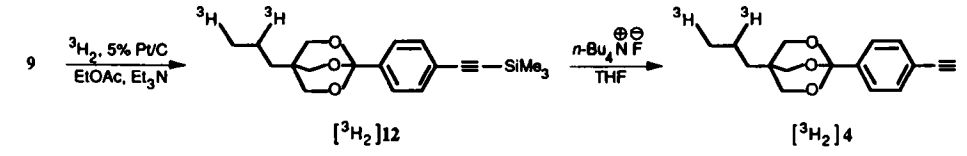
11 R = CMe_3
12 R = $SiMe_3$

TBO 11. After 4 h an 85% conversion was achieved with no evidence of alkynyl reduction. This result led to considering the protection of the ethynyl function with a trimethylsilyl group for two reasons. First, the trimethylsilyl group is unaffected by hydrogenation and is easily introduced and removed, important features for a radiolabeling procedure. Second, the [(trimethylsilyl)ethynyl]phenyl-TBO's such as 12 are a novel type of proinsecticide, i.e., they are only weakly active or inactive in their own right but are activated in the housefly by an oxidative process unknown as to mechanism and ultimate toxicant;[13] the metabolic fate of 12 and the possibility that the ethynyl compound is the activation product could be investigated with this radiolabeled [(trimethylsilyl)ethynyl]phenyl-TBO. Similar hydrogenation of TBO (9) gave after 4 h a quantitative conversion to TBO 12 (Scheme II). Again no reduction of the ethynyl group was observed [if hydrogenation was continued beyond 4 h traces of products from the reduction of the (trimethylsilyl)ethynyl group were evident].*

Selective reduction using this procedure with $^3H_2$ enabled quantitative conversion of TBO 9 to [$^3H_2$]TBO-12, achieved with a specific activity of 58.4 Ci/mmol (Scheme III). Examination of the ^1H and ^3H NMR spectra (Fig. 1) of [$^3H_2$]TBO 12 clearly indicates that T has been incorporated into the 4-propyl substituent. The ^3H NMR spectrum consists of only a multiplet at 0.40-0.55 ppm expected for the CH_2T-CHT-CH_2 group. The normal splitting pattern anticipated for CT-CT coupling from the simple addition is not observed; the complex multiplet that is found indicates uneven addition of tritium across the double bond and vinylic or allylic

*For a preliminary communication on silyl protecting groups for the ethynyl function permitting catalytic hydrogenation of 1° and 2° olefins under competitive conditions see Palmer and Casida[14].

Scheme III



[$^3H_2$]12 [$^3H_2$]4

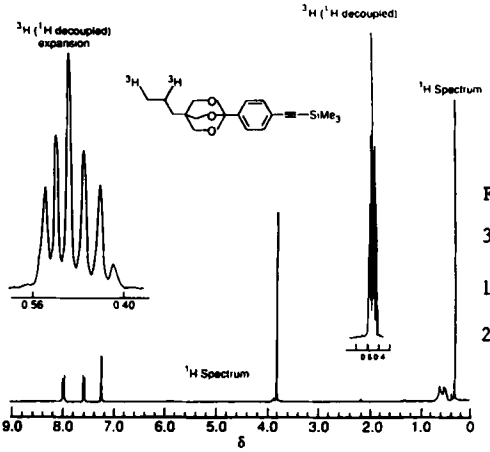


Figure 1

^3H and ^1H NMR spectra of 4-[2,3-$^3H_2$]propyl-1-[4-[(trimethylsilyl)ethynyl]phenyl]-2,6,7-trioxabicyclo[2.2.2]octane in C_6D_6

exchange, possibly prior to olefin addition; this is a well known phenomenon and would contribute to the high specific activity obtained.[15] The ^1H NMR spectrum contains identical signals to those for TBO 12 except that the 7H multiplet at 0.45-0.68 ppm corresponding to $CH_3CH_2CH_2$ has been replaced by a multiplet (approximately 5H) at 0.44-0.58 ppm. Subsequent deprotection of the (trimethylsilyl)ethynyl group with tetrabutylammonium fluoride[5b] afforded [$^3H_2$]TBO 4 in excellent yield with a specific activity of 58.4 Ci/mmol.

In conclusion, this is the first report of a method permitting the selective catalytic reduction with tritium of an olefin moiety in the presence of an alkynyl group.* The method reported here is simple, high yielding and allows labeling at high specific activity of [$^3H_2$]4 suitable as a candidate radioligand for the insect GABA receptor complex. The intermediate [$^3H_2$]12 also permits an investigation into the metabolic activation of this proinsecticide.[13]

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*The trimethylsilyl substituent has been used to protect terminal alkynes during the semi-hydrogenation of internal alkynes to olefins (for a relevant review, see Weber[16]).

EXPERIMENTAL

Catalytic reduction with tritium gas was accomplished at the National Tritium Labeling Facility (University of California, Berkeley). Tritium gas was purchased from Oak Ridge National Laboratory and contained 97.9% T_2, with the largest contaminant being DT (1.76%). Proton NMR spectra were obtained at 300 MHz with a Bruker WM-300 spectrometer for non-tritium containing compounds. NMR spectroscopy on tritium labeled compounds was carried out on an IBM Instruments Inc. AF 300 spectrometer (^3H at 320 MHz, ^1H at 300 MHz) using a $^3H/^1H$ 5-mm dual probe. Mass spectrometry utilized the Hewlett-Packard 5985 system with chemical ionization (230 eV with methane at 0.8 Torr). HPLC analyses were performed on a Waters Associates C-18 μ Bondapak column with a mobile phase of methanol-water-NH_4OH (30:9:1 v/v/v, 2 mL/min). Tritiated samples were counted with a Packard 1500 liquid scintillation counter.

Preparation of 2,2-bis-(Hydroxymethyl)-4-penten-1-ol (7). (a) 4-Penten-1-ol (6) (20g, 0.23 mol) was added dropwise to a stirred suspension of pyridinium chlorochromate (65 g, 0.30 mol) in dry dichloromethane under a nitrogen atmosphere. After stirring for 3 h at room temperature, the mixture was filtered through a florisil column with an ether wash and the combined solvent fractions were evaporated carefully to leave 4-pentenal (15g, 77%) as an unstable liquid which was not purified further. (b) 4-Pentenal (15g, 0.18 mol) was mixed with formalin (175 mL, 2 mol of formaldehyde) and NaOH (0.25 mol in 220 mL of water) and stirred overnight at 50°C. Following neutralization with dilute H_2SO_4 and evaporation to dryness, the portion of the residue soluble in i-propanol was subjected to gradual heating at 0.5 mm Hg (to complete the reduction step) and then stripped of products volatile at up to 110°C. Purification of the residue on silica, eluting with chloroform-methanol (99:1 v/v), gave (7) (10.5g, 40%) as a white solid mp 81-84°C, $[M+1]^+$ 147: ^1H NMR (CD_3COCD_3) δ 2.08-2.12 (dt, 2H, J=7.5, 1.0 Hz, C-CH_2-C), 2.96 and 3.73 (broad, 3H, OH x 3), 3.73 (s, 6H, CH_2O x 3), 4.96-5.07 (m, 2H, CH_2=C), 5.81-5.96 (ddt, 1H, J=17, 10, 7.5 Hz, C=CH-C).

Preparation of 1-(4-Iodophenyl)-4-(prop-2-enyl)-2,6,7-trioxabicyclo[2.2.2]-octane (8). (a) A mixture of (7) (10 g, 68.5 mmol), ethyl carbonate (8.1g, 68.5

mmol) and KOH (0.1 g in 5 mL of dry ethanol) was heated to reflux under nitrogen for 15 min. Ethanol was then distilled off at atmospheric pressure and distillation under reduced pressure afforded 3-hydroxymethyl-3-(prop-2-enyl)oxetane (5.5g, 63%) as an unstable liquid, bp 126-130°C (20 mm Hg): ^{1}H NMR ($CDCl_3$) δ 2.10 (t, 1H, J=6 Hz, OH), 2.42-2.47 (d, 2H, J=7.5 Hz, C-CH_2-C), 3.75 (d, 2H, J=6 Hz, $C\underline{H}_2OH$), 4.45 (AB, 4H, J_{AB}=5 Hz, CH_2OCH_2), 5.08-5.18 (m, 2H, CH_2=C), 5.70-5.85 (ddt, 1H, J=17, 10, 7.5 Hz, C=CH-C). (b) To a stirred solution of the above oxetane (2.3g, 18 mmol) and dry pyridine (2 mL) in dry dichloromethane (50 mL) under a nitrogen atmosphere at 0°C was added a solution of 4-iodobenzoyl chloride (5.0 g, 19 mmol). The mixture was stirred overnight at room temperature, then washed with water, dried (Na_2SO_4) and evaporated to leave 3-(4-iodobenzoyloxymethyl)-3-(prop-2-enyl)oxetane (6.4 g, 99%) as a residue which was not purified further: ^{1}H NMR ($CDCl_3$) δ 2.55 (d, 2H, J=7.5 Hz, C-CH_2-C), 4.42 (s, 2H, CH_2OCO), 4.50 and 4.58 (AB, 4H, J_{AB}=6.5 Hz, CH_2OCH_2), 5.12-5.20 (m, 2H, CH_2=C), 5.72-5.86 (ddt, 1H, J=17, 10, 7.5 Hz C=CH-C), 7.75 and 7.80 (AA'BB', 4H, J=8 Hz, aromatic). (c) Boron trifluoride etherate (0.65 mL) was added to a stirred solution of the above oxetane ester (6.4 g, 18 mmol) in dry dichloromethane (50 mL) under nitrogen at -70°C. The solution was allowed to warm to room temperature, quenched with dry triethylamine, evaporated to dryness, and partitioned between dichloromethane and water. The organic layer was dried (K_2CO_3) and evaporated and the residue purified on basic alumina. Elution with hexane-dichloromethane (4:1 v/v) afforded (8) (4.3 g, 67%) as white flakes mp 140-141°C, $[M+1]^+$ 359:^{1}H NMR ($CDCl_3$) δ 2.01 (d, 2H, J=7.5 Hz, C-CH_2-C), 4.08 (s, 6H, CH_2O x 3), 5.06-5.16 (m, 2H, CH_2=C), 5.56-5.70 (ddt, 1H, J=17, 10, 7.5 Hz, C=CH-C), 7.32 and 7.65 (AA'BB', 4H, J=8 Hz, aromatic).

Preparation of 4-(Prop-2-enyl)-1-[4-[(trimethylsilyl)ethynyl]phenyl]-2,6,7-trioxabicyclo[2.2.2]octane (9). A solution of (8) (2.4 g, 6.7 mmol), (trimethylsilyl)acetylene (2 mL, 20 mmol), bis(triphenylphosphine) palladium (II) chloride (50 mg) and cuprous iodide (10 mg) in dry diethylamine (60 mL) was stirred under a nitrogen atmosphere for 4 h at room temperature. The solution was evaporated and the residue partitioned between water and ether. The organic layer was separated, dried ($MgSO_4$) and evaporated to leave (9) (2.0 g, 91%) as light-

tan flakes mp 163-164°C, $[M+1]^+$ 329: ^1H NMR ($CDCl_3$) δ 0.22 (s, 9H, Me_3Si), 2.01 (d, 2H, J=7.5 Hz, C-CH_2-C), 4.09 (s, 6H, CH_2O x 3), 5.07-5.16 (m, 2H, CH_2=C), 5.57-5.71 (ddt, 1H, J=17, 10, 7.5 Hz, C=CH-C), 7.41 and 7.52 (AA'BB', 4H, J=8 Hz, aromatic).

Preparation of 1-(4-Ethynylphenyl)-4-(prop-2-enyl)-2,6,7-trioxabicyclo-[2.2.2]octane (5). Propenyl TBO 5, prepared from (9) and purified by procedures described for its tert-butyl analog[5b], was obtained as white needles mp 93-95°C, $[M+1]^+$ 257: ^1H NMR ($CDCl_3$) δ 2.02 (2H, d, J=7.5 Hz, C-CH_2-C), 3.07 (1H, s, C≡CH), 4.10 (s, 6H, CH_2O x 3), 5.12 (2H, m, CH_2=CH), 5.65 (1H, m, CH=CH_2), 7.47 and 7.57 (AA'BB', 4H, J=8 Hz, aromatic).

Preparation of 1-[4-(3,3-Dimethylbut-1-ynyl)phenyl]-4-(prop-2-enyl)-2,6,7-trioxabicyclo[2.2.2]octane (10). A solution of (8) (360 mg, 1 mmol), 3,3-dimethylbut-1-yne (1 mL), bis(triphenylphosphine) palladium (II) chloride (30 mg) and cuprous iodide (5 mg) in dry diethylamine (50 mL) was stirred vigorously under a nitrogen atmosphere for 4 h at room temperature. The mixture was evaporated and the residue partitioned between water and ether. The organic layer was separated, dried (K_2CO_3) and evaporated, and the residue purified on basic alumina. Elution with hexane-dichloromethane (4:1 v/v) afforded (10) (300 mg, 96%) as a white solid mp 153-154 °C, $[M+1]^+$ 313: ^1H NMR ($CDCl_3$) δ 1.30 (s, 9H, Me_3C), 2.01 (d, 2H, J=7.5 Hz, C-CH_2-C), 4.08 (s, 6H, CH_2O x 3), 5.06-5.16 (m, 2H, CH_2=C), 5.56-5.70 (ddt, 1H, J=17, 10, 7.5 Hz, C=CH-C), 7.35 and 7.49 (AA'BB', 4H, J=8 Hz, aromatic).

Hydrogenation of 1-[4-(3,3-Dimethylbut-1-ynyl)phenyl]-4-(prop-2-enyl)-2,6,7-trioxabicyclo[2.2.2]octane (10). A mixture of (10) (50 mg), dry triethylamine (0.1 mL) and 5% platinum on activated carbon catalyst (10 mg) in dry ethyl acetate (30 mL) was stirred vigorously under an atmosphere of hydrogen for 4 h at room temperature. The mixture was filtered through celite and the resultant solution evaporated. The residue was shown by NMR to consist of 15% of starting material and 85% of 1-[4-(3,3-dimethylbut-1-ynyl)phenyl]-4-propyl-2,6,7-trioxabicyclo-[2.2.2]octane (11). Purification on a basic alumina column eluting with hexane-dichloromethane (9:1 v/v) gave (11) (40 mg, 80%) as white flakes mp 163-164°C, $[M+1]^+$ 315: NMR ($CDCl_3$) δ 0.93 (t, 3H, J=7 Hz, CH_3CH_2), 1.15-1.30 (m, 4H, CH_2CH_2),

1.30 (s, 9H, Me_3C), 4.08 (s, 6H, CH_2O x 3), 7.35 and 7.50 (AA'BB', 4H, J=8 Hz, aromatic).

Preparation of 4-[2,3-$^3H_2$]Propyl-1-[4-[(trimethylsilyl)ethynyl]phenyl]-2,6,7-trioxabicyclo[2.2.2]octane ([$^3H_2$]12). Platinum on activated carbon catalyst (5%) (9 mg) and a solution of (9) (14 mg, 42.7 μmol) and dry triethylamine (13 μL) in dry ethyl acetate (5 mL) were exhaustively degassed in a microhydrogenation apparatus by the application of several freeze-pump-thaw cycles. Tritium gas was admitted to a pressure of 1 atmosphere and the substrate was thawed. Excess pressure was vented to the vacuum system, and the catalyst was added to the substrate. After the reaction mixture had been stirred at room temperature for 4 h, the substrate was frozen (liquid N_2) and the residual T_2 pumped away. The apparatus was extensively flushed with N_2, and then methanol (2 mL x 2) was added to the mixture and pumped off to remove any labile or dissolved tritium. The catalyst was filtered off and a portion of the filtrate was analyzed by radio HPLC. The radiochromatogram showed a single peak for [$^3H_2$]12 (2.5 Ci, 100%); specific activity 58.4 Ci/mmol: ^3H NMR (C_6D_6) δ 0.40-0.55 (m, CT-CT); ^1H NMR (C_6D_6) 0.28 (s, 9H, Me_3Si), 0.44-0.58 (m, 5H, CH_2-CH-CH_2), 3.77 (s, 6H, CH_2O x 3), 7.56 and 7.96 (AA'BB', 4H, J=8 Hz, aromatic).

Preparation of 4-Propyl-1-[4-[(trimethylsilyl)ethynyl]phenyl]-2,6,7-trioxabicyclo[2.2.2]octane (12). Using an identical hydrogenation procedure to that described above, replacing tritium with hydrogen and using a similar apparatus, (9) was converted quantitatively to (12) (exhibiting identical physical properties to an earlier sample prepared by a different route[5b]): ^1H NMR (C_6D_6) δ 0.28 (s, 9H, Me_3Si), 0.45-0.68 (m, 7H, $CH_3CH_2CH_2$) 3.77 (s, 6H, CH_2O x 3), 7.56 and 7.96 (AA'BB', 4H, J=8 Hz, aromatic).

Preparation of 1-(4-Ethynylphenyl)-4-[2,3-$^3H_2$]propyl-2,6,7-trioxabicyclo-[2.2.2]octane ([$^3H_2$]4). A solution of [$^3H_2$](12) (2.0 Ci, 34 μmol) in dry THF (5 mL) was stirred under a nitrogen atmosphere and tetrabutylammonium fluoride (34 μL of 1 M solution in THF) was added. The mixture was stirred for 1 h at room temperature then evaporated and the residue was partitioned between water and ether. The organic layer was separated, dried (K_2CO_3), filtered and evaporated, and the residue

was taken up in THF and analyzed by radio HPLC. The radiochromatogram showed the corresponding peak for [$^3H_2$](4) (2.0 Ci, yield 100%) (radiochemical purity 94%); specific activity 58.4 Ci/mmol; ^3H NMR (C_6D_6) δ 0.49-0.62 (m, CT-CT); ^1H NMR (C_6D_6) δ 0.44-0.69 (m, 5H, CH_2-CH-CH_2), 2.74 (s, 1H, C≡CH), 3.78 (s, 6H, CH_2O x 3), 7.50 and 7.95 (AA'BB', 4H, J=8 Hz, aromatic). For use as a candidate radioligand, [$^3H_2$]4 was obtained radiochemically pure (100%) by HPLC on a C-18 μBondapak column with methanol/water 1:1 v/v (saturated with ammonia gas) followed by chromatography on a small silica gel column with hexane containing 1% triethylamine.

Preparation of 1-(4-Ethynylphenyl)-4-propyl-2,6,7-trioxabicyclo[2.2.2]octane (4). Using an identical procedure to that described above, (12) was converted in almost quantitative yield to (4) (exhibiting identical physical properties to an earlier sample prepared by a different route[5b]): ^1H NMR (C_6D_6) δ 0.45-0.69 (m, 7H, $CH_3CH_2CH_2$), 2.74 (s, 1H, C≡CH), 3.78 (s, 6H, CH_2O x 3), 7.50 and 7.95 (AA'BB', 4H, J=8 Hz aromatic).

ACKNOWLEDGMENT

We thank Y. Deng of this laboratory for purification of the candidate radioligand and H. Morimoto and P.G. Williams of the National Tritium Labeling Facility (Lawrence Berkeley Laboratory, NIH Grant P41 RR 01237-06) for assistance in the radiosynthesis and ^3H NMR spectroscopy, respectively. This study was supported in part by NIH Grant PO1 ES00049.

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