SYNTHESIS OF TRITIUM LABELED MK-886, A LEUKOTRIENE BIOSYNTHESIS INHIBITOR; EMPLOYMENT OF EPIBROMOHYDRIN AS A MASKED ELECTROPHILIC ACETONE SYNTHON

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SUMMARY

1-(4-Chloro-[3-^{3}H]benzyl)-3-(*t*-butylthio)-α,α-dimethyl-5-(*i*-propyl)-indole-2-propanoic acid (10, MK-886) was prepared by catalytic tritium/halogen exchange on 1-(4-chloro-3-iodobenzyl)-3-(*t*-butylthio)-α,α-dimethyl-5-(*i*-propyl)-indole-2-propanoic acid (9). Compound 9 was prepared by a synthesis converging at the indole benzylation step. The required indole 4 was prepared by means of a Fischer indole synthesis employing the highly functionalized unsymmetrical ketone 3. Ketone 3 was efficiently made in three steps using epibromohydrin as a masked electrophilic acetone synthon. The halogenated benzyl bromide moiety 7 was prepared in three steps from 1-chloro-2-iodo-4-(trifluoromethyl)-benzene.

Key Words: Tritium, indole, acetone synthon, tritium/halogen exchange.

INTRODUCTION

1-(4-Chlorobenzyl)-3-(*t*-butylthio)-α,α-dimethyl-5-(*i*-propyl)-indole-2-propanoic acid (MK-886) is a novel, orally active leukotriene biosynthesis inhibitor, exhibiting potent activity both *in vitro* and *in vivo*.[1] Inhibition of leukotriene biosynthesis may be a therapeutic approach to various human diseases.[2]

Compound 10 was required in radiolabeled form at high specific activity (>10 Ci/mmol) for cellular binding studies. The synthesis of 10

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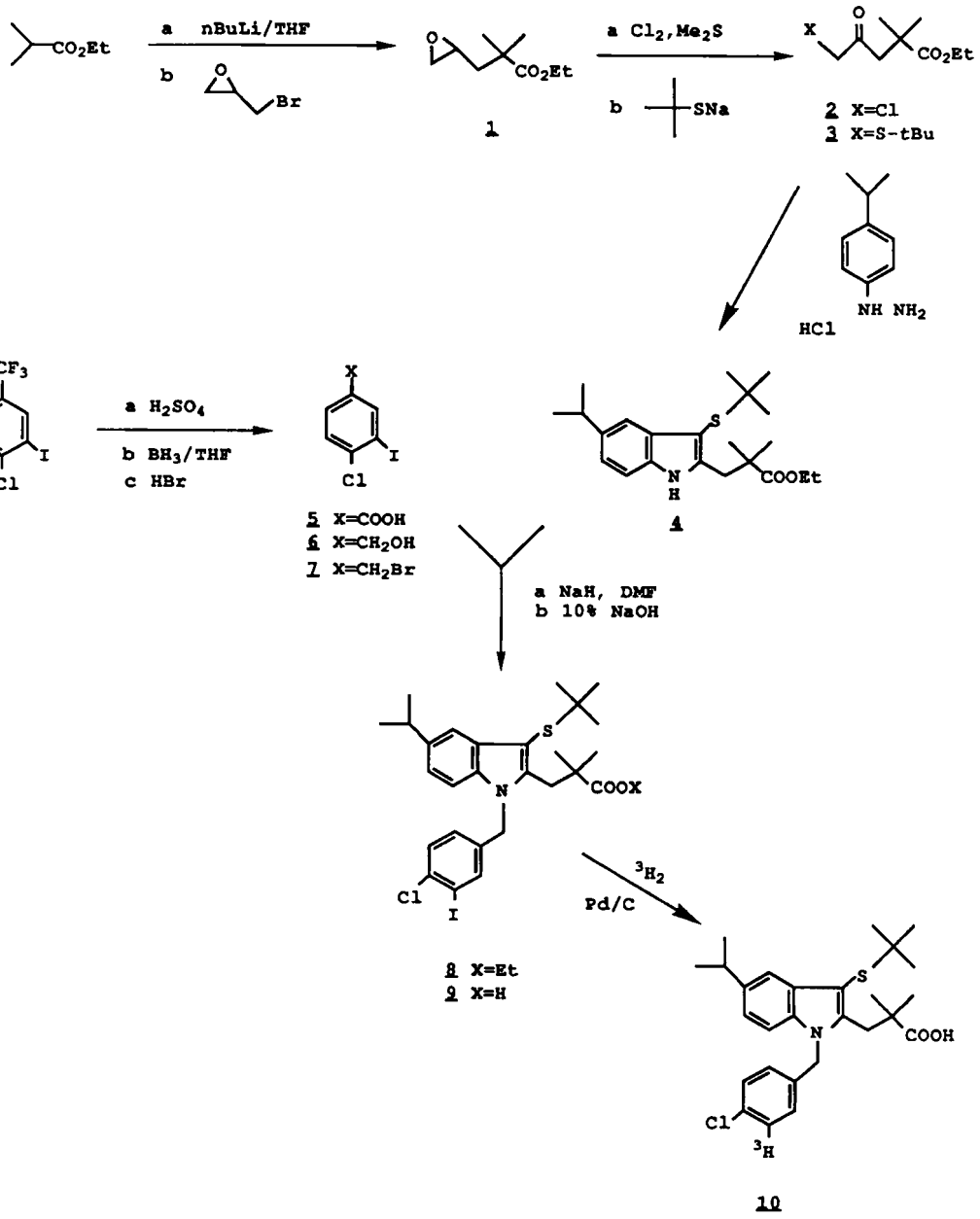
was accomplished (Scheme I) by benzylation of the indole 4 obtained through a Fischer indole synthesis employing ketone 3 which was obtained by a unique use of epibromohydrin as a masked electrophilic acetone synthon. The tritium label was introduced in the last step by catalytic tritium halogen exchange.

SCHEME I



DISCUSSION

The synthesis of compound 10 is shown in Scheme I. Synthesis of the ketone 3 required for the Fischer indole synthesis of 4 was envisioned as a 1,4-dicarbonyl synthesis, for which electrophilic acetone synthons ($CH_3COCH_2^+$) are often key intermediates. However, the preparation of the most commonly used acetone synthon, methoxyallyl bromide, is less than satisfactory as it involves high temperature pyrolysis, which produces the compound in low yield as an inseparable isomeric mixture[3,4,5]. Other recent acetonylating reagents are not without difficulties of their own. 3-Chloro-2-(trimethylsilyloxy)-1-propene[6] requires a multistep preparation, and the preparation of 2-(chloromethyl)-3,5-dioxahex-1-ene[7] requires careful temperature regulation and distillation. Moreover, in our case, the product of the acetonylation reaction would require further functionalization to allow the preparation of 3. What we required was a 1,3-dielectrophilic acetone synthon ($^+CH_2COCH_2^+$) suitable for elaboration into the desired unsymmetrical ketone. This was accomplished by reaction of the lithium enolate of ethyl isobutyrate with epibromohydrin to give the epoxide 1. Although Lewis acid rearrangement of terminal epoxides is known to give aldehyde preferentially, the little-used procedure of Olah,[8,9] employing chlorine and dimethylsulfide, in contrast successfully converted the epoxide into the desired chloroketone 2 in 59% overall yield. The chlorine was then displaced with t-butyl thiol, giving the desired unsymmetrical ketone 3 in 75% yield. Compound 3 was converted into indole 4 in 40% yield by the Fischer indole synthesis. During the preparation of this manuscript, another synthesis of MK-886 was published[15]. This synthesis involved a Fischer indole synthesis using ketone 3 and employed 2,3-dichloro-1-propene as an acetone synthon.

The halogenated benzyl bromide derivative 7 was prepared in three steps beginning with 1-chloro-2-iodo-4-(trifluoromethyl)benzene. The

conversion of this compound to the carboxylic acid 5 was effected in 90% yield using 10% oleum[12]. Borane reduction of the acid gave the corresponding benzyl alcohol 6 in 58% yield[13]. The bromide 7 was prepared in 32% yield from the alcohol using 48% HBr[14].

The benzyl bromide derivative 7 was used to alkylate the indole 4 in DMF with NaH, producing 8 in 68% yield, the ester function of which was hydrolyzed with aqueous NaOH to give the acid 9 in 82% yield. Beginning with 9, the tritium labeled compound 10 was produced in the key iodine/tritium exchange step using 10 Curies of tritium gas. A 23.2 mCi quantity of 10 was obtained after HPLC purification. The radiochemical purity was 99.2% (HPLC), the specific acitivity was 20 Ci/mmol (CI/MS) and both ^{1}H and ^{3}H-NMR indicated specific labeling at the intended position. Notably, there was no dechlorination of the benzyl ring detected as a result of the exchange procedure.

EXPERIMENTAL

General

Ethyl isobutyrate, epibromohydrin, 4-isopropylphenylhydrazine hydrochloride hydrate and sodium hydride were purchased from Aldrich Chemical Co. (Milwaukee, WI). 1-Chloro-2-iodo-4-(trifluoromethyl)benzene was purchased from Lancaster Synthesis, Windham, NH). 10% Oleum was prepared by mixing 9 parts concentrated sulfuric acid with 1 part fuming sulfuric acid. No-carrier added tritium gas (10 curies) was obtained from DuPont/NEN (Boston, MA). 5% Pd/C was purchased from Engelhard (Newark, NJ). All solvents used were HPLC grade or better.

HPLC radioactivity was monitored with either a Ramona Radioactivity Detector using Tru-Count (IN-US, Fairfield, NJ) scintillation cocktail, or a Radiomatic Flo-One Radioactivity Detector using Ready Safe cocktail (Beckman Instruments). Proton NMR spectra were acquired on either a Bruker 350 instrument (250 MHz) or a Bruker AM400 (400 MHz); tritium NMR spectra (426 MHz) were obtained on the latter instrument. Low resolution

mass spectra were obtained on a Finnegan 1020 instrument using direct probe chemical ionization. Elemental analyses are within 0.4% of the calculated values.

Ethyl 2,2-Dimethyl-4,5-epoxypentanoate (1)

A solution of 21 mL of ethyl 2-methylpropanoate (0.156 mol) in 50 mL of THF at -78°C was added to a solution containing 25.2 mL of diisopropylamine (0.180 mol) and 62.4 mL of 2.5 M n-butyllithium in hexane (0.156 mol). The reaction mixture was stirred for 30 minutes at -78°C. The resulting enolate solution was slowly added *via* cannula to 16 mL of epibromohydrin (0.180 mol) in 150 mL of THF at -78°C. The solution was allowed to reach room temperature over 4 hr. Saturated aqueous ammonium chloride solution was added and the solution was stirred for 15 minutes. The product was extracted into ethyl acetate and the organic layer was washed with water, then with brine. The organic layer was separated and dried over $MgSO_4$. TLC of the solution (Analtech GHLF silica gel, 9:1 hexane/ethyl acetate) gave a spot by UV with an R_f of 0.3. The product was purified by flash chromatography (Baker 40-60 mesh silica gel, hexane with 0-5% ethyl acetate step gradient), giving 18 g (60%) of the desired product 1 as an oil, which was used directly in the next step. ^1H NMR (250 MHz, $CDCl_3$) δ4.15 (q, J=7 Hz, 2H, $-CO_2\underline{CH}_2CH_3$), 2.95 (m, 1H, epoxide $\underline{CH}$-CH_2-), 2.73 (q, 1H, epoxide C-$\underline{H}$), 2.4 (q, 1H, epoxide C-$\underline{H}$) 1.75 (q, 2H, $-\underline{CH}_2$-$C(Me)_2$-), 1.3 (q, 6H, $-C(\underline{CH}_3)_2$-), 1.1 (t, J=7 Hz, 3H, $-CO_2CH_2\underline{CH}_3$).

Calcd. for $C_9H_{16}O_3$: C, 62.77 H, 9.36.

Found: C, 62.46 H, 9.44.

Ethyl 5-chloro-2,2-dimethyl-4-oxopentanoate (2)

Ethyl 5-chloro-2,2-dimethyl-4-oxopentanoate was prepared in 98% yield from 1 using chlorine and dimethylsulfide following the procedure of Olah[8] and the resulting oil was used without further purification in the

next step. ^{1}H NMR (250 MHz, $CDCl_3$,) δ 4.12 (q, J=7 Hz, 2H, $-CO_2\underline{CH}_2CH_3$), 4.08 (s, 2H, Cl-$\underline{CH}_2$), 2.85 (s, 2H, $-\underline{CH}_2C(Me)_2-$), 1.26 (s, 6H,$-C(\underline{CH}_3)_2-$), 1.24 (t, J=7 Hz, 3H,$-CO_2CH_2\underline{CH}_3$).

Calcd. for $C_9H_{15}O_3Cl$: C, 52.31 H, 7.32.

Found: C, 52.17 H, 7.40

Ethyl 2,2-dimethyl-5-(*t*-butylthio)-4-oxopentanoate (3)

To an ice-cooled mixture of 0.84 g of 80% sodium hydride (28 mmol) in 100 mL of dry THF was added 3.24 mL of t-butyl thiol (28 mmol). The reaction was warmed to ambient temperature and stirred until hydrogen evolution stopped. A solution containing 5.0 g of compound 2 (24 mmol) in 10 mL of THF was added slowly, causing an exothermic reaction. The reaction mixture was stirred 20 minutes at room temperature, then heated for 20 minutes at 60°C. Ethyl acetate was added and the organic layer washed with water and brine. The organic layer was separated and dried over $MgSO_4$. The solvent was removed *in vacuo*, and TLC of the crude product (Analtech GHLF silica gel, 9:1 hexane/ethyl acetate visualized w/$KMnO_4$) showed a spot at R_f = 0.4. The crude product was purified by flash chromatography (Baker 40-60 mesh silica gel, hexane with 0-3% ethyl acetate step gradient) to give 4.7 grams (75%) of 3 as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.11 (q, J=7 Hz, 2H, $-CO_2\underline{CH}_2CH_3$), 3.25 (s, 2H, t-butyl-S-$\underline{CH}_2$-), 2.91 (s, 2H,$-\underline{CH}_2C(CH_3)_2-$), 1.29 (s, 9H, $-C(\underline{CH}_3)_3$), 1.20 (s, 6H,$-CH_2C(\underline{CH}_3)_2-$), 1.10 (t, J=7 Hz, 3H, $-CO_2CH_2\underline{CH}_3$).

Calcd. for $C_{13}H_{24}O_3S$: C, 59.96 H,9.29

Found: C, 59.59 H, 9.33

Ethyl 3-(*t*-butylthio)-α,α-dimethyl-5-(*i*-propyl)-1H-indole-2-propanoate (4)

A solution of 5.0 grams of 4-isopropylphenylhydrazine hydrochloride hydrate (26.7 mmol) and 3.0 grams of 3 (11.5 mmol) in 150 mL of isopropanol was refluxed for 24 hours. The isopropanol was removed by

evaporation and replaced with ethyl acetate. The organic solution was washed with 5% aqueous sodium bicarbonate solution until basic, then with water, and finally with brine. The organic layer was separated and dried over sodium sulfate. TLC (Analtech GHLF silica gel, 9:1 hexane/ethyl acetate) showed the product at R_f= 0.85, visualized with Van Urk's reagent.[16] The crude product was purified by flash chromatography (Baker 40-60 mesh silica gel, hexane with 0-10% ethyl acetate step gradient) to give 2.0 grams (40%) of compound 4 as an oily solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.15 (s, 1H, -NH), 7.70 (s, 1H, C4-H), 7.30 (d, J=10 Hz, 1H, C7-H), 7.10 (d, J=1 Hz, 1H, C6-H), 4.20 (q, J=7 Hz, 2H, $-CO_2CH_2CH_3$), 3.22 (s, 2H, $-CH_2C(CH_3)_2-$), 2.25 (t, J=7 Hz, 3H, $-CO_2CH_2CH_3$), 1.28 (s, 9H,$-S-C(CH_3)_3$), 1.15 (s, 6H, $-C(CH_3)_2$).
Calcd. for $C_{22}H_{33}O_2NS$: C, 70.36 H, 8.86.
Found: C, 70.20 H, 8.96.

4-Chloro-3-iodobenzoic acid (5)

A suspension of 6.00 grams of 1-chloro-2-iodo-4-(trifluoromethyl)benzene (19.58 mmol) in 10% oleum was stirred at 60 °C for 10 minutes, then at 75 °C for 3 hours. The resulting dark brown solution was cooled to room temperature, then poured into an ice/water mixture. The resulting tan precipitate was isolated by filtration and dissolved in 100 mL of 30% (w/w) aqueous sodium hydroxide. The basic solution was extracted twice with 100 mL of chloroform. The aqueous layer was decolorized with 100 mg of activated charcoal, then cooled to 0°C. Concentrated aqueous HCl was added dropwise to pH 1. The resulting precipitate was collected by filtration, then dried *in vacuo* at 60°C for 24 hours, giving 4.99 grams of 5 (90%) as a white powder; m.p. 218-219°C (lit. 216-217°C)[17]. This product was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ8.57 (d, J=1.7, 1H, C2-H), 8.00 (dd, J=8.3, 1.7, 1H, C6-H), 7.55 (d, J=8.3, 1H, C5-H). Mass spectrum(CH_4): m/z 285 ($(M+H)^+$, 33), 283(M^+, 100), 267 $(M+H-H_2O)^+$, 10),265(25).

4-Chloro-3-iodobenzyl alcohol (6)

To a solution of 1.00 gram of 5 (3.54 mmol) in 10 mL of dry THF at 0°C was added 10.0 mL of 1.0 M borane/THF solution. The cooling bath was removed and the reaction mixture was stirred for 3 hours, at which time TLC (Merck F254 silica gel, 100% methylene chloride, UV at 254 nm) showed almost complete reaction. The excess borane was quenched with 10 mL of water, and the THF was removed in vacuo. The resulting solution was partitioned between 50 mL of ethyl acetate and 20 mL of saturated aqueous potassium carbonate solution. The separated aqueous layer was extracted twice with 50 mL of ethyl acetate. The organic layers were combined and the solvent was removed in vacuo, producing a pale yellow oil. The oil was dried under vacuum (0.05 mm Hg) for 16 hours, giving 552 mg of 6 (58%) which was used without further purification in the next step. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.87 (d, J=1.9, 1H, C2-H), 7.41 (d, J=8.2, 1H, C5-H) 7.27 (dd, J=8.1,1.9 Hz, 1H, C-6H), 4.64 (s, 2H, benzylic -CH_2-). Mass spectrum (CH_4): m/z 270 (M^+,10), 268 (M^+, 32), 253 ($(M-OH)^+$, 32), 251(100).

4-Chloro-3-iodobenzyl bromide (7)

A 1.0 mL quantity of 48% aqueous hydrobromic acid was added to 302 mg of 6 (1.12 mmol) and the solution was stirred at 75-80°C for 1.5 hours, after which time TLC (Merck F254 silica gel, 1:1 hexane/methylene chloride, UV at 254 nm) showed no remaining starting material. The reaction mixture was taken up into 20 mL of water, and powdered sodium bicarbonate was added until gas evolution ceased. The solution was extracted twice with 25 mL of ethyl acetate, and the organic extracts were combined and concentrated in vacuo to give 80 mg of 7 (32%) as an orange-red oil. The product was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.88 (d, J=2.1, 1H, C2-H), 7.40 (d, J=8.1, 1H, C5-H), 7.31 (dd, J=8.2, 2.1 Hz, 1H, C-6H), 4.38 (s, 2H, benzylic -CH_2-). Mass spectrum (NH_3, negative ion): m/z 333 ($(M-H)^-$, 22), 332($(M-H)^-$, 7) 331($(M-H)^-$, 100), 329($(M-H)^-$,73).

Ethyl 1-(4-Chloro-3-iodobenzyl)-3-(*t*-butylthio)-α,α-dimethyl-5-(*i*-propyl)-indole-2-propanoate (8)

To a solution containing 30 mg of 4 (0.08 mmol) and 26.6 mg of 7 (0.08 mmol) in 2.0 mL of dry DMF was added 3.82 mg of sodium hydride (0.16 mmol), and the reaction mixture was stirred at 22°C for 1 h, after which time TLC (Merck F254 silica gel, 1:1 hexane/methylene chloride, UV at 254 nm) indicated complete reaction. The excess sodium hydride was quenched by the addition of 1.0 mL of isopropanol and the reaction mixture was partitioned between 20 mL of ethyl acetate and 10 mL of water. The organic layer was separated, dried over powdered $MgSO_4$ and concentrated *in vacuo* to give 34 mg of 8 (68%) as an orange oil. The ester was used without further purification in the next step. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.64 (s, 1H, C4-H), 7.28 (d, J=8.3 Hz, 1H, C5'-H), 7.26 (d, J=1.9 Hz, 1H, C2'-H) 7.03 (s, 2H, C6-H+C7-H), 6.71 (dd, J=8.3,1.9 Hz, 1H, C6'-H), 5.31 (s, 2H, benzylic $-CH_2-$), 4.00 (q, J=7.2, 2H, $-OCH_2CH_3$), 3.20 (s, 2H, β-CH_2 (indole)), 3.01 (p, J=6.9, 1H, isopropyl hydrogen), 1.18-1.40 (m, 24H, methyl groups). Mass spectrum (CH_4): m/z 628 ($(M+H)^+$,6) 627 $(M=H)^+$,6), 626 ($M+H^+$,22), 331(23), 330(100), 251(27).

1-(4-Chloro-3-iodobenzyl)-3-(*t*-butylthio)-α,α-dimethyl-5-(*i*-propyl)-indole-2-propanoic acid (9)

A solution of 34 mg of 8 (0.054 mmol) in 3 mL of 1:1:1 (v/v/v) THF/ethanol/10% NaOH was stirred at 22°C in the dark for 26 hours. The ethanol and THF were removed *in vacuo*, and the remaining aqueous solution was adjusted to pH 3 with 3N HCl. This solution was extracted twice with 10 mL of ethyl acetate, and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*, giving 26.7 mg of 9 (82%) as a pale yellow oily solid. This material was purified by semi-preparative HPLC (Lichrosorb RP-18, 10 mm I.D. X 250 mm, 90:10:1 (v/v/v) acetonitrile:water:acetic acid, eluted at 3 mL/min, UV at 254 nm),

giving 8.0 mg of 9 (25% overall from 8) as an oily white solid. ^{1}H NMR (400 MHz, CD_3OD): δ7.56 (d,J=1.2 Hz, 1H, C4-H), 7.36 (d, J=8.4, 1H, C5'-H), 7.16 (d, J=8.4, C7-H), 7.12 (d, J=1.9, 1H, C2'-H)), 7.03 (dd, J=8.4, 1.9, 1H, C6-H), 6.91 (dd, J=8.4,1.9, 1H, C6'-H), 5.44 (s, 2H, benzylic $-CH_2-$), 3.25 (s, 2H, β-CH_2 (indole)), 2.98 (quin., J=6.9, 1H, isopropyl -H), 1.28 (d, J=6.9, 6H, $CH(CH_3)_2$), 1.26 (s, 9H, $S-CH(CH_3)_3$), 1.18 (s, 6H, $C(CH_3)_2COOH$). Mass spectrum (CH_4): m/z 600 ($(M+H)^+$, 33), 599 ($(M+H)^+$, 36), 598 ($M+H^+$, 100), 474 ($(M+H-I)^+$, 8), 473 ($(M+H-I)^+$, 9), 472($(M+H-I)^+$, 68).

1-(4-Chloro-[3-^{3}H]benzyl)-3-(*t*-butylthio)-α,α-dimethyl-5-(*i*-propyl)-indole-2-propanoic acid (10)

A 2.1 mg portion of 9 (0.035 mmol) was dissolved in 2.0 mL of 95:5 (v/v) ethanol/triethylamine in a 6 mL round bottom flask. A 2.1 mg portion of 5% Pd/C (Engelhard Lot D-440-D) was added, and the mixture was stirred under 10 Curies of carrier-free tritium gas for 4 hours at room temperature. The excess tritium gas was removed and the mixture was filtered through cotton, rinsing with 1 mL of absolute ethanol. The solvent was removed *via* vacuum transfer from the combined filtrates. The residue was immediately dissolved in 5 mL of absolute ethanol, then the solvent was removed by vacuum transfer. The resulting clear oily residue was taken up into 5 mL of absolute ethanol to give the crude product. A radioactivity assay of the solution showed 43.9 mCi of tritium. HPLC analysis (Beckman octyl 5μm, 4.6 mm I.D. x 25 cm, 90:10:1 (v/v/v) acetonitrile/water/acetic acid, 1.0 mL/min, Ramona detector) showed that about 50% of the radioactivity co-chromatographed with authentic unlabeled 10.

Compound 10 was purified by semi-preparative reverse phase HPLC. The ethanol was removed *via* vacuum transfer and the crude product was immediately dissolved in 2 mL of the HPLC solvent mixture (90:10:1 (v/v/v) acetonitrile/ water/acetic acid, kept at ice bath temperature.

The compound was purified in 400 μL portions on a LiChrosorb RP-18 7 μm column (10 mm I.D. x 25 cm, eluted at 3 mL/min, UV at 254 nm). The volume of the combined eluate fractions was reduced to 3-4 mL by rotary evaporation, and the remaining solvent was removed by vacuum transfer, giving 10 as a white solid, which was immediately dissolved in 4 mL of absolute ethanol and stored at -80°C. Radioactivity assay of this lot showed that 23.2 mCi of tritium was present. HPLC analysis (Beckman octyl 5μm, 4.6 mm I.D. x 25 cm, 90:10:1 (v/v/v) acetonitrile/water/acetic acid, 1.0 mL/min, Ramona radioactivity flow detector) showed that the radiochemical purity was 99.2%.

Proton NMR gave a positive identification when compared to standard. ^{1}H NMR (400 MHz, CD_3OD): δ7.54 (s, 1H, C4-H), 7.20 (d, J=8.5 Hz, 1.67 H, C3',C5'-H), 7.14 (d, J=8.5 Hz, 1H, C7-H), 6.99 (dd, J=8.4, 1.4 Hz, 1H, C6-H), 6.80 (d, J=8.5, 2H, C2',C6'-H), 5.48 (s, 2H, benzylic $-CH_2-$), 3.27 (s, 2H, β-CH_2(indole)), 3.00 (quint., J=6.9, 1H, isopropyl -H), 1.28 (d, J=6.9, 6H, $CH(C\underline{H}_3)_2$), 1.23 (s, 9H, $S-CH(C\underline{H}_3)_3$), 1.16 (s, 6H, $C(C\underline{H}_3)_2COOH$). Mass spectrum ($NH_3$): m/z 474 ($M^+$, 100), 472(9), 400(6). Label distribution by CI/MS: 20.0 Ci/mmol, $t_ø$ 31%, t_1 69%, avg. ^{3}H incorporation: 0.69 atom/molecule.

The ^{3}H-NMR (426 MHz) showed the label to reside exclusively in the expected aromatic position, with the signal at δ7.248 appearing as a doublet (J=8.8 Hz) which is further split by long-range coupling (J=2.5 Hz).

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