# SYNTHESIS OF $^{14}$C-LABELLED LEUKOTRIENE RECEPTOR ANTAGONISTS: 5-SUBSTITUTED-4,6-DITHIANONANEDIOIC ACID DERIVATIVES

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## SUMMARY

Two $^{14}$C-labelled leukotriene receptor antagonists were prepared from two aryl bromides and potassium [$^{14}$C]cyanide. Potassium cyanide was converted to copper(I) [$^{14}$C]cyanide and was subsequently used to displace the bromine atom from two aryl bromides, 2-dodecylbromobenzene and 2-(8-phenyloctyl)bromobenzene. The resulting nitriles were reduced to aldehydes with diisobutylaluminum hydride and the aldehydes were reacted with 3-mercaptopropionic acid to give 5-(2-dodecylphenyl)-4,6-dithianonanedioic acid ($^{14}$C-SK&F 102081) and 5-[2-(8-phenyloctyl)phenyl]-4,6-dithianonanedioic acid ($^{14}$C-SK&F 102922), respectively. These products were snythesized in about 30% overall yield with radiochemical purity of greater than 95%. Their structures were assigned based on the analytical data of the corresponding nonradiolabelled compounds obtained from the nonradioactive preparations.

Key words: 5-(2-dodecylphenyl)-4,6-dithianonanedioic acid, 5-[2-(8-phenyloctyl)phenyl]-4,6-dithianonanedioic acid, leukotriene antagonists.

## INTRODUCTION

4,6-Dithia-5-(2-dodecylphenyl)nonanedioic acid (SK&F 102081) is a selective leukotriene receptor antagonist which blocks leukotriene $D_4$ ($LTD_4$)-induced contraction of guinea pig trachea *in vitro* (1). *In vivo*, SK&F 102081 displays significant activity in blocking $LTD_4$-induced bronchoconstriction. The duration of action, however, is somewhat limited. In order to investigate

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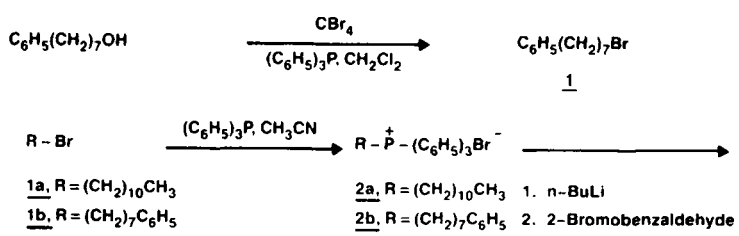
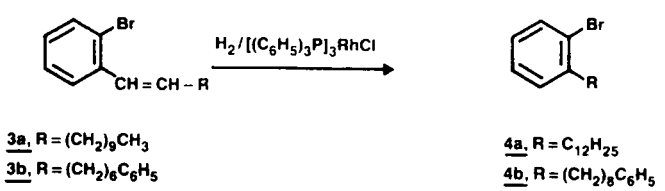
the possible contribution of metabolism to this brevity of pharmacologic action, $^{14}$C-labelled SK&F 102081 was synthesized. Preliminary experiments from metabolism studies in guinea pig indicated that the primary route of metabolic degradation of SK&F 102081 is initiated by omega oxidation. Therefore, 5-[2-(8-phenyloctyl)phenyl]-4,6-dithianonanedioic acid (SK&F 102922) was synthesized to evaluate the effect of blockade of omega oxidation on the rate of metabolism. The metabolism studies of SK&F 102081 and SK&F 102922 have been reported (2,3). Here we report the radiosynthetic scheme used to prepare $^{14}$C-SK&F 102081 (7a) and $^{14}$C-SK&F 102922 (7b).

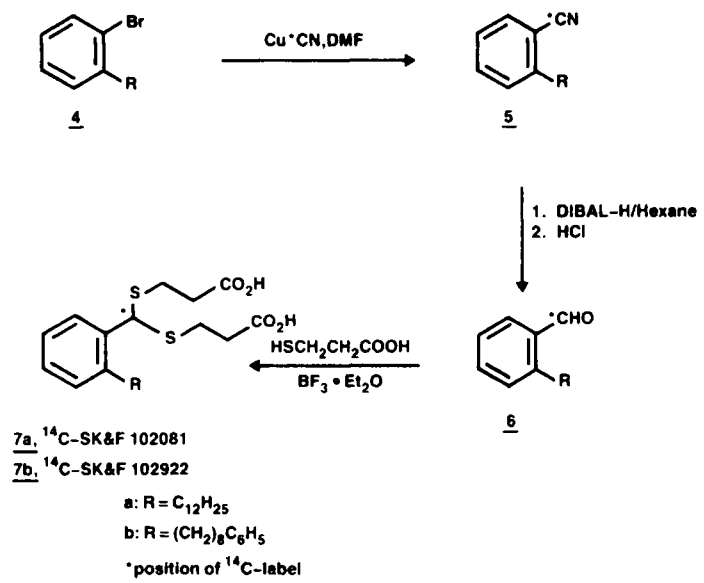
Synthetic scheme 1 was used to prepare the intermediates and the starting material for the radiosynthesis. The structures of the intermediates were confirmed by chemical ionization mass spectrometry (CI-MS), $^{1}$H-NMR and elemental analysis. Synthetic scheme 2 was used to prepare 7a and 7b. Their structures were confirmed based on the elemental (C,H,S) analysis, fast atom bombardment (FAB) mass spectrometry and $^{1}$H-NMR (270 MHz) data of the corresponding nonradiolabelled compounds.

**Scheme 1**



**Scheme 2**




7a, $^{14}$C-SK&F 102081
7b, $^{14}$C-SK&F 102922
a: R = $C_{12}H_{25}$
b: R = $(CH_2)_8C_6H_5$
*position of $^{14}$C-label

## EXPERIMENTAL

Radiochemical Purity: Radiochemical purity of $^{14}$C-SK&F 102081 and $^{14}$C-SK&F 102922 was determined on an HPLC system consisting of three M-6000A solvent delivery systems, a Model 481 UV detector set at 250 nm, a Data Module, a WISP, a Z-module and a Model 721 system controller. After injection the percentage of acetonitrile in 1% acetic acid was increased in a linear fashion over 20 min from 45 to 90% and then held at 90% for an additional 5 min during the analysis of $^{14}$C-SK&F 102081. $^{14}$C-SK&F 102922 was analyzed under similar conditions except that the gradient was lengthened to 25 min. Flow was maintained at 2.5 ml/min. Approximately 70,000-100,000 dpm of $^{14}$C-SK&F 102081 or $^{14}$C-SK&F 102922 was injected onto a Waters 5μ $C_{18}$ NOVA-PAK® column (8 x 100 mm) and 0.5 min fractions of eluant collected directly into minivials. Five milliliters of Atomlite® (New England Nuclear) was added to each vial and the radiochemical content of fractions was determined by the liquid scintillation counting (LSC) method using quantitation against a

Packard minivial standard curve. Radiochemical purity was determined by expressing the radiochemical content of the UV absorbing peak of SK&F 102081 or SK&F 102922 as a percentage of the cumulative radioactivity from all fractions. Before summation, a value approximating two times background (considered the limit of detection) was subtracted from each fraction. Negative values were not included in summation calculations. Radiochemical purity of $^{14}$C-SK&F 102081 was 97.0% and that of $^{14}$C-SK&F 102922 was 95.0% using this method.

Specific Activity: HPLC instrumentation was identical to that used in radiochemical purity determinations. Isocratic solvent systems containing 81% or 72% acetonitrile in 1% aqueous acetic acid were used for quantitation of $^{14}$C-SK&F 102081 or $^{14}$C-SK&F 102922, respectively. Flow was maintained at 2.5 ml/min. Standard curves were developed with 30, 60, 90, 120 or 150 µg/ml solutions of SK&F 102081 or SK&F 102922. Twenty microliters of standard or sample was injected on the column at all times. Samples of $^{14}$C-SK&F 102081 and $^{14}$C-SK&F 102922 used in quantitation were approximately 60 µg/ml. Radiochemical content was determined by summation of all background-subtracted fractions. The specific activity of $^{14}$C-SK&F 102081 was 9.15 mCi/mmol and that of $^{14}$C-SK&F 102922 was 11.57 mCi/mmol using this method.

$^{1}$H-NMR Spectra: $^{1}$H-NMR spectra of SK&F 102081 and SK&F 102922 were obtained using a JEOL GX270 NMR spectrometer. $^{1}$H-NMR of other intermediates were obtained using a Varian EM-390 NMR spectrometer. The solvent used was $CDCl_3$ with tetramethylsilane as a reference.

FAB - Mass Spectra & CI - Mass Spectra: FAB-Mass spectra of SK&F 102081 and SK&F 102922 were obtained using a Finnigan-MAT triple stage quadrupole (TSQ) mass spectrometer equipped with 4500 series ion source and an Ion Tech 11NF saddle field gun. Xenon was used as the primary ionizing beam and glycerol as the target matrix. CI-Mass spectra of other intermediates were obtained using

a Finnigan 3300 series mass spectrometer.

Chemicals: Potassium [$^{14}$C]cyanide was obtained from Pathfinder Laboratories. 1-Bromoundecane, 2-bromobenzaldehyde, triphenylphosphine, n-butyllithium (2.2 M in hexane), 3-mercaptopropionic acid, and boron trifluoride etherate were purchased from Aldrich Chemical Company. 7-Phenyl-1-heptanol was purchased from Columbia Organic Chemicals. Diisobutylaluminum hydride/hexane was purchased from Alfa.

Elemental Analyses: Analytical results for elements indicated were within ± 0.4% of the thoretical values.

Copper(I) [$^{14}$C]Cyanide: A sample of K$^{14}$CN (10 mCi, 25.17 mCi/mmol) was mixed with 26 mg of KCN and was then dissolved in 2 ml of water in a 25 ml round bottom flask. To this solution was added dropwise 55 mg (0.44 mmol) of sodium sulfite in 2 ml of water, followed by addition of 217 mg (0.87 mmol) of $CuSO_4 \cdot 5H_2O$ in 3 ml of water. A white precipitate formed immediately. To this was added 0.4 ml of 1N NaOH to partially neutralize the sulfuric acid produced. The pH was 2.5 at this point. The reaction mixture was stirred for 15 min. The water layer was decanted from the white solid which was washed with water (2 x 10 ml) and acetone (2 x 10 ml). The product was dried overnight in a desicator under vacuum. The yield of Cu$^{14}$CN was 65 mg (88.8%). This batch of compound was used in the synthesis of $^{14}$C-SK&F 102081 (7a). A second synthesis of Cu$^{14}$CN starting with 20 mCi of K$^{14}$CN (39.82 mCi/mmol), 33 mg (0.5 mmol) KCN, 69 mg (0.55 mmol) sodium sulfite and 273 mg (1.09 mmol) $CuSO_4 \cdot 5H_2O$, gave 86 mg (96%) Cu$^{14}$CN which was employed in the synthesis of $^{14}$C-SK&F 102922 (7b).

2-Dodecylbromobenzene (4a): The Wittig reaction was carried out by standard methodology (4). A solution of 80.1 g (341 mmol) of 1-bromoundecane and 98.3 g (375 mmol) of triphenylphosphine was refluxed in 800 ml of acetonitrile for

24 hr. The reaction mixture was cooled to room temperature and the solvent was evaporated. The thick liquid was redissolved in 100 ml of acetonitrile followed by 1.2 liter of ether. The solvent was decanted. This process was repeated four times to yield 110.6 g (65%) of 2a. This was used without further purification.

To a solution of 96.8 g (195 mmol) of 2a in 600 ml freshly distilled THF was added dropwise 88.6 ml (195 mmol) of n-butyllithium (2.2M in hexane) at 0°C under an argon atmosphere over 30 min. After the addition was complete, the reaction mixture was stirred for another 15 min at 0°C and 30 g (162 mmol) of 2-bromobenzaldehyde in 200 ml THF was added dropwise. After stirring at 0°C for additional 15 min, the solvent was evaporated. The residue was sonicated in ether and was left at 0°C overnight. The ether was decanted. The sonication procedure in ether was repeated three times. The gummy residue was purified by flash chromatography (5) (silica, hexane) to give 49.7 g (95%) of 2-dodecenylphenyl bromide 3a with cis to trans isomer ratio about 3 to 1: $^1$H-NMR ($CDCl_3$), δ 0.72-1.00 (unresolved triplet, 3H, methyl), 1.30 (broad singlet, 16H, methylene), 2.00-2.33 (m, 2H, allylic $CH_2$), 5.75 (doublet of triplets, 0.75H, J=8Hz, J-12Hz, ArCH = CH, cis isomer), 6.15 (doublet of triplets, 0.25H, J=8Hz, J=15Hz, ArCH = CH, trans isomer), 6.45 (d, 0.75H, J=12Hz, ArCH = CH, cis isomer), 6.82 (d, 0.25H, J=15Hz, ArCH = CH, trans isomer), 7.00-7.60 (m, 4H, aromatic); CI-MS (Methane), $(M+H)^+$ = 323.

To a solution of 10 g (31.0 mmol) of 3a in 200 ml of toluene/ethanol (1:1) was added 2 g of tris(triphenylphosphine) rhodium (I) chloride (Wilkinson's Catalyst). The suspension was purged with argon for 30 min and then hydrogen was bubbled into the bottle for 1 hr. The olefin 3a was hydrogenated in a Parr shaker (50 psi) for 4 hr. The solution was degassed with argon and the solvent was evaporated. The residue was mixed with hexane and silica gel. The slurry was filtered and the filtrate was concentrated by evaporation. The residue was purified by flash chromatography (5) (silica gel, hexane), to yield

9.3 g (93%) of 4a: $^1$H-NMR δ 0.75-0.95 (unresolved triplet, 3H, methyl), 1.22 (broad singlet, 20H, aliphatic), 2.70 (t, 2H, $ArCH_2$), 6.90-7.60 (m, 4H, aromatic); CI-MS (methane), $(M+H)^+$ = 325.

2-Dodecyl[cyano-$^{14}$C]benzonitrile(5a) and 2-Dodecyl[formyl-$^{14}$C]benzaldehyde (6a): The synthesis of 5a was adapted from the method of Friedman and Schecter (6). To a sample of 65 mg (0.71 mmol) of copper(I) [$^{14}$C]cyanide in a 25 ml round bottom flask was added 2 ml of sieve-dried (4A) DMF. A greenish solid mixture formed. To this mixture was added 231 mg (0.71 mmol) of 2-dodecylbromobenzene in 3 ml of dry DMF. The reaction mixture was refluxed for 3 hr and an additional equivalent mole ratio of copper(I) cyanide was added to drive the reaction to completion. The reaction mixture was again refluxed for 3 hr and was then left at room temperature overnight. To this was added 10 ml of ferric chloride solution (prepared from 4.55 g of ferric chloride monohydrate in 10 ml of 3N hydrochloric acid and 40 ml of water). The product was extracted with 2x15 ml of ether. The ether solution was washed with water (2x20 ml) and 15 ml of saturated sodium chloride solution and was dried over anhydrous magnesium sulfate. The solvent was removed to give a light yellow liquid: IR, 2240 $cm^{-1}$ (CN); TLC (silica gel, ethyl acetate/ hexane 2:100, $R_f$ = 0.53). The cyanide 5a was used without further purification.

The cyanide 5a was dissolved in 5 ml of sieve-dried (4A) hexane and 1 ml of DIBAL-H (diisobutylaluminum hydride)/hexane (1.27 M) was added. The solution was stirred under argon for 30 min and 5 ml of 3N HCl was added. The reaction mixture was stirred for another 15 min. The hexane layer was separated and the aqueous layer was extracted with another 5 ml of hexane. The hexane extracts were combined and washed with water (2x10 ml), and 10 ml of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a light yellow liquid. The crude product was chromatographed through a silica gel column (1.5 x 10 cm) using hexane as

eluting solvent, then ethylacetate/hexane 2.5:100, and finally 5:100. Each fraction was checked by TLC (silica gel, ethyl acetate/hexane 5:100) to determine the proper fractions to be combined. The yield of the aldehyde 6a was 99 mg (50.8%):IR, 1710 $cm^{-1}$(C=O); TLC (silica gel, ethyl acetate/hexane 5:100, $R_f$ = 0.52).

5-(2-Dodecylphenyl)-4,6-dithia[5-$^{14}$C]nonanedioic Acid (7a): To a solution of 99 mg (0.36 mmol) of 6a and 84.9 mg (0.80 mmol) of 3-mercaptopropionic acid in 5 ml of sieve-dried (4A) methylene chloride was added 54 mg (0.38 mmol) of boron trifluoride etherate with ice-cooling. The solution turned cloudy immediately. It was stirred for 15 min and 10 ml of water was added. Another 5 ml of methylene chloride was added and the solution was stirred for 5 min. The methylene chloride layer was separated and was washed with water (3x10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a thick colorless liquid. This crude product was chromatographed through a silica gel column (1.5x10 cm) using hexane/ethyl acetate 5:1 mixture as eluting solvent. The HPLC-LSC method was used to determine radiochemical purity of the fractions. Fractions with more than 96% purity were combined. The solvent was evaporated to give 98 mg of 7a. Fractions with less than 96% but higher than 90% were combined to give 30 mg of 7a. The yield of the condensation was 75.9%. The nonradiolabelled 7a synthesized in a nonradioactive preparation was purified as described above and analytical data were obtained: $^1$H-NMR ($CDCl_3$), δ 5.34 (s, 1H, methine proton); FAB-MS, $(M-H)^-$ = 467. Anal. ($C_{25}H_{40}O_4S_2$) C, H, S.

2-(8-Phenyloctyl)bromobenzene (4b): To an ice-cold solution of 5.0 g (26 mmol) of 7-phenyl-1-heptanol in 100 ml of methylene chloride under argon was added 10.4 g (31.3 mmol) of carbon tetrabromide in one portion. The solution was stirred for 5 min at 0°C and 7.5 g (28.6 mmol) of triphenylphosphine was added in one portion. The solution was stirred for an additional 5 min at 0°C and then 2.5 hr at room temperature. The solvent was evaporated and the crude

product was purified by flash chromatography (5) (silica gel, hexane) to give 6.2 g (94%) of 1-bromo-7-phenylheptane (1b): IR, absence of -OH (3350 $cm^{-1}$); CI-MS(methane), $(M+H)^+$ 255. Anal. ($C_{13}H_{19}Br$) C, H.

A solution of 6.2 g (24.0 mmol) of 1b and 7.0 g (27.0 mmol) of triphenylphosphine in 100 ml of acetonitrile was refluxed for 72 hr under an argon atmosphere. The mixture was cooled and the solvent was evaporated. The residue was azeotroped four times with methylene chloride and then sonicated four times in ether. The ether was decanted each time. The oil was again mixed with ether and the mixture was left overnight at 0°C. The ether was evaporated to give 8.5 g (67%) of 2b. This intermediate was used without further purification.

To a suspension of 8.5 g (16.3 mmol) of 2b in 75 ml of freshly distilled THF was added dropwise under argon at 0°C 6.3 ml (16.3 mmol) of n-butyllithium/hexane (2.6 M) over 10 min. After the addition was complete, the deep-red solution was stirred for an additional 20 min at 0°C. To this solution was added dropwise 3.0 g (16.3 mmol) of 2-bromobenzaldehyde in 10 ml of THF. The reaction mixture was stirred for another 10 min and was then poured into ice-cold 1% aqueous diethylamine/ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The organic extracts were combined, washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated. The residue was stirred in hexane and the bulk of triphenylphosphine oxide was filtered. The filtrate was concentrated and the residue was purified by flash chromatography (5) (silica gel, hexane) to give 4.2 g (75%) of 2-(8-phenyl-1-octenyl)bromobenzene (3b) with cis to trans isomer ratio about 3 to 1: $^1$H-NMR ($CDCl_3$), δ 1.05-1.80 (m, 8H, methylene), 2.15 (m, 2H, allylic $CH_2$), 2.58 (m, 2H, $ArCH_2$), 5.72 (doublet of triplets, 0.75H, J=8Hz, J=12Hz, ArCH = CH, cis isomer), 6.10 (doublet of triplets, 0.25H, J=8Hz, J=15Hz, ArCH = CH, trans isomer), 6.45 (d, 0.75H, J=12Hz, ArCH = CH cis

isomer), 6.75 (d, 0.25H, J=15Hz, ArCH = CH, trans isomer), 6.95-7.60 (m, 9H, aromatic); CI-MS (methane), $(M+H)^+$ = 343. Anal. ($C_{20}H_{23}Br$) C, H.

To a solution of 4.1 g (11.9 mmol) of 3b in 150 ml ethanol/toluene (1:1) was added 1.27 g of tris(triphenylphosphine) rhodium (I) chloride (Wilkinson's Catalyst). The suspension was purged with argon for 45 min and hydrogen was bubbled into the bottle for 1 hr. The olefin 3b was hydrogenated in a Parr shaker under 50 psi at room temperature for 14 hr. The solution was degassed with argon and the solvent was evaporated. The residue was mixed with hexane and silica gel. The slurry was filtered. The filtrate was concentrated and the product was purified by flash chromatography (5) (silica gel, hexane) to yield 2.4 g (60%) of 4b: $^1$H-NMR ($CDCl_3$), δ 1.30 (broad singlet, 8H, aliphatic), 1.50-1.80 (m, 4H, aliphatic), 2.45-2.80 (2 triplets, 4H, $ArCH_2$), 6.85-7.60 (m, 9H, aromatic); CI-MS (methane), $(M+H)^+$ 345 • Anal. ($C_{20}H_{25}Br$) C, H.

2-(8-Phenyloctyl)[cyano-$^{14}$C]benzonitrile(5b) and 2-(8-Phenyloctyl)[formyl-$^{14}$C]benzaldehyde(6b): To a sample of 86 mg (0.96 mmol) of copper(I) [$^{14}$C]cyanide in a 25 ml round bottom flask was added 2 ml of dry DMF. A greenish mixture formed. To this mixture was added 335 mg (0.97 mmol) of 2-(8-phenyloctyl)bromobenzene in 3 ml of dry DMF. The mixture was refluxed for 2.5 hr and an additional equivalent mole ratio of copper(I) cyanide was added to drive the reaction to completion. The reaction mixture was again refluxed for 3.5 hr and left at room temperature overnight. To this reaction mixture was added 10 ml of ferric chloride solution (prepared by dissolving 4.55 g of ferric chloride monohydrate in 10 ml of 3N hydrochloric acid and 40 ml of water). The product was extracted with ether (2 x 15 ml). The ether extract was washed with water (2 x 20 ml) and saturated sodium chloride (15 ml) and was dried over anhydrous magnesium sulfate. The solvent was evaporated to obtain a pale yellow liquid: IR, 2110 $cm^{-1}$ (CN); TLC (silica gel, ethyl acetate/hexane 5:100, $R_f$ = 0.45). The nitrile was used

without further purification. The nitrile 5b was dissolved in 5 ml of dry hexane and 2 ml (2 mmol) of DIBAL-H/Hexane was added. The reaction mixture was stirred for 15 min and 5 ml of 3N HCl was added. The hexane layer was separated and the aqueous layer was extracted with another 5 ml of hexane. The hexane extracts were combined and washed with water (2 x 10 ml) and 10 ml of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a light yellow liquid. The crude product was chromatographed through a silica gel column (1.5 x 10 cm) using hexane as eluting solvent, followed by ethyl acetate/hexane 2.5:100 and finally ethyl acetate/hexane 5:100. Fractions were analyzed by TLC and those containing pure aldehyde were pooled and evaporated to obtain 99 mg (35.0%) of pure aldehyde: IR, 1700 $cm^{-1}$ (C=O); TLC (silica gel, ethyl acetate/hexane 5:100, $R_f$ = 0.45). The aldehyde 6b was not separable from the nitrile 5b by TLC, but absence of the CN stretching frequency at 2110 $cm^{-1}$ indicated complete conversion of nitrile to aldehyde.

5-[2-(8-Phenyloctyl)phenyl]-4,6-dithia[5-$^{14}$C]nonanedioic Acid (7b): To a solution of 99 mg (0.34 mmol) of 6b and 72 mg (0.68 mmol) of 3-mercaptopropionic acid in 5 ml of sieve-dried (4A) methylene chloride was added 54 mg (0.38 mmol) of boron trifluoride etherate. The solution became cloudy immediately. The solution was stirred for 15 min and 20 ml ether was added. The resulting solution was washed with water (2x20 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a colorless viscous liquid. This crude product was chromatographed through a silica gel column (1.5x10 cm) using hexane/ethyl acetate (3:1, 3:2 and 3:3) as eluting solvents. HPLC-LSC method was employed to determine the radiochemical purity of the fractions. Fractions having more than 95% purity were combined and evaporated to yield 117 mg of 7b ($^{14}$C-SK&F 102922). The yield of the condensation was 70.5%. The nonradiolabelled 7b synthesized in a nonradioactive preparation was purified as described above and analytical data were obtained: $^1$H-NMR ($CDCl_3$), $\delta$ 5.34 (s, 1H, methine proton); FAB-MS,

(M - $H^-$ = 487. Anal. ($C_{27}H_{36}O_4S_2$) C, H, S.

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