

SYNTHESIS OF A CARBON-14 RING-LABELED BENZTHIOPHENE VIA DEGRADATION AND RECYCLIZATION OF AN UNLABELED BENZTHIOPHENE

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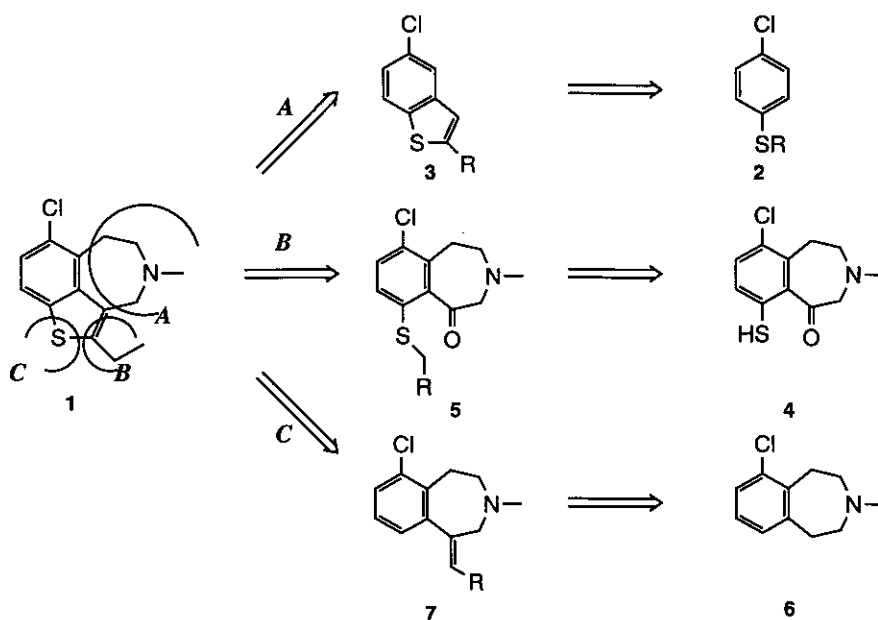
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Abstract- Synthesis of 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methyl-[2- ^{14}C]-thieno[4,3,2-*ef*][3]benzazepine (**1**) has been accomplished *via* degradation, alkylation and recyclization of an unlabelled benzthiophene. Ozonolysis of the benzthiophene (**11a**) gave the benzazepinone disulfide (**13**) which was reduced with tributylphosphine to the thiol (**4**). Direct treatment of the thiol (**4**) with ethyl bromo-[2- ^{14}C]acetate and sodium ethoxide gave the recyclized benzthiophene (**14**). The ester side chain of **14** was reduced with LAH to give ^{14}C -labeled form of the original starting material. Transformation to **1** was readily accomplished by a manganese dioxide oxidation, Wittig reaction, catalytic reduction sequence.

Introduction: Development of 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methyl-[2- ^{14}C]thieno[4,3,2-*ef*]-[3]benzazepine (**1**) as a possible treatment for Benign Prostatic Hypertrophy required that the compound be prepared in carbon-14 labeled form for biotransformation studies. Due to the potential for metabolic instability in the thiophene side chain or the azepine ring, it was preferable that the label be in either the benzene or thiophene ring system. Design of the radiosynthesis of **1** required introduction of a radiolabel with a minimum number of synthetic steps from a readily available radiolabeled starting material.

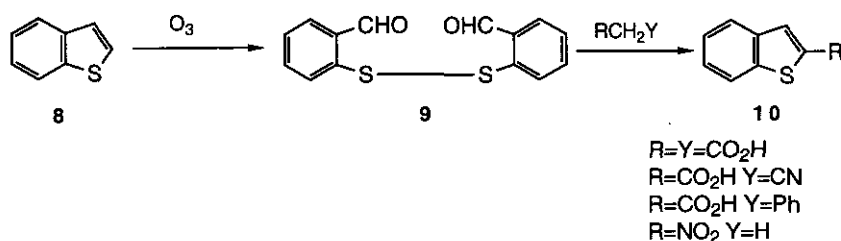
Synthesis with the ^{14}C in the benzene ring of **1** was rejected as this would require a total synthesis of the tricyclic ring system from a ^{14}C -labeled benzene. Retrosynthetic analysis suggested three possible routes for construction of the ring-labeled thiophene. Route A would utilize the well known cyclization of

arylthioacetaldehydes (ArSCH_2CHO), prepared by reaction of an aryl thiol (**2**) with a halo acetaldehyde dialkyl acetal, to form the benzthiophene ring.¹ Ring labeling would thus require a ^{14}C at either C-1 or C-2 in the halo- acetaldehyde dialkyl acetal moiety. Halomethylation of **3** at C-3 of the thiophene ring² followed by reaction with an aminoacetaldehyde dialkyl acetal or an ethanolamine equivalent and subsequent acid catalyzed cyclization would reform the azepine ring.³ Route B involves simple alkylation of a benzazepinone intermediate (**4**) at sulfur with a ^{14}C -labeled ethyl bromoacetate followed by base catalyzed recyclization of **5** to give the carbon-14 labeled tricyclic framework. Such a route is similar to one of the earliest reported syntheses of a benzthiophene in which Friedlander and Lenk⁴ reported on the cyclization of *o*-mercaptobenzaldehyde to benzthiophene-2-carboxylic acid *via* reaction with chloroacetic acid and sodium hydroxide. Route C requires a regioselective oxidation at one of the benzylic carbons⁵ in the azepine (**6**) followed by a Wittig reaction with a ^{14}C -radiolabeled phosphine to give azepine (**7**). Sulfur insertion with thionyl chloride⁶ would reform the thiophene ring. Of the three routes, Route B appeared to offer the most efficient way to synthesize the desired ring-labeled thiophene. Both routes A and C suffer from the need to develop a total synthesis of the labeled precursor, whereas the labeled starting material in Route B, ethyl bromo-[2- ^{14}C]acetate, is commercially available. Route C chemistry also appeared to be more difficult and, as such, to require more development time.

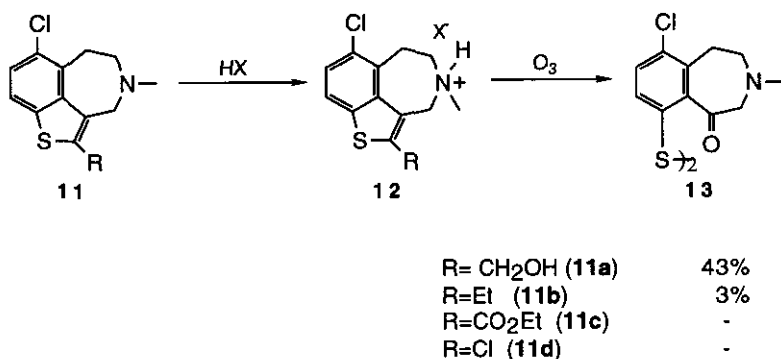


While the key starting material in Route B, benzazepinone (**4**), could be prepared by total synthesis, we

found that it could more rapidly and easily be obtained via degradation of the unlabeled tricyclic framework itself. Meth-Cohn⁷ and von Waceck⁸ have reported that ozonolysis of benzthiophene (**8**) gives the *o*-mercaptobenzaldehyde dimer (**9**). Meth-Cohn⁷ has also found that reaction of the aldehyde dimer **9** with an active methylene compound (e.g. malonic acid, malononitrile, phenylacetic acid, nitromethane) and base (triethylamine) gave the now substituted benzthiophene (**10**):



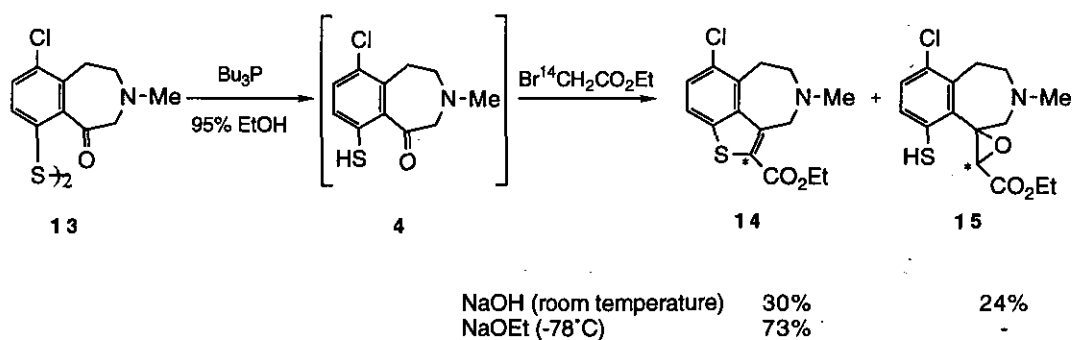
Precursor Synthesis: Application of the Meth-Cohn ozonolysis procedure to our system required that the *N*-methylazepine on the tricyclic system be converted to a salt (**12**, X=trifluoroacetyl) prior to reaction in order to prevent oxidation at nitrogen. Successful ozonolysis of the tricyclic system at the thiophene ring was dependent on the nature of the thiophene side chain. Only when the side chain was hydroxymethyl (R=CH₂OH) were satisfactory yields of the disulfide benzazepinone (**13**) obtained. Ozonolysis where R= ethyl, carboethoxy, or chloro failed to give the desired compound even though starting material was consumed in the reaction:



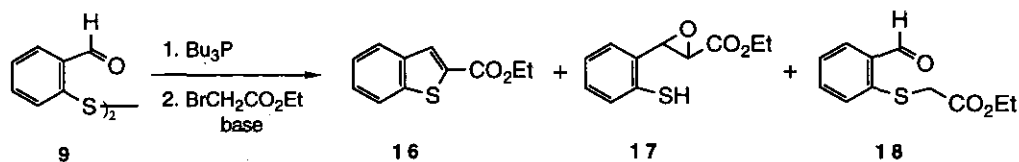
Recyclization: In preparation for alkylation, disulfide (**13**) was first reduced with tributylphosphine⁹ in 95% ethanol to give the corresponding thiol (**4**). Triphenylphosphine¹⁰ and triphenylphosphine on resin¹¹ were also examined as possible reducing agents but tributylphosphine proved to be the more effective

reducing agent. It was not necessary to isolate the thiol; rather, the solvent was removed and the thiol directly treated with ethyl bromoacetate followed by sodium ethoxide in absolute ethanol at -78°C . This gave a 73% yield of the recycled benzthiophene in a one-pot procedure from the disulfide (**13**). This procedure is in contrast to the cyclization procedure of Meth-Cohn where the disulfide was directly treated with the active methylene component. In a model study, direct reaction of phenylacetic acid with our disulfide (**13**) using the Meth-Cohn procedure failed to give any of the expected benzthiophene. Meth-Cohn had obtained a 60% yield of the substituted benzthiophene (**10**) from disulfide (**9**) and phenylacetic acid. Reduction to the thiol was therefore employed in our system prior to reaction with the active methylene component.

Attempted recyclization using triethylamine as had been used by Meth-Cohn gave only a 37% yield of alkylated thiol; no recyclization to the benzthiophene was seen. Aqueous sodium hydroxide gave the expected benzthiophene (**14**), but a significant amount of epoxide (**15**) was also obtained. However, epoxide (**15**) could be cyclized to benzthiophene (**14**) in 66% yield by treatment with sodium ethoxide.



Mechanistically, formation of the epoxide (**15**) is likely the result of a Darzens condensation. Model studies¹² in our laboratories on the reaction of disulfide (**9**) with ethyl bromoacetate indicated that successful cyclization was a function of both base and temperature. Reaction at room temperature with triethylamine as the base, as had been used by Meth-Cohn, afforded approximately a 1:1 mixture of epoxide (**17**) and the alkylated thiol (**18**). At -78°C , formation of the epoxide was suppressed since a 91:9 mixture of **18** (82% yield) and **17** (8% yield) was isolated. Hsiao¹³ also found triethylamine ineffective in cyclizing **18**, though there was no mention of a Darzens product. DBU as base did afford the

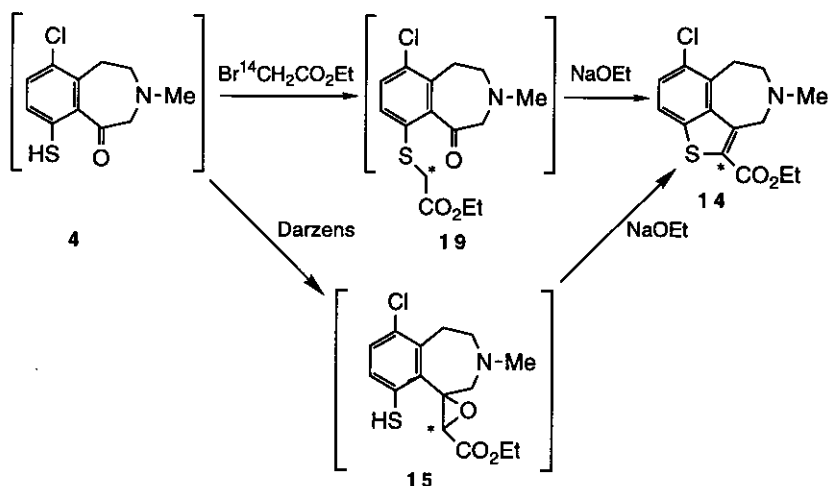


Et ₃ N (room temperature)	-	45%	45%
Et ₃ N (-78°C)	-	8%	82%
NaOH (room temperature)	54%	24%	-
NaOEt (2 eq/room temperature)	59%	-	-
NaOEt (2 eq/-78°C)	73%	-	-
NaOEt (0.5 eq/room temperature)	-	19%	38%

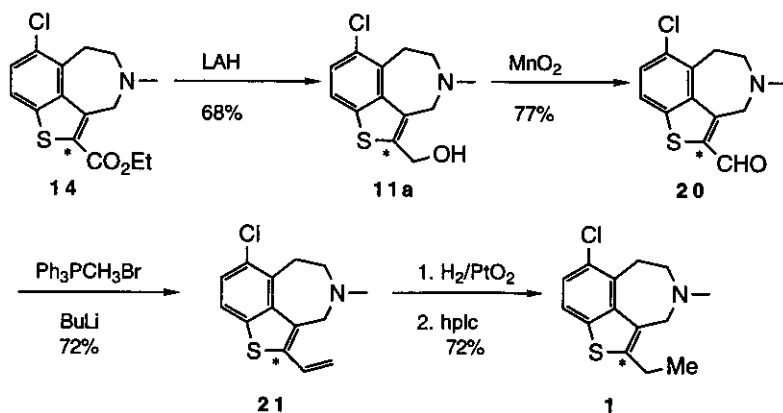
benzthiophene product, however. Our examination of aqueous sodium hydroxide as base, as had been used by Lenk,⁴ showed that it was effective in giving the cyclized benzthiophene (**16**) (54% yield) although a 24% yield of the epoxide (**17**) was still isolated. As noted above, when hydroxide was tried on the actual benzazepinone system, benzthiophene (**14**) was obtained in only 30% yield and a 24% yield of epoxide (**15**) was still obtained. Since the hydroxide reactions were carried out with simultaneous mixing of hydroxide, thiol and bromoacetate it is reasonable to expect that the Darzens pathway could be competitive with sulfur alkylation and this might account for the large amount of epoxide seen. Little, if any, epoxide was isolated when ethoxide used as the base. Reaction at room temperature using two equivalents of sodium ethoxide gave a 59% yield of benzthiophene (**16**) while at -78°C a 73% yield of **16** was obtained. The course of the ethoxide reaction was further investigated in one trial where only 0.5 equivalent of ethoxide was used. The reaction mixture, isolated in 57% yield, contained a 2:1 mixture of **18** and **17**. Clearly, the room temperature ethoxide reactions were still giving a significant amount of epoxide but this intermediate was not isolated since sufficient ethoxide would cyclize **17** to **16**.

In the optimized reaction with our actual benzazepinone system, the reaction proceeds by way of alkylated thiol (**19**) since ethyl bromoacetate and the thiol (**4**) are allowed to react prior to the addition of ethoxide and the reaction is run at -78°C. Addition of ethoxide then leads to formation of **14** with concomitant disappearance of the intermediate (**19**). Should any Darzens product form it would still cyclize to product (**14**).

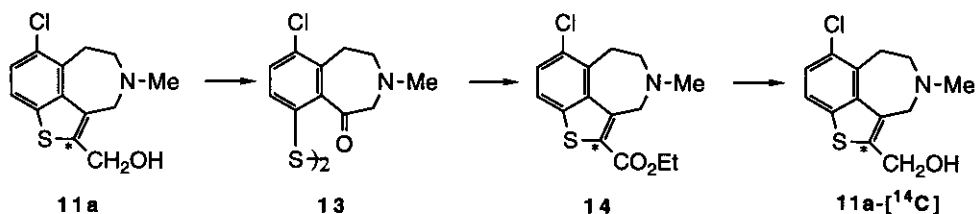
Completion of the Synthesis of 1: The synthesis of the target compound was easily completed by lithium aluminum hydride reduction of the ester (**14**) which gave the original starting material, the now carbon-14 labeled side chain alcohol (**11a**), in 68% yield. Manganese dioxide oxidation to the aldehyde



(**20**) followed by a Wittig reaction gave olefin (**21**). This olefin was extremely unstable radiochemically. Radiochemical purity of **21** decreased by approximately 15% over a 12 hour period. This is not too surprising given the nature of the olefin and its probable susceptibility to polymerization as a result of beta particle decay.¹⁴ Catalytic hydrogenation of the olefin gave the target compound (**1**) in 27% overall yield from **14**. Benzthiophene (**1**) did not display the extreme radiochemical instability seen in the olefin (**21**).



Conclusion: The synthesis of **1** has taken advantage of an advanced unlabeled tricyclic intermediate



(11a) which, after oxidative degradation with ozone, alkylation with ethyl bromo-[2-¹⁴C]acetate, and base catalyzed recyclization, reformed the original tricyclic framework now in carbon-14 labeled form.

EXPERIMENTAL SECTION

Ethyl bromo-[2-¹⁴C]acetate was purchased from American Radiolabeled Chemicals, Inc. (St. Louis, MO) at a specific activity of 50 mCi/mmol. All reagents were of analytical reagent grade or better. ¹H-Nmr spectra were run a Bruker 400 MHz NMR. Radiochemical purity was determined by thin layer chromatography on 5cm x 20cm silica gel GF plates (250 μm, Merck) which were analyzed on a Berthold LB 2832L linear analyzer.

9,9'-Dithiobis(6-chloro-3,4,5,6-tetrahydro-3-1H-benzazepine-1-one) (13) Benzthiophene (11a) (596 mg, 2.23 mmol) was suspended in 35 ml of methanol and 0.24 ml of trifluoroacetic acid (347 mg, 3.04 mmol) added. The now homogeneous solution was cooled to -78°C under a nitrogen atmosphere. Ozone (at 20%) was gently bubbled through the solution for 5 min. Nitrogen was then bubbled through the solution for 10 min and 0.2 ml of dimethyl sulfide added. The yellow solution was warmed to room temperature and concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with saturated NaHCO₃, water, 0.1M K₃Fe(CN)₆, and water. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluted with 1:1 EtOAc/hexane) gave 240 mg (45%) of disulfide (13) as a yellow solid. Ms(Cl, CH₄): 483 (21), 481 (M+H⁺, 34), 244 (25), 243 (16), 242 (97), 241 (19), 240 (100); ¹H-nmr (CDCl₃) δ2.41 (s, 3H, NCH₃), 2.74 (t, 2H, J=6.7 Hz, CH₂CH₂N), 3.06 (t, 2H, J=6.7 Hz, CH₂N), 3.43 (s, 2H, CH₂C=O), 7.36 (d, 1H, J=8.7 Hz, ArH), 7.57 (d, 1H, J=8.7 Hz, ArH); Anal. Calcd for C₂₂H₂₂N₂O₂Cl₂S₂: C, 54.88; H, 4.61; N, 5.82. Found: C, 54.57; H, 4.70; N, 5.46.

7-Chloro-2-carboethoxy-3,4,5,6-tetrahydro-4-methyl-[2-¹⁴C]-thieno[4,3,2-*e*][3]benzazepine ([¹⁴C]14) The disulfide (13) (306 mg, 0.64 mmol) was dissolved in 25 ml of 95% ethanol and 0.183 ml (148 mg, 0.73 mmol) of tributylphosphine was added; the reaction mixture immediately turned reddish in color. The reaction was concentrated *in vacuo*, absolute ethanol added, the solvent again removed *in vacuo*, and the residue dried *in vacuo* (0.06 mm). This procedure was repeated. The residue was then taken up in 25 ml of absolute ethanol and 70 mCi of ethyl bromo-[2-¹⁴C]acetate (50 mCi/mmol, 234 mg, 1.40 mmol)

added at room temperature. The solution was then cooled to -78°C for 20 min and 0.834 ml of a sodium ethoxide in ethanol solution (1.90 mmol) added. The solution was allowed to slowly warm to 0°C over 90 min. The solvent was removed *in vacuo* and the product purified by column chromatography (silica gel, eluted with ethyl acetate). This gave 248 mg (63%) of benzazepine (**14**) as a pale yellow solid. Purity of the product was 96.3% by radio-tlc (ethyl acetate, $R_f=0.13$). A second 19 mg portion of product, at a purity of 92.6%, was obtained by combining early and late eluting fractions.

Epoxide (15). Disulfide (**13**) (60 mg, 0.125 mmol) was suspended in 3 ml of 95% ethanol. To this was added 34 μl of tri-*n*-butylphosphine (0.137 mmol). The solution was stirred 10 min at room temperature and then 311 μl of 1*N* NaOH followed by 31 μl of ethyl bromoacetate (47 mg, 0.275 mmol) were added. The reaction was stirred 10 min and then concentrated *in vacuo* and partitioned between ethyl acetate and water. The ethyl acetate was dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by preparative tlc (2mm x 20cm x 20cm plate, developed 2x with ethyl acetate) gave 23 mg (30%) of benzazepine (**20**) as an oil and 20 mg (24%) of epoxide (**15**) as an oil which was characterized by mass spectroscopy and proton nmr and used as is: Ms (CI, CH_4) 330 (36), 329 (20), 328 ($\text{M}+\text{H}^+$, 100), 312 (32), 311 (15), 310 (85); ^1H -nmr(CDCl_3) δ 1.32 (t, 3H, $J=7.3$ Hz, CH_3), 2.41 (t, 1H, $J=12.5$ Hz, CH_2N), 2.53 (s, 3H, NCH_3), 2.62 (d, 1H, $J=12.5$ Hz, CH_2N) 2.92-3.06 (m, 2H, CH_2) , 3.42-3.47 (m, 2H, CH_2), 4.16 (m, 2H, CH_2CH_3), 4.34 (s, 1H, epoxide CH), 6.93 (d, 1H, $J=8.4\text{Hz}$, ArH), 7.20 (d, 2H, $J=8.4\text{Hz}$, ArH).

9-(Ethoxycarbonylmethyl)thio-6-chloro-3,4,5,6-tetrahydro-3-1*H*-benzazepine-1-one (19). A sample of alkylated thiol (**19**) was prepared by alkylation of thiol (**4**). Thiol (**4**), prepared from disulfide (**13**) (20 mg, 41.5 μmol) as described above, was dissolved in 400 μl of dry THF and 50 μl of triethylamine. To this was added 10 μl of ethyl bromoacetate (15 mg, 89.8 μmol). This was stirred 1 h at room temperature and then 1 h at 50°C . The reaction was concentrated *in vacuo* and purified by preparative tlc (2 mm x 20 cm x 20 cm plate, developed with ethyl acetate). This gave 10 mg (37%) of **19** as an oil which was characterized by mass spectroscopy and proton nmr and used as is: Ms (CI, NH_3) 330 (41), 329 (15), 328 ($\text{M}+\text{H}^+$, 100), 316 (11), 314 (30), 300 (11); ^1H -nmr(CDCl_3) δ 1.24 (t, 3H, $J=7.1\text{Hz}$, CH_3), 2.39 (s, 3H, NCH_3), 2.70-2.73 (m, 2H, Ar CH_2), 3.00-3.03 (m, 2H, CH_2N) 3.37 (s, 2H, $\text{CH}_2\text{C}=\text{O}$) , 3.64 (s, 2H, $\text{CH}_2\text{CO}_2\text{Et}$), 4.17 (q, 2H, $J=7.1$ Hz, CH_2CH_3), 7.36-7.41 (m, 2H, ArH).

7-Chloro-3,4,5,6-tetrahydro-4-methyl-[2-¹⁴C]-thieno[4,3,2-ef][3]benzazepine-2-methanol ([¹⁴C]11a)

The ester (**14**) (248 mg, 0.80 mmol) was dissolved in 15 ml of dry THF, cooled to 0°C under a nitrogen atmosphere, and 91 mg (2.39 mmol) of lithium aluminum hydride was added. The mixture was slowly warmed to room temperature over 90 min. The reaction was quenched by sequential addition of 89 µl of water, 89 µl of 15% NaOH, and 268 µl of water. The mixture was filtered and concentrated to a white solid *in vacuo*. This gave 212 mg of alcohol (**11a**) (99%) as a white solid at a purity of 95.4% by radio-TLC (90:10:0.5 EtOAc/MeOH/Et₃N, R_f=0.14). This was used directly in the next reaction without any purification.

7-Chloro-3,4,5,6-tetrahydro-4-methyl-[2-¹⁴C]-thieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde ([¹⁴C]20)

The alcohol (**11a**) (212mg, 0.79 mmol) was dissolved in 150 ml of methylene chloride and treated with 980 mg of activated (black) manganese dioxide (11.3 mmol). This was stirred 1 h at room temperature under a nitrogen atmosphere. The reaction was filtered through Celite and concentrated to a pale yellow solid *in vacuo*. This gave 161 mg of aldehyde (**20**) (77%) at a radiochemical purity of 95.0% by tlc (90:10:0.5 EtOAc/MeOH/Et₃N, R_f=0.28). This was used directly in the next reaction without any purification.

7-Chloro-2-ethenyl-3,4,5,6-tetrahydro-4-methyl-[2-¹⁴C]-thieno[4,3,2-ef][3]benzazepine([¹⁴C]21)

Methyltri-phenylphosphonium bromide (650 mg, 1.82 mmol) was suspended in 30 ml of dry THF and cooled to -10°C under a nitrogen atmosphere. To this was added 2.27 ml of a 0.8M n-butyllithium solution (1.82 mmol) and the now homogeneous solution was stirred 90 min. To this was added 161 mg (0.61 mmol) of **20** in 5 ml of dry THF. The solution was stirred 10 min, poured into 50 ml of saturated NaCl and extracted with ethyl acetate. The organic layer was dried (MgSO₄), filtered and concentrated to a yellow oil *in vacuo*. This was purified by column chromatography (silica gel, eluted with 90:10:0.5 EtOAc/MeOH/Et₃N). This gave 115 mg of olefin (**21**) (72%) at a radiochemical purity of 93.5% by radio-tlc (90:10:0.5 EtOAc/MeOH/Et₃N, R_f=0.17). Upon storage for 18 h at -78°C, a white precipitate had formed which was insoluble in ethanol. This presumably polymerized material was filtered from an absolute ethanol solution of **21**. This solution was used immediately in the next reaction.

7-Chloro-2-ethyl-3,4,5,6-tetrahydro-4-methyl-[2-¹⁴C]-thieno[4.3.2-*ef*][3]benzazepine ([¹⁴C]1) Olefin (**21**) (100 mg, 0.38 mmol), in 20 ml of absolute ethanol, was treated with 70 mg of PtO₂ (Aldrich) This was hydrogenated under 1 atmosphere of hydrogen gas for 3.5 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by preparative hplc on a LiChrosorb Si60 column (10 mm x 25 cm) eluted at 4.5 ml/min with 98.2:0.6:0.2 CH₂Cl₂/MeOH/NH₄OH (R_f=10.1 min, uv at 237nm). The product fractions were concentrated in vacuo to give 72 mg (72%) of benzthiophene [¹⁴C](1) as a white, crystalline solid. This was diluted with 72 mg of unlabeled **1** at a specific activity of 20.0 mCi/mmol (0.075 mCi/mg). Radiochemical purity as determined by hplc was 99.4% (Whatman Partisil ODS-3, 4.6mm x 25cm, eluted with 70:30 phosphate buffer (pH 3.0)/acetonitrile at 1 ml/min, uv at 220nm, R_f=12.6 minutes). Chemical purity, using the same hplc system, was 99.9% versus an analytically pure reference standard. ¹H-nmr(CDCl₃) δ1.32 (t, 3H, J=7.5 Hz, CH₃), 2.49 (s, 3H, NCH₃), 2.86 (q, 2H, J=7.5 Hz, CH₂CH₃), 3.09-3.13 (m, 2H, CH₂), 3.38-3.41 (m, 2H, CH₂), 3.99 (br s, 2H, CH₂), 7.21 (d, 1H, J=8.5 Hz, ArH), 7.48 (d, 2H, J=8.5 Hz, ArH).

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REFERENCES

1. B. D. Tilak, *Proc. Indian Acad. Sci., Sect. A*, 1950, **32** 390; B. D. Tilak, *Tetrahedron*, 1960, **9**, 76; N. N. Magdesieva, *Adv. Heterocycl. Chem.*, 1970, **12**, 1.
2. G. Dyker and R. P. Kreher, *Chem. Ber.*, 1988, **121**, 1203.
3. J. Likforman and J. Gardent, *Compt. Rend. (C)*, 1969, **268**, 2340; T. A. Post and S. J. Borowski, US Patent 4,541,954 Sept. 17, 1985 (*Chem. Abstr.*, 1985, **104**, P88457d); A. J. Villani, F. Etzkorn, G. A. Rotert, and J. R. Heys, *J. Labelled Comp. and Radiopharm*, 1988, **25**, 1340; J. Bonnic, P. Uriac, H. Bouget, and J. Huet, *C. R. Hebd. Seances Acad. Sci. Ser. C*, 1978, **286**, 83; C. Kaiser, F. E. Ali, W. E. Bondinell, M. Brenner, K. G. Holden, T. W. Ku, H-J Oh, S. T. Ross, N. C. F. Yim, C. L. Zirkle, R. A. Hahn, H. M. Sarau, P. E. Settler, and J. R. Wardell, Jr., *J. Med. Chem.*, 1980, **23**, 975.
4. P. Friedlander and E. Lenk, *Ber.*, 1912, **45**, 2083.

5. W. Klotzer, S. Teitel, J. F. Blount, and A. Brossi, *J. Am. Chem. Soc.* 1971, **93**, 4321.
6. W. B. Wright, Jr. and H. J. Brabander, *J. Heterocycl. Chem.* 1971, **8**, 711.
7. K. J. Brown and O. Meth-Cohn, *Tetrahedron Lett.* 1974, 4069.
8. A. von Waceck, H. O. Eppinger, and A. von Bezard, *Ber.*, 1940, **73**, 521.
9. S. Z. Zard, *Tetrahedron. Lett.*, 1984, **25**, 3707.
10. L. E. Overman, J. Smoot, and J. D. Overman, *Synthesis*, 1964, 59.
11. R. E. Humphrey and J. M. Hawkins, *Anal. Chem.*, 1964, **36**, 1812.
12. Compounds (**16**, **17**, and **18**) were characterized by ^1H -nmr(CDCl_3). Benzthiophene (**16**): δ 1.34 (t, 3H, $J=7.1$ Hz, CH_3), 4.33 (q, 2H, $J=7.1$ Hz, CH_2CH_3) 7.30-7.39 (m, 2H, ArH), 7.77-7.80 (m, 2H, ArH), 7.98 (s, 1H, vinyl H). Epoxide (**17**): δ 1.23 (t, 3H, $J=7.1$ Hz, CH_3), 4.17 (q, 2H, $J=7.1$ Hz, CH_2CH_3), 4.30 (d, 1H, $J=5.8$ Hz, epoxide CH of 1 diastereomer), 4.41 (d, 1H, $J=6.1$ Hz, epoxide CH of 1 diastereomer), 5.41-5.45 (m, 1H, epoxide CH of 1 diastereomer), 5.59 (br s, 1H, epoxide CH of 1 diastereomer), 7.06-7.12 (m, 2H, ArH), 7.15-7.20 (m, 1H, ArH), 7.29-7.32 (m, 1H, ArH). Ester (**18**): δ 1.22 (t, 3H, $J=7.1$ Hz, CH_3), 3.69 (s, 2H, $\text{CH}_2\text{CO}_2\text{Et}$), 4.16 (q, 2H, $J=7.1$ Hz, CH_2CH_3), 7.35-7.39 (m, 1H, ArH), 7.50-7.57 (m, 2H, ArH), 7.85 (dd, 1H, $J=1.2$, 7.7 Hz, ArH), 10.36 (s, 1H, CHO).
13. C-N. Hsiao, L. Bhagavula, and R. J. Pariza, *Syn. Comm.*, 1990, **20**, 1687.
14. E. A. Evans, "Self Decomposition of Radiochemicals," Amersham Corporation, Arlington Heights, IL.

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