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A NEW SYNTHESIS OF BIS-AMINOETHANETHIOL (BAT) CHELATING AGENTS CONTAINING A GAMMA CARBOXYLATE

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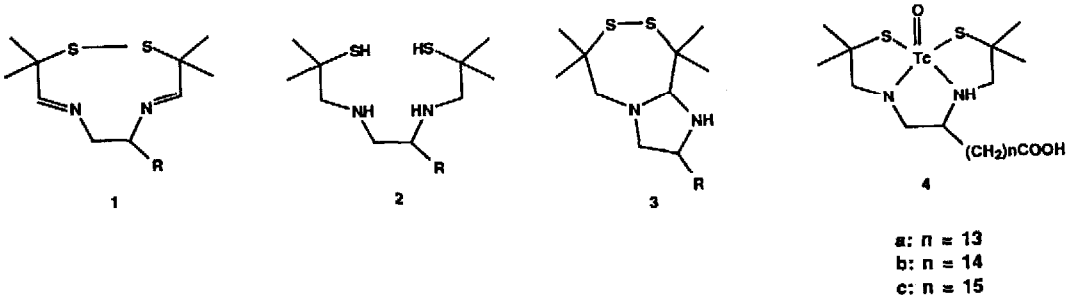
Summary. A new synthesis of bis(aminoethanethiols) containing a long-chain fatty acid moiety is described. The procedure described offers an advantage over literature methods since the use of strong reducing agents such as lithium aluminum hydride is avoided.

The synthesis of substituted bis(aminoethanethiol) (BAT) derivatives has received a considerable amount of attention lately since this ligand system has been shown to form a neutral and lipid-soluble complex with technetium-99m (^{99m}Tc),[1-4] a useful radioisotope in the field of diagnostic nuclear medicine. The preparation of the BAT chelating skeleton generally involves the condensation of an appropriately substituted ethylene diamine with 2,2'-dithiobis (2-methyl-propanal) to give the cyclic diimine-dithiol, **1**; reduction of **1** to the BAT system requires the use of strong reducing agents such as lithium aluminum hydride or Red-Al®.[3-5] Reduction of **1** with sodium borohydride has been shown to result in ring closure to form the imidazolidino [1,2-d]dithiapine, **3**,[6,7] which can be further reduced to **2** by treatment with lithium aluminum hydride.[7] This obligatory requirement of the use of strong reducing agents to effect reduction of either **1** or **3** to produce **2** limits the number of functional groups that can be incorporated into the BAT-skeleton. As part of our on-going research to prepare ^{99m}Tc-labeled fatty acid derivatives for myocardial imaging, it became necessary to develop a new route for the construction of the BAT-skeleton that is compatible with the incorporation of a carboxylate group. We now report the synthetic methodology that enabled us to achieve this goal.

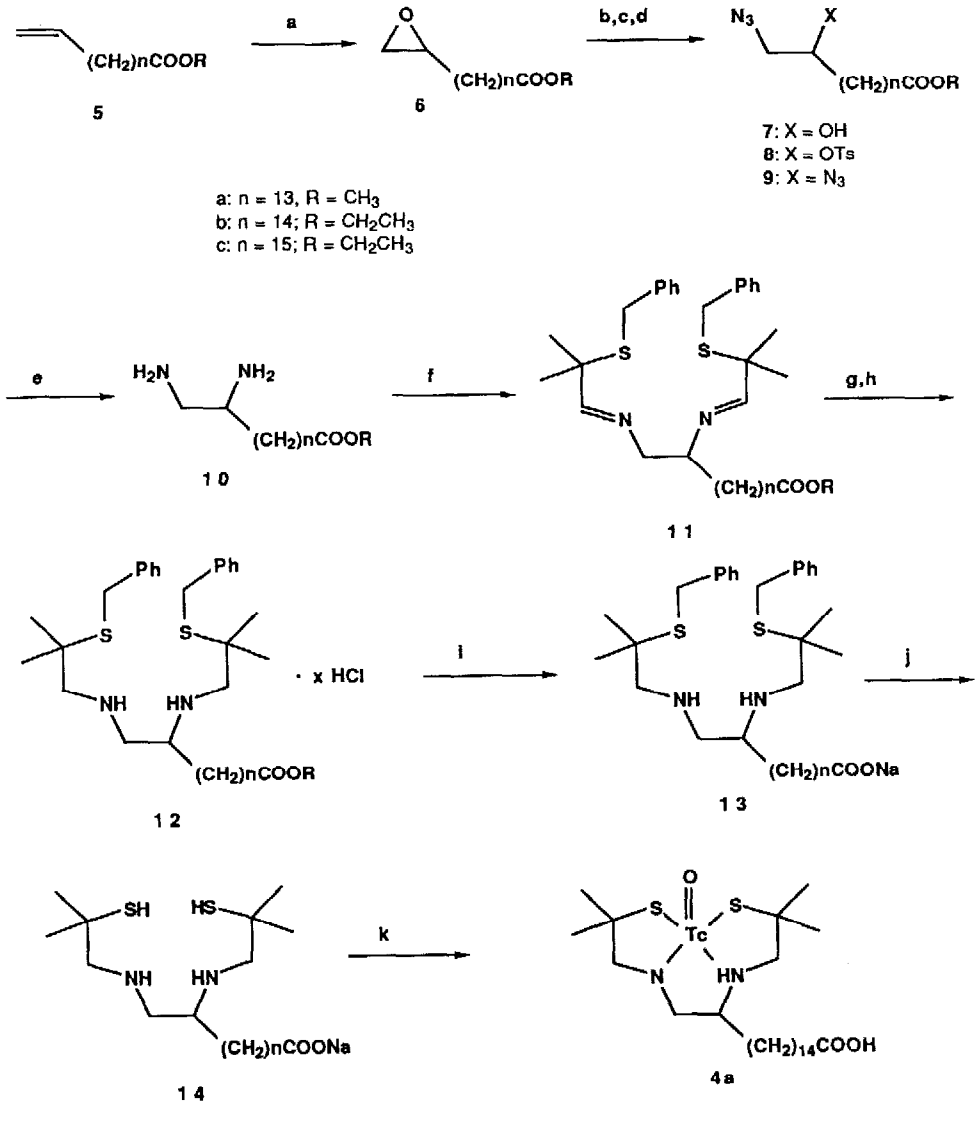


1 2 3 4

a: n = 13
b: n = 14
c: n = 15

Figure 1

Scheme 1

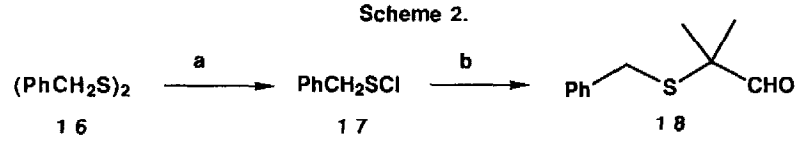


[a]Reagents: a: MCPBA/CH_2CL_2; b: NaN_3/EtOH; c: pTsCl/Pyridine; d: NaN_3/DMF; e: PtO_2/H_2/EtOH; f: 2 eq. **18**/C_6H_6; g: $NaBH_4$/EtOH; h: HCl/EtOH; i: NaOH/EtOH; j: Na/NH_3; k: [^{99}Tc]ammonium pertechnetate/$SnCl_2$/EtOH/H_2O.

The synthesis of the BAT-fatty acids is outlined in Scheme 1; 6-oxo-Δ^{15}-hexadecanoic acid and 7-oxo-Δ^{16}-heptadecanoic acid[8] were esterified (Fisher conditions) and converted to the corresponding methylene derivatives **5a** and **5b** using a modified Wolff-Kishner reduction (yield: 48%).[9] Ethyl 17-octadecenoate, **5c**, was prepared via a simple C1-homologation of **5b** (overall yield:41%).[10] The terminal olefin of **5** was converted to a vicinal diamine by using a modification of the method described by Swift and Swern;[11] in this case the tosylate, **8**, was used as opposed to the mesylate of the literature procedure. The overall yield for the conversion of **6** to **10** ranged from 25 to 65%.[12]

The key step of the synthesis involved the introduction of the 2-methyl-mercaptopropane fragment to form the BAT chelating skeleton. This was achieved via the reductive alkylation of **10** with the S-benzyl aldehyde, **18**; the synthesis of this key intermediate is outlined in Scheme 2. Treatment of benzyl disulfide, **16**, with sulfuryl chloride containing a catalytic amount of triethylamine afforded the corresponding sulfenyl chloride,[13] which is treated in crude form with an excess of isobutyraldehyde to give the S-benzyl aldehyde, **18**, in moderate yield (76%). Condensation of **10** with two equivalents of **18** afforded the diimine, **11**; reduction of the diimine with sodium borohydride in ethanol followed by treatment with ethanolic HCl gave the BAT-fatty ester as either the monohydrochloride (HCl/EtOH/RT for 2 h) or dihydrochloride (HCl/EtOH/reflux for 2 h). The yield for this conversion typically ranged from 26-61%. Treatment of **12** with 3 eq. of ethanolic NaOH gave the corresponding sodium carboxylate, **13**, which was deprotected with sodium in liquid ammonia to afford the BAT-fatty acid

Scheme 2.



16 17 18

a: $SO_2Cl_2/Et_3N/CCl_4$; b: $(CH_3)_2CHCHO/CCl_4$.

as the corresponding sodium salt, **14**. The BAT-fatty acids proved to be viscous oils that were somewhat chemically unstable and were radiolabeled with ^{99m}Tc immediately following deprotection. Radiolabeling was achieved using ^{99m}Tc-stannous glucoheptonate in 50% aqueous ethanol and the radiochemical yield ranged from 49-87%. The chemical instability of **14** is supported by an observed decrease in labeling yield with respect to time (with the yield eventually falling to zero after storage for 4 months); the appearance of high molecular weight components (m/z >1000) in the negative ion FAB-MS spectrum of **14c** supports the formation of polymeric disulfides, although the chemical nature of the decomposition product was not determined. The structure of the Tc-BAT-fatty acid analogs was confirmed by preparing the ^{99}Tc-carrier added complex, **4a**; this complex was characterized spectroscopically and displays the properties consistent with other neutral ^{99}Tc-N2S2 complexes reported in the literature[14] and afforded analytical data consistent with the assigned structure (UV, Tc = 0 absorption at 420 nm; IR, Tc = 0 stretching at 900 cm^{-1}).[12]

The synthetic methodology described here represents a new method for preparing bis(aminoethanethiol) derivatives containing a gamma-carboxylate; the analogs synthesized contained a long-chain fatty acid moiety since our goal was to prepare a ^{99m}Tc-based tracer of myocardial metabolism.[15] Recently, a number of reports have described the synthesis of bifunctional chelates for ^{99m}Tc containing a gamma-carboxylate for coupling to peptides and proteins.[7,16-18] We are currently investigating the use of shorter-chain analogs of **2** and **4** (n = 2-6) as a means

of labeling peptides with ^{99m}Tc.

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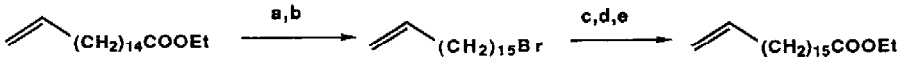
References.

1. Kung, H.F.; Molnar, M.; Billings, J.; Wicks, R.; Blau, M. *J. Nucl. Med.* **1984**, 25, 326.
2. Kung, H.F.; Yu, C.C.; Billings, J.; Molnar, M.; Blau, M. *J. Med. Chem.* **1985**, 28, 1280.
3. Lever, S.Z.; Burns, H.D.; Kervitsky, T.M.; Goldfarb, H.W.; Woo, D.V.; Wong, D.F.; Epps, L.A.; Kramer, A.V.; Wagner, H.N. Jr. *J. Nucl. Med.* **1985**, 26, 1287.
4. Efange, S.M.N.; Kung, H.F.; Billings, J.; Guo, Y.-Z.; Blau, M. *J. Nucl. Med.* **1987**, 28, 1012.
5. Corbin, J.L.; Work, D.E. *J. Org. Chem.* **1976**, 41, 489.
6. Joshua, A.V.; Scott, J.R.; Sondhi, S.M.; Ball, R.G.; Lown, J.W. *J. Org. Chem.* **1987**, 52, 2447.
7. Lever, S.Z.; Baidoo, K.E.; Kramer, A.V.; Burns, H.D. *Tetrahedron Letters* **1988**, 29, 3219.
8. Hunig, S.; Eckardt, W. *Chem. Ber.* **1962**, 95, 2493.
9. Tulloch, A.P. *Chem Phys. Lipids* **1977**, 18, 1.
10. The sequence of reactions for the conversion of **5b** to **5c** is as follows:



a: $LiAlH_4$/THF; b: $(Ph)_3P/CBr_4$/ether; c: NaCN/DMSO; d: $KOH/(CH_2OH)_2$; HCl/EtOH.

11. Swift, G.; Swern, D. *J. Org. Chem.* **1967**, 32, 511.
12. All new compounds were characterized by 1H-NMR, FT-IR, MS and elemental analysis and exhibited spectral and analytical properties consistent with the proposed structures. Compound **14** failed to afford a satisfactory elemental analysis and was characterized by 1H-NMR, FT-IR, and FAB-MS; the corresponding ^{99}Tc-complex **4a** satisfied all of the above criteria.
13. Harpp, D.N.; Friedlander, B.T.; Smith, R.A. *Synthesis* **1979**, 181.
14. Deutsch, E.; Libson, K.; Jurisson, S.; Lindsay, L.F. *Prog. Inorg. Chem.* **1983**, 30, 75.
15. Liang, F.H.; Virzi, F.; Hnatowich, D.J.; *Nucl. Med. Biol.* **1987**, 14, 555.
16. Fritzberg, A.R. *Nuklearmedizin* **1987**, 26, 7.
17. Fritzberg, A.R.; Abrams, P.G.; Beaumier, P.L.; Kasina, S.; Morgan, C.; Rao, T.N.; Reno, J.M.; Sanderson, J.A.; Srinivasan, A.; Wilbur, D.S.; Vanderheyden, J.-L. *Proc. Natl. Acad. Sci.* **1988**, 85,4025.
18. Franz, J.; Volkert, W.A.; Barfield, E.K.; Holmes, R.A. *Nucl. Med. Biol.* **1987**, 14, 569.

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