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An Efficient Synthetic Route to 2-(1,2-Dithiolan-3-yl)acetic acid. Trisnorlipoic Acid and Amide Derivatives.

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Abstract: A simple, efficient synthesis of 2-(1,2-dithiolan-3-yl)acetic acid from Meldrum's acid, acrolein and thioacetic acid is described. The isopropyldene 2,4-*bis*(acetylthio)butane-1,1-dicarboxylate formed in the three-component, single container process, can be methanolized to the corresponding dimethyl ester and then hydrolyzed, oxidized to the disulfide and decarboxylated to 2-(1,2-dithiolan-3-yl)acetic acid. The acid can be converted by conventional reagents into a variety of amide derivatives. © 1997 Elsevier Science Ltd.

α-Lipoamide is recognized as an important factor in a number of biochemical processes.[1] One key role for this cofactor is in the transformation of pyruvic acid to acetyl CoA in the cocarboxylase complex where, attached to a lysine, it transfers the acetyl function from thiamine to CoASH.[2] The cofactor plays a major role in a variety of other oxidation-reduction enzyme structures.[3–5] The easy availability of a variety of analogs of lipoamide might not only provide insight into a further understanding of its role in metabolism but such materials and derivatives also have the potential to serve as models of the biochemical events, metabolic inhibitors and antagonists. In a wholly different area, materials of this type are becoming increasingly important as the attachment group for tethering enzymes, antibodies and other bioprobes to gold surfaces.[6] This potential to construct a variety of analogs having shorter or less flexible or more functionalized tethering arms between the acid or amide functional group and the disulfide ring came about from our interest in extrapolating the Michael addition chemistry of thiols to Meldrum's acid derivatives.[7]

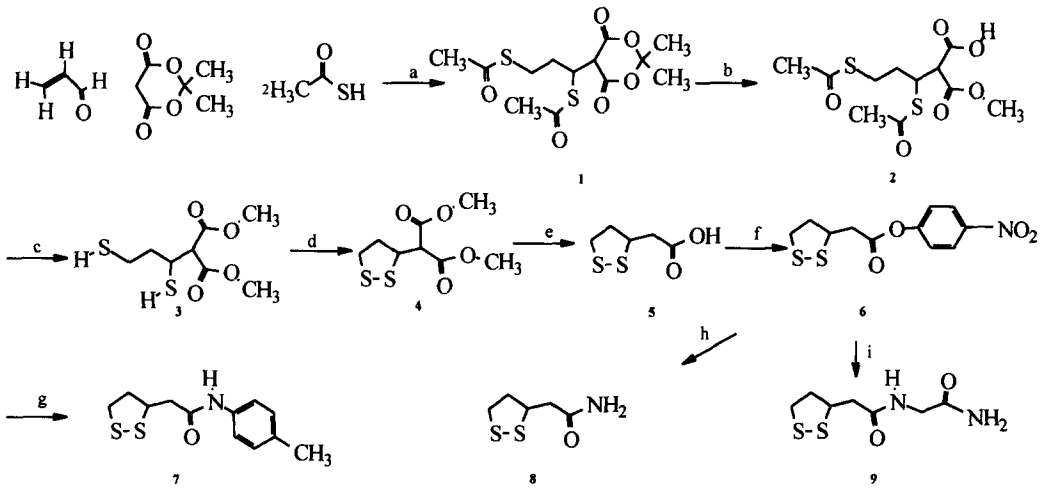
The main question in the synthesis of α-lipoic acid or its analogues is the method of forming the 5-membered 1,2-dithiolan-3-yl ring system. Traditionally, 1,3-diol tosylates or halides were converted to the dithiols by the reaction with sulfur nucleophiles.[8–12] Here, we offer a simple, efficient pathway for the formation of this dithiolane system through the formal consecutive Michael addition of thioacetic acid to Meldrum's acid adduct of acrolein. After hydrolysis, decarboxylation of the Meldrum's acid moiety and formation of the disulfide, trisnorlipoic acid and its derivatives were produced.

Treatment of acrolein with 2 equivalents of thioacetic acid in acetone followed by the addition Meldrum's acid in the presence of a catalytic amount of piperidine acetate gave diacylthioated propyl Meldrum's acid **1**[13] in almost quantitative yield. Both our previous work[7] and the importance of the timing sequence of the addition to obtain good and consistent yields, implied a pathway of 1) Michael addition of the thioacetic acid to acrolein, 2) aldol condensation of the resulting thioacetyl aldehyde with Meldrum's acid, followed by 3) elimination and 4) a second Michael addition of thioacetate to the alkylidene Meldrums acid.

Other α, β-unsaturated aldehydes behave in the same fashion to give related structures as a mixture of diastereoisomers.

The obvious direct, one step acidic deprotection of the two thioacyl functions with the simultaneous cleavage of the Meldrum's acid moiety of **1** to give dimercapto diester **3** could not be realized. The only product isolated was the cyclic dithioketal of **3,** dimethyl 2-(1, 3-dimercaptopropyl)malonate S, S acetonide. In the course of the reaction, even under the dilute and aqueous conditions, the acetone released from the Meldrum's acid hydrolysis was captured by dithiol. To repress this event, it was necessary to accomplish ring cleavage and deacylation in separate steps. Refluxing **1** in methanol 3 hr under neutral conditions to give ester acid dithioacetate **2**.[14] Then after workup but without purification, ester acid dithioacetate **2** upon acid catalyzed methanolysis affords dimercapto diester **3** and this, again without isolation, was taken up into ethyl acetate and oxidized with iodine and aqueous $KHCO_3$ to 1,2-dithiolan-3-yl malonic ester **4**[15]. Simultaneous aqueous acidic hydrolysis and decarboxylation of **4** produced 2-(1,2-dithiolan-3-yl)acetic acid (**5**[16,17], trisnorlipoic acid). Attempts to decarboxylate **2** resulted in both decarboxylation and elimination of the thioacetate and any attempts at base hydrolysis also yielded elimination products.

Coupling[18] of **5** with *p*-nitrophenyl trifluoroacetate gave disulfide *p*-nitrophenyl ester **6**[19]. This *p*-nitrophenyl ester derivative **6** was further transformed into N-*p*-tolyl 2-(1,2-dithiolan-3-yl)acetamide[20] [7], 2-(1,2-dithiolan-3-yl)acetamide[21] [**8**] (trisnorlipoamide) and 2-(1,2-dithiolan-3-yl)acetylglycinamide[22] [**9**] (a rigid segment heteroatom analog of lipoamide) by treatment with *p*-toluidine, NH_4OAc or glycinamide, respectively. Alternatively, amides could be directly constructed using acid **5**, the amine and DCC [5 → 7].



Scheme 1

a) piperidine acetate b) MeOH, reflux c) MeOH/HCl, reflux d) I_2/ aq. $KHCO_3$ e) 6M HCl, reflux f) *p*-nitrophenyl trifluoroacetate g) *p*-toluidine h) ammonium acetate i) glycine amide

Chemical studies and biochemical investigations of these derivatives, as well as others, are ongoing in collaboration with the research group of Dr. Charles Williams Jr. at the Veterans Administration Hospital, Ann Arbor.

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13 Isopropyldene 2,4-bis(acetylthio)butane-1,1-dicarboxylate **[1].** To a solution of acrolein (0.95 g,15.2 mmol) in acetone (2 mL) at rt was added dropwise with stirring 2.2 mL (30.4 mmol) of thioacetic acid. After 20 min, solid piperidinium acetate (0.1 g) was added followed by a solution of Meldrum's acid (2.24 g, 15.2 mmol) in acetone (6 mL). Over 2 h the solution became solid and then the mixture was diluted with an equal amount of H_2O and the resulting mixture was stirred for 10 min, then filtered and the product washed with water. The solid was dried under vacuum to afford **1** (5.03 g, 99%) as a white solid.: Crystallization from $CHCl_3$ gave white crystals mp 113-115°C. **FTIR** (KBr) 1787, 1730, 1701, 1678, 1390, 1349, 1260, 1209, 1137, 949, 873, 626. **^{1}H NMR** ($CDCl_3$) δ 4.52 (ddd, J = 10.2, 4.5, 2.6 Hz, 1H), 4.12 (d, J = 2.6 Hz 1H), 3.05 (ddd, J = 13.8, 7.9, 5.8 Hz, 1H), 2.83 (ddd, J = 13.8, 7.5, 7.5 Hz, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.18 (dddd, J = 14.7, 10.2, 7.5, 5.8 Hz, 1H), 1.99 (dddd, J = 14.7, 7.9, 7.5, 4.5 Hz, 1H), 1.85 (s, 3H), 1.78 (s, 3H). **^{13}C NMR** ($CDCl_3$) δ 195.7, 194.4, 163.3, 163.1, 105.4, 51.1, 38.9, 32.1, 30.4, 30.2, 28.2, 26.5, 26.3. Anal. Calcd.for $C_{13}H_{18}O_6S_2$: C,46.67; H,5.42. Found: C,46.38; H,5.23.

14 2-Carbomethoxy-3,5-bis(acetylthio)-pentanoic acid. Methanolysis of **1**. A solution of **1** (0.57 g, 1.7 mmol) in methanol (4 mL) was refluxed for 3 h. The reaction mixture was cooled and concentrated under reduced pressure to afford the mixture of diastereomers **2** (0.53 g, 99%) as pale yellow oil. This mixture was used without further purification. **FTIR** (neat) 3248, 1743, 1701, 1690, 1431, 1133. **^{1}H NMR** ($CDCl_3$) δ 4.20-4.14 (m, 1H), 3.87 (d, J = 5.1 Hz, 1H), 3.79 (s, 3H), 3.76(s, 3H), 3.07-2.98(m, 1H), 2.88-2.80 (m, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.07-1.98 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ 196.0, 194.8, 194.8, 167.4, 55.3, 52.6, 41.2, 41.2, 32.1, 31.9, 30.2, 30.2, 26.3, 26.3. **HRMS** m/z (M^+) calcd.for $C_{11}H_{16}O_6S_2$ $(M+H)^+$: 309.0466. Found: 309.0467.

15 Dimethyl 2-(1, 2-Dithiolan-3-yl)malonate [**4**]. A stirred solution of diastereomers of ester acid **2** (7.48 g, 24.2 mmol) in methanol (30 mL) containing conc. HCl (2mL) was refluxed for 20 h. The mixture was cooled and then concentrated under reduced pressure to afford the dimercapto diester **3** as a pale yellow oil. The dimercapto diester **3** was dissolved in ethyl acetate (40 mL), cooled to 0°C and the resulting solution was treated with 10% cold $KHCO_3$ (150 mL) and the mixture was stirred at 0°C for 10 min. Iodine (6.7 g, 24.2 mmol) in ethyl acetate (80 mL) was then added dropwise with stirring until the brown

iodine color persisted. After a few minutes, an aqueous solution of 10% sodium thiosulfate was added to quench the excess iodine. The aqueous layer was extracted with ethyl acetate (75 mL x 2). The combined organic extracts were dried (Na_2SO_4) and evaporated and the residue was purified by silica gel chromatography (hexane:EtOAc, 15 : 1) to give disulfide diester **4** (3.84 g, 67.1%). **FTIR** (neat) 1735, 1730, 1457, 1270, 1194, 1092, 951. **^{1}H NMR** ($CDCl_3$) δ 4.24 (ddd, J = 10.6, 6.9, 4.9 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72 (d, J = 10.6 Hz, 1H), 3.23 (ddd, J = 10.9, 7.6, 6.9 Hz, 1H), 3.13 (ddd, J = 10.9, 7.6, 6.9 Hz, 1H), 2.52 (dddd, J = 13.3, 6.9, 6.9, 4.9 Hz, 1H), 2.03 (dddd, J = 13.3, 7.6, 6.4, 4.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ 167.8, 167.5, 56.7, 52.6, 52.1, 39.6, 37.2. **HRMS** m/z (M^+) calcd.for $C_8H_{12}O_4S_2$ $(M+H)^+$: 236.0177. Found: 236.0183.

16 Trisnorlipoic acid **5**: 2-(1,2-Dithiolan-3-yl)acetic acid A mixture of disulfide diester **3** (0.61 g, 2.58 mmol) in a 1:1 mixture of conc. HCl and water (2 mL) was refluxed for 4 h. After cooling, the reaction mixture was brought to pH 8 and washed with $CHCl_3$ (15 mL x 2). The aqueous layer was acidified to pH 3 and extracted with $CHCl_3$ (30 mL x 2). The combined extracts were dried (Na_2SO_4), filtered and evaporated to afford acid **5** (0.32g, 76%) as a pale yellow oil[17]. **FTIR** (neat) 3300-2400, 1679, 1426, 1262, 952. **^{1}H NMR** ($CDCl_3$) δ 4.05-3.97 (m, 1H), 3.25-3.11 (m, 2H), 2.84 (A part of an AB system, dABq, JAB = 16.8 Hz, J = 8.2 Hz, 1H), 2.76 (B part of an AB system, dABq, JAB = 16.8 Hz, J = 6.4 Hz, 1H), 2.04-1.95 (m, 1H). Acidic H was searched for but not found. **^{13}C NMR** ($CDCl_3$) δ 177.5, 49.5, 40.0, 39.5, 39.1. **HRMS** m/z (M^+) Calcd.for $C_5H_8O_2S_2$$(M+H)^+$: 163.9966. Found: 163.9972.

17 Like lipoic acid this product upon standing, even in the refrigerator, polymerizes to a gummy material through disulfide exchange. The depolymerization to monomeric acid can be accomplished through solution in NaOH, acidification, extraction and solvent evaporation. See Thomas, R. C.; Reed, L. J. *J. Am. Chem. Soc.* 1956, *78*, 6148.

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19 Compound **6**: mp 52-53 °C. **FTIR** (KBr) 1761, 1521, 1350, 1205. **^{1}H NMR** ($CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 4.16-4.08 (m, 1H), 3.29-3.16 (m, 2H), 3.08 (A part of an AB system, dABq, JAB = 16.8 Hz, J = 8.7 Hz, 1H), 2.98 (B part of an AB system, dABq, JAB = 16.8 Hz, J = 5.9 Hz, 1H), 2.64-2.55 (m, 1H), 2.09-2.01 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ 168.8, 155.0, 145.4, 125.2, 122.4, 49.6, 40.3 39.4, 39.3. Anal. Calcd.for $C_{12}H_{15}NO_4S_2$: C, 46.30; H, 3.89; N, 4.91. Found: C, 46.23; H, 4.00; N, 4.77

20 Compound **7**: 67% yield as a white solid mp 108 °C. **FTIR** (KBr) 3315, 3259, 1660, 1514, 1309, 818. **^{1}H NMR** ($CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 4.20-4.12 (m, 1H), 3.25-3.12 (m, 2H), 2.75 (A part of AB system, dABq, JAB = 14.0 Hz, J = 8.1 Hz, 1H), 2.69 (B part of AB system, d_{ABq}, JAB = 14.0 Hz, J = 6.1 Hz, 1H), 2.62-2.51 (m, 1H), 2.31(s, 3H), 2.11-2.00 (m, 1H). Anal. Calcd.for $C_{12}H_{15}NOS_2$: C,56.88; H,5.97; N,5.53. Found: C,56.76; H,5.94; N,5.37.

21 Compound **8**: 72% yield as pale yellow solid mp 124-125 °C. **FTIR** (KBr) 3366, 3249, 1658, 1632. **^{1}H NMR** (d^6-acetone) δ 6.92 (s, 1H), 6.44 (s, 1H), 4.02 (ddt, J = 8.3, 6.1, 6.1 Hz, 1H), 3.25-3.20 (m, 1H), 3.19-3.08 (m, 1H), 2.64 (A part of an AB system, dABq, JAB = 15.4 Hz, J = 6.2 Hz, 1H), 2.58 (B part of an AB system, dABq, JAB = 15.4 Hz, J = 8.4 Hz, 1H), 2.53-2.45 (m, 1H), 2.02-1.95 (m, 1H). **^{13}C NMR** (d^6-acetone) δ 173.4, 52.2, 42.2, 41.0, 40. Anal. Calcd.for $C_5H_9NOS_2$: C,36.78; H,5.56; N,8.58. Found: C,36.45; H,5.20; N,8.47

22 Compound **9:** 73% yield as pale yellow solid mp 117-119 °C. **FTIR** (KBr) 3308, 3187, 3090, 1685, 1653. **^{1}H NMR** (d^6-DMSO) δ 8.26-8.15 (m, 1H), 7.30 (s, 1H), 7.04 (s, 1H), 3.97-3.90 (m, 1H), 3.66 (A part of an AB system, dABq, JAB = 16.8 Hz, J = 5.6 Hz, 1H), 3.60 (B part of an AB system, dABq, J_{AB} = 16.8 Hz, J = 5.6 Hz, 1H), 3.23-3.16 (m, 1H), 3.14-3.08 (m, 1H), 2.63 (A' part of an A'B' system, dABq, $J_{A'B'}$ = 15.1 Hz, J = 6.0 Hz, 1H), 2.51 (B' part of an A'B' system, dABq, $J_{A'B'}$ = 15.1 Hz, J = 8.7 Hz, 1H), 2.44-2.35 (m, 1H), 2.00-1.91 (m, 1H). **HRMS** m/z (M^+) calcd.for $C_7H_{12}N_2O_2S_2$$(M+H)^+$: 220.0340. Found: 220.0347

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