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Enantioselective synthesis of *R*-(+)-α and *S*-(−)-α-lipoic acid

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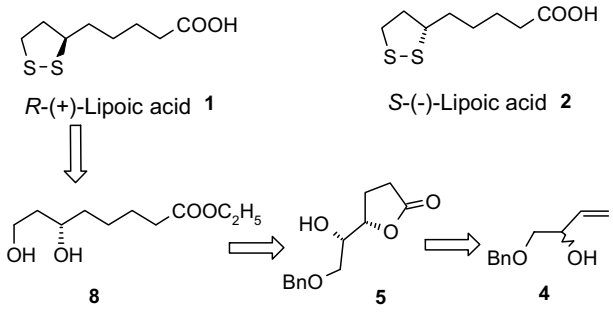
Abstract—An efficient synthesis of α-lipoic acid from the readily available *cis*-2-butene-1,4-diol employing a Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation as the key steps, is described.

R-(+)-α-Lipoic acid is the coenzyme associated with α-ketoacid dehydrogenase.[1] α-Lipoic acid was first isolated by Reed et al. in 1950 and characterized as the cyclic disulfide 5-[3-(1,2-dithiolanyl)]-pentanoic acid.[1a,2] The absolute configuration of natural α-(+)-lipoic acid was confirmed as *R* by the synthesis of its unnatural (−)-antipode from *S*-malic acid by Golding and co-workers[3] Lipoic acid is an important and powerful biological anti-oxidant that can directly scavenge free radicals and protect cells from oxidative damage.[4] Lipoic acid and its derivatives are highly active as anti-HIV[5] and anti-tumour agents.[6] The *R*-(+)-enantiomer is much more effective than the *S*-(−)-enantiomer at enhancing insulin-stimulated glucose transport and nonoxidative and oxidative glucose metabolism.[7]

The biological properties of both the enantiomers of α-lipoic acid have fostered significant interest in their synthesis.[8] The first asymmetric synthesis of (+)-lipoic acid was reported by Elliot in which the rather expensive (*S*,*S*)- pentane-2,4-diol was used as the starting material and source of optical purity.[9] Most of the syntheses of lipoic acid employ a Chiron approach. Our synthesis of α-lipoic acid comprises simple experimental procedures, which readily provide either enantiomer of lipoic acid starting from the readily available achiral precursor *cis*-2-butene-1,4-diol.

Our retrosynthetic analysis, as shown in Scheme 1, conceived the hydroxy lactone **5** as the key intermediate,



Scheme 1. Retrosynthetic analysis for **1**.

which would be derived from the allyl alcohol **4** by a Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation, to install the requisite chirality.

Enantiomerically pure hydroxy lactone **5**, the versatile intermediate for our synthesis, obtained in four steps from *cis*-2-butene-1,4-diol **3**,[10] was treated with triphenylphosphine, iodine and imidazole to give the iodo lactone **6**. Reduction of the lactone using DIBAL-H at −78 °C followed by an in situ two-carbon Wittig reaction gave the unsaturated ester **7**. Removal of the benzyl protection, removal of iodine and reduction of the double bond was achieved in one pot using W2 Raney nickel in the presence of hydrogen at room temperature and pressure for 24 h to give the diol **8**. The diol **8**, a well known intermediate for the synthesis of (+)-lipoic acid, was treated with mesyl chloride to deliver the dimesylate **9**. The dimesylate on reacting with Na_2S and elemental sulfur in DMF at 90 °C for 24 h gave ethyl lipoate **10**, which on hydrolysis with 1M ethanolic KOH gave *R*-(+)-α-lipoic acid. Having accomplished the synthesis of natural *R*-(+)-lipoic acid we turned our attention to

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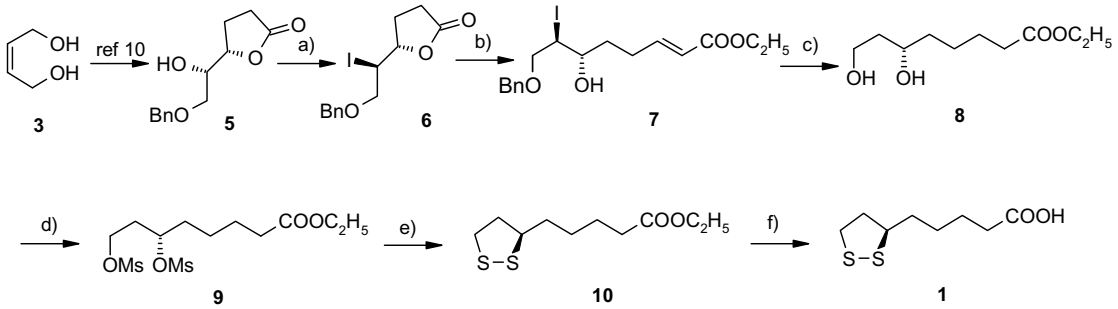

Scheme 2. Reagents and conditions: (a) PPh_3, I_2, imidazole, 70 °C, 3 h, 94%; (b) DIBAL-H, DCM, −78 °C, 1 h, $Ph_3PCHCOOC_2H_5$, 24 h; rt, 96%; (c) W2 Raney nickel, H_2, rt, 24 h, 84%; (d) CH_3SO_2Cl, Et_3N, DCM, 0 °C, 4 h, 92%; (e) Na_2S, S, DMF, 90 °C, 24 h, 72%; (f) 1 M ethanolic KOH, rt, 24 h, 75%.

synthesize unnatural *S*-(−)-lipoic acid. Accordingly we prepared the enantiomer of hydroxy lactone **5** by using AD-mix-β and then applying the same sequence of reactions as used to synthesize *R*-(+)-α-lipoic acid. The physical and spectroscopic data of all the synthetic materials are in good agreement with the proposed structures and those of **1** and **2** are in good agreement with the literature data[11] (Scheme 2).

In summary both *R*-(+)-α-and *S*-(−)-α-lipoic acid were synthesized efficiently in 34% overall yield in 8 steps from the allyl alcohol **4**, which in turn was obtained from the readily available cis-2-butene-1,4-diol as the common achiral precursor. The synthesis of other biologically active compounds from the versatile intermediate **5** are being investigated in our laboratory.

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11. All new compounds were characterized and gave satisfactory spectral data. Compound **5**: $[\alpha]_D^{24}$ +40.59 ($c = 1$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 2.25 (2H, m), 2.48 (2H, m), 2.69 (1H, m), 3.59 (2H, m), 3.84 (1H, m), 4.57 (3H, m), 7.33 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.37, 28.11, 70.57, 71.60, 73.14, 79.87, 127.51, 128.13, 137.47, 177.75 ppm. Compound **6**: $[\alpha]_D^{24}$ −19.77 ($c = 1$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 2.04 (1H, m), 2.42 (1H, m), 2.49 (2H, m), 3.72 (1H, dd, $J = 10.56$, 5.87 Hz), 3.83 (1H, dd, $J = 10.56$, 5.08 Hz), 4.31 (1H, m), 4.55 (3H, m), 7.32 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 27.60, 28.44, 33.96, 71.38, 72.88, 78.80, 127.43, 128.24, 137.25, 175.66 ppm. Compound **7**: $[\alpha]_D^{24}$ −24.67 ($c = 1$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 1.29 (3H, t, $J = 7.05$ Hz), 1.70 (1H, m), 1.90 (1H, m), 2.38 (2H, m), 2.97 (1H, br), 3.65–3.91 (3H, m), 4.20 (3H, m), 4.56 (2H, s), 5.8 (1H, dt, $J = 15.65$, 1.57 Hz), 6.96 (1H, dt, $J = 15.65$, 6.65 Hz), 7.32 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.08, 27.98, 33.86, 37.75, 59.84, 72.49, 72.89, 73.22, 121.45, 127.48, 127.74, 128.25, 137.00, 148.14, 166.11 ppm.
Compound **1**: mp: 48 °C, $[\alpha]_D^{24}$ +106.29 ($c = 0.1$, benzene). ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 1.52 (2H, m), 1.68 (4H, m), 1.91 (1H, m), 2.37 (2H, t, $J = 7.05$ Hz), 2.63 (1H, m), 3.18 (2H, m), 3.55 (1H, m), 12.45 (1H, br). ^{13}C NMR (50 MHz) δ: 24.44, 28.74, 33.88, 34.65, 38.48, 40.21, 56.20, 179.85 ppm.