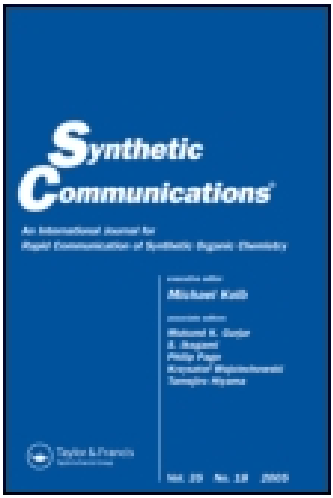

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New and Concise Approach to (R)-α-Lipoic Acid

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New and Concise Approach to (*R*)-α-Lipoic Acid

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Abstract: A concise enantiospecific synthesis of (*S*)-6,8-bis(methylsulfonyloxy)-octanoic acid (**2**), a ready precursor of (*R*)-(+)-α-lipoic acid (**1**), is reported. The key step of the synthesis is the coupling of the tosylate derived from (*R*)-malic acid with phenylpropyl magnesium bromide. A recently reported green procedure was used for the oxidative unmasking of the phenyl group, used as a latent carboxyl group.

Keywords: Asymmetric synthesis, lipoic acid, malic acid

(*R*)-(+)-α-Lipoic acid (**1**) (thioctic acid; 6,8-dithiooctanoic acid) is an important protein-bound coenzyme and growth factor first isolated in 1951 from processed insoluble liver residue.[1] Since then, lipoic acid has been found to be widely distributed in animal and plant tissue,[2] and displays an extremely high level of biological activity. Being a readily bioavailable compound capable of scavenging a number of free radicals and protecting cells from oxidative damage[3a] as well as from ionizing radiation–induced damage,[3b] α-lipoic acid is termed the ideal antioxidant.[4] Lipoic acid was also shown to possess protective and curative effects in heavy-metal-poisoned animals.[5] It was also found to be a potent growth-promoting factor, which stimulated reparative regeneration of soft tissues.[6] Recently, it has also been reported that α-lipoic acid and its derivatives are highly active as anti-HIV[7] and antitumor agents.[8] The

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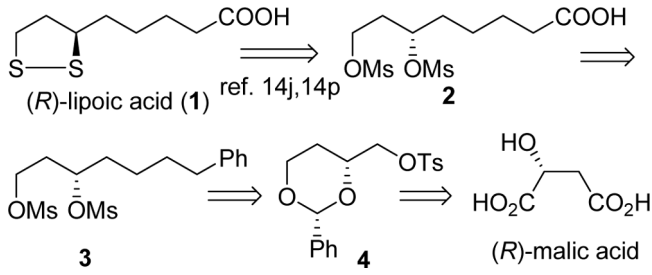
racemic α-lipoic acid can be used to treat various liver diseases including metal poisoning[9] and alcoholic liver diseases.[10] Moreover, (*R*)-(+)-α-lipoic acid is effective to a great extent in the treatment of various diseases such as mushroom poisoning,[11] diabetes, and neurodegenerative disorders.[12]

It has been shown that the (*R*)-enantiomer is much more effective than the (*S*)-enantiomer at enhancing insulin-stimulated glucose transport and nonoxidative and oxidative glucose metabolism.[13]

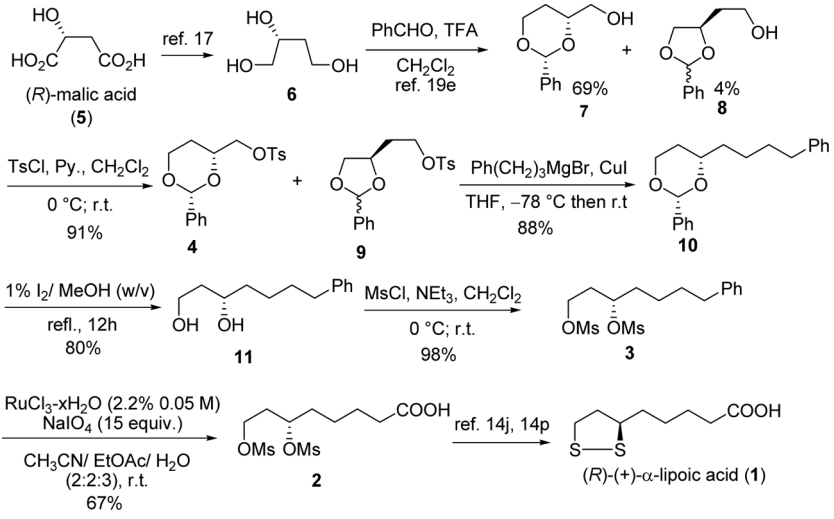
The biological properties of (*R*)-(+)-α-lipoic acid have created significant interest in its synthesis.[14] In continuation of our effort in developing malic acid–based synthetic methodologies,[15] we now report a new and concise synthesis of (*S*)-6,8-bis(methylsulfonyloxy) octanoic acid (**2**), a ready precursor to (*R*)-(+)-α-lipoic acid (**1**),[14j,14p] starting from (*R*)-malic acid.

Although (*R*)-malic acid has been used as a chiron for the first enantioselective synthesis of α-lipoic acid (*S*-**1**, and *R*-**1**),[14a,14b] the reported approach to (*S*)-**1** required a total of 15 synthetic steps starting from (*S*)-malic acid. As depicted retrosynthetically in Scheme 1, our approach is much shorter; only seven steps are required for the synthesis of (*S*)-6,8-bis(methylsulfonyloxy)octanoic acid (**2**) and one more step for (*R*)-lipoic acid. Our approach features the use of tosylate **4** as the key intermediate and phenyl group as a latent carboxyl group.[16]

The synthesis started from the known (*R*)-1,2,4-butanetriol (**6**),[17–19] easily available from (*R*)-malic acid either by lithium aluminum hydride (LAH) reduction of malate, or by Hanessian's one-pot method [BH_3•SMe_2, $B(OMe)_3$, THF, rt].[18] In the presence of trifluoroacetic acid (TFA), treatment of triol **6** with benzaldehyde at refluxing dichloromethane afforded regio- and diastereoselectively a mixture of two inseparable isomeric acetals in 73% yield, which contained 95% of *cis*-1,3-dioxane **7** and 5% of **8**[19] (Scheme 2). The two regioisomers, although inseparable by column chromatography, can be easily separated



Scheme 1. Retrosynthetic analysis of (*R*)-(+)-α-lipoic acid (**1**).



Scheme 2. Asymmetric synthesis of (*R*)-(+)-α-lipoic acid (**1**).

by recrystallization of their tosylate derivatives **4**[18c] and **9**. In the presence of a catalytic amount of CuI, the coupling of tosylate **4** with phenylpropyl magnesium bromide proceeded smoothly, which afforded the chain elongation product **10** in 88% yield.

For the cleavage of the acetal, compound **10** was treated with a solution of 4:1 *v*/*v* mixture of $AcOH/H_2O$, which gave the desired diol **11** in 67% yield. The yield was improved to 80% by using Szarek's method,[20] namely, by refluxing a methanolic solution of dioxane **10** in the presence of a catalytic amount of iodine. Bismesylation of **11** under standard conditions gave bismesylate **3** in 98% yield.

Next, we proceeded to investigate the oxidative cleavage of the phenyl group into a carboxyl group using ruthenium tetraoxide as an oxidant. Although subjection of **3** to the standard conditions established by Sharpless[21] (2.2% $RuCl_3$, 4.1 mol. equiv. $NaIO_4$ in CCl_4–MeCN–H_2O, 2/2/3, *v*/*v*) led to the desired product **2** in 68% yield, a recent report about the replacement of environmentally harmful CCl_4 by EtOAc[22] attracted our attention. To our delight, the greener solvent system (EtOAc–MeCN–H_2O, 2/2/3, *v*/*v*)[22] worked similarly well (room temperature, 5 days), affording bismesylate acid **2** in 67% yield. Because bismesylate **2** has been converted previously into (*R*)-α-lipoic acid,[14j,14p] our synthesis of **2** constitutes a formal enantioselective synthesis of (*R*)-α-lipoic acid.

In summary, starting from (*R*)-malic acid, a concise enantioselective synthesis of (*S*)-6,8-bis(methylsulfonyloxy)octanoic acid (**2**) was achieved in seven steps with an overall yield of 26%. In combination with the works of Page[14j] and Sudalai,[14p] our approach to (*R*)-(+)-α-lipoic acid (**1**) required only eight steps.

EXPERIMENTAL

General

Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Av400 spectrometer with tertramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by Applied Biosystem 32000 Trap (ESI direct injection). Optical rotations were measured with Rutoph-Autopol IV automatic polarimeter. High resolution mass spectroscopy (HRMS) spectra were recorded on a QSTAR Pulsar/LC/MS/MS System, ESI-QTOF instrument (Applied Biosystem, Canada). Melting points were determined on a Yanaco MP-500 melting-point apparatus and were corrected. Tetrahydrofuran (THF) used in the reactions was dried by distillation over metallic sodium and benzophenone; dichloromethane was distilled over P_2O_5. Silica gel (Zhifu, 300–400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (60–90 °C) mixtures.

(2*R*,4*R*)-4-Hydroxymethyl-2-phenyl-l,3-dioxane (7)

Trifluoroacetic acid (0.2 mL) and benzaldehyde (5.5 mL, 53.9 mmol) were added successively to a stirred CH_2Cl_2 solution (190 mL) of the known triol **6** (4.08 g, 38.0 mmol), easily available from (*R*)-malic acid.[17–19] After refluxing for 33 h, the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ at 0 °C. The mixture was extracted with CH_2Cl_2 (4 × 15 mL). The organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification of the residue (ethyl acetate–petroleum ether, 1:3) gave a colorless oil (5.45 g, 73%). According to the ^{1}H NMR integration, the resultant oil contained 95% of the regioisomer **7** and 5% of the regioisomeric dioxolane, with the former being diastereomeric pure and the latter being a ca. 1:1 mixture of the *trans*- and *cis*-diastereoisomers. The two regioisomeric dioxolanes cannot be separated by flash

chromatography. IR (film) ν_{max}: 3418 (br), 3065, 3035, 2923, 2859, 1635, 1454, 1363, 1103 cm^{-1}. The data for **7**[19b]: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.40–1.44 (m, 1H, *H*-5), 1.84–1.94 (m, 1H, *H*-5), 2.35 (br s, 1H, –O*H*), 3.60–3.67 (m, 2H, *H*-4, *H*-6), 3.93–3.99 (m, 2H, CH_2OH), 4.26–4.30 (m, 1H, *H*-6), 5.53 (s, 1H, *H*-2), 7.39–7.54 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.7, 65.5, 66.5. 77.5, 101.2, 126.1, 126.1, 128.2, 128.2, 128.9, 138.3; MS (ESI) m/z 217 ($M + Na^+$, 100).

(2*R*,4*R*)-4-Tosyloxymethyl-2-phenyl-l,3-dioxane (4)

Pyridine (4 mL) and a CH_2Cl_2 solution (10 mL) of *p*-TsCl (2.82 g, 15.0 mmol) were added successively to a stirred solution of dioxolane **7** (2.35 g, 12.0 mmol) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) in anhydrous CH_2Cl_2 (6 mL) at 0 °C. After stirring for 48 h at room temperature, the reaction was quenched with 5 mL of water and extracted with CH_2Cl_2 (4 × 15 mL). The organic layers were washed successively with saturated aqueous $CuSO_4$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash-chromatographic purification of the residue (ethyl acetate–petroleum ether, 1:3) gave a white solid (3.81 g, 91%). Recrystallization of the crude solid from pentane–ether–CH_2Cl_2 (2/1/1) gave isomerically pure dioxolane **4**[19e] (3.27 g, 86%) as white crystals. Mp 69–70 °C (pentane–ether–CH_2Cl_2, 2/1/1) [lit.[19e] mp 65 °C (ether–pentane, 1/2)]; $[\alpha]_D^{20} + 2.1$ (*c* 1.4, $CHCl_3$) [lit.[19e] $[\alpha]_D^{25} + 3.0$ (*c* 1.1, $CHCl_3$), $[\alpha]_D^{25} - 2.1$ (*c* 0.89, $CHCl_3$) for the (*S*,*S*)-enantiomer]; IR (film) ν_{max}: 3065, 3030, 2964, 2851, 1594, 1454, 1361, 1177, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.54 (m, 1H, *H*-5), 1.76–1.83 (m, 1H, *H*-5), 2.42 (s, 3H, PhCH_3), 3.91–3.98 (m, 1H, *H*-6), 4.04–4.10 (m, 1H, *H*-4), 4.11–4.15 (m, 2H, CH_2OTs), 4.25–4.30 (m, 1H, *H*-6), 5.45 (s, 1H, *H*-2), 7.26–7.78 (m, 9H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 27.2, 66.3, 71.5, 74.1, 101.0, 126.0, 126.0, 127.9, 127.9, 128.2, 128.2, 128.9, 129.8, 129.8, 132.7, 137.9, 144.9. MS (ESI) m/z 371 ($M + Na^+$, 100).

(2*R*,4*S*)-2-Phenyl-4-(4-phenylbutyl)-1,3-dioxane (10)

A solution of bis-tosylate **4** (576 mg, 1.70 mmol) in THF (3 mL) and CuI (250 mg) were added successively to a cooled (−78 °C) THF solution of 3-phenylpropyl magnesium bromide, freshly prepared from 1-bromo-3-phenylpropane (1.2 mL, 8.27 mmol) and magnesium (298 mg, 12.0 mmol) in anhydrous Et_2O (6 mL) followed by diluting with anhydrous THF (8 mL). After stirred for 48 h at room temperature, the reaction was quenched with aqueous NH_4Cl (11 mL) and extracted with CH_2Cl_2

(4×10 mL). The organic layers were washed with successively with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash-chromatographic purification of the residue (ethyl acetate–petroleum ether, 1:20) gave **10** (430 mg, 88%) as a colorless oil. $[\alpha]_D^{20}$ −29 (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 3062, 3026, 2933, 2843, 1598, 1495, 1453, 1363, 1242, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.43–1.81 (m, 8H, *H*-5, $(CH_2)_3CH_2Ph$), 2.62 (t, $J = 7.6$ Hz, 2H, CH_2Ph), 3.79–3.82 (m, 1H, *H*-4), 3.94 (td, $J = 12.2$, 2.4 Hz, 1 H, *H*-4), 4.04–4.10 (m, 1H, *H*-3), 5.49 (s, 1H, *H*-2), 7.16–7.49 (m, 9H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6, 31.4, 31.3, 35.8, 67.1, 77.1, 101.1, 125.6, 126.0, 126.0, 128.1, 128.1, 128.2, 128.2, 128.4, 128.4, 128.6, 138.9, 142.6; HRMS calcd. for $[C_{20}H_{24}O_2 + NH_4]^+$: 314.2115; found: 314.2117. Anal. calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.19; H, 8.57.

(*S*)-7-Phenylheptane-1,3-diol (11)

A methanolic (130 mL) solution of **10** (1.30 g, 4.39 mmol) and I_2 [1.270 g, 1% (w/v)] was refluxed for 12 h. The resulting mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ until the iodine's characteristic brown color disappeared. After concentration under reduced pressure, the residue was extracted with CH_2Cl_2 (4×10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash-chromatographic purification of the residue (ethyl acetate–petroleum ether, 1:1) gave **11** (0.729 g, 80%) as a colorless oil, and 16% of the starting material was recovered. $[\alpha]_D^{20}$ − 2.8 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 3353 (br), 3077, 3054, 3025, 2933, 2857, 1602, 1489, 1059cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35–1.74 (m, 8H, *H*-2, $(CH_2)_3CH_2Ph$), 2.54 (br s, 2H, 2O*H*), 2.62 (t, $J = 7.7$ Hz, 2H, CH_2Ph), 3.79–3.89 (m, 3H, *H*-1, *H*-3), 7.16–7.20 (m, 3H, Ph-*H*), 7.25–7.29 (m, 2H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 31.4, 35.9, 37.6, 38.2, 61.8, 72.2, 125.7, 128.3, 128.3, 128.4, 128.4, 142.5; HRMS calcd. for $[C_{13}H_{20}O_2 + NH_4]^+$: 226.1802; found: 226.1804. Anal. calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; Found: C, 74.39; H, 9.92.

(*S*)-7-Phenylheptan-1,3-diol Dimesylate (3)

Methanesulfonyl chloride (0.8 mL, 10.2 mmol) was added to a CH_2Cl_2 solution (23 mL) of diol **11** (0.961 g, 4.62 mmol) and triethylamine (4.5 mL, 32.3 mmol) at 0 °C. After stirring for 5 h, the reaction was quenched with 5 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers

were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash-chromatographic purification of the residue (CH_2Cl_2–petroleum ether, 3:1) gave **3** as a colorless oil (1.65 g, 98%). $[\alpha]_D^{20} + 19$ (*c* 1.4, $CHCl_3$); IR (film) ν_{max}: 3027, 2937, 2863, 1602, 1495, 1453, 1352, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.41–1.47 (m, 2H, *H*-4), 1.64–1.82 (m, 4H, *H*-5, *H*-6), 2.01–2.11 (m, 2H, *H*-2), 3.04 (t, $J = 7.6$ Hz, 2H, CH_2Ph), 2.99–3.04 (m, 6H, Ms-*H*), 4.32–4.35 (m, 2H, *H*-1), 4.85–4.88 (m, 1H, *H*-3), 7.16–7.20 (m, 3H, Ph-*H*), 7.26–7.29 (m, 2H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 30.9, 34.0, 34.7, 35.5, 37.4, 38.6, 65.6, 78.8, 125.8, 128.3, 128.3, 128.4, 128.4, 141.9. HRMS calcd. for $[C_{15}H_{24}O_6S_2 + NH_4]^+$: 382.1353; found: 382.1351. Anal. calcd. for $C_{15}H_{24}O_6S_2$: C, 49.43; H, 6.64. Found: C, 49.78; H, 6.77.

(*S*)-6,8-Bis(methylsulfonyloxy)octanoic Acid (2)

$NaIO_4$ (11.19 g, 52.3 mmol) in one portion and a 0.05 M aqueous solution of $RuCl_3 \bullet xH_2O$ (1.6 mL, 2.2%) were added successively to a solution of compound **3** (1.27 g, 3.49 mmol) in a mixed solvent system containing EtOAc–CH_3CN–H_2O [15 mL/15 mL/22 mL, 2/2/3 (v/v)] at 0 °C. The mixture was stirred at room temperature for 5 days. After addition of brine, the resulting mixture was filtered, and the aqueous phase was extracted with CH_2Cl_2 (4×15 mL). The combined organic layers were washed successively with $NaHSO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 40 °C. After purification of the residue by flash chromatography and eluting with ethyl acetate, the known bismesylate **2**[14j,14p] was obtained as a colorless oil (0.793 g, 68%), which solidified upon standing at 0 °C. White crystals were obtained after recrystallization from ether. Mp 56–57 °C (ether) [lit.[14j] mp 54–55 °C (ether)]; $[\alpha]_D^{20} + 20$ (*c* 1.0, $CHCl_3$) [lit.[14p] $[\alpha]_D^{25} + 22$ (*c* 1.0, $CHCl_3$)]; IR (film) ν_{max}: 3568 (br), 3029, 2941, 2872, 1712, 1349, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.44–1.53 (m, 2H, *H*-5), 1.65–1.83 (m, 4H, *H*-3, *H*-4), 2.05–2.16 (m, 2H, *H*-7), 2.40 (t, $J = 7.2$ Hz, 2H, *H*-2), 3.06–3.07 (m, 6H, Ms-*H*), 4.32–4.93 (m, 2H, *H*-6), 4.87–4.93 (m, 1H, *H*-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.1, 24.2, 33.5, 34.0, 34.6, 37.4, 38.7, 65.6, 78.4, 178.8; HRMS calcd. for $[C_8H_{14}O_2S_2 + NH_4]^+$: : 350.0938; Found: 350.0939.

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REFERENCES

1. (a) Reed, L. J.; Gounsalus, I. C.; De Busk, B. G.; Homberger, C. S. Crystalline α-lipoic acid: A catalytic agent associated with dehydrogenase. *Science* **1951**, *114*, 93–94; (b) Sigel, H. The hydrophobic and metal-ion coordinating properties of α-lipoic acid—An example of intramolecular equilibria in metal-ion complexes. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 389–400.
2. Schmidt, U.; Grafen, P.; Goedde, H. W. Biochemistry and chemistry of lipoic acids. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1969**, *32*, 423–469.
3. (a) Bast, A.; Haenen, G. R. M. M. Interplay between lipoic acid and glutathione in the protection against microsomal lipid peroxidation. *Biochim. Biophys. Acta* **1988**, *963*, 558–561; (b) Prasad, K. N.; Cole, W. C.; Haase, G. M. Radiation protection in humans: Extending the concept of as low as reasonably achievable (ALARA) from dose to biological damage. *Brit. J. Radio.* **2004**, *77*, 97–99.
4. Packer, L.; Tritschler, H. J.; Wessel, K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. *Free Rad. Biol. Med.* **1997**, *22*, 359–378.
5. Maruyama, S.; Hachisu, M.; Iwanaga, H.; Ino, Y.; Ogasawara, S.; Yamada, S. Pharmacological study on acute toxicity of mercuric chloride in mice. *Showa Igakkai Zasshi* **1977**, *37*, 449–454; *Chem. Abstr.* **1979**, *90*, 115983y.
6. Bilch, G. L.; Suslova, O. I.; Mukhin, V. P.; Poroolla, V. I.; Galankin, B. N.; Bogomolova, R. A. Possible use of lipoic acid during acute cholecystitis and cholecystopancreatitis (experimental clinical study). *Izuch. Biol. Deistuiya Prod. Org. Sint. Prir. Soedin* **1976**, 122–130; *Chem. Abstr.* **1978**, *88*, 164426 m.
7. Baur, A.; Harrer, T.; Peukert, M.; Jahn, G.; Kalden, J. R.; Fleckenstein, B. Alpha-lipoic acid is an effective inhibitor of human immunodeficiency virus (HIV-1) replication. *Klin. Wochenschr.* **1991**, *69*, 722–724; *Chem. Abstr.* **1992**, *116*, 207360b.
8. Bingham, P. M.; Zachar, Z. Preparation of lipoic acid derivatives as antitumor agents. *PCT Int. Appl.* WO 00 24,734, 2000; *Chem. Abstr.* **2000**, *132*, 308192j.
9. Muller, L. Protective effects of DL-alpha-lipoic acid on cadmium-induced deterioration of rat hepatocytes. *Toxicology* **1989**, *58*, 175–185.
10. Bustamante, J.; Lodge, J. K.; Marcocci, L.; Tritschler, H. J.; Packer, L.; Rihn, B. H. Alpha-lipoic acid in liver metabolism and disease. *Free Rad. Biol. Med.* **1998**, *24*, 1023–1039.
11. Plotzker, R.; Jensen, D.; Payne, J. A. Case report: Amanita virosa acute hepatic necrosis: Treatment with thioctic acid. *Am. J. Med. Sci.* **1982**, *283*, 79–82.

12. Alterkrich, H.; Stoltenburg-Didinger, G.; Wagner, H. M.; Herrmann, J.; Walter, G. Effects of lipoic acid in hexacarbon-induced neuropathy. *Neurotoxicol. Tetratol.* **1990**, *12*, 619–622.
13. Streeper, R. S.; Henriksen, E. J.; Tritschler, H. Differential effects of lipoic acid stereoisomers on glucose metabolism in insulin-resistant skeletal muscle. *Am. J. Physiol.* **1997**, *273*, E185–191.
14. (a) Brookes, M. H.; Golding, B. T.; Howes, D. A.; Hudson, A. T. Proof that the absolute configuration of natural α-lipoic acid is R by the synthesis of its enantiomer [(*S*)-(−)-α-lipoic acid] from (*S*)-malic acid. *J. Chem. Soc., Chem. Commun.* **1983**, *19*, 1051–1053. The same group has completed a synthesis of the natural enantiomer; (b) Brookes, M. H.; Golding, B. T.; Hudson, A. T. Syntheses of α-(*R*)- and α-(*S*)-lipoic acid from (*S*)-malic acid. *J. Chem. Soc., Perkin Trans. 1* **1988**, 9–12; (c) Elliott, J. D.; Steele, J.; Johnson, W. S. An efficient, asymmetric synthesis of *R*-(+)-α-lipoic acid. *Tetrahedron Lett.* **1985**, *26*, 2535–2528; (d) Rao, A. V. R.; Gurjar, M. K.; Garyali, K.; Ravindranathan, T. Enantiospecific synthesis of (R)-(+)-α-lipoic acid from D-glucose. *Carbohydr. Res.* **1986**, *148*, 51–55; (e) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. Enantioselective synthesis of R-(+)-α-lipoic acid. *J. Chem. Soc., Chem. Commun.* **1986**, *18*, 1408–1409; (f) Rao, A. V. R.; Punrandare, A. V.; Reddy, E. R.; Gurjar, M. K. Syntheses of (R)-(+)-α-lipoic acid. *Synth. Commun.* **1987**, *17*, 1095–1102; (g) Rao, A. V. R.; Mysorekar, S. V.; Yadav, J. S. Syntheses of 1,3-diols: Its application to the syntheses of α-lipoic acid. *Synth. Commun.* **1987**, *17*, 1339–1347; (h) Rao, A. V. R.; Mysorekar, S. V.; Gurjar, M. K.; Yadav, J. S. Synthesis of (3*R*,4*R*)-1,5-hexadiene-3,4-diol and its unsymmetrical derivatives: Application to (*R*)-(+)-α-lipoic acid. *Tetrahedron Lett.* **1987**, *28*, 2183–2186; (i) Menon, R. B.; Kumar, M. A.; Ravindranathan, T. Stereospecific synthesis of α-lipoic acid. *Tetrahedron Lett.* **1987**, *28*, 5313–5314; (j) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. An enantioselective synthesis of *R*-(+)-α-lipoic acid. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 1615–1618; (k) Gopalan, A. S.; Jacobs, H. K. Baker's yeast reduction of alkyl 6-chloro-3-oxohexanoates: Synthesis of *R*-(+)-α-lipoic acid. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 1897–1900; (l) Rao, B. V.; Rao, A. S. A common strategy for the synthesis of (+)-hepialone and (+)-α-lipoic acid. *Synth. Commun.* **1995**, *25*, 1531–1543; (m) Laxmi, Y. R. S.; Iyengar, D. S. Chemoenzymic synthesis of methyl (6*S*)-(−)-6,8-dihydroxyoctanoate: A precursor to (*R*)-(+)-α-lipoic acid. *Synthesis* **1996**, *5*, 594–596; (n) Adger, B.; Bes, M. T.; Grogan, G.; McCaque, R.; Pedragosa, M. S.; Roberts, S. M.; Villa, R.; Wan, P. W. H.; Willetts, A. The synthesis of (*R*)-(+)-lipoic acid using a monooxygenase-catalyzed biotransformation as the key step. *J. Bioorg. Med. Chem.* **1997**, *5*, 253–261; (o) Chavan, S. P.; Praveen, C. A concise and stereoselective synthesis of (+)- and (−)-deoxoprosophylline. *Tetrahedron Lett.* **2004**, *45*, 421–423; (p) Upadhya, T. T.; Nikalje, M. D.; Sudalai, A. Asymmetric dihydroxylation and hydrogenation approaches to the enantioselective synthesis of *R*-(+)-α-lipoic acid. *Tetrahedron Lett.* **2001**, *42*, 4891–4893; (q) Chavan, S. P.; Praveen, C.; Ramakrishna, G.; Kalkote, U. R. Enantioselective synthesis of *R*-(+)-α and *S*-(−)-α-lipoic acid.

Tetrahedron Lett. **2004**, *45*, 6027–6028; (r) Zimmer, R.; Hain, U.; Berndt, M.; Gewald, R.; Reissig, H. U. Enantioselective synthesis of (*S*)- and (*R*)-6-hydroxy-8-nonene-carboxylates by asymmetric catalysis: A formal synthesis of (*R*)-α-lipoic acid and its (*S*)-antipode. *Tetrahedron: Asymmetry* **2000**, *11*, 879–887; (s) Zhang, S.; Chen, X.; Zhang, J.; Wang, W.; Duan, W. An enantioselective formal synthesis of (+)-(*R*)-α-lipoic acid by an L-proline-catalyzed aldol reaction. *Synthesis* **2008**, *3*, 383–386; (t) Bringmann, G.; Herzberg, B.; Adam, G. A short and productive synthesis of (*R*)-α-lipoic acid. *Zeitschrift Naturforsch. B, Chem. Sci.* **1999**, *54*, 655–661.

15. For two accounts, see (a) Huang, P.-Q. Recent advances on the asymmetric synthesis of bioactive 2-pyrrolidinone-related compounds starting from enantiomeric malic acid. In *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; J. L. Vicario, D. Badia, L. Carrillo (Eds.); Research Signpost: Kerala, 2005; p. 197; (b) Huang, P.-Q. Asymmetric synthesis of hydroxylated pyrrolidines, piperidines and related bioactive compounds: From N-acyliminium chemistry to N-alpha-carbanion chemistry. *Synlett* **2006**, *8*, 1133–1149.
16. For a review of the synthetic application of oxidative degradation of benzene rings, see Mander, L. N.; Williams, C. M. Oxidative degradation of benzene rings. *Tetrahedron* **2003**, *59*, 1105–1136.
17. For reviews on the use of both enantiomers of tartaric acid as chirons, see (a) Coppola, G. M., Schuster, H. F. *α-Hydroxy Acids in Enantioselective Syntheses*; Wiley-VCH: Weinheim, 1997; (b) Gawronski, J.; Gawronska, K. *Tartaric and Malic Acids in Synthesis: A Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents*; Wiley: New York, 1999; (c) Ghosh, A. K.; Koltun, E. S.; Bilcer, G. Tartaric acid and tartrates in the synthesis of bioactive molecules. *Synthesis* **2001**, *9*, 1281–1301; (d) Yoda, H. Recent advances in the synthesis of naturally occurring polyhydroxylated alkaloids. *Curr. Org. Chem.* **2002**, *6*, 223–243.
18. (a) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. Structure and synthesis of dihydroxypentyluracil from bacteriophage SP-15 deoxyribonucleic acid. *J. Am. Chem. Soc.* **1973**, *95*, 8749–8757; (b) Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. Facile access to (*S*)-1,2,4-butantriol and its derivatives. *Can. J. Chem.* **1984**, *62*, 2146–2149.
19. (a) Sanchez-Sancho, F.; Valverde, S.; Herradon, B. Stereoselective syntheses and reactions of chiral oxygenated α,β-unsaturated-γ- and δ-lactones. *Tetrahedron: Asymmetry* **1996**, *7*, 3209–3246; (b) Toshima, H.; Sato, H.; Ichihara, A. Total synthesis of (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide, a new biologically active δ-lactone produced by Seiridium unicorne. *Tetrahedron* **1999**, *55*, 2581–2590; (c) Yadav, J. S.; Rao, K. V.; Reddy, M. S.; Prasad, A. R. Stereoselective synthesis of (−)-tetrahydrolipstatin via a radical cyclization based strategy. *Tetrahedron Lett.* **2006**, *47*, 4393–4395; (d) Hungerbuhler, E.; Seebach, D.; Wasmuth, D. Doppelt und dreifach funktionalisierte, enantiomerenreine C4-synthese baustrine aus β-hydroxybuttersäure, Äpfelsäure und weinsäure. *Helv. Chim. Acta* **1981**, *64*, 1467–1487; (e) Yang, G. L.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P.; Arthur,

G. Convergent *C*-glycolipid synthesis via the Ramberg–Bäcklund reaction: Active antiproliferative glycolipids. *Org. Lett.* **1999**, *1*, 2149–2151.
20. Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. A new, facile method for cleavage of acetals and dithioacetals in carbohydrate derivatives. *Tetrahedron Lett.* **1986**, *27*, 3827–3830.
21. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. A greatly improved procedure for ruthenium tetroxide catalyzed oxidations of organic compounds. *J. Org. Chem.* **1981**, *46*, 3936–3938.
22. Zimmermann, F.; Mend, E.; Oget, N. Ruthenium catalysed oxidation without CCl_4 of oleic acid, other monoenic fatty acids, and alkenes. *Tetrahedron Lett.* **2005**, *46*, 3201–3203.