Biosci. Biotechnol. Biochem., **63** (11), 2025–2027, 1999

Note

Synthesis of Methyl (*S*)-(−)-6,8-Dihydroxyoctanoate as a Precursor of (*R*)-(+)-α-Lipoic Acid

Makoto GANAHA, Satoshi YAMAUCHI, and Yoshiro KINOSHITA†

Department of Agricultural Chemistry, Faculty of Agriculture, Ehime University, Tarumi 3-5-7, Matsuyama, Ehime 790-8566, Japan

Received June 7, 1999; Accepted June 25, 1999

The synthesis of methyl (*S*)-(−)-6,8-dihydroxyoctanoate as a precursor of (*R*)-(+)-α-lipoic acid was accomplished by using methyl (*S*)-(−)-(2-oxocyclohexyl)acetate, which had been obtained from baker's yeast reduction, as a chiral starting material.

Key words: yeast reduction; γ-ketoester; asymmetric reduction; (*R*)-(+)-α-lipoic acid

We have previously reported[1] that baker's yeast reduction of alkyl (2-oxocyclohexyl)acetate (γ-keto ester) afforded (2*S*)-*trans*-alcohols, (2*S*)-*cis*-alcohols, and unaltered (1*S*)-ketones with high optical purity.

(*R*)-(+)-α-Lipoic acid **1**, which is a cofactor in the biochemical decarboxylation of keto acids and has also been reported to be a growth factor for a variety of microorganisms, has previously been synthesized[2,3] from naturally available chiral starting materials or by asymmetric synthesis.

We now apply our procedure[1] of baker's yeast reduction to synthesize methyl (*S*)-(−)-6,8-dihydroxyoctanoate **2**, a precursor of (*R*)-(+)-α-lipoic acid (Fig.).

We planned to synthesize lipoic acid by using the product from baker's yeast reduction as the starting material. (*S*)-Keto-ester **3**, which had been obtained from the baker's yeast reduction, was converted to lactones **4** (77% yield) and **5** (12% yield) by Baeyer-Villiger oxidation[4] (*m*CPBA in the presence of a phosphate buffer at pH 8). The Baeyer-Villiger oxidation (**3**→**4**), the key step in the present synthesis, has been reported to proceed with the complete retention of configuration.[5] We first carried out the Baeyer-Villiger oxidation with *m*CPBA in the presence of $NaHCO_3$, but the enantiomeric excess was low (59%). To avoid racemization of the substrate, the reaction was performed with the pH 8 buffer. In this case, oxidation proceeded with perfect retention of the configuration (>99% ee.). Major isomer **4** was then reduced to triol **6** with $LiAlH_4$ (86%), and the resulting 1,3-dihydroxy moiety was protected as acetonide-derivative **7** (75%). Conversion to **9** was accomplished by the stepwise oxidation of primary alcohol **7** to corresponding aldehyde **8** with PDC in dichloromethane[6] (75%) and then to carboxylic acid **9** with *m*CPBA.[7] Acid **9** was esterified by ethereal CH_2N_2, and the exposure of acetonide **10** to *p*-TsOH in MeOH gave dihydroxy-ester **2** (56% from **8**, $[\alpha]_D^{22}$ −5.2° (*c* 1.728, $CHCl_3$); lit.[3a] $[\alpha]_D^{25}$ −4.1° ($CHCl_3$)).

The enantiomeric excess of **2** was determined by an HPLC analysis of its derivative. First, racemic (±)-**2** was converted to trityl ether (±)-**11** with TrCl and then treated with (−)-menthyl chloroformate to afford the corresponding diastereomeric carbonate mixture. HPLC analysis gave well-separated 1:1 signals for the diastereomers. Next, in a similar manner, optically active **2** was converted to **11** and then transformed to corresponding carbonate **12**. An HPLC analysis of **12** showed it to be of >99% ee.

Conversion of **2** into (*R*)-(+)-lipoic acid **1** has already been achieved by several workers.[3] Thus, a formal synthesis of (*R*)-(+)-lipoic acid **1** was achieved. The present method provides easy access to natural (*R*)-(+)-lipoic acid of high optical purity.

Experimental

Column chromatography was performed on silica gel (Wakogel C-300, 200–300 mesh). IR spectra were determined with a Shimadzu FTIR-8100 instrument, while ^{1}H-NMR spectra were recorded with a JNM-EX400 FT-NMR instrument. Specific rotation values were determined with a Horiba SEPA-200 instrument. Dry baker's yeast of the "saf-instant" brand from S. I. Lesaffre (France) was used. HPLC analyses were carried out in a pre-packed column (Cica-Merck, LiChrospher Si 60, UV detection at 270 nm, hexane-EtOAc=35:1 at 2 ml/min) with a Shimadzu LC-6AD instrument fitted with a UV-VIS detector (Shimadzu SPD-6AV). EIMS data were measured with a Hitachi M-80 spectrometer.

*(S)-6-Methoxycarbonylmethyl-6-hexanolide (**4**).* To a vigorously stirred mixture of **3** (704 mg, 4.14 mmol) in $CHCl_3$ (12 ml) and a pH 8 sodium phosphate buffer (0.1 M, 12 ml) at 0°C was added *m*CPBA (1.43 g, 8.28 mmol). The resulting mixture was stirred from 0°C to rt for 24 h. The organic layer was separated, and the resulting aqueous layer was extracted with CH_2Cl_2. The combined organic layers were successively washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (eluting with 10:1 benzene-EtOAc) to give **4** (593 mg, 77% yield) and (*S*)-2-methoxycarbonylmethyl-6-hexanolide **5** (96 mg, 12% yield). **4**: $[\alpha]_D^{18}$ +29.5° (*c* 3.386, $CHCl_3$); ^{1}H-NMR δ_H ($CDCl_3$): 4.72–4.82 (1H, m), 3.71 (3H, s), 2.81 (1H, dd, *J*=16.1, 7.32 Hz), 2.64–2.71 (2H, m), 2.55 (1H, dd, *J*=16.1, 5.86 Hz),

† To whom correspondence should be addressed. FAX: +81-89-977-4364; E-mail: ykin@agr.ehime-u.ac.jp

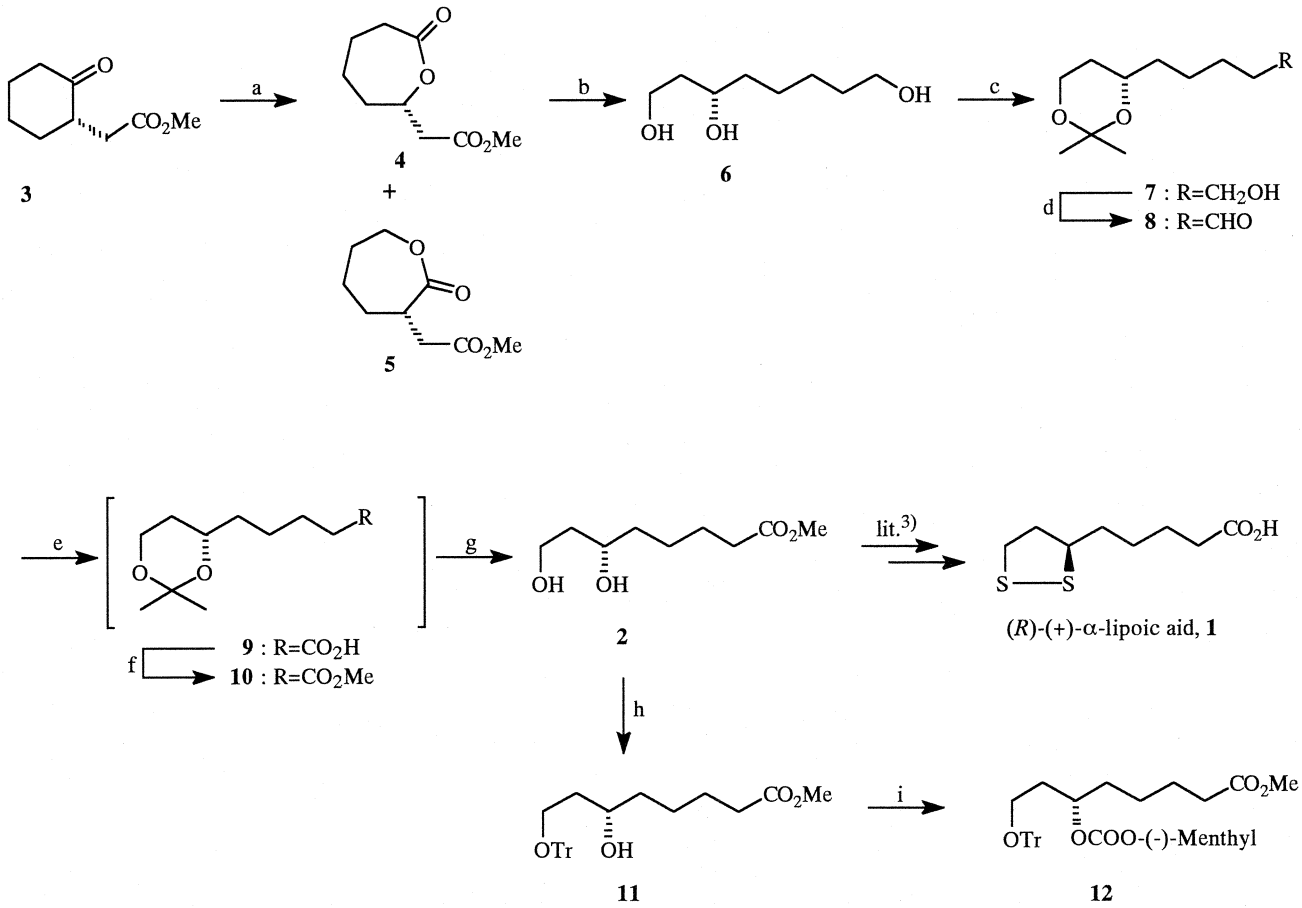

Fig. Synthesis of Methyl (*S*)-6,8-dihydroxyoctanoate (**2**).
a: *m*CPBA, $CHCl_3$, pH 8 buffer solution, 0°C to rt. (77% for **4**, 12% for **5**); b: $LiAlH_4$, THF, rt. (86%); c: $Me_2C(OMe)_2$, *p*-TsOH, DMF, rt. (75%); d: PDC, CH_2Cl_2, rt. (75%); e: *m*CPBA, CH_2Cl_2, rt.; f: CH_2N_2, ether; g: *p*-TsOH, MeOH, rt. (e–g, 56%); h: TrCl, Py., CH_2Cl_2, rt. (76%); i: (−)-menthyl chloroformate, Py., 4-DMAP, toluene, rt.

1.90–2.03 (3H, m), 1.54–1.73 (3H, m); IR ($CHCl_3$): 1732, 1728 cm^{-1}; HRMS *m/z* (M^+): calcd. for $C_9H_{14}O_4$, 186.0892; found, 186.0888. **5**: $[\alpha]_D^{18}$ −36.3° (*c* 1.212, $CHCl_3$); ^{1}H-NMR δ_H ($CDCl_3$): 4.30–4.36 (2H, m), 3.69 (3H, s), 3.14–3.22 (1H, m), 2.90 (1H, dd, *J*=17.1, 7.81 Hz), 2.39 (1H, dd, *J*=17.1, 6.34 Hz), 1.90–2.06 (2H, m), 1.47–1.82 (4H, m); IR ($CHCl_3$): 1728 cm^{-1}; CIMS *m/z*: (MH^+) 187.

(S)-1,3,8-Octanetriol (6). To an ice-cold solution of **4** (522 mg, 2.80 mmol) in THF (30 ml) was added $LiAlH_4$ (851 mg, 22.4 mmol) over 10 min. After the mixture had been stirred at room temp. for 22 h, the reaction was quenched by successively adding H_2O while cooling, 10% aqueous NaOH and H_2O. The resulting solid was removed by filtration, and the filter cake was washed with $CHCl_3$. The combined filtrate and washings were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (eluting with 10:1 $CHCl_3$–MeOH) to afford **6** (393 mg, 86% yield): $[\alpha]_D^{19}$ +4.3° (*c* 5.748, EtOH) (lit.[8] $[\alpha]_D$ +4.58° (*c* 1.66, EtOH)); ^{1}H-NMR δ_H ($(CD_3)_2SO$): 4.27–4.33 (2H, m), 4.24 (1H, d, *J*=5.37 Hz), 3.43–3.56 (3H, m), 3.32–3.41 (2H, m), 1.19–1.55 (10H, m); IR ($CHCl_3$): 3100–3580 cm^{-1}.

(S)-4-(5-Hydroxypentyl)-2,2-dimethyl-1,3-dioxane (7). To a stirred solution of **6** (347 mg, 2.14 mmol) in DMF (2.6 ml) were added 2,2-dimethoxypropane (0.394 ml, 334 mg, 3.20 mmol) and *p*-TsOH·H_2O (40 mg), and the mixture was stirred at room temp. for 20 h. Triethylamine was then added dropwise until the pH value became basic, and the mixture was concentrated. The residue was purified by chromatography (eluting with 2:1 hexane-EtOAc) to give **7** (323 mg, 75% yield): $[\alpha]_D^{20}$ −11.2° (*c* 5.018, $CHCl_3$); ^{1}H-NMR δ_H ($CDCl_3$): 3.95 (1H, td, *J*=11.97, 2.93 Hz), 3.78–3.87 (2H, m), 3.64 (2H, t, *J*=6.35 Hz), 1.45 (3H, s, overlapping m), 1.38 (3H, s, overlapping m), 1.23–1.63 (11H, m); IR ($CHCl_3$): 3150–3600 cm^{-1}; CIMS *m/z*: (MH^+) 203; HRMS *m/z* (M^+-CH_3): calcd. for $C_{10}H_{19}O_3$, 187.1334; found, 187.1341.

(S)-6,8-(Dimethylmethylenedioxy)octanal (8). To a stirred solution of **7** (276 mg, 1.37 mmol) in CH_2Cl_2 (2 ml) was added PDC (770 mg, 2.05 mmol), and the mixture was stirred at room temp. for 19 h. After dry ether (2 ml) had been added, the mixture was stirred for 30 min. It was then filtered through Celite, and the resulting filtrate was purified by chromatography (eluting with ether) to afford **8** (206 mg, 75% yield): IR ($CHCl_3$):

1723 cm^{-1}. This compound was unstable and was therefore used immediately.

Methyl (S)-6,8-dihydroxyoctanoate (2). To a stirred solution of **8** (161 mg, 0.806 mmol) in CH_2Cl_2 (3 ml) was added *m*CPBA (278 mg, 1.61 mmol), and the mixture was stirred at room temp. for 1.5 h. It was then cooled in an ice-bath, and the resulting precipitate was filtered off. The filtrate was treated with an ethereal solution of CH_2N_2 and allowed to stand for 20 min. The excess CH_2N_2 was decomposed by adding acetic acid, and the solution was concentrated. To the residue in methanol (9 ml) was added *p*-TsOH·H_2O (0.15 g), and the mixture was stirred at room temp. for 30 min. Triethylamine was then added dropwise until the pH value became basic, and the mixture was concentrated. The residue was purified by chromatography (eluting with EtOAc) to give dihydroxy-ester **2** (86 mg, 56% yield in 3 steps): $[\alpha]_D^{22}$ −5.2° (*c* 1.728, $CHCl_3$); ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 3.78–3.95 (3H, m), 3.67 (3H, s), 2.77 (1H, br.s), 2.62 (1H, br.s), 2.34 (2H, t, J=7.57 Hz, 1.30–1.77 (8H, m); IR ($CHCl_3$): 3450, 1728 cm^{-1}; Found: C, 56.17; H, 9.27. Calcd. for $C_9H_{18}O_4$: C, 56.82; H, 9.54.

Methyl (S)-6-hydroxy-8-trityloxyoctanoate (11). To a stirred solution of **2** (24 mg, 0.13 mmol) in CH_2Cl_2 (1 ml) were added pyridine (0.090 ml, 88 mg, 1.1 mmol) and TrCl (45 mg, 0.16 mmol), and the mixture was stirred at room temp. for 6 h under N_2. The reaction was quenched by adding sat. NH_4Cl, and the organic phase was separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (eluting with 5:1 benzene-EtOAc) to afford trityl ether **11** (42 mg, 76% yield): $[\alpha]_D^{22}$ −21.7° (*c* 0.830, $CHCl_3$); ^{1}H-NMR δ_H ($CDCl_3$): 7.13–7.46 (15H, m), 3.70–3.80 (1H, m), 3.66 (3H, s), 3.32–3.42 (1H, m), 3.18–3.27 (1H, m), 2.88–2.97 (1H, br.s), 2.30 (2H, t, J=7.33 Hz), 1.20–1.80 (8H, m); IR ($CHCl_3$): 3500, 1732 cm^{-1}; Found: C, 77.09; H, 7.43. Calcd. for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46.

Determination of the enantiomeric excess of **2**. A mixture of trityl ether **11** (14 mg, 0.031 mmol), pyridine (0.076 ml, 0.94 mmol), 4-DMAP (cat.), and (−)-menthyl chloroformate (0.13 ml, 0.63 mmol) in toluene (0.7 ml) was stirred at room temp. for 4 h under N_2. The reaction mixture was successively washed with cold 0.5 M HCl, sat. $NaHCO_3$ and brine, and dried over Na_2SO_4. A sample of racemic **11** was similarly prepared from racemic **3**. The carbonate of the latter compound showed two well-separated peaks with an area ratio of 1:1 by HPLC (retention times: (*R*)-(−)-menthyl carbonate, 32.9 min; (*S*)-(−)-menthyl carbonate, 35.4 min). HPLC analysis of the first sample gave a single peak. Thus, the sample of **2** was of >99% ee.

Acknowledgments

The authors express their sincere gratitude to the members of Advanced Instrumentation Center of Chemical Analysis at Ehime University for NMR and EIMS measurements.

References

1) Ganaha, M., Funabiki, Y., Motoki, M., Yamauchi, S., and Kinoshita, Y., Reduction of alkyl (2-oxocyclohexyl)acetates by baker's yeast. *Biosci. Biotechnol. Biochem.*, **62**, 181–184 (1998).
2) (a) Elliott, J. D., Steele, J., and Johnson, W. S., Asymmetric synthesis *via* acetal templates. 12. Highly diastereoselective coupling reactions with a ketene acetal. An efficient, asymmetric synthesis of *R*-(+)-α-lipoic acid. *Tetrahedron Lett.*, **26**, 2535–2538 (1985); (b) Page, P. C. B., Rayner, C. M., and Sutherland, I. O., Enantioselective synthesis of (*R*)-(+)-α-lipoic acid. *J. Chem. Soc., Chem. Commun.*, 1408–1409 (1986); (c) Rao, A. V. R., Mysorekar, S. V., Gurjar, M. K., and Yadav, J. S., Synthesis of (3*R*, 4*R*)-1,5-hexadien-3,4-diol and its unsymmetrical derivatives: Application to (*R*)-(+)-α-lipoic acid. *Tetrahedron Lett.*, **28**, 2183–2186 (1987); (d) Menon, R. B., Kumar, M. A., and Ravindranathan, T., Stereospecific synthesis of α-lipoic acid. *Tetrahedron Lett.*, **28**, 5313–5314 (1987); (e) Gopalan, A. S. and Jacobs, H. K., Stereochemical control of yeast reductions: Synthesis of *R*-(+)-α-lipoic acid. *Tetrahedron Lett.*, **30**, 5705–5708 (1989); (f) Page, P. C. B., Rayner, C. M., and Sutherland, I. O., An enantioselective synthesis of *R*-(+)-α-lipoic acid. *J. Chem. Soc., Perkin Trans 1*, 1615–1618 (1990); (g) Gopalan, A. S. and Jacobs, H. K., Bakers' yeast reduction of alkyl 6-chloro-3-oxohexanoates: Synthesis of (*R*)-(+)-α-lipoic acid. *J. Chem. Soc., Perkin Trans. 1*, 1897–1900 (1990).
3) (a) Dasaradhi, L., Fadnavis, N. W., and Bhalerao, U. T., A novel enantiospecific synthesis of (*S*)-(−)-methyl 6,8-dihydroxyoctanoate, a precursor of (*R*)-(+)-α-lipoic acid. *J. Chem. Soc., Chem. Commun.*, 729–730 (1990); (b) Brookes, M. H., Golding, B. T., and Hudson, A. T., Syntheses of α-(*R*)- and α-(*S*)-lipoic acid from (*S*)-malic acid. *J. Chem. Soc., Perkin Trans. 1*, 9–12 (1988); (c) Adger, B., Bes, M. T., Grogan, G., McCague, R., P-Moreau, S., Roberts, S. M., Villa, R., Wan, P. W. H., and Willetts, A. J., Application of enzymic Baeyer-Villiger oxidations of 2-substituted cycloalkanones to the total synthesis of (*R*)-(+)-lipoic acid. *J. Chem. Soc., Chem. Commun.*, 1563–1564 (1995).
4) Wang, J., Busson, R., Blaton, N., Rozenski, J., and Herdewijn, P., Enantioselective approach to the synthesis of cyclohexane carbocyclic nucleosides. *J. Org. Chem.*, **63**, 3051–3058 (1998).
5) Hassall, C. H., The Baeyer-Villiger oxidation of aldehydes and ketones. In "Organic Reactions, Vol. IX," eds. Adams, R., Blatt, A. H., Cope, A. C., Curtin, D. Y., and Mcgrew, F. C., John Wiley & Sons Inc., New York, pp. 73–106 (1957).
6) Corey, E. J. and Schmidt, G., Useful procedures for the oxidation of alcohols involving pyridinium dichromate in aprotic media. *Tetrahedron Lett.*, 399–402 (1979).
7) Coe, J. W. and Roush, W. R., Studies of an intramolecular Diels-Alder approach to the nargenicins: Involvement of boatlike transition states in the cyclizations of substituted 1,7,9-decatrien-3-ones. *J. Org. Chem.*, **54**, 915–930 (1989).
8) Liu, C. and Coward, J. K., Stereospecific synthesis of (*R*)- and (*S*)-*S*-adenosyl-1,8-diamino-3-thiooctane, a potent inhibitor of polyamine biosynthesis. Comparison of asymmetric induction vs enantiomeric synthesis. *J. Med. Chem.*, **34**, 2094–2101 (1991).