Carbohydrate Research, 148 (1986) 51–55
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

ENANTIOSPECIFIC SYNTHESIS OF (*R*)-(+)-α-LIPOIC ACID FROM D-GLUCOSE*

A. V. RAMA RAO, MUKUND K. GURJAR, KAMINI GARYALI, AND T. RAVINDRANATHAN
National Chemical Laboratory, Pune 411 008 (India)
(Received September 25th, 1985; accepted for publication, October 18th, 1985)

ABSTRACT

The first enantiospecific synthesis of natural (*R*)-(+)-α-lipoic acid in 13 steps starting from D-glucose is described.

INTRODUCTION

Interest in the total synthesis of α-lipoic acid arose because of its physiological properties[1]. It is a cofactor in the biochemical decarboxylation of α-keto acids and a growth factor for a variety of micro-organisms, and it reduces the blood sugar of diabetic rabbits during a glucose tolerance test[2]. Although several syntheses of (±)-α-lipoic acid have been reported, natural (*R*)-(+)-α-lipoic acid (**1**) has been obtained by resolution of the racemate[3]. A recent communication[4] on the asymmetric synthesis of (*R*)-(+)-α-lipoic acid prompted this report of an enantiospecific synthesis.

RESULTS AND DISCUSSION

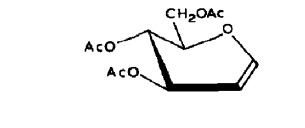
In planning our synthesis of **1**, the first objective was the aldehyde **10**, a useful precursor for C–C bond formation.

3,4,6-Tri-*O*-acetyl-D-glucal (**2**) was converted[5] into crystalline ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**3**). Hydrogenation of **3** over freshly prepared Raney nickel afforded 93% of the 2,3-dideoxy derivative **4**, Zemplén deacetylation[6] of which (→**5**) followed by conventional benzylation afforded 89% of the 4,6-di-*O*-benzyl derivative **6**. Treatment of **6** with propanedithiol–boron trifluoride etherate–dichloromethane at room temperature afforded 80% of the dithiane derivative **7**, the ^{1}H-n.m.r. spectrum of which was consistent with the assigned structure.

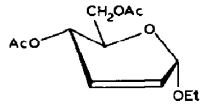
Using the procedure of Barton and McCombie[7], **7** was converted into 85% of the xanthate derivative **8** by reaction with sodium hydride–carbon disulfide–methyl

*NCL Communication No. 3852.

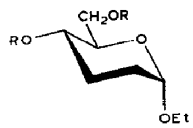
0008-6215/86/$ 03.50



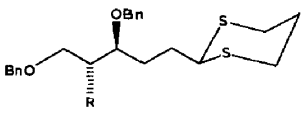
2



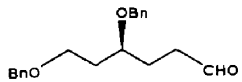
3



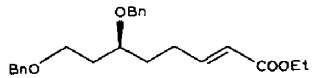
4 R = Ac
5 R = H
6 R = Bn



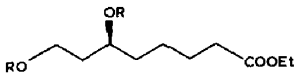
7 R = OH
8 R = OC—SMe
‖
S
9 R = H



10



11



12 R = H
13 R = Ms

1 R = H
14 R = Et

iodide. The ^{1}H-n.m.r. spectrum of **8** contained a downfield signal at δ 5.95 (m) for H-4′. Treatment of **8** with a boiling mixture of tributyltin hydride–toluene–α,α-azobisisobutyronitrile for 18 h gave 96% of **9**, hydrolysis of which with mercuric oxide–boron trifluoride etherate in aqueous acetone yielded the desired aldehyde **10**.

The next stage involved C_2 homologation of **10**. Accordingly, **10** and ethoxycarbonylmethylenetriphenylphosphorane were heated under reflux in benzene to give the α,β-unsaturated ester **11** (80%). The large $J_{2,3}$ value (16 Hz) of **11** confirmed the *trans* configuration. Hydrogenation of **11** over excess of Raney nickel effected reduction of the double bond and debenzylation to give 90% of the diol **12**, which was converted into (*R*)-(+)-α-lipoic acid (**1**) following the strategy developed by Golding and his co-workers[8].

Treatment of **12** with methanesulfonyl chloride–triethylamine in dichloromethane gave the dimesylate **13** in almost quantitative yield. The ^{1}H-n.m.r. spectrum of **13** contained two singlets for mesyl groups, and signals at δ 4.28 (t) and 4.80 (m) for H-8,8′ and H-6, respectively. Reaction of **13** with sodium sulfide and sulfur in *N,N*-dimethylformamide at 90° afforded 70% of the expected ethyl (*R*)-(+)-α-lipoate (**14**), which gave n.m.r. signals at δ 3.18 (t) and 3.60 (m) for H-8,8′ and H-6, respectively. The upfield shifts of the signals for these protons were expected because of the shielding effect of the sulfur atom. Hydrolysis of **14** with 0.1M potassium hydroxide in ethanol at room temperature afforded 75% of (*R*)-(+)-α-lipoic acid (**1**), $[\alpha]_D$ +95° (benzene); lit.[3] +91°; lit.[4] +102°.

EXPERIMENTAL

All evaporations were performed under diminished pressure. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian FT-80A or Bruker WH-90 spectrometer. Optical rotations were measured with a JASCO DIP-181 polarimeter. All solvents were purified and dried. Light petroleum refers to the fraction b.p. 60–80°. Dry-packed column chromatography was performed on silica gel (60–120 mesh).

*Ethyl 4,6-di-*O*-benzyl-2,3-dideoxy-α-*D*-erythro-hexopyranoside* (**6**). — To a solution of the diacetate **4**[6] {10.4 g, 40 mmol; $[\alpha]_D$ +120.5° (*c* 1.2, chloroform); lit.[6] $[\alpha]_D$ +118° (ethanol)} in dry methanol (50 mL) was added sodium (40 mg). After 18 h, the mixture was neutralized with Amberlite IR-120 (H^+) resin and concentrated, and benzene was distilled from the residue to afford the diol **5**[6] (7.0 g, 100%).

To a solution of **5** (5 g, 28.4 mmol) in dry tetrahydrofuran (50 mL) under nitrogen was added sodium hydride (50% oil dispersion; 5 g, 210 mmol) during 1 h. The solution was cooled, benzyl bromide (7 mL, 58 mmol) was added, and the mixture was left overnight at room temperature. Methanol (5 mL) was added, the solution was concentrated, and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was dried and concentrated. Column chromatography (ethyl acetate–light petroleum, 1:10→1:4) of the residue afforded **6** (8.9 g, 89%), $[\alpha]_D$ +100.5° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 1.19 (t, 3 H, CH_2CH_3), 1.7 (m, 4 H, H-2,2′,3,3′), 3–4 (m, 6 H, H-4,5,6′ and CH_2CH_3), 4.1–4.6 (m, 4 H, 2 CH_2Ph), 4.76 (bs, 1 H, H-1), 7.21 (d, 10 H, 2 Ph).

Anal. Calc. for $C_{22}H_{28}O_4$: C, 74.2; H, 7.9. Found: C, 74.0; H, 7.7.

2-[(3S,4R)-3,5-Dibenzyloxy-4-hydroxypentyl]-1,3-dithiane (**7**). — To a solution of **6** (5 g, 14 mmol) in dichloromethane (20 mL) was added propane-1,3-dithiol (2 g, 18.5 mmol) and boron trifluoride etherate (2 mL). The mixture was stirred for 2 h at room temperature, then neutralised with sodium carbonate, filtered, and concentrated. Column chromatography (ethyl acetate–light petroleum, 1:10→1:1) of the residue afforded **7** (4.6 g, 80%), $[\alpha]_D$ +8° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 1.4–2.4 (m, 7 H, 3 CH_2 at C-1,2′,5 and OH), 2.80 (q, 4 H, 2 CH_2 at C-4,6), 3.5 (m, 3 H, CH_2 at C-5′ and H-4′), 3.9 (m, 2 H, H-2,3′), 4.48 (s, 2 H, CH_2Ph), 4.51 (s, 2 H, CH_2Ph), 7.3 (d, 10 H, 2 Ph).

Anal. Calc. for $C_{23}H_{30}O_3S_2$: C, 66.0; H, 7.2; S, 15.3. Found: C, 66.4; H, 7.2; S, 15.1.

2-[(3S)-3,5-Dibenzyloxypentyl]-1,3-dithiane (**9**). — To a stirred solution of **7** (2.5 g, 6 mmol) in dry tetrahydrofuran (30 mL) under nitrogen was added sodium hydride (50% oil dispersion; 1.2 g, 25 mmol). After 1 h, dry carbon disulfide (2 mL) was added, followed, after 20 min, by methyl iodide (2 mL). The mixture was stirred for 24 h at room temperature, methanol (3 mL) was added, the mixture was concentrated, and the residue was partitioned between chloroform and water. The chloroform layer was dried and concentrated. Short-column chromatography (ethyl

acetate–light petroleum, 1:4) of the residue gave the xanthate **8** (2.65 g, 85%). ^{1}H-N.m.r. data: δ 1.7–2.4 (m, 6 H, 3 CH_2 at C-1′,2′,5), 2.56 (s, 3 H, SMe), 2.75 (q, 4 H, 2 CH_2 at C-4,6), 3.8 (m, 4 H, CH_2 at C-5 and H-2,3′), 4.50 (s, 2 H, CH_2Ph), 4.53 (dd, 2 H, CH_2Ph), 5.95 (m, 1 H, H-4′), 7.25 (d, 10 H, 2 Ph).

A solution of **8** (2.1 g, 4.13 mmol) in dry toluene (30 mL) containing α,α-azobisisobutyronitrile (15 mg) was heated under nitrogen and freshly prepared tributyltin hydride (3 mL) was added. The mixture was boiled under reflux for 18 h and then concentrated. Column chromatography (ethyl acetate–light petroleum, 0:1→1:9) of the residue afforded **9** (1.61 g, 96%), $[\alpha]_D$ +14.5° (*c* 0.7, chloroform). ^{1}H-N.m.r. data: δ 1.6–2.3 (m, 8 H, 4 CH_2 at C-1′,2′,4′,5), 2.78 (q, 4 H, 2 CH_2 at C-4,6), 3.5 (m, 3 H, CH_2 at C-5′ and H-3′), 3.95 (t, 1 H, H-2), 4.42 (s, 2 H, CH_2Ph). 4.44 (dd, 2 H, CH_2Ph), 7.25 (s, 10 H, 2 Ph).

Anal. Calc. for $C_{23}H_{30}O_2S_2$: C, 68.7; H, 7.5; S, 15.9. Found: C, 68.1; H, 7.2; S, 15.8.

Ethyl (S)-6,8-dibenzyloxyoct-2-enoate (**11**). — To a stirred suspension of red mercuric oxide (1.06 g, 3.5 equiv.) and boron trifluoride (0.52 mL, 3 equiv.) in aqueous 17% acetone (15 mL) under nitrogen was added dropwise a solution of **9** (0.56 g, 1.4 mmol) in tetrahydrofuran (3 mL). After 20 h, the mixture was neutralised with a solution of sodium hydroxide in aqueous 75% acetone. The precipitate was removed, the acetone was evaporated, and the aqueous solution was extracted repeatedly with chloroform and then concentrated to dryness. The residue was extracted with chloroform, and the extract was dried and concentrated to afford **10**, which was chromatographically homogeneous and was used without further purification.

A solution of **10** (0.35 g, 1.12 mmol) in dry benzene (5 mL) was treated with ethoxycarbonylmethylenetriphenylphosphorane (1.17 g, 3 equiv.). The mixture was heated under reflux for 10 h and then concentrated. Column chromatography (ethyl acetate–light petroleum, 1:20) of the residue gave **11** (0.30 g, 80%), $[\alpha]_D$ +3° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 1.24 (t, 3 H, CH_3CH$_2$), 1.4–2.0 (m, 4 H, H-5,5′,7,7′), 2.3 (m, 2 H, H-4,4′), 3.5 (m, 3 H, H-6,8,8′), 4.13 (q, 2 H, CH_3CH_2), 4.42 (s, 4 H, 2 CH_2Ph), 5.71 (dt, 1 H, *J* 16 and 1.5 Hz, H-2), 6.88 (dt, 1 H, *J* 16 and 6.5 Hz, H-3), 7.24 (d, 10 H, 2 Ph).

Anal. Calc. for $C_{24}H_{30}O_4$: C, 75.4; H, 7.9. Found: C, 75.3; H, 7.9.

Ethyl (S)-6,8-dimesyloxyoctanoate (**13**). — A solution of **11** (0.4 g, 1.05 mmol) in ethanol (10 mL) was hydrogenated over freshly prepared W2 Raney nickel (4 g) at normal pressure and temperature for 18 h, then filtered through Celite, and concentrated to afford the saturated diol **12** (0.192 g, 90%).

To a solution of **12** (0.102 g, 0.5 mmol) in dry dichloromethane (2 mL) at 0° was added triethylamine (1 mL) and methanesulfonyl chloride (0.24 mL, 3 mmol). After storage for 4 h at 0°, the mixture was poured into aqueous sodium hydrogencarbonate and extracted with dichloromethane, and the extract was dried and concentrated. Column chromatography (ethyl acetate–light petroleum, 1:1) of the residue gave **13** (0.18 g, 100%), $[\alpha]_D$ +17° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 1.22

(t, 3 H, CH_3CH_2), 1.3–2.5 (m, 10 H, 5 CH_2), 3.00 (s, 6 H, 2 OMs), 4.15 (q, 2 H, CH_3CH_2), 4.28 (t, 2 H, H-8,8′), 4.80 (m, 1 H, H-6).

Anal. Calc. for $C_{12}H_{24}O_8S_2$: C, 40.0; H, 6.7; S, 17.8. Found: C, 40.0; H, 6.7; S, 17.5.

Ethyl (R)-(+)-α-lipoate [ethyl (5R)-5-(1,2-ditholan-3-yl)pentanoate] (**14**). — A solution of **13** (0.36 g, 1 mmol) in dry *N,N*-dimethylformamide (3 mL) containing powdered sodium sulfide nonahydrate (0.24 g, 1 mmol) and sulfur (32 mg, 1 mmol) was heated at 90° for 24 h, then poured into ice–water, and extracted with light petroleum. The extract was washed with water, dried, and concentrated. Short-column chromatography (benzene) of the residue afforded **14** (0.164 g, 70%), $[\alpha]_D$ +61° (*c* 0.3, chloroform); ν_{max}^{liquid} 1730 cm^{-1} (COOEt). ^{1}H-N.m.r. data: δ 1.27 (t, 3 H, CH_3CH_2), 1.4–2.8 (m, 10 H, 5 CH_2), 3.18 (t, 2 H, H-8,8′), 3.6 (m, 1 H, H-6), 4.13 (q, 2 H, CH_3CH_2). Mass spectrum: *m/z* 234 (M^+).

Anal. Calc. for $C_{10}H_{18}O_2S_2$: C, 51.3; H, 7.7; S, 27.35. Found: C, 51.2; H, 7.8; S, 27.1.

(R)-(+)-α-lipoic acid [(5R)-5-(1,2-dithiolan-3-yl)pentanoic acid] (**1**). — A solution of **14** (0.117 g, 0.5 mmol) in ethanol (5 mL) was treated with 0.1M potassium hydroxide (5.5 mL) in the dark and under nitrogen at room temperature. After 24 h, ethanol was evaporated, and the aqueous solution was extracted with light petroleum, then acidified with 5M hydrochloric acid to pH 1, and repeatedly extracted with ether. The combined extracts were concentrated and short-column chromatography (benzene–ethyl acetate, 20:1) of the residue afforded **1** (63 mg, 75% based on recovered **14**), m.p. 44°, $[\alpha]_D$ +95° (*c* 0.1, benzene); ν_{max}^{liquid} 1695 cm^{-1} (COOH); lit.[4] m.p. 43–45°, $[\alpha]_D$ +102° (benzene); lit.[3] $[\alpha]_D$ +91° (benzene). ^{1}H-N.m.r. data: δ 1.3–2.8 (m, 10 H, 5 CH_2), 3.10 (t, 2 H, H-8,8′), 3.53 (m, 1 H, H-6). Mass spectrum: *m/z* 206 (M^+).

Anal. Calc. for $C_8H_{14}O_2S_2$: C, 46.6; H, 6.8; S, 31.1. Found: C, 46.55; H, 6.6; S, 30.7.

REFERENCES

1 L. J. Reed, I. C. Counsalus, B. G. DeBusk, and C. S. Homberger, Jr., *Science*, 114 (1951) 93–94; H. Sigel, *Angew. Chem. Int. Ed. Engl.*, 21 (1982) 389–400.
2 C. V. Natraj, V. M. Gandhi, and K. K. G. Menon, *J. Biosci.*, 6 (1984) 37–46.
3 E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, 77 (1955) 5144–5149; D. S. Acker and W. J. Wayne, *ibid.*, 79 (1957) 6483–6487.
4 J. D. Elliott, J. Steele, and W. S. Johnson, *Tetrahedron Lett.*, (1985) 2535–2538.
5 R. J. Ferrier and N. Prasad, *J. Chem. Soc.*, C, (1969) 575–580.
6 C. L. Stevens, P. Blumberg, and D. L. Woods, *J. Am. Chem. Soc.*, 86 (1964) 3592–3594.
7 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, (1975) 1574–1585.
8 M. H. Brooks, B. T. Golding, D. A. Howes, and A. T. Hudson, *J. Chem. Soc., Chem. Commun.*, (1983) 1051–1053.