A Short Enantioselective Formal Synthesis of Methyl (*S*)-(−)-6,8-Dihydroxyoctanoate: A Key Intermediate for the Synthesis of *R*-(+)-α-Lipoic Acid

Maitreyee (Sarma) Bezbarua, Anil K. Saikia, Nabin C. Barua,* Dipak Kalita, Anil C. Ghosh

Organic Chemistry Division, Regional Research Laboratory, Jorhat 785006, Assam, India

Fax +91(376)321158

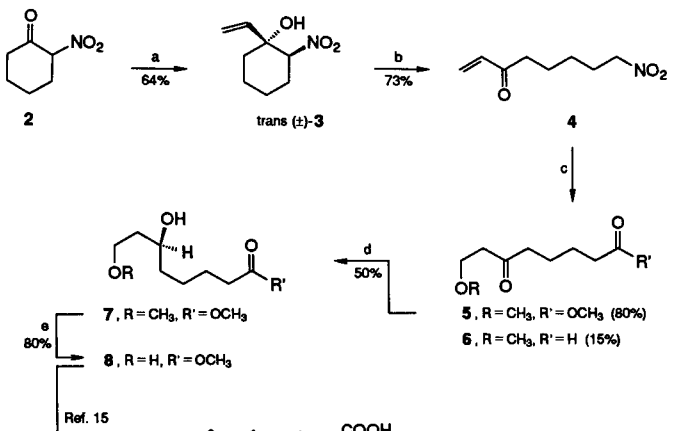
Received 27 December 1995; revised 29 March 1996

Dedicated to Prof. U.R. Ghatak on his 65th birthday.

A short enantioselective formal synthesis of methyl (*S*)-(−)-6,8-dihydroxyoctanoate starting from readily available 2-nitrocyclohexanone using a novel retro-Henry reaction is described.

R-(+)-α-Lipoic acid [(*R*)-**1**] is widely distributed in plants and animals and is a vital cofactor in the multienzyme complexes. It also finds diverse uses in biology, medicine, cosmetics, and photography. Most recently *R*-(+)-α-lipoic acid has been reported to inhibit HIV-1 replication in T-cells and in HeLa-CD$^+$ cells at non-toxic concentration of 35–70 μg/mL.[1] Because of its importance, ever since its isolation in 1950 by Reed et al.,[2] this biologically important molecule has been the target of various synthetic efforts.[3–8] In continuation of our work in exploring the chemistry of nitroaliphatic compounds, we have recently developed a retro-Henry cleavage reaction[9] for a short two-step synthesis of ω-oxo nitroaliphatics starting from easily available 2-nitrocyclohexanone. In this communication we describe a short efficient formal synthesis of methyl (*S*)-(−)-6,8-dihydroxyoctanoate, [(*S*)-**8**], which is a key intermediate for the synthesis of *R*-(+)-α-lipoic acid [thioctic acid; 6,8-dithiooctanoic acid; (*R*)-**1**] (Scheme). Reaction of 2 equivalents of vinylmagnesium bromide with 2-nitrocyclohexanone (**2**), as per the procedure described by Ballini et al.,[10] gave exclusively *trans*-(+)-**3** in 64% yield which on exposure to anhydrous copper sulfate adsorbed on silica gel in anhydrous benzene under reflux gave ω-nitro α,β-unsaturated ketone **4** in 73% yield as an oil. Conversion of **4** to oxo ester **5** was achieved by modifying the procedure reported by Jacobson[11] by treating compound **4** successively with a sodium methoxide in methanol and sulfuric acid in methanol system which gave in addition to **5** in 80% yield, an aldehyde **6** in 15% yield. The Jacobson's procedure is reported to give dimethyl acetals under these conditions, however to our surprise our products were ester **5** and aldehyde **6** and no trace of the corresponding acetal was detected.

The oxo ester **5** was enantiospecifically reduced with baker's yeast according to the procedure described in the literature[12,13] to yield the chiral alcohol (*S*)-**7**. Selective hydrolysis of the methyl ether (*S*)-**7** with tetrabutylammonium iodide in $CHCl_3$ gave the chiral 1,3-diol (*S*)-**8** in 80% yield. Conversion of (*S*)-**8** into *R*-(+)-α-lipoic acid [(*R*)-**1**] has already been reported in the literature.[3,4,6a,15]



(a) $CH_2=CHMgBr$/THF, −30 to 0°C; (b) anhyd $CuSO_4 \cdot SiO_2$/anhyd benzene, reflux; (c) NaOMe/MeOH,H_2SO_4, −30 to 0°C; (d) baker's yeast/glucose/H_2O, 48 h; (e) Bu_4NI/$Et_2O \cdot BF_3$/$CHCl_3$.

Scheme

Mass spectra were obtained by EI at 70 eV using INCOS 50 GC-MS equipment. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions at 60 MHz and 300 MHz using TMS as an internal standard. IR spectra were recorded as thin films unless otherwise stated. 2-Nitrocyclohexanone (**2**) and *trans*-2-nitro-1-vinylcyclohexan-1-ol (**3**) were prepared following literature[10] procedure. Petroleum ether (PE) used refers to bp 60–80°C.

1-Nitrooct-7-en-6-one (4):

A mixture of 2-nitro alcohol **3**[10] (0.68 g, 3.98 mmol) and $CuSO_4$/SiO_2 (3.5 g) in anhyd benzene (25 mL) was refluxed for 4 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the residue was washed with acetone. The combined filtrates were evaporated under reduced pressure and the product was purified by chromatography on silica gel (EtOAc/PE, 1 : 10) to give **4** (0.5 g, 73%) as an oil.

IR: ν = 1675, 1540 cm^{-1}.

^{1}H NMR: δ = 5.9 (m, 2H, $HC=CH_2$), 5.5 (m, 1H, $CH=CH_2$), 4.2 (t, J = 7 Hz, 2H, CH_2NO_2), 2.35 (t, J = 6.5 Hz, 2H, $CH_2C=O$), 1.2 (br, 6H, CH_2).

MS: m/z = 171 (M^+), 144, 125, 111, 97, 83, 69, 55.

$C_8H_{13}NO_3$	calc.	C 56.13	H 7.65	N 8.18
(171.2)	found	56.25	7.50	8.23

Methyl 8-Methoxy-6-oxooctanoate (5):

A solution of **4** (0.15 g, 0.87 mmol) in methanolic NaOMe (7 mL) was added dropwise to a solution of 9.74 N H_2SO_4 in MeOH (7 mL) at −35°C. After complete addition of the substrate, CH_2Cl_2 (20 mL) was added. The mixture was washed with ice cold water and then with dil NaOH solution, dried (Na_2SO_4) and concentrated under reduced pressure. Finally the crude residue was purified by chromatography to obtain **5** (0.12 g, 80%) as an oil along with compound **6** (oil; 0.023 g, 15%). The compounds **5** and **6** were successively eluted with EtOAc/PE (1 : 3) as solvent.

5:

IR: $\nu = 1705, 1725\ cm^{-1}$.

^1H NMR (300 MHz): $\delta = 3.66$ (s, 3H, CO_2CH_3), 3.63 (t, $J = 6.25$ Hz, 2H, OCH_2), 3.3 (s, 3H, OCH_3), 2.64 (t, $J = 6.2$ Hz, 2H, CH_2CO_2Me), 2.47 (m, 2H, $COCH_2$), 2.33 (m, 2H, CH_2CO), 1.6 (m, 4H, CH_2).

MS: $m/z = 203$ ($[M+1]^+$), 170, 139, 111, 59, 55.

$C_{10}H_{18}O_4$	calc.	C 59.39	H 8.97
(202.2)	found	59.45	8.85

6:

IR: $\nu = 1705\ cm^{-1}$.

^1H NMR (300 MHz): $\delta = 9.8$ (t, $J = 2.3$ Hz, CHO), 3.63 (t, $J = 6.18$ Hz, 2H, OCH_2), 3.33 (s, 3H, OCH_3), 2.6 (t, $J = 6.18$ Hz, 2H, CH_2CO), 2.46 (m, 4H, $COCH_2$ and CH_2CHO), 1.2 (m, 4H, CH_2).

MS: $m/z = 171$ ($[M-1]^+$), 139, 111, 97, 83.

$C_9H_{16}O_3$	calc.	C 62.77	H 9.36
(172.2)	found	62.69	9.45

Methyl (*S*)-(−)-6-Hydroxy-8-methoxyoctanoate (7):

A suspension of baker's yeast (128.28 g) and D-glucose (6.5 g) in water (2.3 mL) was stirred for 30 min at 32 °C. A solution of **5** (0.1 g, 0.49 mmol) in MeOH (2 mL) was added and the mixture was allowed to stand at r.t. for 48 h. The mixture was filtered through a Celite pad and washed with EtOAc (150 mL). The filtrate was acidified with 2N HCl till pH 1 and extracted with EtOAc. The organic extract was dried (Na_2SO_4), evaporated and the residue was purified by preparative TLC (EtOAc/PE, 1 : 3) to give **6** (0.05 g, 50%) as an oil; $[\alpha]_D^{25} -10.6$ ($c = 0.15$, $CHCl_3$).

IR: $\nu = 3350, 1705\ cm^{-1}$.

^1H NMR (300 MHz): $\delta = 3.55$ (s, 3H, CO_2CH_3), 3.4 (m, 2H, OCH_2), 3.35 (s, 3H, OCH_3), 2.5 (br, 1H, OH), 2.3 (t, $J = 7.4$ Hz, 2H, CH_2CO_2Me), 1.55 (q, $J = 5.4$ Hz, 7H, CH_2CH (OH) CH_2CH_2), 1.4 (m, 2H, CH_2).

MS: $m/z = 205$ ($[M+1]^+$), 187, 171, 155, 139, 113, 87.

$C_{10}H_{20}O_4$	calc.	C 58.80	H 9.87
(204.3)	found	58.94	9.82

Methyl (*S*)-(−)-6,8-Dihydroxyoctanoate (8):

To a mixture of (*S*)-**7** (0.05 g, 0.26 mmol) and Bu_4NI (0.1 g, 0.27 mmol) in anhyd $CHCl_3$ (5 mL) was added $BF_3 \cdot OEt_2$ (0.04 g, 0.27 mmol) and the mixture was refluxed for 4 h. The mixture was then treated with sat. $NaHCO_3$ solution (50 mL) and extracted with $CHCl_3$. The organic layer was washed with aq $Na_2S_2O_3$ solution (20 mL) followed by water (50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (EtOAc/PE, 1 : 3) to furnish the pure diol **8** (0.04 g, 80%) as an oil; $[\alpha]_D^{25} -3.8$ ($CHCl_3$) (Lit.[14] $[\alpha]_D^{25} -3.9$ ($CHCl_3$) for *S*-isomer).

IR: $\nu = 3370, 2940, 1735, 1460\ cm^{-1}$.

^1H NMR: $\delta = 1.51$ (m, 8H, CH_2), 2.25 (t, $J = 7.3$ Hz, 2H CH_2CO_2Me), 3.35 (m, 3H, $CH_2OH + CHOH$), 3.62 (s, 3H, OCH_3), 4.53 (s, 2H, OH).

MS: $m/z = 191$ ($[M+1]^+$), 173, 163, 141, 130.

Authors are grateful to DST, New Delhi for financial support.

(1) Baur, A.; Harrer, T.; Peukert, M.; Jahn, G.; Kalden, J.R.; Fleckenstein, B. *Klin. Wochenschr.* **1991**, *69*, 722; *Chem. Abstr.* **1992**, *116*, 207360.
(2) Reed, L.J.; DeBusk, B.G.; Gunsalus, I.C.; Hornberger, C.S. Jr. *Science* **1951**, *114*, 93.
(3) Golding, B.T.; Brookes, M.H.; Howes, D.A.; Hudson, A.T. *J. Chem. Soc., Chem. Commun.* **1983**, 1051.
(4) Elliott, J.D.; Steele, J.; Johnson, W.S. *Tetrahedron Lett.* **1985**, *26*, 2535.
(5) (a) Bullock, M.W.; Brockman, J.A., Jr.; Patterson, E.L.; Pierce, J.V.; von Saltza, M.H.; Sanders, F.; Stokstad, E.L.R. *J. Am. Chem. Soc.* **1954**, *76*, 1828.
(b) Walton, E.; Wagner, A.F.; Peterson, L.H.; Holly, F.W.; Folkers, K. *J. Am. Chem. Soc.* **1954**, *76*, 4748.
(c) Reed, L.J.; Ching-I Niu *J. Am. Chem. Soc.* **1955**, *77*, 416.
(d) Braude, E.A.; Linstead, R.P.; Wooldridge, K.R.H. *J. Chem. Soc.* **1956**, 3074.
(e) Segre, A.; Viterbo, R.; Parisi, G. *J. Am. Chem. Soc.* **1957**, *79*, 3503.
(f) Lewis, B.A.; Raphael, R.A. *J. Chem. Soc.* **1962**, 4263.
(g) Tsuji, J.; Yasuda, H.; Mandai, T. *J. Org. Chem.* **1978**, *43*, 3606.
(6) (a) Rama Rao, A.V.; Gurjar, M.K.; Guryali, K.; Ravindranathan, T. *Carbohydr. Res.* **1986**, *148*, 51.
(b) Rama Rao, A.V.; Purandare, A.V.; Reddy, E.R.; Gurjar, M.K. *Synth. Commun.* **1987**, *17*, 1095.
(c) Rama Rao, A.V.; Mysorekar, S.V.; Gurjar, M.K.; Yadav, J.S. *Tetrahedron Lett.* **1987**, *28*, 2183.
(7) Bulman Page, P.C.; Rayner, C.M.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* **1986**, 1408.
(8) Brooks, D.W.; Kellogg, R.P.; Cooper, C.S. *J. Org. Chem.* **1987**, *52*, 192.
(9) Saikia, A.K.; Hazarika, M.J.; Barua, N.C.; Bezbarua, M.S.; Ghosh, A.C. *Synthesis* **1996**, 981.
(10) Ballini, R.; Bartoli, G.; Gariboldi, P.V.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1993**, *58*, 3368.
(11) Jacobson, R.M. *Tetrahedron Lett.* **1974**, 3215.
(12) Gopalan, A.S.; Jacobs, H.K. *Tetrahedron Lett.* **1989**, *30*, 5705.
(13) Dasaradhi, L.; Fadnavis, N.W.; Bhalerao, U.T. *J. Chem. Soc., Chem. Commun.* **1990**, 729.
(14) Brookes, M.H.; Golding, B.T.; Hudson, A.T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 9.
(15) Menon, R.B.; Kumar, M.A.; Ravindranathan, T. *Tetrahedron Lett.* **1987**, *28*, 5313.