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Asymmetric dihydroxylation and hydrogenation approaches to the enantioselective synthesis of *R*-(+)-α-lipoic acid

T. T. Upadhya,† M. D. Nikalje and A. Sudalai*

Process Development Division, National Chemical Laboratory, Pune 411008, India

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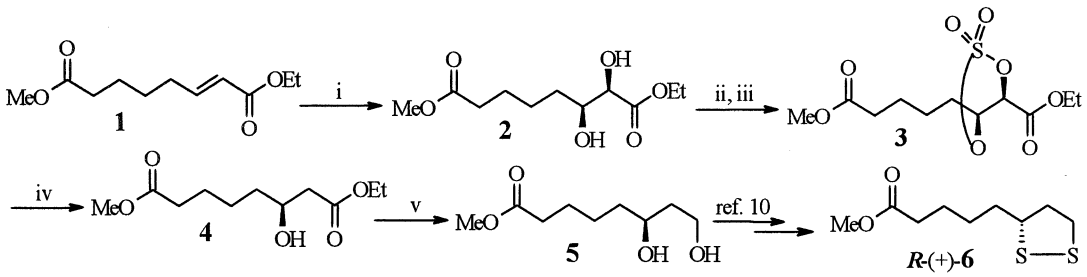
Abstract—The asymmetric synthesis of methyl (*S*)-6,8-dihydroxyoctanoate (**5**) and (*S*)-6,8-dimethylsulfonyloxyoctane-1-carboxylic acid (**13**), key precursors to *R*-(+)-α-lipoic acid (**6**) is described using OsO_4-catalyzed asymmetric dihydroxylation and Ru-catalyzed asymmetric hydrogenation, respectively, as the key steps in the reaction sequence. These methods lead to an efficient formal synthesis of *R*-(+)-α-lipoic acid in 90% ee.

R-(+)-α-Lipoic acid (**6**) plays an important role as a protein-bound transacylating cofactor of several multienzymatic keto acid dehydrogenase complexes and as a growth factor for a variety of microorganisms.[1] Recently, it has also been reported that lipoic acids and their derivatives are highly active as anti-HIV[2] and anti-tumor agents.[3] Generally, it is reported that the enantioselective synthesis of **6** has been achieved either from 'chiral pool' starting materials or by asymmetric synthesis[4] including mostly bakers' yeast reductions. In this communication, we describe a short, efficient and enantioselective synthesis of **6** starting from easily available starting materials and by employing two powerful asymmetric catalytic methods, i.e. asymmetric dihydroxylation (ADH)[5] and asymmetric hydrogenation (AH),[6] as the key reactions to control the absolute configuration at the C-3 position.

We envisaged that methyl (*S*)-6,8-dihydroxyoctanoate (**5**) and (*S*)-6,8-dimethylsulfonyloxyoctane-1-carboxylic acid (**13**) could serve as two key precursors for the synthesis of **6** (Schemes 1 and 2). In order to obtain **5** the olefinic diester (**1**),[7] obtained readily from ε-caprolactone in three steps, was subjected to OsO_4-catalyzed asymmetric dihydroxylation[6] using hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2$–PHAL] as chiral lig-



Scheme 1. (i) OsO_4, $(DHQD)_2$–PHAL, $K_3Fe(CN)_6$, K_2CO_3, rt, 95%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 92%; (iii) $RuCl_3$ (cat.), $NaIO_4$, 85%; (iv) $NaBH_4$, DMAC, 20% H_2SO_4, 63%; (v) $NaBH_4$, Et_3N, MeOH:DMF (2:1), AcOH, 0°C, 5 h.

Keywords: asymmetric reactions; diols; disulfide; hydrogenation; hydroxylation.

* Corresponding author. E-mail: sudalai@dalton.ncl.res.in

† Present address: Max-Planck Institute fur Molekulare Physiologie, Otto-Hahn Str. 11, 44227 Dortmund, Germany.

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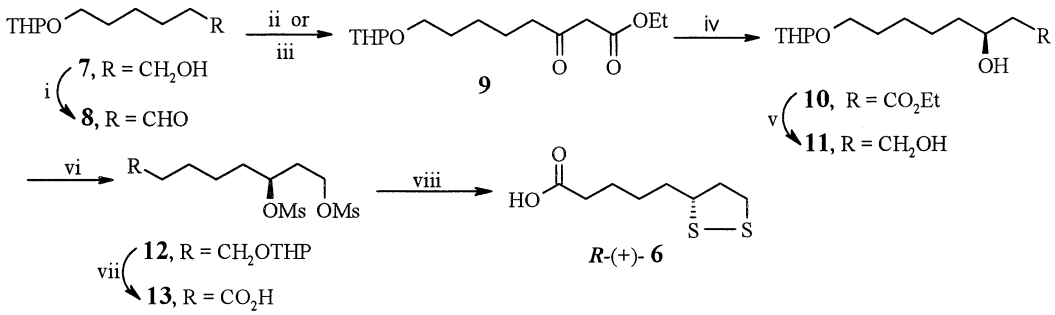

Scheme 2. (i) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, 75%; (ii) N_2CHCO_2Et, CH_2Cl_2, $SnCl_2$, 1 h, rt, 83%; (iii) Zn, $BrCH_2CO_2Et$, benzene, 4 h, followed by PCC, NaOAc, CH_2Cl_2, 4 h, 65%; (iv) (*S*)-BINAP–Ru(II), H_2 (400 psi), MeOH, 100°C, 6 h, 90%; (v) $NaBH_4$, $CuSO_4$, EtOH, 7 h; (vi) MsCl, Et_3N, CH_2Cl_2, 0°C, 6 h; (vii) *p*TSA, MeOH, 10 h; followed by oxidation with PCC, CH_2Cl_2, 3 h and Ag_2O, NaOH, EtOH, 1 h, 62%; (viii) KOH, H_2O, $Na_2S{\cdot}9H_2O$, DMF, HCl, 80°C, 28 h, 45%.

and affording the diol **2**‡ in 95% yield and 96% ee (from ^{1}H NMR analysis of its diacetate using Eu(III) chiral shift reagent). The diol **2** was then converted to cyclic sulfate **3** (85% yield) using standard conditions.[8] Reduction of **3** at the α-position with $NaBH_4$–*N*,*N*′-dimethylacetamide (DMAC) resulted[8] in selective formation of the (3*S*)-alcohol **4** in 86% yield {gum, $[\alpha]_D^{25}$ +13.59 (*c* 1.2 in EtOH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1, 24.7, 24.9, 33.8, 36.1, 41.3, 51.4, 60.6, 67.7, 172.8, 173.9}. Further selective reduction of one of the ester groups in **4** is achieved by following the reported method[9] [$NaBH_4$–Et_3N, MeOH:DMF (2:1), 0°C] to furnish **5** (85% yield), the spectroscopic data of which is identical to the reported values.[10] Conversion of (*S*)-**5** diol into **6** has already been reported in the literature.[10]

‡ **Spectroscopic data for selected compounds**

Diol ***2***: Gum; $[\alpha]_D^{25}$ +9.39 (*c* 1.2, EtOH); IR (neat, cm^{-1}): *v* 3600–3200, 2948, 2866, 1731, 1645–1633, 1440, 1369, 1269–1120, 1026, 864, 734; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2–1.4 (t, *J*=6.0 Hz, 3H), 1.4–1.73 (m, 7H), 2.1 (s, 1H), 2.27–2.34 (t, *J*=7.0 Hz, 2H), 3.64 (s, 3H), 3.79–3.87 (m, 1H), 4.00–4.01 (d, *J*=2.0 Hz, 1H), 4.20–4.30 (q, *J*=7.0 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.0, 24.6, 25.1, 33.1, 33.7, 51.2, 61.6, 72.2, 73.3, 173.3, 173.7; MS (*m*/*z* % rel. intensity): 248 (M^+, 2), 199 (2), 143 (3), 125 (20), 113 (68), 104 (92), 95 (22), 85 (21), 76 (100), 67 (40).

Cyclic sulfate ***3***: Gum; $[\alpha]_D^{25}$ +54.25 (*c* 1.2, EtOH), IR (neat, cm^{-1}): *v* 2985, 2954, 2873, 1768, 1737, 1438, 1394, 1302, 1209, 1163, 1041–1029, 948, 885, 842, 651; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31–1.38 (t, *J*=7.5 Hz, 3H), 1.54–1.74 (m, 4H), 1.95–2.06 (m, 2H), 2.32–2.38 (t, *J*=6.0 Hz, 2H), 3.67 (s, 3H), 4.28–4.39 (q, *J*=7.5 Hz, 2H), 4.85–4.96 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.6, 23.77, 23.99, 32.30, 32.2, 51.1, 63.0, 79.8, 83.8, 164.5, 173.2.

Alcohol ***10***: Viscous liquid; IR (neat, cm^{-1}): *v* 3500–3300, 1723, 1670, 1635, 1532, 1448, 1442, 1366, 1335, 1296, 1190, 1099, 998, 926, 888, 813, 767, 631, 576, 420; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2–1.35 (t, *J*=8.0 Hz, 3H), 1.35–1.7 (m, 14H), 2.4–2.55 (m, 2H), 3.4–3.6 (m, 4H), 3.95–4.1 (m, 1H), 4.1–4.25 (q, *J*=7.2 Hz, 2H), 4.55 (brs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1, 19.5, 25.3, 25.5, 26.1, 29.6, 30.7, 36.6, 41.6, 60.3, 61.9, 67.3, 67.9, 98.6, 172.5; elemental analysis: $C_{15}H_{28}O_5$ requires C, 62.50; H, 9.70%. Found: C, 62.51; H, 9.90%.

Mesylate ***13***: Mp 48°C, $[\alpha]_D^{25}$ +22 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): *v* 3550–3300, 1728, 1697, 1460, 1405, 1380, 1350, 1198, 1178, 1090, 970, 822, 535, 420; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2–1.75 (m, 6H), 2.05–2.15 (m, 2H), 2.45 (t, *J*=6.4 Hz, 2H), 3.05 (s, 6H), 4.25 (t, *J*=5.0 Hz, 2H), 4.75–4.9 (m, 1H), 10.30 (brs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 24.0, 33.2, 34.0, 34.5, 37.5, 38.6, 64.9, 78.0, 180.0 one signal is missing due to overlap; elemental analysis: $C_{10}H_{20}O_8S_2$ requires C, 36.15; H, 6.02; S, 19.28%. Found: C, 36.22; H, 6.08; S, 19.30%.

Our strategy for the synthesis of 6,8-dimethylsulfonyloxyoctane-1-carboxylic acid (**13**) starts from commercially available 1,6-hexanediol. Monoprotection of 1,6-hexanediol (1 mol of dihydropyran, *p*TSA, anhydrous ether, 0°C) afforded **7** in 81% yield which underwent Swern oxidation affording aldehyde **8** (75%). Two-carbon chain extension from aldehyde **8** to β-keto ester **9** was achieved by two routes: (i) C–H insertion of ethyl diazoacetate[11] with **8** in the presence of a catalytic amount of anhydrous $SnCl_2$ at 25°C afforded **9** in 83% yield; (ii) Reformatsky reaction of **8** with ethyl bromoacetate in refluxing benzene gave the crude alcohol followed by its oxidation with PCC produced **9** in 65% yield. Although it is reported in the literature[6] that asymmetric hydrogenation of β-keto esters using (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]dichlororuthenium [(*S*)-(−)-BINAP–Ru(II) complex] proceeds at 4 atmospheres of H_2, we found that the reduction of β-keto ester **9** under similar conditions did not proceed at all and recovered only the starting materials.

However, increasing the pressure of H_2 (400 psi) and temperature (100°C) brought about the hydrogenation of **9** smoothly in an enantioselective manner to give the optically active alcohol **10**‡ in 90% yield. The optical purity of the alcohol **10** was found to be 96% from ^{19}F NMR analysis of the ester formed by reaction with (*S*)-(−)-α-methoxy-α-trifluromethylphenylacetyl chloride. Reduction of the ester function in **10** using $NaBH_4$–$CuSO_4$ in EtOH yielded the diol **11**, which was subsequently mesylated under standard conditions to yield **12**. The transformation of **12** into **13**‡ was achieved sequentially in three steps of deprotection (*p*TSA, MeOH) and oxidations (PCC and Ag_2O); the overall yield being 62%.

The absolute configuration of natural (+)-α-lipoic acid is *R*. This was achieved by a step that involves a single inversion of configuration, i.e. the displacement of *O*-methanesulfonate by a thiolate nucleophile. Accordingly, disulfide displacement[12] of the methanesulfonate groups of the potassium salt of the 3(*S*)-acid (**13**) proceeded with inversion of configuration at C-3 to give *R*-(+)-α-lipoic acid in 45%. {$[\alpha]_D^{25}$ −93.2 (*c* 0.9 in benzene) [lit.[13] −104 (*c* 0.88 in benzene) agreeing well with the published spectroscopic data[13]}.

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