An Efficient, Highly Enantioenriched Route to L-Carnitine and α-Lipoic Acid via Hydrolytic Kinetic Resolution

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Abstract: A general and practical approach for the synthesis of C-4 chiral building blocks using Jacobsen’s hydrolytic kinetic resolution technique to resolve terminal epoxides and diols in high enantiomeric excess and excellent yields is described. The utilization of these building blocks for the synthesis of biologically important natural products L-carnitine and α-lipoic acid is illustrated.

Keywords: L-carnitine, α-lipoic acid, hydrolytic kinetic resolution, terminal epoxide, enantiomerised

(R)- and (S)-Carnitine (3-hydroxy-4-trimethylammonobutyric acid, 1) have attracted considerable attention in recent years, owing to their interesting biological properties and their use as Pharmaceuticals.1–3 (R)-Carnitine 1, also known as vitamin B7, plays an important role in the β-oxidation of fatty acids, acting as a carrier of fatty acids over the mitochondrial membrane. Since fatty acid oxidation is a critical step by which cells derive energy, carnitine is important for cellular energetics. The antipode, S enantiomer of 1, acts as a competitive inhibitor of carnitine acyltransferase6 causing depletion of carnitine. α-(R)-Lipoic acid 3 is an important protein bound coenzyme and growth factor found in animal tissues, plants, and microorganisms. It plays a major role in several biochemical processes and has been identified as a crucial co-factor with pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH) multi-enzyme complexes responsible for the production of acetyl-CoA in metabolic pathways7 (Figure 1). The increasing demand for this class of compound is exemplified by numerous synthetic routes including optical resolution, fermentation, the chiron approach (asymmetric synthesis from natural products), and catalytic asymmetric synthesis, along with their associated patents.8 There is still a need, however, for straightforward syntheses that have significant practical value.

Chiral epoxides are versatile building blocks for the synthesis of enantiomerically pure complex molecules. Asymmetric epoxidation of olefins presents a powerful strategy for the synthesis of enantiomerically enriched epoxides. Great success has been achieved in the epoxidation of allylic alcohols, unfunctionalized cis-olefins, and conjugated trisubstituted olefins.9 However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomerically pure form. Terminal epoxides are available inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, by an economical and operationally simple method.

[2-(Phenylmethoxy)ethyl]oxirane 4 has been extensively used as a versatile C-4 chiral building block in the preparation of a variety of biologically important compounds including pactamycin and milbemycin,10 1,3-polyols (macrolide antibiotics)11 and most recently, (R)/(S)-adenosyl-1,8-diamino-3-thiooctane.12 Despite the extensive use of this chiral epoxide, there is still no method for its preparation in both high yields and enantiomeric purity. In this paper, we wish to describe a more convenient synthesis of the enantiomerically pure epoxides (R)- and (S)-4 by employing Jacobsen’s hydrolytic kinetic resolution (HKR), as the key step, to resolve the terminal epoxides. The HKR method uses readily accessible cobalt-based chiral salen complex 5 as a catalyst and constitutes a very attractive approach for the preparation of highly enantioselective chiral epoxides and diols of high optical purity in excellent yields.13 The salient features of HKR include the accessibility of racemic terminal epoxides and the use of water as the reagent/nucleophile for epoxide ring-opening, which allows access to highly enantioenriched (>99% ee) products in close to theoretical yields. Also HKR is a practical and scaleable reaction protocol involving low loadings (0.2–2.0 mol%) of a recyclable catalyst and the separation of the product from unreacted epoxide is simple due to large boiling point and polarity differences.

The substrate for HKR, racemic epoxide 4, was obtained from the commercially available 3-buten-1-ol by benzylation with one equivalent of sodium hydride and benzyl bromide in THF in 90% yield followed by epoxidation with MCPBA in dichloromethane. Subsequent HKR of 4
with (R,R)-salen-Co(III)-OAc complex 5 (0.5 mol%) and H₂O (0.55 equiv) at ambient temperature afforded a mixture of epoxide (R)-4 in 47% yield (98% optical yield) and the 1,2-diol 6 in 43% yield (Scheme 1). The diol 6 could be recycled, via the Mitsunobu reaction with DIAD and triphenylphosphine in refluxing benzene, to afford the corresponding epoxide (S)-4 in 80% yield with 96% optical yield. Both epoxides are expected to serve as good precursors for the synthesis of biologically interesting natural products. Although both epoxides have been synthesized independently, by long synthetic routes, starting from chiral pool aspartic acid, malic acid etc., the present synthetic modification, to obtain both epoxides (R)- and (S)-4 in just one or two steps from (±)-4, was a significant improvement. Utilization of the C-4 chiral building blocks for the synthesis of L-carnitine 1 and α-(R)-lipoic acid 3 was then investigated.

Thus, hydrogenolysis of the benzyl ether on chiral epoxide (R)-4 gave the required epoxy alcohol 7 in 85% yield (Scheme 2). Conversion of 7 into the corresponding (3R)-(−)-4-amino-3-hydroxybutyric acid (GABOB), a well-known neuromodulator, was accomplished in a straightforward manner in two steps. The primary alcohol in compound 7 was oxidized to the corresponding carboxylic acid and subsequent nucleophilic opening of the epoxy acid with a solution of concentrated ammonium hydroxide furnished 2. Methylation of enantiomerically pure (R)-2 was carried out under basic conditions to yield (R)-carnitine 1 in 65% yield.

Upon re-examination of the structure of α-(R)-lipoic acid 3, we realized that (R)-2-(benzoxyl)ethyl]oxirane (4) could be an ideal precursor (Scheme 3). Thus, the regiospecific opening of epoxide (R)-4 with but-3-enylmagnesium bromide (3 equiv) in THF containing 10 mol% lithium tetrachlorocuprate at −78 °C furnished 1-benzyl-oxoct-7-en-3-ol (8) in 90% yield. The hydroxy group in 8 was protected as benzyl ether by reaction with benzyl bromide in the presence of sodium hydride and TBAI in DMF. The next step was to elaborate the terminal olefin into the corresponding acid function. Thus, compound 9 was subjected to hydroboration–oxidation, using borane–DMS–hydrogen peroxide in THF to afford the primary alcohol 10 in 88% yield. Oxidation of the primary alcohol to the carboxylic acid was achieved with a mixture of sodium chlorite and bleach, catalyzed by TEMPO and followed by esterification with diazomethane to afford the ester 11. Removal of the benzyl group by hydrogenolysis gave the diol 12, which was converted to α-(R)-lipoic acid 3, by the standard sequence of reactions. Mesylation of diol 12 followed by disulfide displacement with a mixture of sodium sulfide and sulfur in DMF at 90 °C for 24 hours and finally saponification with potassium carbonate in methanol and water yielded lipoic acid 3. The spectral data and optical rotation of 3 were in good agreement with the reported data.

In summary, we have demonstrated a very simple and practical method for the synthesis of enantiomerically pure (R)-carnitine and α-(R)-lipoic acid using Jacobsen’s HKR technique as the key step and source of chirality. The extension of the synthetic methodology described to other biologically active compounds, employing the versatile intermediate 4, is being investigated in our laboratory.

Scheme 1

![Scheme 1 Diagram](image1)

Scheme 2

![Scheme 2 Diagram](image2)
(R)- and (S)-(2-Benzylxoy)ethyl]oxirane (4)
A stirred solution of (±)-4 (8.0 g, 44.94 mmol) and (R,R)-salen Co(III)-OAc catalyst 5 (145 mg, 0.225 mmol) was cooled to 0 °C, then H$_2$O (0.45 mL, 25.0 mmol) was added dropwise over a period of 45 min. The reaction mixture was then stirred at r.t. for 5 h, diluted with EtOAc, dried (Na$_2$SO$_4$), and concentrated. The brown residue was chromatographed (EtOAc–hexane, 1:9); the first fraction eluted contained (R)-4 and the second fraction eluted afforded (S)-dial (6) (3.8 g, 43%). Subsequently, 6 (3.5 g, 17.85 mmol), Ph$_3$P (7.0 g, 26.7 mmol), and DIAD (5.16 mL, 26.75 mmol) in benzene (70 mL) were heated under reflux for 20 h. The solvent was removed, Et$_2$O (80 mL) was added, and the Ph$_3$P precipitate was removed by filtration. The filtrate was concentrated and the resulting residue was purified by column chromatography (EtOAc–hexane, 1:9) to give (S)-4 (2.55 g, 80%); [α]$_D$ = –13.9 (c 2.0, CHCl$_3$) [Lit.$^{a,b}$+14.5 (c 2.51, CHCl$_3$)].

(3R)-4-Trimethylamino-3-hydroxybutyric Acid [R-Carnitine] (1)
Methylation of (3R)-2 (200 mg, 1.68 mmol) was carried out by the reported method$^{a,b}$ to furnish (R)-1 (175 mg, 65% yield) as a clear colorless gum, which was recrystallized from i-PrOH; mp 193–195 °C (Lit.$^{b}$mp 197–198 °C); [α]$_D$ = 22.6 (c 1.0, H$_2$O) [Lit.$^{a,b}$ [α]$_D$ = 23.7 (c 0.86, H$_2$O)]; 95% ee.

(5)-1-Benzoyloxy-7-en-3-ol (8)
Mg (1.5 g, 62.5 mmol), 4-bromo-1-butene (8.1 g, 60 mmol), and a few drops of 1,2-dibromoethane in anhyd THF (25 mL) were gently warmed until the reaction commenced. The reaction mixture was then stirred at r.t. for 1 h and then cooled to –78 °C. A solution of Li$_2$CuCl$_4$ (0.09 g, 0.4 mmol) in THF was introduced into the reaction mixture. After stirring for 1 h, (R)-4 (3.1 g, 17.5 mmol) in THF (15 mL) was added dropwise. The mixture was stirred at –78 °C for an additional 3 h and then allowed to warm to r.t. overnight. The reaction was quenched with a cold sat. aq solution of NH$_4$Cl (10 mL). The organic layer was separated and the aqueous layer extracted with Et$_2$O (2 × 25 mL). The combined organic layer was washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude residue was chromatographed (EtOAc–
PE, 1:2) to give 8 (3.7 g, 90%) as a light yellow oil; [α]D +5.5 (c 0.5, CHCl3).

1H NMR (CDCl3): δ = 1.28–1.51 (m, 4 H), 1.59–1.61 (m, 2 H), 1.98–2.01 (m, 2 H), 2.85 (br s, 1 H), 3.52–3.54 (m, 2 H), 3.61–3.64 (m, 1 H), 4.42 (s, 2 H), 5.1–5.85 (m, 3 H), 7.23 (s, 5 H).

MS (CI): m/z (%) = 91 (100), 107 (81), 131 (18), 159 (47), 235 [54, (M + 1)].

Anal. Calcd for C14H22O2: C, 81.44; H, 8.70. Found: C, 81.37; H, 8.49.

(S)-6,8-Dibenzoyloxy-1-ene (9)

To a solution of alcohol 8 (2.35 g, 10.0 mmol) in anhyd DMF (15 mL) was added TBAI (7.49 g, 20.0 mmol) followed by NaH (60% wt in mineral oil, 0.36 g, 15.0 mmol) at 0 °C under a N2 atmosphere.

A solution of 2 M BH3·DMS (4.6 mL, 9.22 mmol) in THF (5 mL) was carefully introduced at 0 °C to decompose excess BH3·DMS, followed by the addition of 1 M aq NaOEt (30 mL) and water (25 mL) and then concentrated to give the crude carboxylic acid, which was esterified by dissolution in a solution of CH2N2 (excess) in Et2O and the resulting solution was left to stand overnight.

The crude methyl ester was purified by column chromatography (EtOAc–PE, 1:2) to give 9 (2.76 g, 85%) as a colorless oil; [α]D +19.5 (c 0.5, CHCl3).

1H NMR (CDCl3): δ = 1.48–1.51 (m, 4 H), 1.75–1.77 (m, 2 H), 2.01–2.03 (m, 2 H), 3.49–3.52 (m, 3 H), 4.40 (s, 2 H, OCHPh), 4.39 (d, J = 8.3 Hz, 1 H, CH2Ph), 4.45 (d, J = 8.3 Hz, 1 H, CH2Ph), 4.95–5.89 (m, 3 H, CH2=CHPh), 7.23 (s, 10 H).

MS (CI): m/z (%) = 91 (100), 107 (21), 127 (8), 159 (47), 235 [54, (M + 1)].

Anal. Calcd for C17H20O2: C, 71.84; H, 6.9; S, 31.15. Found: C, 71.80; H, 6.9; S, 31.15.

(S)-6,8-Dibenzoyloxy-1-ol (10)

To a solution of alkyne 9 (2.5 g, 7.7 mmol) in anhyd THF (15 mL) was added a solution of 2 M BH3·DMS (4.6 mL, 9.22 mmol) at 0 °C under a N2 atmosphere. After stirring for 2 h at r.t., MeOH (5 mL) was carefully introduced at 0 °C to decompose excess BH3·DMS, followed by the addition of 1 M aq NaOEt (30 mL) and 30% H2O2 (14.0 mL). The reaction mixture was then stirred at r.t. for 2 h. The solvent was removed under vacuum, diluted with H2O (2 mL), and extracted with CHCl3 (2 × 100 mL). The combined organic phases were washed with H2O (5 mL), brine (5 mL), dried (Na2SO4), and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc–PE, 1:9) to afford 10 (2.32 g, 88%) as a colorless liquid; [α]D +20.5 (c 1.0, CHCl3).

1H NMR (CDCl3): δ = 1.49–1.51 (m, 8 H), 2.25 (t, J = 7.3 Hz, 2 H), 2.65 (s, 3 H), 3.2–3.35 (m, 3 H), 4.50 (s, 2 H).

MS (Cl, NH3): m/z (%) = 130 (3), 141 (21), 163 (18), 174 (17), 191 [100, (M + 1)].

Anal. Calcd for C17H20O2: C, 71.42; H, 6.9; S, 32.07. Found: C, 71.42; H, 6.9; S, 32.07.

α-(R)-Lipoic Acid (3)

Mp 44–46 °C (Lit.8a 46–48 °C); [α]D +101 (c 1.0, CH2Cl2) [Lit.8b +104, (c 0.88, benzene)].

1H NMR (CDCl3): δ = 1.50–1.53 (m, 2 H), 1.67–1.70 (m, 6 H), 1.86–1.88 (m, 1 H), 2.35 (t, J = 7.3 Hz, 2 H), 2.92–2.95 (m, 1 H), 3.06–3.08 (m, 2 H), 3.47–3.49 (m, 1 H), 11.05 (br s, 1 H).

13C NMR (75 MHz): δ = 24.4, 28.8, 33.7, 34.6, 38.3, 40.3, 56.2, 180.0.

MS (EI): m/z (%) = 81 (100), 95 (7), 105 (25), 123 (64), 155 (17), 173 (12), 206 (70, M+).

Anal. Calcd for C5H10O2S: C, 46.55; H, 6.85; S, 31.1. Found: C, 46.8; H, 6.9; S, 31.15.

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References

