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Expeditious biomimetically-inspired approaches to racemic homocitric acid lactone and per-homocitrate

Hong-Bin Chen, Ling-Yan Chen, Pei-Qiang Huang,* Hong-Kui Zhang, Zhao-Hui Zhou and Khi-Rui Tsai

Department of Chemistry, Key Laboratory for Chemical Biology of Fujian Province and State Key Laboratory for Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, PR China

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Abstract—Two concise and flexible biomimetically-inspired approaches to homocitric acid lactone (**3**) and its higher homolog, triethyl per-homocitrate (**12**), are presented herein. The key steps include an efficient indium metal-mediated allylation–oxidative cleavage procedure and a one-step ethoxycarbonylmethylation of α-oxo-diesters.

1. Introduction

The mechanism of biological nitrogen fixation has been extensively studied in many laboratories over the world as an important interdisciplinary research. It has been shown that nitrogenases, mainly MoFe-nitrogenase, catalyze the ATP-dependent reduction of N_2 to ammonia with obligatory evolution of at least one H_2 at ambient temperature.[1] In addition, this enzyme can also catalyze the reduction of several types of substrates besides N_2 and H^+. Recent progress in mechanistic study of this complex metalloenzyme revealed that, (*R*)-homocitric acid (**1**) as a chelating ligand bound to $Mo^{IV/III}$ of FeMo-cofactor plays critical roles in nitrogen fixation.[2] Moreover, (*R*)-homocitric acid is also a key intermediate in the biosynthetic pathway to the essential amino acid lysine[3] in fungi and euglenids. Because this pathway is absent in plants and mammalians, (*R*)-homocitric acid and its derivatives are considered to be promising candidates for potential anti-fungal therapy in medicine, and anti-fungal agents for crop protection.[4] For further studies in both areas, it requires convenient methods to synthesize homocitric acid. Although several methods have been developed to synthesize homocitric acid lactone, a more stable version of homocitric acid,[5–7] almost all of them are either lengthy, low yielding, expensive, unscalable, or involving toxic reagents. As a consequence, current supply of homocitric acid is quite limited and very costly. In addition, the higher homolog of homocitric acid, namely per-homocitric acid is also important for elucidating the mechanism of nitrogenase-catalyzed biological nitrogen fixation. However, the method for the synthesis of per-homocitric acid is still not available (Chart 1).[8]

1. n = 1, (*R*)-homocitric acid
2. n = 2, (*R*)-per-homocitric acid
3. (*R*)-homocitric acid lactone

Chart 1. Structure of homocitric acid and per-homocitric acid.

In continuation of our studies on the nitrogenase,[9,7e] we have turned our attention to explore the roles that homocitrate played in the process of biological nitrogen fixation. To this end, an efficient, simple, and scalable route to homocitric acid and per-homocitric acid is required. We describe herein two expeditious, practical, and flexible approaches to both racemic homocitric acid lactone and triethyl per-homocitrate.

Inspired by the biosynthesis of homocitrate (Fig. 1),[6b,10,3] our retrosynthetic analysis of homocitric acid and its higher homologs (Scheme 1) implies the installation of the C-2 side chain to α-oxo-dicarboxylic acids or their diesters. Although such a C_2^d synthon has recently been shown to be introducible, albeit in modest yields (54–58%),[11] via silyl ketene acetate, to facilitate the product isolation and purification, we elected to use firstly the allyl group as a synthetic equivalent[12] of the requisite C_2^d synthon, and to use α-ketodiesters[13] as the substrates.

Keywords: Homocitric acid; Homocitric acid lactone; Per-homocitric acid; Indium; Allylation.
* Corresponding author. Tel.: +86 592 2180992; fax: +86 592 2186405; e-mail: pqhuang@xmu.edu.cn

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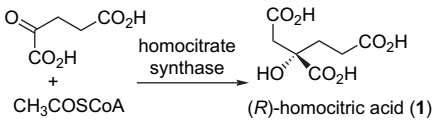
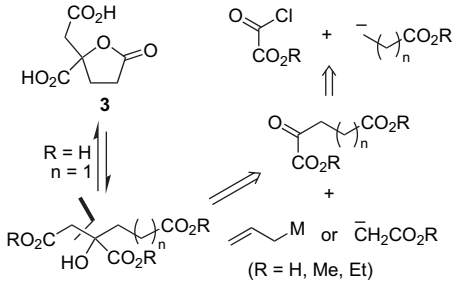


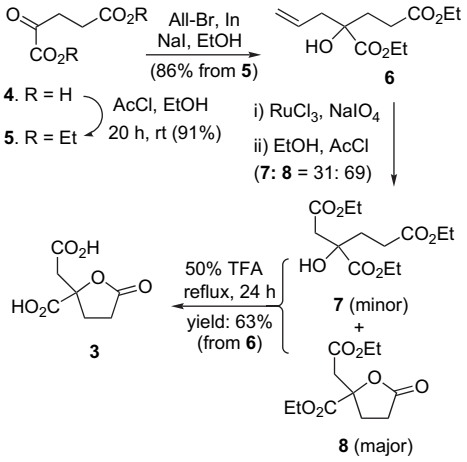
Figure 1. Biosynthetic pathway for homocitric acid.



Scheme 1. Retrosynthetic analysis of homocitric acid and per-homocitric acid.

2. Results and discussion

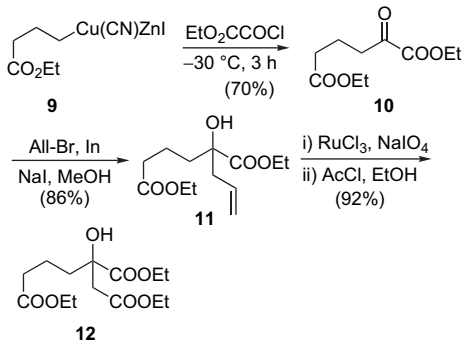
The synthesis of homocitric acid lactone (**3**) started from the di-esterification of commercially available α-oxo-glutaric acid (**4**) (Scheme 2). Thus treatment of α-oxo-glutaric acid with acetyl chloride containing absolute ethanol gave diethyl α-oxo-glutarate **5** in 91% yield. The efficient allylation of **5** was the key step for our strategy. Among numerous allylation methods,[14] modern indium metal-mediated Barbier-type allylation[15] appeared to be the most attractive in terms of its simplicity and low toxicity. Indeed, simply by stirring a mixture of diethyl α-oxo-glutarate **5**, allyl bromide, indium metal, and sodium iodide in a mixed solvent system (H_2O–ethanol 6/1) at rt, the desired carbinol **6** was obtained in 86% yield.[16]



Scheme 2.

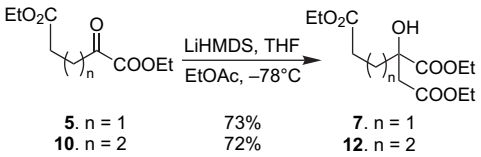
Next, we proceeded to investigate the oxidative cleavage of the double bond of the allyl group into a carboxyl group using ruthenium tetraoxide as an oxidant. Although subjection of **6** to the standard conditions established by Sharpless[12] (2.2% $RuCl_3$, 4.1 mol equiv $NaIO_4$ in CCl_4–MeCN–H_2O, 2/2/3) led to the desired product in satisfied yield, a recent report on replacing environmentally harmful CCl_4 by EtOAc[17] drew our attention. To our delight, mixed solvent system (EtOAc–MeCN–H_2O, 2/2/3, v/v)[17] worked similarly well (rt, 1 h). To facilitate the product isolation, the crude acid-diester was transformed into the corresponding triester by treating with CH_3COCl–EtOH at rt, which gave a separable mixture of **7** and **8** in a ratio of 31/69. The mixture of triester–lactone **7/8** was treated with a 50% solution of aqueous trifluoroacetic acid to give homocitric acid lactone (**3**) in an overall yield of 63% from **6**. It is worth to mention that only one flash chromatography purification and two simple filtrations through silica gel were required for the synthesis of homocitric acid lactone **3** from **4**.

The method was extended to the synthesis of per-homocitric acid triester (**12**). For this purpose, zinc–copper reagent **9**, prepared by the known procedure,[18] was treated with ethyl oxalyl chloride at −30 °C to afford the desired diethyl α-oxo-adipate **10** in 70% yield (Scheme 3). Indium-mediated allylation of α-oxo-adipate **10**, followed by RuO_4-mediated oxidative cleavage of the C=C bond under improved conditions (2.2% $RuCl_3$, 6.0 mol equiv $NaIO_4$ in EtOAc–MeCN–H_2O, 2/2/3, v/v),[17] and esterification furnished compound **12** in an overall yield of 79% from **10**.



Scheme 3.

We next turned our attention to investigate a biomimetically-inspired one-step approach to triethyl homocitrate **7** and triethyl per-homocitrate **12** by using ethyl lithioacetate as a C_2^d synthon. Treatment of diethyl α-oxo-glutarate **5** with ethyl lithioacetate, in situ generated from ethyl acetate and LiHMDS, afforded **7** in 73% yield (Scheme 4).[19] Similarly, subjection of diethyl α-oxo-adipate **10** to react with ethyl lithioacetate provided **12** in 72% yield.



Scheme 4.

3. Conclusion

In conclusion, we have developed a simple, convenient, and flexible synthesis of homocitric acid lactone (**3**) and its higher homolog (as triester **12**) starting from two α-oxo-diesters. The use of Barbier-type indium-mediated allylation

reaction, and substitution of harmful carbon tetrachloride by ethyl acetate in the RuO_4-mediated oxidative olefin cleavage, combined with simple purification procedure for the synthesis of homocitric acid lactone or per-homocitrate, render the present method more environmentally benign. Moreover, an even simpler one-step synthesis of triethyl homocitrate **7** and its higher homolog, triethyl per-homocitrate **12**, has also been achieved. The easy access to homocitric acid lactone and its higher homologs, will contribute, in its own right, to the studies of the mechanism of biological nitrogen fixation.

4. Experimental section

4.1. General

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 330 FTIR spectrometer using film KBr pellet technique. NMR spectra were recorded in $CDCl_3$ on a Bruker AV400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (parts per million) units downfield from TMS. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus LC–MS apparatus. Flash column chromatography was carried out on silica gel (300–400 mesh). THF was distilled over sodium.

4.1.1. Diethyl 2-allyl-2-hydroxypentanedioate (6). To an ethanolic solution (20 mL) of **5** (4.04 g, 20.0 mmol) were successively added an aqueous solution (120 mL) of sodium iodide (0.30 g, 2.0 mmol), allyl bromide (4.84 g, 3.5 mL, 40.0 mmol), and indium metal (2.76 g, 24.0 mmol). The reaction mixture was stirred at room temperature until indium metal completely dissolved. The mixture was diluted with 4 N HCl (15 mL) and extracted with ethyl ether (5× 50 mL). The combined organic phases were successively washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc–PE 1/8, R_f=0.35) to afford **6** (4.20 g, 17.2 mmol, yield: 86%) as a pale yellow oil. IR (film) ν_{max}: 3513, 3077, 1735, 1644, 1223, 1181; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.82–5.70 (m, 1H), 5.15–5.07 (m, 2H), 4.29–4.18 (m, 2H), 4.12 (q, J=7.0 Hz, 2H), 3.31 (s, 1H, *OH*, D_2O exchangeable), 2.52–2.38 (m, 3H), 2.25–2.15 (m, 1H), 2.15–1.99 (m, 2H), 1.30 (t, J=7.0 Hz, 3H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.5, 173.2, 131.9, 119.2, 76.3, 62.1, 60.5, 43.8, 33.5, 28.8, 14.3, 14.2; MS (ESI, *m/z*): 244 $(M+H)^+$, 266 $(M+Na)^+$. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.93; H, 8.19.

4.1.2. Homocitric acid lactone (3). To a solution of **6** (2.44 g, 10.0 mmol) in EtOAc (20 mL) and MeCN (20 mL) were successively added H_2O (30 mL), $NaIO_4$ (12.8 g, 60.0 mmol), and ruthenium trichloride hydrate (0.05 N in H_2O, 4.4 mL, 2.2% mol equiv). The dark brown suspension was stirred vigorously at rt for ca. 1 h. Then the reaction mixture was quenched with *iso*-propanol and filtered to remove the insoluble solids. The filtrate was concentrated under reduced pressure. The remaining aqueous solution was extracted with EtOAc (5×40 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The oily residue was dissolved in 20 mL of absolute ethanol and cooled to 0 °C before acetyl chloride (0.39 g, 0.36 mL, 5.0 mmol) was added dropwise. The resulting mixture was warmed to rt and stirred overnight. Ethanol was removed under reduced pressure and the residue was passed through a short silica gel column eluting with EtOAc–PE (60–90 °C, 1/1) to give a residue, which is a mixture of **7** and **8** (*method 1*). An analytical sample was obtained by flash chromatographic purification and the crude mixture was used in the next step as it was.

The crude mixture of **7/8** was dissolved in 50% trifluoroacetic acid (10 mL) and refluxed for 24 h. After cooling, the solvent was removed under reduced pressure. The residue was washed with anhydrous diethyl ether to give **3** (1.18 g, 6.3 mmol; overall yield from **6**: 63%) as colorless crystals. Mp: 166–168 °C (Et_2O) (lit.[6b] 161–162 °C). IR (film) ν_{max}: 3421, 1787, 1730, 1703, 1222, 1200, 1177, 1064 cm^{-1}; ^{1}H NMR (methanol-d_4, 400 MHz) δ: 2.93 (d, J=17.0 Hz, 1H), 2.68 (d, J=17.0 Hz, 1H), 2.45–2.31 (m, 2H), 2.31–2.20 (m, 1H), 2.20–2.09 (m, 1H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 178.7, 174.1, 172.4, 84.7, 42.1, 32.3, 28.7; HRMS calcd for $[C_7H_8O_6-1]^-$: 187.0240, found: 187.0237.

4.1.3. Compound 8. Pale yellow oil. IR (film) ν_{max}: 2981, 1793, 1739, 1376, 1178, 1070; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.28 (q, J=7.1 Hz, 2H), 4.16 (q, J=7.1 Hz, 2H), 3.11 (d, J=16.7 Hz, 1H), 2.96 (d, J=16.7 Hz, 1H), 2.74–2.52 (m, 3H), 2.40–2.30 (m, 1H), 1.32 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.5, 170.5, 168.5, 82.9, 62.4, 61.2, 41.6, 31.2, 27.8, 14.1, 14.0; MS (ESI, *m/z*): 244 $(M+H^+)$, 266 $(M+Na^+)$. Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.13; H, 6.60.

4.1.4. Triethyl homocitrate (7).

4.1.4.1. *Method 2* (via enolate addition to 5). To a solution of HMDS (0.63 g, 0.83 mL, 3.90 mmol) in 2.6 mL of anhydrous THF at 0 °C was added dropwise *n*-BuLi (2.5 M solution in *n*-hexane, 2.93 mmol, 1.17 mL). After stirring for about 30 min, the mixture was cooled to −78 °C and to which was added EtOAc (0.26 g, 0.76 mL, 2.93 mmol). After stirring at −78 °C for 30 min, a THF solution (5.50 mL) of **5** (0.39 g, 1.95 mmol) was added dropwise. The mixture was stirred at −78 °C for another 3 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl ether (3×8 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc–PE 1/6) to afford **7** (0.28 g, 0.98 mmol) in 73% yield. Pale yellow oil. IR (film) ν_{max}: 3505, 2982, 2938, 1736, 1446, 1373, 1191 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.22–4.31 (m, 2H), 4.13 (2q, overlapped, each J=7.1 Hz, 4H), 3.77 (s, 1H, *OH*, D_2O exchangeable), 2.94 (d, J=16.2 Hz, 1H), 2.68 (d, J=16.2 Hz, 1H), 2.46–2.54 (m, 1H), 2.21–2.29 (m, 1H), 2.02–2.07 (m, 2H), 1.31 (t, J=7.1 Hz, 3H), 1.25 (2t, overlapped, each J=7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.6, 172.9, 170.5, 74.2, 62.2, 60.9, 60.6, 43.5, 33.9, 28.3, 14.1; MS (ESI, *m/z*): 290 $(M+H^+)$, 312 $(M+Na^+)$. Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 53.62; H, 7.60.

4.1.5. Triethyl per-homocitrate (12).

4.1.5.1. *Method 1* (via indium-mediated allylation of 10 followed by subsequent oxidative cleavage and esterification). Following the procedure described for the allylation of **5**, **11** was synthesized in 86% yield from **10**.

Compound **11**: pale yellow oil. IR (film) ν_{max}: 3517, 3073, 2980, 1735, 1637, 1222, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.83–5.70 (m, 1H), 5.16–5.08 (m, 2H), 4.30–4.21 (m, 2H), 4.13 (q, J=7.1 Hz, 2H), 3.25 (s, 1H, *OH*, D_2O exchangeable), 2.48–2.35 (m, 2H), 2.35–2.24 (m, 2H), 1.88–1.77 (m, 2H), 1.74–1.65 (m, 1H), 1.55–1.45 (m, 1H), 1.31 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.8, 173.2, 132.2, 119.0, 76.7, 62.0, 60.3, 43.9, 38.0, 34.2, 19.1, 14.3, 14.2. MS (ESI, *m/z*): 259 $(M+H)^+$, 281 $(M+Na)^+$. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.51; H, 8.49.

Compound **12** was prepared in 92% yield from **11** by following the procedure described for the synthesis of **7/8**.

4.1.5.2. *Method 2* (via enolate addition to 10). To a solution of HMDS (0.500 g, 0.65 mL, 3.08 mmol) in 2.0 mL anhydrous THF at 0 °C was added dropwise *n*-BuLi (2.5 M solution in *n*-hexane, 2.31 mmol, 0.90 mL). After stirring for about 30 min, the mixture was cooled to −78 °C. To which was added EtOAc (0.65 mL, 2.51 mmol) and the stirring was continued at −78 °C for about 30 min. To the resulting mixture was added dropwise **10** (0.33 g, 1.54 mmol) in 4.50 mL anhydrous THF. The reaction mixture was stirred at −78 °C for another 3 h and then quenched with saturated NH_4Cl. The resulting mixture was extracted with diethyl ether (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc–PE 1/6) to afford **12** (0.34 g, 1.12 mmol, yield: 72%) as a pale yellow oil. IR (film) ν_{max}: 3517, 2980, 1735, 1641, 1446, 1372, 1222, 1175, 1025 cm^{-1}; IR (film) ν_{max}: 3508, 2982, 2938, 1739, 1736, 1732, 1374, 1183, 1096, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.32–4.21 (m, 2H), 4.12 (2q, overlapped, each J=7.0 Hz, 4H), 3.75 (s, 1H, *OH*, D_2O exchangeable), 2.91 (d, J=16.2 Hz, 1H), 2.67 (d, J=16.2 Hz, 1H), 2.36–2.23 (m, 2H), 1.84–1.58 (m, 4H), 1.30 (t, J=7.0 Hz, 3H), 1.24 (2t, overlapped, each J=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 173.0, 170.6, 74.8, 62.0, 60.8, 60.3, 43.5, 38.4, 34.0, 18.8, 14.2, 14.1, 14.0; MS (ESI, *m/z*): 305 $(M+H)^+$, 327 $(M+Na)^+$. Anal. Calcd for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 55.15; H, 8.04.

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