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A facile method for synthesis of (*R*)-(−)- and (*S*)-(+)-homocitric acid lactones and related α-hydroxy dicarboxylic acids from D- or L-malic acid

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Abstract—We report here a simple and convenient route for the stereoselective synthesis of (*R*)-(−)- and (*S*)-(+)-homocitric acid lactones, which play very important roles in biochemistry. The method involves only three steps, starting from the readily available methyl 3-iodopropionate and D-malic acid or L-malic acid, respectively. The stereoconfiguration of the target molecules has been achieved via a self-regeneration approach with over 98% diastereoselectivity and significantly improved yield over the previous methods.

Homocitrate is an important component of the FeMo-cofactor in nitrogenase, where nitrogen fixation has been thought to occur. The FeMo-cofactor was first identified by Shah and Brill in 1977,[1] and its crystallographic structure was determined by Rees and co-workers.[2] Since then, there have been extensive investigations on the biological functions of FeMo-cofactor,[3] and on the synthetic Mo/Fe/S cluster models.[4] However, the mechanism of fixation/activation of molecular dinitrogen remains unclear, and in particular the role of homocitrate coordinated to molybdenum has not been well understood. This is partly due to the lack of convenient methods to synthesize (*R*)-(−)-homocitrate, which is not commercially available (Fig. 1).

There are two reports on asymmetric synthesis of (*R*)-(−)-homocitrate based on Seebach's work,[5] which starts from α-hydroxy carboxylic acid and utilizes pivalaldehyde as a protecting group to form a dioxolanone ring in order to achieve a high regioselectivity created by the bulkiness of the *tert*-butyl group. Biellmann started from L-lactic acid or L-serine and arrived at the target

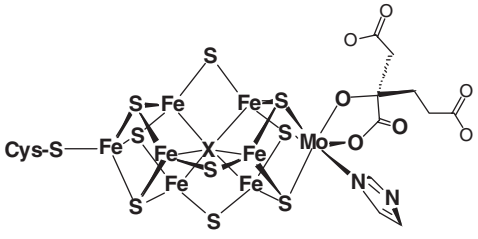

Figure 1. FeMo-cofactor structure of nitrogenase.

in five steps with an overall yield of 3%.[6] The improved synthesis from D-malic acid was reported thereafter by Ma and Palmer, but still the overall yield of homocitrate lactone is 12% and it requires six steps.[7] In this paper, we report a new and facile route for the synthesis of (*R*)-(−)- and (*S*)-(+)-homocitric acid lactones with much improved yields (total yields are >30%) and good stereoselectivity (>98% ee). The method is based on the work of Ma and Palmer but we could accomplish the synthesis in only three steps featuring methyl 3-iodopropionate as the electrophilic reagent by modification of the reaction conditions.

The asymmetric synthetic route to (*R*)-(−)-homocitrate and other corresponding carboxylic acids is summarized in Scheme 1.

Keywords: Homocitric acid lactones; α-Hydroxy dicarboxylic acids; Nitrogenase.
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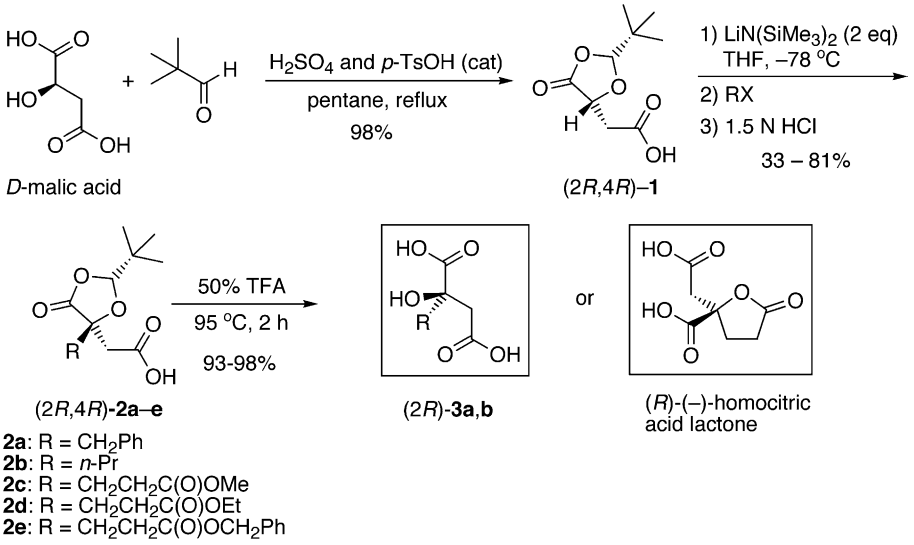


Scheme 1.

The first step is the synthesis of protected D-malic acid by pivalaldehyde, which could be repeated according to Seebach's report.[5]

The following step is alkylation of dianion species of compound **1**. According to the reported method, (2*R*,4*R*)-**1** was treated by 2 equiv of $LiN(SiMe_3)_2$ at −78 °C and then 1.5 equiv of benzyl bromide was added. The solution was allowed to warm to −20 °C and kept for another 5 h to give the corresponding adducts (2*R*,4*R*)-**2a** in 81% yield (>98% ee, entry 1 in Table 1), which is almost similar to the reported results.[5–7] We expected 3-iodopropionic acid ester to be the proper electrophile for a straightforward synthesis of (*R*)-(−)-homocitrate and (*S*)-(+)-homocitrate. However, the reaction with methyl 3-iodopropionate did not afford the adduct by the same procedure. Similarly, the reaction with *n*-propyl iodide was found unsuccessful (entry 2).[8] We examined the reaction with *n*-propyl iodide using D,L-**1** prepared from D,L-malic acid under various reaction time and temperature, and we found a clue to get the adduct although the yield was only 10%, when the temperature was kept −10 °C for 10 h (entry 3). The work-up process after this alkylation reaction was also optimized altogether. Compounds **2** are sensitive to acid and base in the solution. When the acidity was too high, the protecting group, pivalaldehyde, was easily removed. The resulting dicarboxylic acid compound could not be separated by flash column chromatography using silica gel. The basic solution condition is apparently not suitable because the desired compound would dissolve in the aqueous phase as carboxylates. Meanwhile, the colour of the solution will turn red even to black red due to the oxidation of the excess of I^- in the air, which will be troublesome in the course of separation of desired compounds. Thus, we employed the 1 N HCl solution to quench the reaction and adjusted pH value near to 3. The organic layer was then washed with saturated solution of sodium sulfite to reduce I_2 into I^-.

When the reaction temperature was over 0 °C, the diasteroselectivity decreased to 90% (entry 5). Finally the optimized conditions were to keep the temperature at −5 °C for 14 h, and the adduct D,L-**2c** was obtained in 35% (entry 4). ^1H NMR clearly shows that no epimer exists, and at the same time, we could obtain single crystals of compound D,L-**2c** and the structure was deter-

Table 1. The alkylation reactions of compound **1**

Entry	Substrates	Electrophiles	Reaction conditions[a]	Yield (%)	$[\alpha]_D^{22}$	de%[b]
1	(2*R*,4*R*)-**1**	Benzyl bromide	−20 °C, 5 h	81	−64.2	>98
2	D,L-**1**	*n*-Propyl iodide	−20 °C, 5 h	0	—	—
3	D,L-**1**	*n*-Propyl iodide	−10 °C, 16 h	10	—	>96[c]
4	D,L-**1**	*n*-Propyl iodide	−5 °C, 10 h	35	—	>96[c]
5	(2*R*,4*R*)-**1**	*n*-Propyl iodide	0 °C, 10 h	38	—	90
6	(2*R*,4*R*)-**1**	*n*-Propyl iodide	−5 °C, 10 h	35	−24.8	>96
7	(2*R*,4*R*)-**1**	Methyl 3-iodopropionate	−5 °C, 10 h	33	−20.0	>98
8	(2*R*,4*R*)-**1**	Ethyl 3-iodopropionate	−5 °C, 10 h	26	−17.4	>98
9	(2*R*,4*R*)-**1**	Benzyl 3-iodopropionate	−5 °C, 10 h	30	−12.9	>98
10	(2*S*,4*S*)-**1**	Methyl 3-iodopropionate	−5 °C, 10 h	34	+19.9	>98

[a] The electrophiles were added at −78 °C and they were gradually warmed to these temp and stirred.
[b] The de value were calculated by the integration of ^1H NMR from Varian Inova-500M spectrometer.
[c] One pair of enantiomers, (2*R*,4*R*) and (2*S*,4*S*), were obtained selectively.

mined by X-ray analysis.[9] It is clear that there is a pair of enantiomers in the unit cell, since space group is *P*-1 and $Z = 2$ (Fig. 2).[10] The relative configuration is the predicted one, which is in agreement with the results Seebach referred to as the self-regeneration of stereocentres (SRS) approach.[11]

Under these optimized conditions, the reaction of (2*R*,4*R*)-**1** and methyl 3-iodopropionate as an electrophile afforded (2*R*,4*R*)-3-(2-*tert*-butyl-5-carboxymethyl-4-oxo-[1,3]dioxolan-5-yl)-propionic acid methyl ester [(2*R*,4*R*)-**2c**] in 33% yield (entry 7). Similarly, (2*S*,4*S*)-**2c** was obtained in 34% from (2*S*,4*S*)-**1** (entry 10). Their optical rotation values match well except for the direction. When the reaction of (2*R*,4*R*)-**1** was performed over 0 °C, a diastereomer, (2*R*,4*S*)-**2c**, was also isolated, whose X-ray structural analysis clearly shows that methyl propionate group is located on the same side as *tert*-butyl group (Fig. 3).[9] Other spectroscopic data are consistent with the X-ray structure.[12]

When ethyl 3-iodopropionate and benzyl 3-iodopropionate were used as an electrophilic reagent, the corresponding adducts were obtained in 26% and 30% yield, respectively (entries 8 and 9).

The last step is to remove the protecting group (Scheme 2). We tried using formic acid or trifluoroacetic acid in various concentrations to remove pivalaldehyde protection. Homocitric acid is not a stable form and hence a five member lactone ring was spontaneously formed after removing pivalaldehyde protection to give (*R*)-(−)-homocitric acid lactone in 98% yield. (*S*)-(+)-homocitric acid lactone was also synthesized in the same procedure. The overall yields of (*R*)-(−)- and (*S*)-(+)-homocitric acid lactone are 32% and 33% from D- and L-malic acid, respectively.

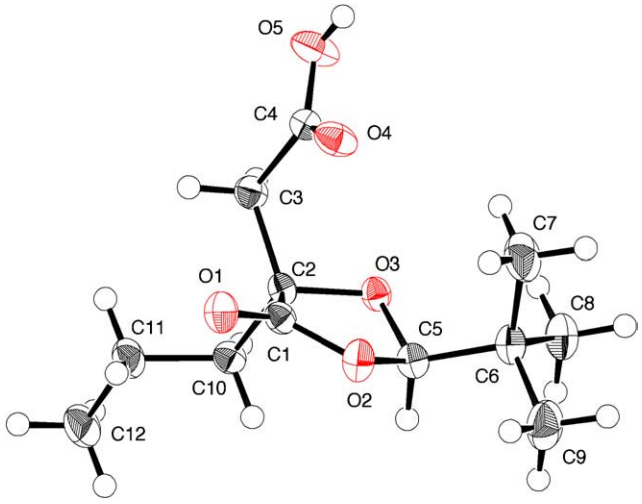


Figure 2. The ORTEP3 structure of D,L-**2b**.

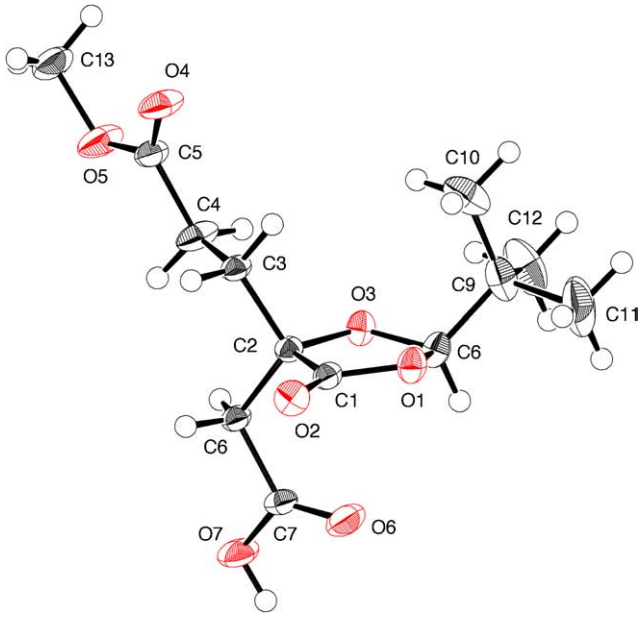
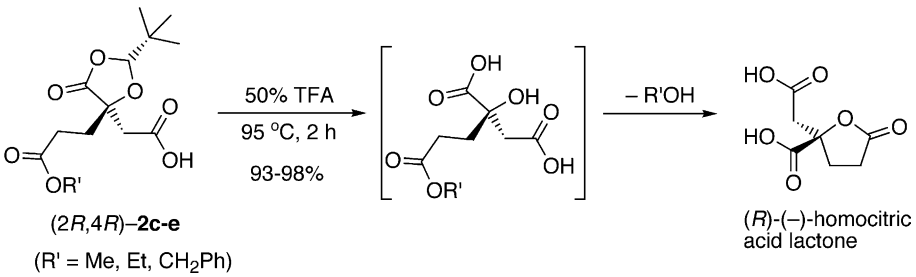


Figure 3. The ORTEP3 structure of (2*R*,4*S*)-**2c**.

The optical rotations were measured. (*R*)-(−)- and (*S*)-(+)-homocitric acid lactone were already synthesized by Biellmann[6] and their optical rotations were reported in a complicated system.[13] We measured the optical rotations of (*R*)-(−)- and (*S*)-(+)-homocitric acid lactone in methanol, and also in the presence of molybdate complex according to the reported method.[13] The results are as following; (*R*)-(−)-homocitric acid lactone: $[\alpha]_D^{22}$ −21.2 (*c* 1.22, CH_3OH), $[\alpha]_D^{22}$ −51.8 (*c* 0.25, condition see Ref. 13); (*S*)-(+)-homocitric acid lactone: $[\alpha]_D^{22}$ +21.3 (*c* 1.12, CH_3OH). $[\alpha]_D^{22}$ +52.2 (*c* 0.22, condition see Ref. 13).

In conclusion, we have developed a new and simple method for the synthesis of (*R*)-(−)- and (*S*)-(+)-homocitric acid lactone with high stereoselectivity in higher yield. We believe such a facile method will significantly



Scheme 2.

facilitate the research of nitrogenase and nitrogenase models.

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Supplementary data

Experimental details and spectroscopic data for all new compounds are included in Supplementary data which can be obtained on-line at doi:10.1016/j.tetlet.2005.03.180.

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9. X-ray data for D,L-**2b** and (2*R*,4*S*)-**2c**; the data collection was made with a Rigaku-AFC8 diffractometer equipped with a Rigaku Saturn CCD detector. The structure was solved by direct methods and refined by full-matrix least-squares on *F* by teXsan software package of Rigaku/MSC. Crystal data for D,L-**2b**: $C_{12}H_{20}O_5$, $M = 244.29$, triclinic, space group $P\bar{1}$, $a = 5.964(1)$, $b = 9.246(2)$, $c = 12.610(3)$ Å, $\alpha = 98.848(10)$, $\beta = 103.231(9)$, $\gamma = 91.11(1)°$, $V = 667.7(2)$ Å^3, $Z = 2$, $D_{calcd} = 1.215$ g/cm^3, $T = 173$ K, μ(Mo-Kα) = 0.94 cm^{-1}, $R = 0.054$, $R_w = 0.071$, GOF = 1.91, 158 variables, 2856 unique reflections [$I > 0\sigma(I)$]. For (2*R*,4*S*)-**2c**: $C_{13}H_{20}O_7$, $M = 288.30$, monoclinic, space group $P2_1$, $a = 10.06(1)$, $b = 6.346(5)$, $c = 12.77(1)$ Å, $\beta = 112.09(2)°$, $V = 755.2(10)$ Å^3, $Z = 2$, $D_{calcd} = 1.268$ g/cm^3, $T = 173$ K, μ(Mo-Kα) = 1.03 cm^{-1}, $R = 0.036$, $R_w = 0.046$, GOF = 1.31, 184 variables, 2816 unique reflections [$I > 0\sigma(I)$]. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 265287 for D,L-**2b** and CCDC 265288 for (2*R*,4*S*)-**2c**.
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12. (2*R*,4*R*)-**2c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.20 (s, 1H), 3.71 (s, 3H), 2.89 (d, 1H, $J = 16.5$ Hz), 2.86 (d, 1H, $J = 16.5$ Hz), 2.43–2.52 (m, 2H), 2.26–2.32 (m, 1H), 2.08–2.14 (m, 1H), 0.96 (s, 9H); mp: 75–77 °C. $[\alpha]_D^{22}$ −20.0. (2*R*,4*S*)-**2c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.32 (s, 1H), 3.72 (s, 3H), 2.94 (d, 1H, $J = 17$ Hz), 2.88 (d, 1H, $J = 17$ Hz), 2.54–2.60 (m, 1H), 2.42–2.48 (m, 1H), 2.22–2.28 (m, 1H), 2.12–2.18 (m, 1H), 0.99 (s, 9H); mp: 108–110 °C. $[\alpha]_D^{22}$ +26.2.
13. Krebs, H. A.; Eggleston, L. V. *Biochemistry* **1943**, *37*, 334, According to their method, we prepared the media from 2.5 mL of Na_3-citrate (1 M), 0.5 mL of glacial acetic acid, 4.5 mL $(NH_4)_2MoO_4$ (29%) and 2.5 mL distilled water.