(±)-*erythro*-γ,δ-Dihydroxycarboxylic Acid Lactones from a β-Lithiopropionate Equivalent and α-Chloroaldehydes[1]

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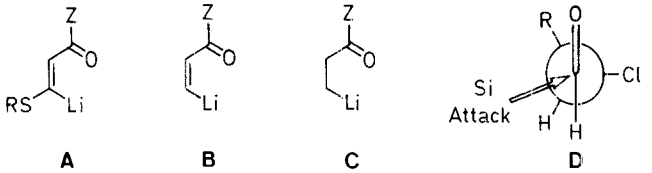
Reaction of β-ethylthio-β-lithioacrylate **1A** with α-chloroaldehydes furnished predominantly the *erythro* products **3**, which were isolated as γ-lactones **4**. At room temperature intermediates **3** are transformed into the (±)-*erythro*-γ,δ-dihydroxycarboxylic acid γ-lactones **8**. Raney nickel treatment provided interesting natural γ-lactone derivatives; thus, from *erythro*-**8c** the socalled L-factor *erythro*-**9c** was obtained. Similarly, from β-methoxy β-lithioacrylate **10A** the (±)-*erythro*-γ,δ-dihydroxycarboxylic acid δ-lactone *erythro*-**11** was gained.

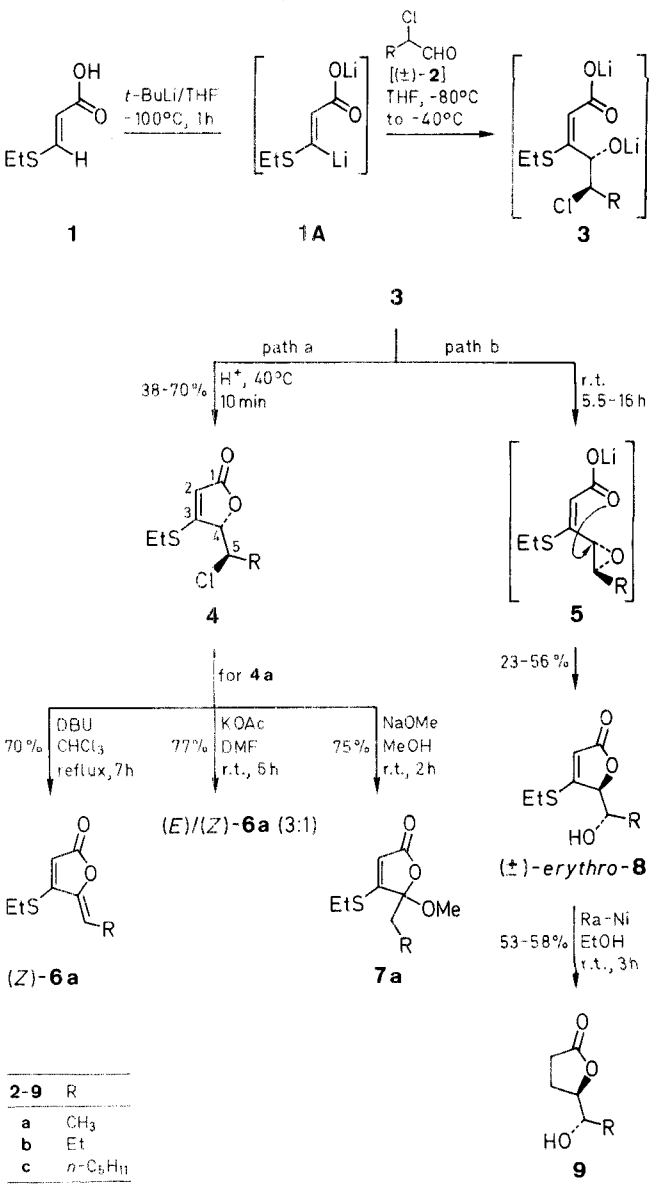
γ,δ-Dihydroxycarboxylic acid lactones are ubiquitous in nature, exhibiting often interesting physiological properties.[2,3] For instance, the (−)-isomer of compound *erythro*-**9a** (Scheme **B**) is a constituent of *Osmunda japonica THUN.* providing a derivative with antifeedant properties.[3] The (+)-isomer of compound *erythro*-**9c** was isolated from *Streptomyces griseus*[2] and named L-factor because it was claimed to be responsible for the formation of the antibiotic leukaemomycin.[4] Various synthetic methodologies have been developed for this type of compounds.[5–10] In addition, they have been used as intermediates in natural product syntheses[11] including carbohydrates.[1,12]

We have demonstrated that the readily accessible β-C-lithiated acrylates **A** (Scheme **A**) serve as versatile β-lithioacrylate **B** and β-lithiopropionate equivalents **C** providing, for instance, γ- and δ-lactones in short routes by reaction with carbonyl compounds, epoxides, and oxetanes, respectively, as electrophilic-nucleophilic species.[10,12,13] Thus, γ,δ-dihydroxy substituted derivatives are also readily obtained with derivatives of α-hydroxy aldehydes and α-hydroxy epoxides;[1,10,12] the usefulness of α-chloroaldehydes in this reaction is demonstrated here.[14]



Scheme **A**

The dilithiated species **1A**, generated from the readily available β-ethylthioacrylic acid **1** with *tert*-butyllithium,[13] afforded with α-chloroaldehydes **2a–c** (racemates) at low temperature diastereoselectively the addition products **3**, which on acidic aqueous workup (path a) provided the *erythro*-γ-lactones (±)-*erythro*-**4a–c**, respectively, in good yields (Table 2). The ^{1}H-NMR of the crude demonstrated the presence of minor amounts of the corresponding *threo*-isomers (Table 1), which could not be isolated in pure form. The relative configurations were assigned by comparison of the ^{1}H-NMR data with previous results[1,12] where H-4 of the *erythro*-isomer exhibits a downfield shift (Table 2) compared with the corresponding *threo*-isomers [δ (H-4): **4a** = 4.97; **4b** = 5.04; **4c** = 5.05]. The



2-9	R
a	CH_3
b	Et
c	n-C_5H_{11}

Scheme **B**

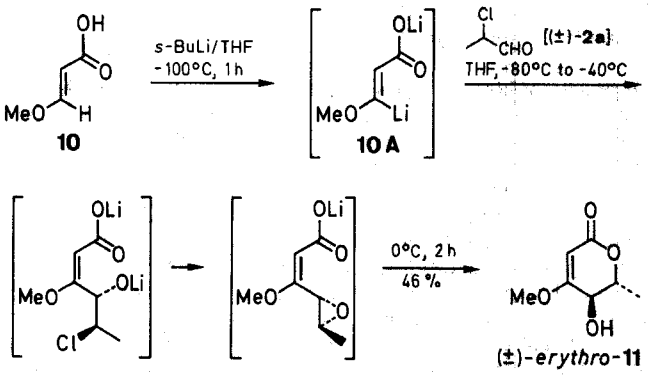
Table 1. *erythro*/*threo*-Selectivities Obtained for the Reactions of **1A** and **10A** with (±)-**2a–c**

Starting materials	Products and Ratios (Path a)[a]	Products and Ratios (Path b)[a]
1A + (±)-**2a**	(±)-*erythro*-**4a** : (±)-*threo*-**4a** (9 : 1)	(±)-*erythro*-**8a** : (±)-*threo*-**8a** (6 : 1)
1A + (±)-**2b**	(±)-*erythro*-**4b** : (±)-*threo*-**4b** (9 : 1)	(±)-*erythro*-**8b** : (±)-*threo*-**8b** (9 : 1)
1A + (±)-**2c**	(±)-*erythro*-**4c** : (±)-*threo*-**4c** (7 : 1)	(±)-*erythro*-**8c** : (±)-*threo*-**8c** (7 : 1)
10A + (±)-**2a**		(±)-*erythro*-**11** : (±)-*threo*-**11** (> 19 : 1)

[a] See experimental.

preferred formation of the *erythro*-isomers is in accordance with previous findings[1,12] and with the Cram-Felkin-Anh model predictions (see **D**).[15]

Base treatment, for instance of the product (±)-*erythro*-**4a** gave varying results: Treatment with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) afforded cleanly the *Z*-isomer *Z*-**6a**; this is ascribed to a E1cb mechanism favoring the formation of the thermodynamically more stable isomer. However, with potassium acetate due to a prevailing E2 mechanism the major isomer was the *E*-isomer *E*-**6a** (*E*/*Z* = 3:1). The structural assignments are based on the ^{1}H-NMR chemical shifts of H-5.[16] Sodium methoxide in methanol furnished via elimination and reversed methanol addition butenolide (±)-**7a**. Chlorine substitution was directly obtained from the reaction mixture containing intermediates **3** by warming up to room temperature (path b). The γ,δ-dihydroxycarboxylic acid lactones (±)-**8a–c** were found in almost the same *erythro*/*threo* ratios in the crude (Table 1); the *erythro*-isomers (±)-*erythro*-**8a–c** were isolated in pure form (Table 2). The stereochemical result is due to double inversion of configuration with formation of epoxides **5** and subsequent invertive opening. Raney nickel treatment of compounds (±)-*erythro*-**8a** and (±)-*erythro*-**8c** led to the lactones (±)-*erythro*-**9a** and (±)-*erythro*-**9c**, respectively, which had ^{1}H-NMR data identical to those published previously,[8,17] thus independently proving the structural assignments.



Scheme C

Table 2. Compounds **4**, **6**, **8**, **9** and **11** Prepared

Product	Yield (%)	mp[a] (°C)	Molecular Formula[b] or Lit. Data	^{1}H-NMR (250 MHz, $CDCl_3$/TMS)[c] δ, *J* (Hz)
(±)-*erythro*-**4a**	66	oil[d]	$C_8H_{11}ClO_2S$ (206.7)	1.43 (t, 3H, *J* = 7.3, SCH_2CH_3); 1.48 (d, 3H, *J* = 6.7, $CHCH_3$); 2.98 (q, 2H, *J* = 7.3, SCH_2CH_3); 4.23 (dq, 1H, *J* = 3.3, 6.7, H-5); 5.10 (dd, 1H, *J* = 1.2, 3.3, H-4); 5.77 (d, 1H, *J* = 1.2, H-2)
(±)-*erythro*-**4b**	70	oil[d]	$C_9H_{13}ClO_2S$ (220.7)	1.09 (t, 3H, *J* = 7.3, CH_2CH_3); 1.42 (t, 3H, *J* = 7.3, SCH_2CH_3); 1.75–1.97 (m, 2H, $CH-CH_2CH_3$); 2.99 (q, 2H, *J* = 7.3, SCH_2CH_3); 3.98–4.05 (m, 1H, H-5); 5.13 (dd, 1H, *J* = 1.2, 3.6, H-4); 5.76 (d, 1H, *J* = 1.2, H-2)
(±)-*erythro*-**4c**	38	oil[e]	$C_{12}H_{19}ClO_2S$ (262.8)	0.90 (t, 3H, *J* = 6.7, CH_3); 1.42 (t, 3H, *J* = 7.3, SCH_2CH_3); 1.26–1.82 [m, 8H, $(CH_2)_4$]; 2.98 (q, 2H, *J* = 7.3, SCH_2CH_3); 4.09 (dt, 1H, *J* = 3.3, 10.3, H-5); 5.13 (dd, 1H, *J* = 1.2, 3.3, H-4); 5.77 (d, 1H, *J* = 1.2, H-2)
(*Z*)-**6a**	70[f]	77–78	$C_8H_{10}O_2S$ (170.2)	1.41 (t, 3H, *J* = 7.3, SCH_2CH_3); 1.92 (d, 3H, *J* = 7.3, $=CCH_3$); 2.97 (q, 2H, *J* = 7.3, SCH_2CH_3); 5.40 (q, 1H, *J* = 7.3, H-5); 5.77 (s, 1H, H-2)
(*E*)-**6a**	77[g]	52	$C_8H_{10}O_2S$ (170.2)	1.45 (t, 3H, *J* = 7.3, SCH_2CH_3); 2.04 (d, 3H, *J* = 7.9, $=CCH_3$); 2.98 (q, 2H, *J* = 7.3, SCH_2CH_3); 5.82 (d, 1H, *J* = 1.5, H-2); 5.87 (dq, 1H, *J* = 1.5, 7.9, H-5)
(±)-**7a**	75	oil	$C_9H_{14}O_3S$ (202.3)	0.89 (t, 3H, *J* = 7.3, CH_2CH_3); 1.43 (t, 3H, *J* = 7.3, SCH_2CH_3); 1.81 (dq, 1H, *J* = 7.3, 14.6, CH_2CH_3); 2.06 (dq, 1H, *J* = 7.3, 14.6, CH_2CH_3); 2.96 (q, 2H, *J* = 7.3, SCH_2CH_3); 3.21 (s, 3H, OCH_3); 5.78 (s, 1H, H-2)
(±)-*erythro*-**8a**	56	85[e]	$C_8H_{12}O_3S$ (188.3)	1.21 (d, 3H, *J* = 6.4, $CHCH_3$); 1.41 (t, 3H, *J* = 7.4, SCH_2CH_3); 2.74 (d, 1H, *J* = 7.0, OH); 2.97 (q, 2H, *J* = 7.4, SCH_2CH_3); 4.02 (m, 1H, H-5); 4.98 (dd, 1H, *J* = 1.2, 3.9, H-4); 5.73 (d, 1H, *J* = 1.2, H-2)
(±)-*erythro*-**8b**	41	74[d]	$C_9H_{14}O_3S$ (202.3)	1.03 (t, 3H, *J* = 7.3, CH_2CH_3); 1.42 (t, 3H, *J* = 7.3, SCH_2CH_3); 1.50–1.65 (m, 2H, CH_2CH_3); 2.01 (d, 1H, *J* = 7.3, OH); 2.96 (q, 2H, *J* = 7.3, SCH_2CH_3); 3.67–3.77 (m, 1H, H-5); 4.97 (dd, 1H, *J* = 1.2, 5.5, H-4); 5.71 (d, 1H, *J* = 1.2, H-2)
(±)-*erythro*-**8c**	22	92[e]	$C_{12}H_{20}O_3S$ (244.4)	0.88 (t, 3H, *J* = 4.9, CH_3); 1.21–1.63 [m, 8H, $(CH_2)_4$]; 1.41 (t, 3H, *J* = 7.3, SCH_2CH_3); 2.95 (br s, 1H, OH); 2.97 (q, 2H, *J* = 7.3, SCH_2CH_3); 3.78–3.84 (m, 1H, H-5); 4.97 (dd, 1H, *J* = 1.2, 4.2, H-4); 5.73 (d, 1H, *J* = 1.2, H-2)
(±)-*erythro*-**9a**	58	oil	oil[17]	–[h]
(±)-*erythro*-**9b**	53	oil	oil[8]	–[h]
(±)-*erythro*-**11**	46	111–112	$C_7H_{10}O_4$ (158.2)	1.47 (d, 3H, *J* = 6.4, $CHCH_3$); 3.73 (br s, 1H, OH); 3.81 (s, 3H, OCH_3); 4.17 (dd, 1H, *J* = 2.4, 7.6, H-4); 4.39 (dq, 1H, *J* = 6.4, 7.6, H-5); 5.14 (s, 1H, H-2)

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.3.
[c] Recorded on a Bruker WM 250 spectrometer.
[d] Chromatographed on silica gel (eluent: petroleum ether (bp 35–65°C)/EtOAc, 1:1).
[e] Chromatographed on silica gel (eluent: petroleum ether (bp 35–65°C)/EtOAc, 7:3).
[f] From **4a** and DBU.
[g] From **4a** and KOAc, *E*-**6a**/*Z*-**6a** = 3:1.
[h] ^{1}H-NMR data are in accordance with the reported values.[8,17]

The same reaction course was observed for the dilithiated species **10A** generated from β-methoxy acrylic acid **10**[18] with *sec*-butyllithium. With (±)-**2a**, for instance, exclusively the *erythro*-isomer (±)-*erythro*-**11** was obtained via the intermediates in Scheme **C** (*erythro*:*threo* > 19:1; the *threo*-isomer was not detected). This compound was isolated as the more stable δ-lactone; the structure was assigned by comparing the ^{1}H-NMR data of (±)-*erythro*-**11** (Table 2) with literature data of similar compounds.[19]

Preparation of Lactones (±)-*erythro*-4a–c; General Procedure (Path a):
t-BuLi (3.6 mL of a 1.4 M solution in pentane, 5 mmol) is added dropwise with stirring to a solution of (*E*)-β-ethylthioacrylic acid **1**[13] (300 mg, 2.27 mmol) in dry THF (50 mL) at −100 °C under N_2. The mixture is stirred for 1 h at the same temperature, then heated to −80 °C. Then freshly distilled appropriate α-chloroaldehyde **2**[20] (1.1 equiv) is introduced dropwise into the reaction flask with a syringe. Stirring is continued for 1 h at −80 °C and 1 h at −40 °C. The mixture is poured into ice water (30 mL), acidified to pH 1 with 3 N HCl, and extracted with ether (3 × 50 mL). The combined ether extract is dried ($MgSO_4$), and concentrated. Evaporation is continued for 10 min at 40 °C. The remaining liquid is poured into a sat. $NaHCO_3$ (30 mL), extracted with ether (3 × 30 mL), and the combined ether extract is dried ($MgSO_4$). After concentration, the residue is purified by column chromatography (silica gel; eluents: see Table 2).

(*Z*)-3-Ethylthio-2,4-hexadien-4-olide (*Z*-6a):
A solution of (±)-*erythro*-**4a** (250 mg, 1.21 mmol) and DBU (230 mg, 1.51 mmol) in dry $CHCl_3$ (30 mL) is refluxed for 7 h. After cooling, the mixture is diluted with water (30 mL), acidified to pH 1 with 3 N HCl, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract is washed with sat. $NaHCO_3$, and dried ($MgSO_4$). After concentration, the residue is purified by column chromatography [silica gel; eluent: petroleum ether (bp 35–65 °C)/EtOAc, 8:2].

(*E*)-3-Ethylthio-2,4-hexadien-4-olide (*E*-6a):
A solution of (±)-*erythro*-**4a** (300 mg, 1.45 mmol) and KOAc (200 mg, 2.03 mmol) in DMF (25 mL) is stirred at room temperature for 6 h. The mixture is diluted with water (25 mL), and extracted with ether (4 × 50 mL). The organic extracts are washed with water (4 × 50 mL), dried ($MgSO_4$), and concentrated. The residue is chromatographed on a silica gel column using petroleum ether (bp 35–65 °C)/EtOAc, 8:2 as eluent.

(±)-3-Ethylthio-4-methoxy-2-hexen-4-olide [(±)-7a]:
To a solution of (±)-*erythro*-**4a** (70 mg, 0.33 mmol) in dry MeOH (30 mL) is added NaOMe (0.18 mL) of a 2 M solution in MeOH. The mixture is stirred at room temperature for 2 h, neutralized with ion exchange resin Amberlite IR 120 (H^+), filtered, and concentrated. The remaining colorless oil is purified by column chromatography (silica gel; eluent: petroleum ether (bp 35–65 °C)/EtOAc, 8:2).

Preparation of Lactones (±)-*erythro*-8a–c; General Procedure (Path b):
t-BuLi (3.6 mL of a 1.4 M solution in pentane, 5 mmol) is added dropwise with stirring to a solution of (*E*)-β-ethylthioacrylic acid **1**[13] (300 mg, 2.27 mmol) in dry THF (50 mL) at −100 °C under N_2. The mixture is stirred for 1 h at the same temperature, then heated to −80 °C. Then freshly distilled appropriate α-chloroaldehyde **2**[20] (1.1 equiv) is introduced dropwise into the reaction flask with a syringe. After 1 h at −80 °C and 1 h at −40 °C, the mixture is allowed to reach room temperature, and the stirring is continued for an additional time *t* [(±)-**8a**: *t* = 12 h; (±)-**8b**: *t* = 16 h; (±)-**8c**: *t* = 5.5 h]. The mixture is then poured into ice water (30 mL), acidified to pH 1 with 3 N HCl, and extracted with ether (3 × 50 mL). The combined ether extract is washed with a sat. $NaHCO_3$ (2 × 50 mL), and dried ($MgSO_4$). After concentration, the residue is purified by column chromatography (silica gel; eluents: see Table 2).

Desulfurization of (±)-*erythro*-8a and 8c; General Procedure:
To a solution of (±)-*erythro*-**8a** or (±)-*erythro*-**8c** (300 mg; 1.59 mmol and 1.22 mmol, respectively) in dry EtOH (30 mL) is added Raney nickel W2 (1 g). The mixture is stirred for 3 h, the catalyst is filtered and carefully washed with EtOH. After concentration of the combined ethanol solution, the residue is treated with brine (30 mL), extracted with CH_2Cl_2 (3 × 30 mL), and dried ($MgSO_4$). After concentration, the residue is purified by column chromatography [silica gel; eluents: petroleum ether (bp 35–65 °C)/EtOAc; (±)-*erythro*-**9a**: 1:5; (±)-*erythro*-**9c**: 6:4].

(±)-*erythro*-4-Hydroxy-3-methoxy-2-hexen-5-olide [(±)-*erythro*-11]:
s-BuLi (6.0 mL of a 1.1 M solution in cyclohexane/isopentane 92:8, 6.6 mmol) is added dropwise with stirring to a solution of (*E*)-β-methoxyacrylic acid[18] (300 mg, 2.94 mmol) in dry THF (50 mL) at −100 °C under N_2. The mixture is stirred for 1 h at the same temperature, then α-chloropropionaldehyde[20] (302 mg, 3.26 mmol) is introduced dropwise into the reaction flask with a syringe. Stirring is continued for 1 h at −80 °C, 2 h at −40 °C, and 2 h at 0 °C. The mixture is poured into ice water (30 mL), acidified to pH 1 with 3 N HCl and extracted with ether (4 × 50 mL). The combined ether extract is washed with a sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue is purified by column chromatography [silica gel; eluent: petroleum ether (bp 35–65 °C)/EtOAc, 1:5].

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