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Absolute Configurations of 2-Alkylmalic Acids

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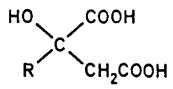
The absolute configurations of some naturally occurring 2-alkylmalic acids (V, VII–X) have all been shown to be *R* by asymmetric syntheses of (*S*)-III, -VI and -VIII (Fig. 1) and CD measurements on molybdate complexes of the synthetic and the natural acids. The key compound in the syntheses is the epoxide (*R*)-XII, obtained in 14 % enantiomeric excess by asymmetric synthesis.

Several 2-alkylmalic acids (I), as well as 2-benzylmalic acid (VIII), occur naturally. Thus, 2-methylmalic acid (citramalic acid, II) is produced by microorganisms and has been detected in or isolated from many fruits. Both (+)- and (−)-citramalic acid have been found. 2-Ethylmalic acid (III) and 2-propylmalic acid (IV) are also synthesised by microorganisms. 2-Isopropylmalic acid (V) is an intermediate in the leucine biosynthesis; its (−)-form has been isolated from different sources, *e.g.* a culture broth of a mutant of *Saccharomyces cerevisiae*.[1]



I:	R= alkyl	VI:	R= $CH_2CH_2CH_2CH_3$
II:	R= CH_3	VII:	R= $CH_2CH(CH_3)_2$
III:	R= CH_2CH_3	VIII:	R= $CH_2C_6H_5$
IV:	R= $CH_2CH_2CH_3$	IX:	R= $CH_2CH_2CH(CH_3)_2$
V:	R= $CH(CH_3)_2$	X:	R= $CH_2CH_2CH_2C(CH_3)_2OH$

2-Isobutylmalic acid [2] (VII) and 2-benzylmalic acid [3] (VIII) are components of two Orchidaceae alkaloids, and 2-(3-methylbutyl)malic acid [4] (IX) and 2-(4-hydroxy-4-methyl-pentyl)malic acid [4] (X) are components of alkaloids from *Cephalotaxus harringtonia*. The absolute configuration has been determined only for citramalic acid. By correlation with (*S*)-(+)-mevalolactone, (+)-citramalic acid has been shown to possess the *S*-configuration.[5,6] The fermentation product 2-hydroxymethylmalic acid (itatartaric acid) has been correlated with citramalic acid.[7] Strong evidence for the *R*-configuration of the natural forms of VII and VIII has recently been obtained from asymmetric synthesis coupled with CD studies.[8]

CD spectra of α-hydroxy acids as molybdate complexes give information on their absolute configurations at the α carbon atoms.[9] It was, however, uncertain whether the Cotton effects of (*S*)-2-methylmalic acid and the (*S*)-2-substituted malic acids with larger substituents would be strictly comparable. For that reason syntheses of the latter acids were performed.

Ethyl chloropyruvate was condensed with the lithium enolate [10] obtained from (−)-menthyl acetate and lithium diisopropylamide, and the resulting mixed ester was transformed into the partially racemic diethyl ester XI. Treatment of XI with lithium hydride in hexamethylphosphortriamide gave the epoxide XII. Opening of the epoxide ring by catalytic hydrogenation afforded, as predominant enantiomer, (*S*)-(+)-diethyl citramalate [10] the specific rotation of which showed that the epoxide (*R*)-XII was present in 14 % enantiomeric excess. The asymmetric syntheses using ethyl pyruvate [10] and ethyl chloropyruvate thus both yielded 2-substituted malic acids in which the *S*-forms predominated. The (*S*)-diethyl esters XIII, XIV, and XV (Fig. 1) were prepared by cleavage of the epoxide ring in (*R*)-XII with the ap-

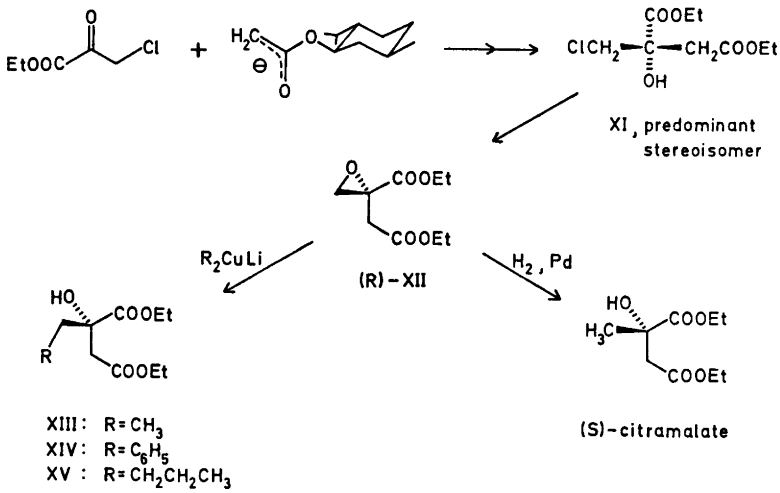


Fig. 1. Reaction scheme for the asymmetric syntheses of (*S*)-XIII, -XIV, and -XV (esters of (*S*)-III, -VIII, and -VI).

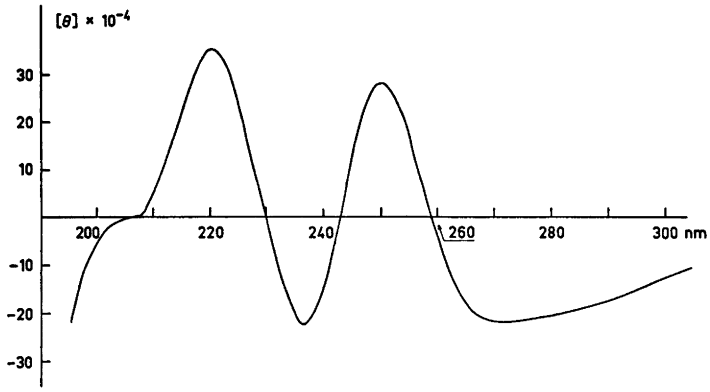


Fig. 2. CD spectrum of (*R*)-(−)-V molybdate complex, 2 mM solution in water, pH 3.3, cell 0.5 mm.

propriate cuprate reagents. Epoxide ring opening reactions with lithium dimethylcuprate and lithium diphenylcuprate have been described by Johnson *et al.*,[11] and the reactions between XII and these copper reagents gave the esters XIII and XIV (Fig. 1) in good yields. The diethyl ester of (*S*)-2-butylmalic acid (XV) was synthesised analogously. It seems reasonable to assume that the molybdate complexes of this acid and (*S*)-VII should give similar CD curves.

Molybdate complexes of the synthetic (*S*)-2-alkylmalic acids were prepared and investigated by CD. All these complexes and those of (*S*)-malic acid [9] and (*S*)-citramalic acid [8] show similar Cotton effects. A sample of (−)-2-isopropylmalic acid [(−)-V], isolated by Sai,[1] shows the opposite Cotton effects (Fig. 2) and consequently has the *R*-configuration. The natural forms of VII and VIII also show the opposite Cotton effects,[8] as do the natural forms of IX and X, and all these acids consequently also have the *R*-configuration.

EXPERIMENTAL

General methods were the same as previously described.[8] The diethyl 2-alkylmalates, purified by preparative GLC, were hydrolysed with 4 M hydrochloric acid (reflux 3 days). The solutions were concentrated (40°, 15 mm) and the acids were dried in a vacuum. Molybdate solu-

tions having pH values between 3.3 and 3.5 (2.0 mol of sodium molybdate per mol hydroxy acid) were prepared from these crude acids and CD spectra were recorded as previously described.[8]

Ethyl chloropyruvate was prepared according to Stekol,[13] starting with 144 g of ethyl pyruvate and 135 ml of sulphuryl chloride. In the distillation (55–58°, 7–8 mm) two fractions were taken. The first fraction (96 g) consisted of (NMR) 75 % ethyl chloropyruvate, 10 % ethyl pyruvate and 15 % ethyl dichloropyruvate. The second fraction (28 g) consisted of (NMR) 90 % ethyl chloropyruvate, 3 % ethyl pyruvate and 7 % ethyl dichloropyruvate.

Diethyl 2-(chloromethyl)malate (XI). A mixture of diisopropylamine (28.5 g, 0.28 mol) in tetrahydrofuran (150 ml) and butyllithium in ether (270 ml, 1.0 M) was stirred under nitrogen at −10° for 40 min. The resulting solution of lithium diisopropylamide was cooled to −78°, a solution of (−)-menthyl acetate (46.6 g, 0.25 mol) in tetrahydrofuran (250 ml) was added during 45 min, and the mixture stirred at the same temperature for 30 min. Ethyl chloropyruvate (42.8 g, 0.29 mol) was then added during 30 min, the temperature being kept at −78°, and the mixture was stirred for another 15 min before the temperature was allowed to rise to 0°. The mixture was poured into dilute hydrochloric acid-ice, the aqueous layer (pH 4–5) was extracted with chloroform, and the chloroform phase was dried (Na_2SO_4) and concentrated. NMR of the product showed comparable amounts of ethyl (−)-menthyl 2-(chloromethyl)malate and (−)-menthyl acetate. The crude product was treated with ethanol (1 l) and conc. sulphuric acid (30 ml) under reflux for 5 days. Part of the ethanol was evaporated. Partition between water and chloroform gave a product which on distillation (90–92°, 0.5 mm) yielded 16.1 g of an 80/20 mixture of XI and (−)-menthol. Redistillation yielded pure (GLC) XI, $[\alpha]_{578}^{24}$ −1.1° (*c* 6.6, chloroform). MS (*m/e*, relative intensity): M^+ = 238 (not observed), 189 (8), 167 (28), 165 (86), 121 (32), 119 (100), 79 (8), 77 (26), 29 (71). NMR (CCl_4): τ 5.70 (q, 2 H), τ 5.81 (q, 2 H), τ 6.00 (s, 1 H), τ 6.30 (s, 2 H), τ 7.12 and 7.28 (AB spectrum, 2 H, J = 16 Hz), τ 8.67 (t, 3 H), τ 8.73 (t, 3 H).

The *epoxide XII* was prepared by treatment of XI (7.2 g, 0.030 mol) with lithium hydride (0.48 g, 0.060 mol) in hexamethylphosphortriamide (HMPA, 15 ml, 65°, 1.5 h). The reaction mixture was poured into dilute hydrochloric acid-ice, extracted three times with ether, and the extract dried (Na_2SO_4) and concentrated. GLC indicated a 50 % conversion to XII (higher yields were obtained in some pilot experiments). As the distilled (60–62°, 2 mm) sample of XII contained approximately 10 % of XI, XII was purified by preparative GLC. The substance thus obtained was indistinguishable (GLC, MS) from a sample of XII obtained by epoxidation of diethyl itaconate.[7] MS: M^+ = 202 (not observed), 157 (27), 129 (40), 128 (29), 101 (95), 29 (100).

Hydrogenation of XII. The epoxide XII (100 mg) in ethanol (4 ml) was hydrogenated in the presence of palladium on charcoal (60 mg) and anhydrous potassium carbonate (50 mg). Diethyl citramalate, indistinguishable (GLC, MS) from an authentical sample was isolated by preparative GLC, $[\alpha]_{578}^{24}$ +2.9° (*c* 4.6, chloroform). MS: M^+ = 204 (not observed), 159 (3), 131 (87), 103 (17), 85 (73), 43 (100), 29 (35). Pure (+)-diethyl citramalate shows $[\alpha]_{578}^{24}$ +20.1°.[10]

2-Ethylmalic acid. A solution of lithium dimethylcuprate (2 mmol) in ether (10 ml) was prepared at 0°.[12] The epoxide XII (0.15 g, 0.75 mmol) in ether (2 ml) was added, and after 10 min at 0° the reaction mixture was poured into dilute hydrochloric acid. Separation of the ether layer and drying (Na_2SO_4) followed by preparative GLC (indicating 100 % ring opening) afforded diethyl 2-ethylmalate, $[\alpha]_{578}^{24}$ +1.3° (*c* 2.4, chloroform). MS: M^+ = 218 (not observed), 189 (2), 145 (63), 99 (50), 57 (100), 29 (50).

2-Butylmalic acid. Propyllithium in ether (2 ml, 0.75 M) was added to a stirred suspension of copper(I) iodide (150 mg, 0.80 mmol) in ether (10 ml), kept at −20° under nitrogen. After 1 min a solution of XII (72 mg, 0.36 mmol) in ether (5 ml) was added dropwise. The mixture was kept between −10° and −20° for 40 min and worked up as above. Preparative GLC, indicating 95 % purity of the product, gave diethyl 2-butylmalate, $[\alpha]_{578}^{24}$ +2.2° (*c* 0.7, chloroform). MS: M^+ = 246 (not observed), 189 (2), 173 (40), 127 (18), 85 (100), 57 (42), 29 (53).

2-Benzylmalic acid. Triethyl phosphite (830 mg, 5 mmol) in 5 ml of ether was added to a stirred suspension of copper(I) iodide (475 mg, 2.5 mmol) in 5 ml ether, and the mixture was stirred under nitrogen at room temperature for 15 min, a clear solution being produced.[14] The temperature was lowered to −60°, a solution of phenyllithium (6.7 ml, 0.75 M, 5.0 mmol) in ether was added, and after 10 min at −60°, a solution of XII (75 mg, 0.38 mmol) in ether was added. The temperature was then allowed to rise to −10°, and the reaction product isolated as above. The alkaloid phalaenopsine,[3] subjected to ethanolysis, afforded a sample of diethyl 2-benzylmalate which was indistinguishable (GLC, MS) from the sample obtained from XII. The latter showed $[\alpha]_{578}^{24}$ +1.8° (*c* 0.9, chloroform). MS: M^+ = 280 (not observed), 262 (13), 207 (25), 189 (20), 161 (16), 119 (27), 115 (44), 91 (100).

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