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Studies on Orchidaceae Glycosides. 5.* The Absolute Configuration of (+)-*erythro*-Isobutyltartaric Acid, a Component of the Glucoside Loroglossine

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(+)-*erythro*-Isobutyltartaric acid, a component of the glucoside loroglossine, is shown to have the 2*R*,3*S* configuration. Syntheses of the 2*S*,3*R* and 2*R*,3*R* isomers of isobutylerythritol and dimethyl (2*S*,3*S*)-isobutyltartrate from 2,3-*O*-isopropylidene-D-glyceraldehyde are described. The circular dichroism curves of the molybdate complexes of the 2*R*,3*S* and the 2*S*,3*S* isomers of isobutyltartaric acid are discussed.

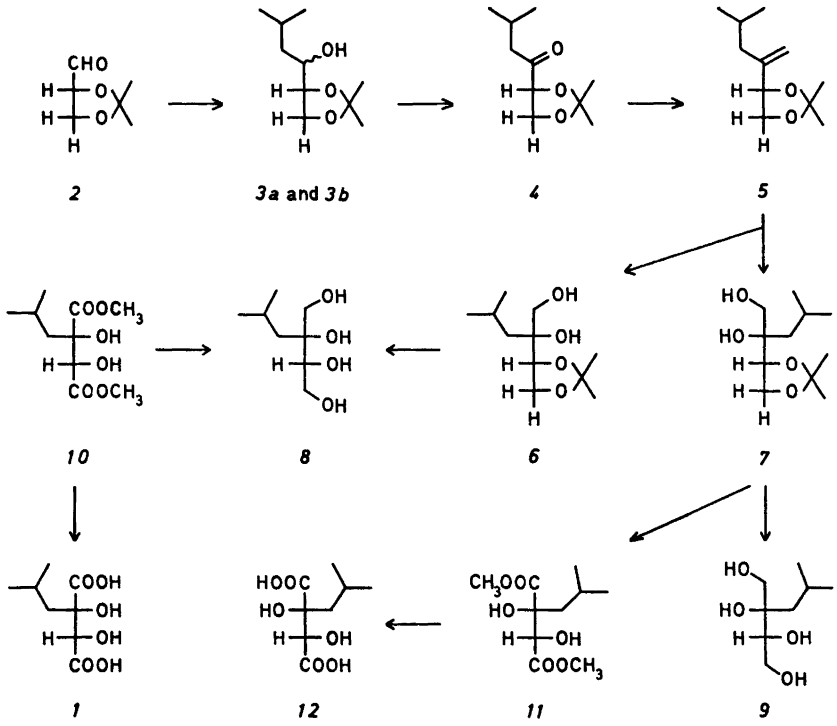
In a recent paper [2] the structures of the Orchidaceae glucosides loroglossine and militarine were reported. Loroglossine was shown to be a diester of isobutyltartaric acid and 4-*O*-β-D-glucopyranosylbenzyl alcohol. The relative configuration of the acid was demonstrated by synthesis to be *erythro*, but its absolute configuration was not determined.

In this communication we report a determination of the absolute configuration of the diacid part of loroglossine, (+)-*erythro*-isobutyltartaric acid (*1*), by correlation with D-glyceraldehyde.

2,3-*O*-Isopropylidene-D-glyceraldehyde(*2*),[3] obtained from D-mannitol, gave on reaction with isobutylmagnesium bromide two diastereomeric alcohols *3a* and *3b*. The crude mixture of the alcohols was transformed to the ketone *4* by oxidation with dimethyl sulfoxide in the presence of dicyclohexylcarbodiimide, pyridine and trifluoroacetic acid.[4] In a Wittig reaction with methylenetriphenylphosphorane,[5] *4* gave the olefin *5*, which on hydroxylation with osmium tetroxide [6] yielded the diols *6* and *7* in the ratio 2:3. These were separated by preparative TLC on silica gel. Acid hydrolysis of *6* and *7* gave the isobutylerythritols *8* and *9*, respectively. The former was found to be indistinguishable from the isobutylerythritol obtained by reduction of dimethyl (+)-*erythro*-isobutyltartrate (*10*).[2] Since *8* is derived from D-glyceraldehyde, it follows that (+)-*erythro*-isobutyltartaric acid (*1*) has the 2*R*,3*S* configuration.

In order to compare the CD curves of the molybdate complexes of (2*R*,3*S*)- and (2*S*,3*S*)-isobutyltartaric acid (*1* and *12*), the latter acid was synthesized in a low yield from *7* by oxidation with nitric acid.[7] Attempts to prepare (2*R*,3*S*)-isobutyltartaric acid (*1*) from *6* in the same way or by oxidation of *8* with oxygen in the presence of platinum [8] were unsuccessful. Instead, this acid (*1*) was obtained by hydrolysis of its dimethyl ester (*10*). From Fig. 1 it is apparent that the configuration at C-2 in *1* and *12* has a dominant influence on the CD curves of their molybdate complexes. Thus a 2*R* configuration gives rise to a strong positive Cotton effect at about 210 nm and a weaker negative effect at 260 – 270 nm (for the conditions used, see Experimental). The CD curves also show two negative Cotton effects at about 230 nm and 300 – 330 nm which, however, are too weak to be useful for the assignment of the configuration at C-3 in alkyltartaric acids (*cf.* Ref. 13). It is interesting to note that the CD curve of the molybdate

* For Paper 4 in this series, see Ref. 1.



complex of *1* is similar to that of (*R*)-2-isobutylmalic acid, which shows positive Cotton effects at 215 and 250 nm, and negative ones at 238 and 270 nm.[9]

Other alkyltartaric acids than *1* have been found in Nature. 4-Hydroxybenzyltartaric acid (piscidic acid) and 2-(3,4-dihydroxybenzyl)-tartaric acid (fukiic acid) have been isolated from *Piscidia erythrina* and *Petasites japonicus*, respectively. Both acids were shown to have the 2*R*,3*S* configuration by application of Horeau's method and degradation into hibiscus acid.[10,11] Recently a methyl derivative of fukiic acid, 2-(4-hydroxy-3-methoxybenzyl)tartaric acid, has been isolated from *Piscidia erythrina*.[12] Isopentyltartaric acid, which is a component of the alkaloid isoharringtonine, has also been shown to possess the 2*R*,3*S* configuration. This assignment was based on a comparison of the CD spectra of the molybdate complexes of isopentyltartaric acid, piscidic acid and its hexahydro derivative.[13]

EXPERIMENTAL

General conditions were the same as in an earlier communication.[2] The CD spectra were measured on a Jasco J-40 spectropolarimeter. Preparative GLC. Column: 0.35 × 180 cm, 10 % Carbowax 20 M on Chromosorb W (60 – 80 mesh), Varian 1400 chromatograph. Carrier gas: N_2, 40 ml/min. Plates precoated with silica gel F_{254} (Merck) were used for TLC, and silica gel 60 was used (230 – 400 mesh, Merck) for column chromatography.

(1R,2R)- and (1S,2R)-1-Isobutyl-2,3-O-isopropylideneglycerol (3a *and* 3b *respectively*). A solution of 2,3-*O*-isopropylidene-D-glyceraldehyde *2*, (0.07 mol) in ether (20 ml) was added dropwise with stirring to an ethereal solution of isobutylmagnesium bromide (0.18 mol, 250 ml). The reaction mixture was stirred at room temperature for 3 h, poured into ice-water and extracted with ether. The evaporation residue of the dried etheral layer (8.2 g) contained two epimeric alcohols in the ratio 1:3. Small amounts of the two epimers were isolated by preparative GLC (115 °C, retention times: major product 12 min, minor product 19 min).

Major product. $[\alpha]_{578}^{22}$ −15.4° (*c* 2.20, methanol). NMR ($CDCl_3$): δ 0.92 (d, 3 H, *J* 6.5 Hz), 0.96 (d, 3 H, *J* 6.6 Hz), 1.39 (s, 3 H), 1.45 (s, 3 H), 1.10 – 1.52 (8 H), 1.62 – 2.10 (m, 1 H), 2.10 (broad, 1 H, exchangeable in D_2O), 3.68 – 4.14 (4. H).

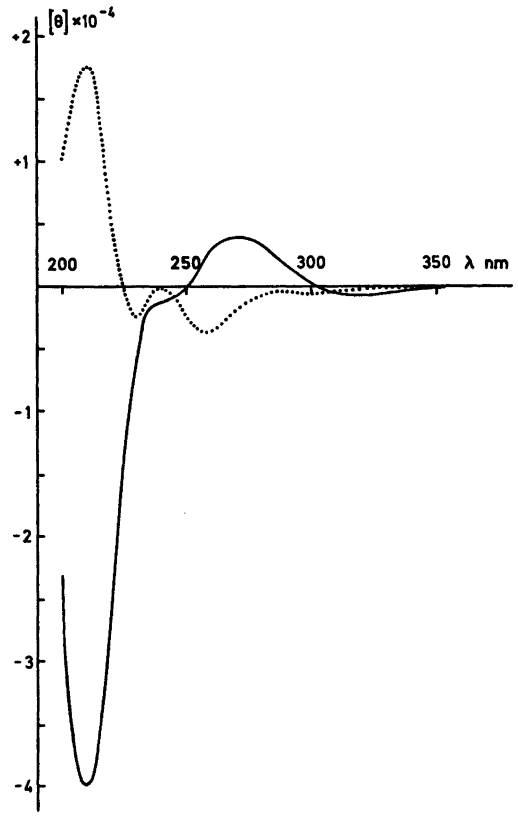


Fig. 1. CD curves of molybdate complexes of (2*R*,3*S*)-2-isobutyltartaric acid (*1*,···) and (2*S*,3*S*)-2-isobutyltartaric acid (*12*, ——) in water.

Minor product. $[\alpha]_{578}^{22}$ +32.8° (*c* 1.79, methanol). NMR ($CDCl_3$): δ 0.89 (d, 3 H, *J* 6.5 Hz), 0.96 (d, 3 H, *J* 6.7 Hz), 1.37 (s, 3 H), 1.44 (s, 3 H), 1.20–2.04 (8 H), 2.11 (d, 1 H, exchangeable in D_2O, *J* 5 Hz), 3.40–4.30 (4 H).

(R)-Isovaleryl-2,2-dimethyldioxolane (4). Dicyclohexylcarbodiimide (0.47 mol), pyridine (0.16 mol) and trifluoroacetic acid (0.09 mol) were carefully added to a cooled mixture of benzene (195 ml) and dimethyl sulfoxide (195 ml). A solution of the crude mixture of the epimers *3a* and *3b* (0.03 mol) in benzene (130 ml) was added to this reagent. The reaction mixture was heated to 50 °C for 17 h. A small amount of a crystalline precipitate was filtered off and ether (650 ml) was added to the filtrate. The solution was washed with a saturated solution of oxalic acid in water (2 × 100 ml). During this procedure a crystalline precipitate formed, which was filtered off and washed with ether (2 × 50 ml). The combined ethereal layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 100 ml) and by water (100 ml), dried and concentrated. The residue was combined with the two precipitates above. Chromatography on silica gel (6.5 × 75 cm, dichloromethane) gave *4* (4.15 g) as a pale yellow oil.

A pure sample was obtained by preparative GLC (125 °C, retention time 5 min). $[\alpha]_{578}^{22}$ +43.3° (*c* 0.46, methanol). IR, ν_{max} ($CHCl_3$): 1715 cm^{-1}. NMR ($CDCl_3$): δ 0.91 (d, 3 H, *J* 6.4 Hz), 0.98 (d, 3 H, *J* 6.7 Hz), 1.41 (*q*, 3 H, *J* 0.6 Hz), 1.50 (*q*, 3 H, *J* 0.6 Hz), 1.90–2.70 (3 H), 3.80–4.50 (3 H).

(S)-4-Methyl-2-(2,2-dimethyldioxolanyl)-1-pentene (5). Triphenylmethylphosphonium bromide (0.012 mol) was added in portions with stirring to a solution of butyllithium (0.013 mol, 6 ml of a 20 % solution in hexane) in ether (30 ml).[5] The mixture was stirred at room temperature for 3.5 h. (*R*)-Isovaleryl-2,2-dimethyldioxolane (*4*, 0.010 mol) in ether (50 ml) was added dropwise after which the solution was refluxed for 15 h, cooled and filtered. The filtrate was washed with water, dried and concentrated. Chromatography of the residue on silica gel (4.6 × 24 cm, chloroform) gave *5* (0.7 g) as an oil.

A pure sample was obtained by preparative GLC (80 °C, retention time 10 min). $[\alpha]_{578}^{22}$ +32.6° (*c* 0.97, methanol). NMR ($CDCl_3$): δ 0.92 (d, 6 H, *J* 6 Hz), 1.41 (s, 3 H), 1.46 (s, 3 H), 1.5–2.2 (m, 3 H), 3.58 (dd, 1 H, $J_1 = J_2$ 8.0 Hz), 4.10 (dd, 1 H, J_1 8.0 Hz, J_2 6.5 Hz), 4.49 (dd, 1 H, J_1 6.5, J_2 8.0 Hz), 4.87 (s, broad, 1 H), 5.19 (s, broad, 1 H).

(2R,3S)1,2-O-Isopropylidene-3-isobutyleryth-ritol (6) and (2R,3R)-1,2-O-isopropylidene-3-isobutylerythritol (7). A mixture of osmium tetroxide (3.23 mmol) and *4* (3.21 mmol) in pyridine (13 ml) was stirred at room temperature for 2 h.[6] A solution of sodium hydrogen sulfite (1.48 g), water (25 ml) and pyridine (16 ml) was added and the mixture was stirred for 30 min. The reaction mixture was extracted with chloroform (5 × 10 ml), and the organic phase was dried and concentrated to a syrup (0.56 g). A part of this syrup (140 mg) was chromatographed on a preparative silica gel plate, (chloroform–methanol, 19:1). Three fractions were obtained: A (R_F 0.38, 25 mg) contained the pure 3*S* epimer (*6*), B (60 mg) a mixture of the 3*S* and 3*R* epimers and C (R_F 0.45, 40 mg) the pure 3*R* epimer (*7*).

3S Epimer (6): needles from hexane at +4 °C, m.p. 36–38 °C $[\alpha]_{578}^{20}$ +7.1° (*c* 0.34, methanol). (Found: C 60.1; H 10.2; O 29.4. Calc. for $C_{11}H_{24}O_4$: C 60.5; H 10.2; O 29.3). NMR (pyridine-d_5): δ 1.07 (d, 3 H, *J* 6.7 Hz), 1.14 (d, 3 H, *J* 6.4 Hz), 1.44 (s, 3 H), 1.53 (s, 3 H), 1.91 (d, 2 H, *J* 6 Hz), 2.00–2.40 (m, 1 H), 3.96 and 4.02 (AB part of an ABX system, J_{AB} 12 Hz, $J_{AX} = J_{AB}$ 5.2 Hz, collapses to an AB system on addition of D_2O), 4.12–4.77 (3 H), 5.20 (s, 1 H, exchangeable in D_2O), 6.30 (t, 1 H, exchangeable in D_2O, *J* 5.2 Hz).

3R Epimer (*7*): $[\alpha]_{578}^{22}$ +9.8° (*c* 0.43, methanol). NMR ($CDCl_3$): δ 0.94 (d, 3 H, *J* 6.4 Hz), 1.00 (d, 3 H, *J* 6.2 Hz), 1.26 (d, 2 H, 6.1 Hz), 1.38 (s, 3 H), 1.44 (s, 3 H), 1.52–2.08 (m, 1 H), 2.70 (s, 1 H, exchangeable in D_2O), 3.56 and 3.72 (AB system, J_{AB} 11 Hz), 3.88–4.24 (3 H).

(2S,3R)-2-Isobutylerythritol (8). A. From (2*R*,3*S*)-1,2-*O*-isopropylidene-3-isobutylerythritol (*6*): A solution of *6* (15 mg) in acetic acid (70 %) was heated at 70 °C for 15 min. The reaction mixture was evaporated and the residue was purified by chromatography on silica gel (1.5×7 cm, chloroform–methanol 9:1). *8* (11.5 mg) was obtained as a syrup, $[\alpha]_{578}^{23}$ +6.1° (*c* 1.15, methanol). NMR (pyridine-d_5): δ 1.09 (d, 3 H, *J* 7 Hz), 1.15 (d, 3 H, *J* 5 Hz), 1.68–2.50 (3 H), 4.00–4.52 (5 H), 4.9–6.6 (broad, exchangeable in D_2O).

B. From dimethyl (+)-*erythro*-2-isobutyltartrate [2] (*10*): A solution of *10* (38.5 mg) in ether (10 ml) was treated with lithium aluminium hydride (60 mg) for 100 min at room temperature. The reaction mixture was diluted with water and filtered. The filtrate was passed through a mixture of equal amounts of Dowex 50 W-X8 (H^+) and Amberlite IRA 400 (OH^-) (1×11 cm). Evaporation of the eluate and chromatography of the residue on silica gel (1×5 cm, chloroform-methanol 9:1) gave *8* (13 mg), $[\alpha]_{578}^{23}$ +6.9° (*c* 1.30, methanol). The NMR spectrum of this sample was indistinguishable from that described under A.

(2R,3R)-2-Isobutylerythritol (9). A solution of *7* (30 mg) in acetic acid (70 %, 10 ml) was heated at 75 °C for 35 min. The solvent was evaporated and the residue was purified on silica gel (1.5×10 cm, chloroform–methanol 9:1). *(2R,3R)*-2-Isobutylerythritol (*9*) was obtained as a syrup (11.8 mg), $[\alpha]_{578}^{21}$ +13.9° (*c* 1.18, methanol). NMR (pyridine-d_5): δ 1.12 (d, 3 H, *J* 7 Hz), 1.16 (d, 3 H, *J* 7 Hz), 1.64–2.55 (3 H), 4.18 (s, 2 H), 4.24–4.50 (3 H), 4.95, 5.16 and 6.3 (broad, 4 H, exchangeable in D_2O).

(2R,3S)-2-Isobutyltartaric acid (1). Dimethyl (+)-*erythro*-2-isobutyltartrate [2] (*10*, 27.8 mg) was refluxed with aqueous hydrochloric acid (2 M, 10 ml) for 70 h. Evaporation of the reaction mixture gave *1* as an amorphous solid, $[\alpha]_{578}^{22}$ +18.8° (*c* 0.69, methanol). NMR (CD_3OD): δ 0.90 (d, 3 H, *J* 6 Hz), 0.96 (d, 3 H, *J* 6 Hz), 1.45–2.10 (3 H), 4.33 (s, 1 H), 4.90 (s, OH). The acid was used without further purification in the preparation of the solution for CD measurement (water; 3.0 mM solution with respect to *1* and 2.7 mM with respect to sodium molybdate. Acidification with hydrochloric acid to pH 3.0). The CD curve is shown in Fig. 1.

Dimethyl(2S,3S)-2-Isobutyltartrate (11). A solution of *7* (103 mg) in nitric acid [7] (32 %, 0.6 ml) was heated at 55 °C for 24 h and then concentrated to a syrup. Water (0.5 ml) was added and the solution was again concentrated. This procedure was repeated twice and the residue was then dried under reduced pressure, dissolved in methanol (1.5 ml) and treated with an excess of diazomethane in ether. The methylation product was purified by preparative GLC (160 °C, retention time 13 min) giving *11* (9.8 mg), m.p. 38–44 °C, $[\alpha]_{578}^{22}$ +12.5° (*c* 0.98, methanol). The NMR spectrum of *11* was indistinguishable from that of the racemic compound.[2]

(2S,3S)-2-Isobutyltartaric acid (12). A solution of *11* (9 mg) in aqueous hydrochloric acid (2 M, 10 ml) was refluxed for 68 h. Evaporation of the reaction mixture gave *12* as an amorphous solid (7.8 mg), $[\alpha]_{578}^{22}$ +9.9° (*c* 0.39, methanol). Before measuring its NMR spectrum, the hydroxylic protons were replaced by deuterium. NMR (CD_3OD): δ 0.90 (d, 3 H, *J* 6 Hz), 0.96 (d, 3 H, *J* 6 Hz), 1.45–2.10 (3 H), 4.25 (s, 1 H). The solution for the CD measurement was prepared as above. The CD curve is shown in Fig. 1.

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