Necic Acid Synthons. Part 5.[1] Total Synthesis of (±)-Retronecic Acid and Related Compounds *via* Zinc-Mediated Coupling of Halogeno-esters

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Zinc-mediated coupling of suitably substituted halogeno esters affords access to (±)-retronecic acid (**2**) and related intermediates. These approaches lead to racemic retronecic acid on the one hand and to a diastereoisomeric mixture of the acid on the other.

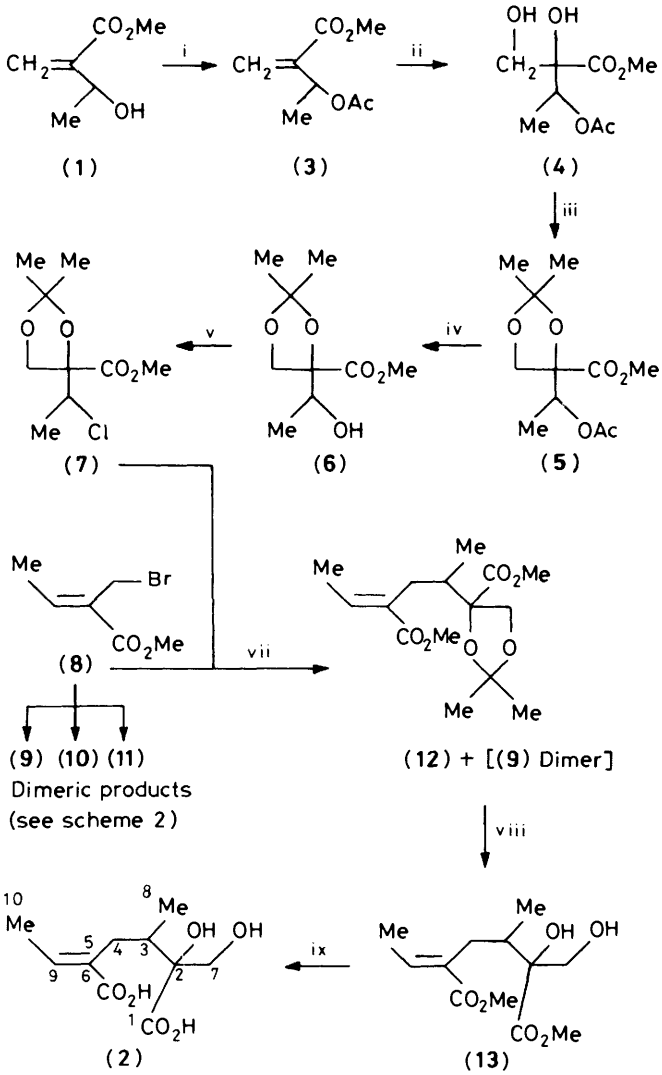
In earlier communications[2,3] we have indicated the potential of 3-hydroxy-2-methylene alkanoate esters (**1**) and their halogenated derivatives as versatile necic acid synthons. This area of research has attracted considerable interest in recent years[4–6] and we now report two related syntheses of retronecic acid (**2**). In these syntheses a single synthon (**1**) provides both the 'left'- and 'right-hand' side of the target molecule (**2**). The approaches have involved (*i*) a convergent synthesis requiring functional elaboration *prior* to coupling (route 1) and (*ii*) controlled elaboration of the 'right-hand' side *after* coupling (route 2). Zinc-mediated coupling of halogeno esters is a key step in both approaches.

Results and Discussion

Route 1.—The initial objective in the convergent synthesis (Scheme 1), was the preparation of the protected halogeno diol (**7**) containing all the functionality required for the 'right-hand' side of retronecic acid (**2**). Coupling of this halogeno diol (**7**) with a suitable 'left-hand' synthon *via* an organometallic intermediate was then expected to provide access to the target molecule (**2**).

In the first stereochemically critical step of this route, the acetoxy compound (**3**) was perhydroxylated,[7] using osmium tetraoxide, to give the diol (**4**). The p.n.d. ^{13}C n.m.r. spectra of the isolated crystalline product, and, in fact, of all subsequent products in the sequence, were consistent with the presence of a *single* pair of enantiomers, *i.e.* no splitting of any of the signals was observed. A ^{13}C n.m.r. spectrum of the crude product mixture of (**4**), prior to crystallisation, however, revealed doubling of most of the signals. Isolation of racemic diol (**4**) may thus be attributed to diastereoselective crystallisation rather than chiral induction during perhydroxylation. Protection of the diol (**4**) as the acetonide (**5**) followed by base hydrolysis of the acetate and then halogenation with hexachloroacetone–triphenylphosphine[8,9] afforded halogen diol (**7**).

Initial attempts to prepare organometallic derivatives of the bromo ester (**8**) (or its acid analogue) proved unsuccessful. Thus, treatment of the bromo ester (**8**) with (*i*) Mg–THF, and (*ii*) Ph_3SnCl afforded the dimeric products (**9**), (**10**), and (**11**), whilst reaction of the acid derivative of the bromo ester (**8**) with both BuLi–THF and BuLi–THF simply resulted in alkylation. However, when the bromo ester (**8**) was added dropwise to a stirred suspension of Zn dust in DMSO[10,11] containing a 1.5 molar excess of the chloro diol (**7**), an exothermic reaction ensued with the formation of a 3:1 mixture of the dimeric compound (**9**) and the required diester (**12**), which could be separated by flash chromatography. Deprotection of the diester (**12**), followed by hydrolysis and neutralisation afforded (±)-retronecic acid (**2**), which was shown (^1H and ^{13}C n.m.r., mixed m.p.) to be indistinguishable from the natural product.

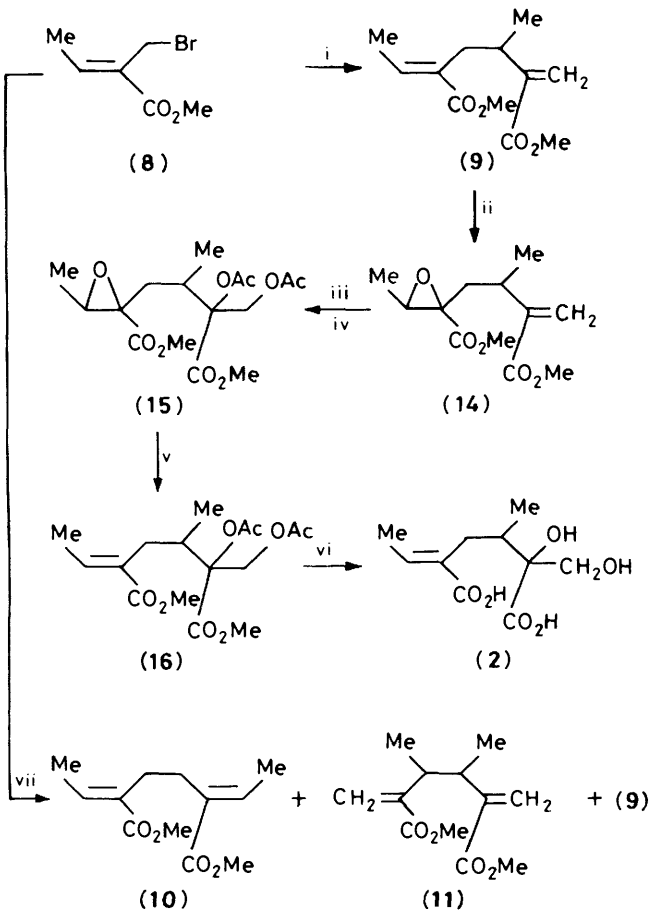


Scheme 1. Conversion of methyl 3-hydroxy-2-methylenebutanoate (**1**) into retronecic acid (**2**) by route 1.

Reagents: i, H^+–Ac_2O; ii, OsO_4; iii, 2,2-dimethoxypropane–H^+; iv, (*a*) K_2CO_3, (*b*) HOAc; v, hexachloroacetone–PPh_3; vi, Mg–THF; vii, Zn dust–DMSO; viii, HCl–dioxane; ix, KOH, ion exchange.

Route 2.—This approach is based on the premise that retronecic acid (**2**) consists of two halves which are essentially identical and which are derivable from the synthon methyl (*E*)-

2-bromomethylbut-2-enoate (**8**) (Scheme 2). 'Dimerisation' was achieved by slow addition of a 1.5 molar solution of the bromo ester (**8**) in DMSO to a stirred slurry of Zn dust (1 mol) in DMSO.[10,11] From this reaction the desired diene (**9**) was isolated in 85% yield. By contrast, use of a Grignard reagent rather than Zn gave a mixture of dienes (**9**), (**10**), and (**11**), (in the ratio of *ca.* 11:7:1) separable by fractional distillation. In neither case was there evidence of the organometallic intermediate attacking the ester group.



Scheme 2. Conversion of methyl (*E*)-2-bromomethylbut-2-enoate (**8**) into retronecic acid by route 2.

Reagents: i, Zn dust–DMSO–25 °C; ii, *m*-chloroperbenzoic acid; iii, OsO_4; iv, Ac_2O–DMAP; v, Cr^{II}; vi, KOH–Ion exchange; vii, Mg–THF–heat.

Elaboration of (**9**) to the target molecule (**2**) consisted of (*i*) selective protection of the internal double bond[12] as an epoxide to give (**14**), (*ii*) perhydroxylation of (**14**) with a catalytic amount of OsO_4 in aqueous H_2O_2[7,13] and subsequent acetylation to yield (**15**), and (*iii*) final deoxygenation of the epoxy diol. This last step proved to be difficult since obvious reagents for reductive elimination such as a Zn–Cu couple,[14] anhydrous Cr^{II} complexes,[15] and hexamethyldisilane in KOH[16] were ineffective and resulted in the diene (**9**). Protection of the diol groups, as in (**15**), and subsequent selective reduction of the epoxide group with a 2 molar excess of an acidic solution of the Cr^{II} reagent,[17] finally afforded the protected diester of retronecic acid (**16**) in low yield. Hydrolysis of the ester yielded the acid (**2**) which was shown to consist of a diastereoisomeric mixture of almost equal parts of the (±)-(2*S*, 3*R*)-isomer (naturally occurring retronecic acid) and (±)-isoretronecic acid (2*R*, 3*R*). The isomer allocation is based on ^1H n.m.r. and ^{13}C n.m.r. investigations of the reaction mixture (Tables 1 and 2).

Table 1. ^1H N.m.r. chemical shifts of natural and synthetic necic acids.

Proton group	Chemical shift (δ) Natural retronecic acid	Synthetic retronecic acid (**2**)	Synthetic isoretronecic acid
CH_2CHMe	0.77	0.77	0.74
$MeCH$	1.76	1.76	1.76
CH_2CH	2.20	2.20	2.20
CH_2OH	3.75	3.74	3.84
$MeCH$	6.94	6.94	6.94

Experimental

N.m.r. spectra were recorded on a Varian T60 or a Varian FT80A instrument using deuteriochloroform as the solvent unless otherwise stated. Mass spectra were run on a Varian CH7 instrument. The synthesis of compounds (**1**) and (**8**) has been described in earlier papers.[2,3] Ether refers to diethyl ether.

Methyl 3-Acetoxy-2-methylenebutanoate (**3**).—Concentrated H_2SO_4 (3 drops) was added to a stirred mixture of the hydroxy ester (**1**) (55.0 g, 0.417 mol) and acetic anhydride (75.0 g, 0.735 mol). The exothermic reaction was cooled in an ice-bath. After 30 min, the mixture was poured into water (100 ml), the organic layer separated and the *aqueous* phase extracted with ether (50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to afford an oil, which was distilled to give methyl 3-acetoxy-2-methylenebutanoate (**3**) (61.0 g, 85%), b.p. 60—62 °C/2.5 mmHg (lit.,[18] 56 °C/0.5 mmHg); δ_H 1.37 (3 H, d, CH*Me*), 2.03 (3 H, s, COMe), 3.78 (3 H, s, COMe), 5.70 (1 H, q, C*H*Me) and 5.83 and 6.3 (2 H, 2 × s, CH_2=C); *m/z* 172 (M^+, 6%) and 129 (100).

Methyl 3-Acetoxy-2-*hydroxy*-2-*hydroxymethylbutanoate* (**4**).—To a stirred solution of the allylic acetate (**3**) (20.0 g; 0.12 mol) in acetone (100 ml), at 0 °C, was added dropwise a mixture of the OsO_4 catalyst (20 ml) and H_2O_2 (8.8M, 30%; 20 ml).[13] The reddish mixture was then stirred overnight at *ca.* 5 °C. Water (50 ml) was added and the yellow solution was allowed to warm to room temperature. The solution was saturated with NaCl, extracted with ethyl acetate (3 × 75 ml), dried ($MgSO_4$), and concentrated to afford crystals of *methyl* 3-*acetoxy*-2-*hydroxy*-2-*hydroxymethylbutanoate* (**4**) (4.9 g, 42%), m.p. 88—90 °C (EtOAc); $\delta_H(CD_3COCD_3)$ 1.2 (3 H, d, CH*Me*), 1.95 (3 H, s, COMe), 3.60 (3 H, s, CO_2Me), 3.63—4.30 (4 H, m, CH_2OH,OH), and 5.11 (1 H, q, CHMe); $\delta_C(CD_3COCD_3)$ 13.9 (*Me*CH), 20.2 (CO*Me*), 52.1 (OMe), 65.0 (OCH_2), 71.6 (MeC*H*), 80.7 (CCO_2Me), 169.4 (MeCO), and 173.5 (CO_2Me); *m/z* 206 (M^+, 1%) and 102 (100) (Found: C, 46.7; H, 7.1. $C_8H_{14}O_6$ requires C, 46.6; H, 6.9%).

4-(1-*Acetoxyethyl*)-4-*methoxycarbonyl*-2,2-*dimethyl*-1,3-*dioxolane* (**5**).—A solution of the diol (**4**) (10.3 g; 50.0 mmol) and toluene-*p*-sulphonic acid (100 mg; 0.5 mmol) in 2,2-dimethoxypropane (75 ml) was stirred at room temperature for 16 h. The solvent was evaporated and the residue diluted with ether (100 ml), washed with water (840 ml), aqueous $NaHCO_3$ (10%; 30 ml), and finally with saturated *aqueous* NaCl (20 ml). The ethereal solution was dried ($MgSO_4$) and concentrated to afford 4-(1-*Acetoxyethyl*)-4-*methoxycarbonyl*-2,2-*dimethyl*-1,3-*dioxo*-

Table 2. ^{13}C N.m.r. chemical shifts (p.p.m.; D_2O) of natural and synthetic necic acids

	Chemical shift (p.p.m.)			
		Synthetic retronecic acid (**2**)		
Carbon number	Natural retronecic acid	Route 1	Route 2	Synthetic isoretronecic acid
1	178.2	178.2	178.2	178.2
6	172.6	172.6	172.3	172.3
9	143,3	143.1	143.3	143.0
5	131.0	131.1	131.0	131.3
2	82.3	82.3	82.4	82.8
7	67.0	67.0	67.0	66.7
3	37.6	37.6	37.6	37.9
4	28.4	28.4	28.4	27.1
10	15.1	15.0	15.1	15.1
8	12.7	12.7	12.7	13.7

lane (5) (99.9 g, 80%), m.p. 39—41 °C (ether–pentane); δ_H 1.25 (3 H, d, CH*Me*), 1.4 and 1.46 [6 H, 2 × s, CMe_2], 2.03 (3 H, s, COMe), 3.73 (3 H, s, COMe), 4.1 (2 H, dd, CH_2), and 5.16 (1 H, q, C*H*Me); δ_C 13.5 (*Me*CH) 20.0 (CO*Me*), 24.5 and 25.1 (Me_2C), 51.7 (CO_2Me), 68.2 (OCH_2), 70.6 (Me*CH*), 84.9 (CCO_2Me), 111.4 (Me_2C), 168.8 (*C*OMe), and 171.2 (CO_2Me); *m/z* 231 (M^+ − 15, 33%) and 130 (100) (Found: C, 53.5; H, 7.6. $C_{11}H_{18}O_6$ requires C, 53.6; H, 7.4%).

4-(1-*Hydroxymethyl*)-4-*methoxycarbonyl*-2,2-*dimethyl*-1,3-*dioxolane* (**6**).—A solution of the acetonide (**5**) (10.0 g, 40.7 mmol) and anhydrous K_2CO_3 (9.2 g, 66.7 mmol) in dry methanol (300 ml) was stirred at room temperature for 16 h. Acetic acid (20 ml) was added, the solution was concentrated and water was (50 ml) added to the slurry. The mixture was extracted with ethyl acetate (3 × 75 ml), dried (anhyd. $MgSO_4$), and concentrated to afford 4-(1-*hydroxymethyl*)-4-*methoxycarbonyl*-2,2-*dimethyl*-1,3-*dioxolane* (**6**) (6.25 g, 75%), m.p. 48—50 °C (tetrachloromethane–pentane); δ_H 1.18 (3 H, d, CH*Me*), 3.81 (3 H, s, COMe), and 4.13 (2 H, dd, CH_2); δ_C 16.9 (*Me*CH), 25.0 and 25.5 (Me_2C), 51.9 (CO_2Me), 68.1 (OCH_2), 69.1 (Me*C*H), 86.6 (CCO_2Me), 111.1 (Me_2C), and 172.7 (CO_2Me); *m/z* 189 (M^+ − 15, 50%) and 101 (100) (Found: C, 52.7; H, 7.9. $C_9H_{16}O_5$ requires C, 52.9; H, 7.9%).

4-(1-*Chloroethyl*)-4-*methoxycarbonyl*-2,2-*dimethyl*-1,3-*dioxolane* (**7**).—Triphenylphosphine (9.0 g, 34.3 mmol) was added in small portions to a stirred solution of the alcohol (**6**) (6.0 g, 29.4 mmol in hexachloroacetone (30 ml, 193 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 20 h. A solution of 10% aqueous $NaHCO_3$ (70 ml) was added and the mixture stirred vigorously for 2 h. Thereafter the solution was extracted with ether (3 × 50 ml), dried ($MgSO_4$), and concentrated to afford an oil which was distilled to give 4-(1-*chloroethyl*)-4-*methoxycarbonyl*-2,2-*dimethyl*-1,3-*dioxolane* (**7**) (3.6 g, 55%), b.p. 78—80 °C/3 mmHg; δ_H 1.47 [6 H, m, CMe_2], 1.55 (3 H, q, CH*Me*), 3.8 (3 H, s, COMe), 4.32 (2 H, dd, CH_2), and 4.47 (1 H, q, C*H*Me); δ_C 19.4 (*Me*CH), 25.3 and 25.8 (Me_2C), 52.7 (CO_2Me), 57.5 (Me*C*H), 68.7 (OCH_2), 86.0 (CCO_2Me), 112.3 (Me_2C), and 171.6 (CO_2Me); *m/z* 207 (M^+ − 15, 67%) and 84 (100) (Found: M^+, 222.06591. $C_9H_{15}ClO_4$ requires *M*, 222.06586).

4-*Methoxycarbonyl*-4-[(3*E*)-3-*methoxycarbonyl*-1-*methylpent*-3-*enyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**12**).—The chloroacetonide (7) (11.12 g, 50.0 mmol) was added to a suspension of activated zinc dust (1.35 g, 20.7 mmol) in dry dimethyl sulphoxide (8 ml), at room temperature under nitrogen. To this mixture was added dropwise, during 4 h, a solution of the bromo ester (**8**) (4.0 g, 20.7 mmol) in dry dimethyl sulphoxide (4 ml). The mixture was stirred overnight, by which time most of the zinc had reacted. The solution was diluted with ethyl acetate (40 ml), washed with 3M-HCl (20 ml), dried ($MgSO_4$), concentrated, and chromatographed [flash chromatography; elution with light petroleum (b.p. 40—60 °C–ethyl acetate (5:1)] to afford the diene (**9**) (3.35 g, 71%) and 4-*methoxycarbonyl*-4-[(3*E*)-3-*methoxycarbonyl*-1-*methylpent*-3-*enyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**12**) (0.78 g, 22%); δ_H 0.83 (3 H, d, CH*Me*), 1.43 (6 H, s, CMe_2), 1.83 (3 H, d, =CH*Me*), 1.96—2.20 (1 H, m, CH), 2.30 (2 H, m, $CHCH_2$), 3.73 and 3.83 (6 H, 2 × s, 2 × CO_2Me), 4.18 (2 H, dd, CH_2) and 6.95 (1 H, q, =C*H*Me); δ_C 12.8 (*Me*CH), 14.2 (*Me*CH=C), 25.0 and 25.6 (Me_2C), 28.2 (CH_2C=C), 38.1 (Me*C*H), 51.1 and 51.6 (2 × CO_2Me), 69.8 (OCH_2), 86.6 [*C*(O)CO_2Me], 110.6 (Me_2C), 130.7 (MeCH=*C*), 138.8 (Me*C*H=C), 167.4 (C=*C*CO_2Me), and 173.4 [C(O)*C*O_2Me]; *m/z* (M^+ − 15, 10%) and 151 (100) (Found: M^+, 300.157 30. $C_{15}H_{24}O_6$ requires *M*, 300.157 28).

(±)-*Dimethyl Retronecate* (**13**).—A solution of the acetonide (**12**) (0.7 g; 2.33 mmol) in 2M-HCl–dioxane (1:1; 8 ml) was stirred for 8 h at room temperature. The solvents were evaporated and the residual oil was taken up in chloroform (30 ml). The solution was dried ($MgSO_4$) and concentrated to afford (±)-dimethyl retronecate (**13**) (0.55 g, 90%); δ_H 0.88 (3 H, d, CH*Me*), 1.81 (3 H, d, =CH*Me*), 2.26 (3 H, m, $CHCH_2$), 3.8 (8 H, 2 × s, CH_2OH, 2 × CO_2Me), 4.33 (2 H, s, 2 × OH), and 6.93 (1 H, q, =C*H*Me); δ_C 12.9 (*Me*CH), 14.7 (MeCH=C), 28.3 (CH_2C=C), 37.0 (Me*C*H), 51.7 and 52.8 (2 × CO_2Me), 66.9 (OCH_2), 82.3 (CCO_2Me), 130.9 (MeCH=*C*), 139.7 (Me*C*H=C), 168.3 (C=*C*CO_2Me), and 175.8 [C(O)*C*O_2Me]; *m/z* 260 (M^+, 2%) and 81 (100) (Found: M^+, 260.1259. Calc. for $C_{12}H_{20}O_6$: *M*, 260.125 96).

(±)-*Retronecic Acid* (**2**).—A mixture of dimethyl retronecate (**13**) (0.45 g, 1.72 mmol) and KOH (0.5 g, 10 mmol) in absolute ethanol (15 ml) was heated under reflux for 3 h. The solvent was evaporated and the solid residue dissolved in H_2O (1.3 ml). This solution was passed through a cation exchange column (Zeocarb 225 SRC H, H-form; 10 g). The aqueous solution, pH range 3—6 was collected, evaporated to dryness and cooled to afford (±)-*retronecic acid* (**2**) (0.18 g, 45%), m.p. 179—180 °C (H_2O) (lit.,[19] 180—181 °C); $\nu_{max.}$ 3 348 (OH), 1 716 and 1 685 cm^{-1} (CO_2H); δ_H (80 MHz; D_2O; DSS), 0.8 (3 H, q, *J* 7 Hz, CH*Me*), 1.82 (3 H, d, *J* 6.9 Hz, =CH*Me*), 2.26 (3 H, m, $CHCH_2$), 3.78 (2 H, dd, CH_2OH), and 6.85 (1 H, q, =C*H*Me); δ_C (D_2O; dioxane), 12.65 (*Me*CH), 14.98 (*Me*CH=C), 28.37 (CH_2=C), 37.62 (Me*C*H), 66.98 (OCH_2), 82.29 (CCO_2H), 131.19 (MeCH=*C*), 143.13 (Me*C*H=C), 172.57 (C=*C*CO_2H), and 178.24 [C(O)*C*O_2H]; *m/z* 196 (M^+ − 36, 5%), 183 (29), 178

(16), 169 (70), 127 (40), 109 (60), and 81 (100) (Found: C, 51.4; H, 6.65. Calc. for $C_{10}H_{16}O_6$ C, 51.7; H, 6.95%).

Dimethyl 5-Ethylidene-3-methyl-2-methylenehexane-2,5-dicarboxylate (**9**).—Zinc dust (99.8%), activated by treatment with aqueous hydrochloric acid (50%) was washed with water and acetone and then dried *in vacuo* for 2 h at 100 °C. To a stirred slurry of the metal (1.85 g, 28.30 mmol) in dry dimethyl sulphoxide (10 ml) was added at 25 °C methyl (*E*)-2-bromomethylbut-2-enoate (**8**) (10.0 g, 51.81 mmol) in dry dimethyl sulphoxide (15 ml) over 1 h. The mixture became slightly warm as the zinc dissolved, and was stirred at room temperature for 16 h. It was then diluted with ethyl acetate (15 ml) and the resulting solution was washed several times with dilute aqueous hydrochloric acid. The combined ethyl acetate extracts were washed consecutively with saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and distilled under reduced pressure to give *5-ethylidene-3-methyl-2-methylenehexane-2,5-dioate* (**9**) (b.p. 137 °C/11 mmHg) (5.0 g, 85%); δ_H 1.08 (3 H, d, CH_2CHMe), 1.82 (3 H, d, *Me*CH=), 2.50 (2 H, d, $=CCH_2CH$), 2.9 (1 H, m, CH_2CHMe), 3.73 (6 H, s, 2 × CO_2Me), and 5.50 and 6.08 (2 H, d, *J* 1.5 Hz, C=CH_2); δ_C (20 MHz; TMS), 13.98 (q, Me), 18.35 (q, *Me*CH=), 32.25 (t, CH_2), 34.56 (d, CH_2CH), 50.89 (q, CO_2Me), 51.00 (q, CO_2Me), 122.90 (t, C=CH_2), 131.14 (s, C=CH_2), 138.17 (d, MeCH=), 144.93 (s, CH=*C*), 166.79 (s, CO_2Me), and 167.54 (s, CO_2Me); *m/z* 226 (M^+, 6%), 194 (22), 135 (63), 114 (25), 113 (19), 84 (100), and 81 (44) (Found: C, 63.1; H, 8.0. $C_{12}H_{18}O_4$ requires C, 63.5; H, 8.0%).

Dimethyl 3-Methyl-5,6-epoxyhept-1-ene-2,5-dicarboxylate (**14**).—To a solution of (**9**) (20 g, 8.85 mmol) in dry dichloromethane (10 ml) was added a slurry of *m*-chloroperbenzoic acid (70%) (2.88 g, 11.57 mmol) in dichloromethane (15 ml). The mixture was heated under reflux for 48 h, cooled, and filtered. The filtrate was washed with water and aqueous NaOH, then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was separated on a silica column (ethyl acetate–light petroleum; 1:5) to give the *epoxy alkene* (**14**) (1.8 g, 84%) as an oil for which no satisfactory elemental analysis was obtained. δ_H (60 MHz; TMS), 1.18 (3 H, d, *Me*CH), 1.34 (3 H, d, *Me*CH–O–CO), 1.53—3.01 (3 H, m, CH_2CHMe), 3.13 (1 H, q, MeC*H*–O–C), 3.76 (6 H, s, 2 × CO_2Me), 5.59 (1 H, s, C=C*H*), and 6.16 (1 H, s, C=C*H*); δ_C (20 MHz; TMS), 13.28 (q, Me), 19.51 (q, *Me*CH–O–C), 32.95 (d, *C*HCH$_2$), 51.52 (q, CO_2Me), 51.91 (q, CO_2Me), 57.24 (d, *CH*–O–C), 59.88 (s, O*C*–*CH*), 123.98 (t, C–CH_2), 144.54 (s, *C*=CH_2), 166.59 (s, CO_2Me), and 171.32 (s, CO_2Me); *m/z* 242 (M^+ 1%), 183 (10), 166 (9), 155 (11), 151 (13), and 129 (100).

Dimethyl 1,2-Diacetoxy-3-methyl-5,6-epoxyheptane-2,5-dicarboxylate (**15**).—The osmium tetraoxide reagent in t-butyl alcohol was prepared as described by Daniels and Fischer.[13] To a stirred solution of (**14**), (1.0 g, 4.1 mmol) in acetone (5 ml) and ether (1.6 ml) at 0 °C was added the OsO_4 catalyst (0.7 ml) and H_2O_2 (0.7 ml, ±11.5 mmol). After 24 h at room temperature the solution was diluted with ether and stirred for a further 20 min. It was then washed with brine and concentrated under reduced pressure to afford an oil (0.6 g, 53%) of *dimethyl-1,2-dihydroxy-3-methyl-5-epoxyheptane-2,5-dicarboxylate*; δ_H (60 MHz; TMS), 1.34 (3 H, d, *Me*CH), 1.37 (3 H, d, *Me*CH), 1.62—3.95 (7 H, m, $CH_2CHC(OH)CH_2OH$), 3.32 (1 H, q, MeC*H*–CO), and 3.73 (6 H, s, 2 × CO_2Me). This *diol* (0.3 g, 1.09 mmol), triethylamine (0.44 m, 1.6 mmol), Ac_2O (0.31 ml, 1.6 mmol), and dimethylaminopyridine[20] (0.022 g, 0.087 mmol) was stirred at room temperature for 4 days. The solution was paritioned between diethyl ether and 2M-hydrochloric acid, the organic phase washed with saturated aqueous Na_2CO_3, dried (Na_2SO_4), and concentrated under reduced pressure to yield (**15**) as an oil (0.26 g, 66%); δ_H (60 MHz; TMS), 1.03 (3 H, br d, *Me*CHCH$_2$), 1.33 (3 H, d, *Me*CH=), 2.04 (3 H, s, OCO*Me*), 2.07 (3 H, s, OCO*Me*), 2.29—3.42 (3 H, m, CH_2CH), 3.74 (6 H, s, 2 × CO_2Me), and 4.84 (2 H, dd, CH_2OCOMe); $\nu_{max.}$ 1 750 (CO) and 730 cm^{-1} (C–O–C).

Dimethyl (E)-1,2-Diacetoxy-3-methylhept-5-ene-2,5-dicarboxylate (**16**).—Chromium trichloride hexahydrate (2.17 g) in water (2.6 ml) and 12M-hydrochloric acid (4.5 ml) was reduced with granulated zinc under nitrogen.[17] The mixture was filtered through glass wool (N_2 atmosphere) into a solution of (**15**) (1.5 g, 4.17 mmol) in acetone (18.7 ml). After being stirred for 16 h at room temperature, the mixture was poured into water and extracted with dichloromethane. From the organic layer the *diacetate* (**16**) (0.2 g, 15%) was obtained as an oil, δ_H (60 MHz; TMS), 0.92 (3 H, br d, *Me*CHCH$_2$), 1.87 (3 H, d, *Me*CH=), 2.18 (6 H, s, 2 × CO_2Me), 2.25—3.00 (3 H, m, CH_2CHMe), 3.80 (3 H, s, CO_2Me), 3.85 (3 H, s, CO_2Me), 4.80 (2 H, dd, CH_2OCOMe), 7.03 (1 H, q, MeC*H*=); δ_C (20 MHz; TMS), 13.12 (q, Me), 14.27 (q, *Me*CH=), 20.44 (q, OCO*Me*), 20.60 (q, OCO*Me*), 26.77 (t, CH_2CH), 36.30 (d, $CHCH_2$), 51.32 (q, CO_2Me), 51.88 (q, CO_2Me), 61.18 (t, CH_2OCOMe), 82.81 (s, *C*OCOMe), 131.23 (s, *C*=CH), 139.00 (d, MeCH=), 167.72 (s, C=O), 168.75 (s, C=O), 169.61 (s, C=O), and 169.92 (s, C=O); *m/z* 344 (M^+, 0.3%), 225 (10.7), 224 (12.0), 211 (14.5), 197 (12.5), 192 (12.6), 169 (18.0), and 165 (33.5) (Found: M^+, 344.146 766. $C_{16}H_{24}O_8$ requires M^+, 344.147 103).

5-Ethylidene-2-hydroxy-2-hydroxymethyl-3-methylhexanedioic acid (**2**) *(Retronecic Acid) and Isoretronecic Acid.*—Compound (**16**) (95 mg; 276 mmol) and potassium hydroxide (84 mg, 1.2 mmol) in ethanol (2 ml) were heated under reflux for 2 h. The solution was cooled, then concentrated to dryness under reduced pressure. The residue in water (2 ml) was passed through a cation exchange resin (Zeocarb 225 SRC, H form; 2 g). From the eluate an oily residue was obtained which crystallised from ethyl acetate (52 mg, 80%) as a mixture of equal parts of retronecic acid and isoretronecic acid, m.p. 155 °C (lit.,[19] 180—181.5 °C); δ_H (80 MHz; D_2O; dioxane) (Found: C, 51.6; H, 6.9. $C_{10}H_{16}O_6$ requires C, 51.7; H, 6.9%); *m/z* 196 (3%), 183 (24), 178 (12), 169 (60), 127 (33), 109 (56), 81 (100). ^1H N.m.r. and ^{13}C n.m.r. spectra data for retronecic acid and isoretronecic acid are shown in Tables 1 and 2.

Dimethyl Octa-2,6-diene-3,6-dicarboxylate (**10**).—Methyl (*E*)-2-bromomethylbut-2-enoate (**8**) (5.0 g, 25.91 mmol) and magnesium turnings (0.45 g, 18.51 mmol) in dry tetrahydrofuran (25 ml) were heated under reflux for 4 h and then stirred at room temperature for 16 h. Water (25 ml) was added and the pH adjusted to 5 with 2M-hydrochloric acid. Extraction with ether gave a mixture of (**9**), (**10**), and (**11**) in the ratio of 11:7:1 (^1H n.m.r.). Separation by distillation afforded (**9**) and (**10**) as pure substances. The *octadiene* (**10**) (0.8 g, 28%) crystallised, m.p. 66—68 °C (from methanol); δ_H (60 MHz; TMS), 1.83 (6 H, d, 2 × *Me*CH), 2.47 (4 H, s, 2 × CH_2), 3.70 (6 H, s, 2 × CO_2Me), 6.83 (2 H, q, 2 × MeC*H*); *m/z* 226 (M^+, 13%), 195 (100), 167 (16), 135 (84), 113 (13), 107 (66), and 81 (47) (Found: C, 63.8; H, 7.8. $C_{12}H_{18}O_4$ requires C, 63.7; H, 7.9%). Only trace quantities of compound (**11**) could be isolated.

Acknowledgements

The authors thank the Council for Scientific and Industrial Research for financial assistance.

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Received 7th May 1985; *Paper* 5/743