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NEW SYNTHETIC ROUTE TO (1R)-CIS-(-)-PERMETHRIN, (1R)-CIS-(+)-CYPERMETHRIN AND (1R)-CIS-(+)-DELTAMETHRIN (DECIS) FROM (+)-3-CARENE.

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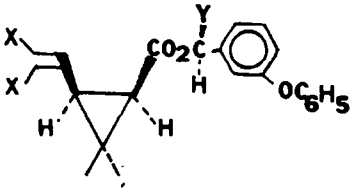
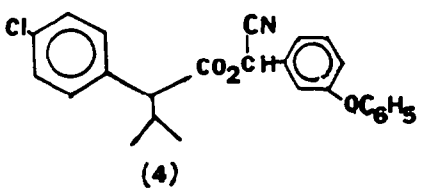
Abstract - (+)-4∝-Acetyl-2-carene (6), readily available from (+)-3-carene (5), was converted to (1R)-cis-(+)-3-(2',2'-dihalovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acids (21) and (22) in eleven steps and in overall yields of 23% and 14%, respectively. Alternatively, (-)-5-keto-3-carene (23), an oxidation product of (+)-3-carene (5) was converted to (1R)-cis-(-)-permethrin (1) in five steps and in an overall yield of 20%. In yet another flexible approach, (-)-(23) was converted to (1R)-cis-(+)-(21) and (1R)-cis-(+)-(22) in seven steps and in an overall yields of 33% and 23%, respectively. These results coupled with the literature reports for the conversion of (1R)-cis-(+)-(21) and (22) to (1R)-cis-(-)-(1), (1R)-cis-(+)-cypermethrin (2) and (1R)-cis-(+)-deltamethrin (decis) (3) constitute two efficient methods for the synthesis of (1R)-cis-synthetic pyrethroid from (+)-3-carene (5).

Ever since the discovery of permethrin (1) by Elliot[1], esters of 3-(2,2-dihalovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acids have become one of the most important classes of agricultural insecticides. The discovery fueled hectic research and development activity in academic and in major commercial agro-chemical laboratories[2], as a result of which several potent insecticidal compounds have emerged. Notable among these are cypermethrin (2) and (1R)-cis-(+)-deltamethrin (Decis) (3) by Elliot's group[3] and fenvalerate (4) by Ohno et al[4].



(1) ; X = Cl , Y = H
(2) ; X = Cl , Y = CN
(3) ; X = Br , Y = CN



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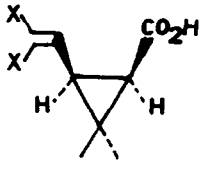


(21), X = Br
(22) X = Cl

The high potency, low mammalian toxicity[5] and biodegradability[5] of these compounds, coupled with the ingenuity of organic chemists to develop elegant cost-effective

routes, paved the way for commercial production of these insecticides in 1976. A total 3000 tons of (1), (2) and (3) were manufactured in 1979[6] which doubled in 1983 to 6500 tons[7] and a further increase in production (upto 10,000 tons/year) is expected in the near future. Thus, these compounds, commonly known as synthetic pyrethroid, suddenly emerged as the most important group of modern insecticides whose technical and economic significance already compares favourably with that of the insecticidal esters of phosphoric acids and carbanates. The research of Elliot's group also demonstrated that a particular stereoisomeric form, e.g. (1R)-cis-, in Decis (3) exhibits greater insecticidal activity than the mixed cis/trans esters[5,8]. In view of this considerable attention was focussed recently on the synthesis of (1R)-cis-cyclopropane carboxylic acids[2]. One such approach, namely, the conversion of (+)-3-carene (5), (a naturally occuring terpene from Pinus sylvestries L and Pinus longifolia Roxb; and possessing the desired cis-geometry at the cyclopropane ring junction) to (1R)-cis-(+)-3-(2,2-dihalovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acids (21) and (22) has received considerable attention in recent years[2,9]. We report herein two independant approaches for the successful conversion of (+)-3-carene (5) to (1R)-cis-(+)-acids (21) and (22), which can subsequently be converted to (1), (2) and (3) in one stereoisomeric form.

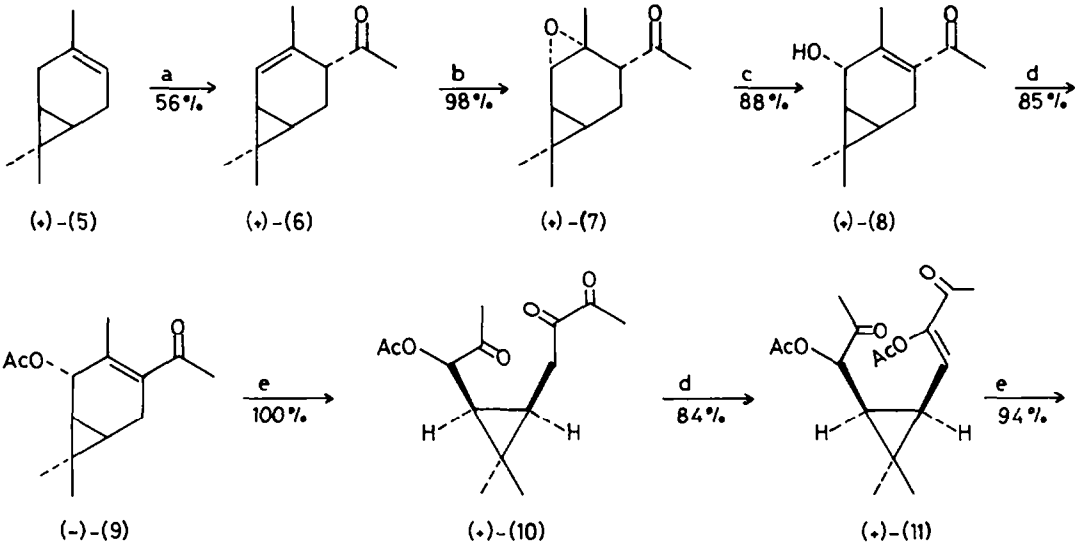
RESULTS AND DISCUSSIONS :

In our first synthesis 4α-acetyl-2-carene (6), readily obtainable[10] from (+)-3-carene (5) in 56% yield, is the starting point of the work (Scheme 1). Epoxidation of (6) to the desired (+)-4α-acetyl-2α, 3α-epoxycarane (7) was carried out with m-chlorobenzoic acid (mCPBA) in chloroform in 98% isolated yield. Our attempt to epoxidize (6) and (7) with other oxidants proved unsuccessful. For example, the reaction of (6) with peracetic acid alone or in conjunction with buffers such as anhydrous sodium acetate[11], anhydrous sodium carbonate[12], a combination of hydrogen peroxide/sodium tungstate under phase-transfer conditions[13], hydrogen peroxide/ethyl chloroformate[14] or oxone[15] led to a complex mixture of products with only negligible amount of (7). On the other hand, no reaction was observed with molybdenum peroxide/t-butyl hydroperoxide[16] and molybdenum dioxyacetyl acetonate/t-butyl hydroperoxide[17]. The success with mCPBA is presumably due to the precipitation of m-chlorobenzoic acid (which drives the reaction forward) and low acidity of the reaction mixture. Rearrangement of the epoxide (7) to (+)-4-acetyl-2α-hydroxy-3-carene (8) was effected with 10% aqueous sodium hydroxide at 25°C in 88% isolated yield. Subsequent acetylation of (8) with acetic anhydride and triethyl-amine afforded (-)-acetate (9) in 85% isolated yield.

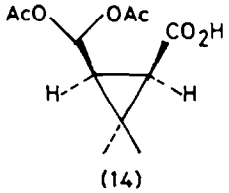
Ozonization of (9) in dichloromethane at -78°C proceeded uneventfully to provide after reductive work-up cis-(+)-3-(1'-acetoxy-2'-oxopropyl)-2,2-dimethyl-1-(2',3'-dioxobutyl)-cyclopropane (10) in quantitative yield. Subsequent enol-acetylation of (10) with acetic anhydride and triethyl-amine gave cis-(+)-3-(1'-acetoxy-2-oxopropyl)-2,2-dimethyl-1-(2'-acetoxy-3'-oxo-1'-butenyl)-cyclopropane (11) in 84% yield. Ozonization of (11) at -78°C followed by reductive work-up afforded cis-(-)-3-(1-acetoxy-2-oxopropyl)-2,2-dimethyl-cyclopropane-1-carbaldehyde (12) in almost quantitative yield.

As shown below, this intermediate (12) could be converted to the desired pyrethroids by several routes.For example, oxidation of (12) with aqueous potassium permanganate followed by acidic work-up yielded directly cis-(+)-4α-acetyl-6,6-dimethyl-3-oxo-bicyclo-(3.1.0)-hex-2-one (13) in 65% yield. In another approach, the aldehyde (12) was treated with two moles of mCPBA in dichloromethane at 25°C to effect both the

Scheme 1



Reagents: (a) $AC_2O/ZnCl_2$, 50°C; (b) mCPBA, $CHCl_3$, 0°C;
(C) 10% aq. NaOH, EtOH, 25°C; (d) AC_2O/Et_3N, EE, 25°C;
(e) O_3, CH_2Cl_2, −78°C; (f) $KMnO_4$, 25°C, H_3O^+,
(g) mCPBA, CH_2Cl_2, 25°C; (h) 70% CH_3CO_3H, CH_2Cl_2, 25°C;
(i) $CHBr_3$ / alc.KOH, THF, −10°C;
(j) $CHCl_3$, KO t Bu, −50°C, DMF−THF;
(k) p-TsOH, $2H_2O$ (Cat), 80°C;
(l) Zn−ACOH, EE, 25°C.



(14)

oxidation of formyl group to carboxyl group and Bayer-villiger oxidation at the carbonyl centre. In this case the desired compound (14) was not isolated; instead, reaction with a catalytic amount of p-toluene sulfonic acid gave cis-(-)-4α-acetoxy-6,6-dimethyl-3-oxobicyclo-(3.1.0)-hex-2-one (15) in 50% yield. Alternatively, (15) can be obtained in excellent yield by the Bayer-Villiger oxidation of (13) with mCPBA (12 h, 25°C) for 70% peracetic acid (12 h, 40°C). Addition of bromoform and chloroform to (-)-(15) in presence of base yielded (1R)-cis-(-)-3-(1'-hydroxy-2', 2',2'-tribromomethyl)-cyclopropane-1-carboxylic acid (17) and (1R)-cis-(-)-3-(1'-hydroxy-2',2',2'-trichloroethyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (18), in 94% and 70% yields, respectively, which were subsequently converted to (1R)-cis-(+)-(21) and (1R)-cis-(+)-(22) following literature procedures[18, 21]. The addition of bromoform to (-)-(15) to synthesize (-)-(17) can also be accomplished under phase transfer condition, albeit in only 15% yield, the major product being (-)-lactol (16) (65%). Conversion of the acid (+)-(21) and (+)-(22) to (1R)-cis-(-)-(1)[19], (1R)-cis-(+)-(2)[19, 20] and (1R)-cis-(+)-(3)[19, 20] is reported in literature. This therefore completes the formal synthesis optically active (1), (2) and (3) from (+)-(5).

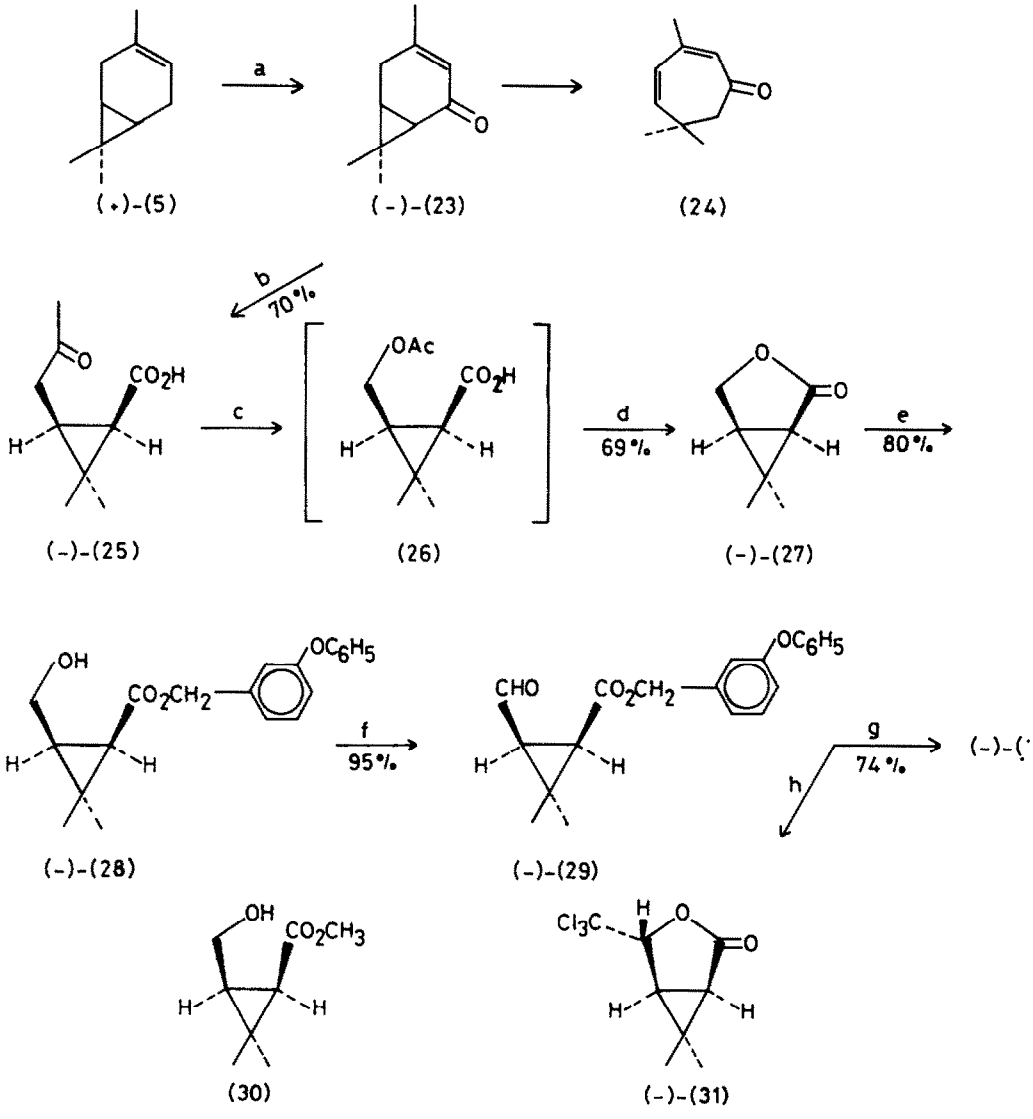
An important drawback of this otherwise simple and highly efficient synthesis is the usage of ozone, a reagent unsuitable for large scale operations. Therefore our effort to find a safer route to (-)-(1), (+)-(2) and (+)-(3) which excludes ozone usage and is also amenable to large scale operations - has led to an alternative synthetic strategy which is described below.

(-)-5-Keto-3-carene (23), readily prepared in our laboratory by the catalytic oxidation of (+)-3-carene (5)[22] or by the t-butyl chromate oxidation of (+)-(5)[23], is the starting point of our work (Scheme 2). We have noted earlier that (23) is prone to rearrangement to the dienone (24) at high temperature (~130°C) and/or in the presence of stronger acids or bases. We have therefore attempted the oxidation (-)-(23) with potassium permanganate under milder condition - namely under ambient condition in an acetic acid - water mixture. This led to the formation of the desired acid (-)-(25) in 70% yield. Subsequent Bayer-Villiger oxidation of (-)-(25) with equimolar mCPBA in dichloromethane at 25°C is slow (72 h); however the reaction could be expedited (24 h) with one molar excess of the oxidant. The resultant acid (26) although not isolated in pure form due to contamination with m-chlorobenzoic acid, could be smoothly hydrolysed with aqueous hydrochloric acid to the pure (1R)-cis-(-)-γ-lactone (27) in 69% yield. To our knowledge this is the shortest route[9a] to (-)-(27) from (+)-3-carene reported so far.

The conversion of (±)-γ-lactone (27) to the methyl-3-hydroxy-methyl-2,2-dimethyl cyclopropane carboxylate (30), as reported by Krief et al[24], involves the hydrolysis of (±)-(27) with aqueous base followed by esterification of the acid with diazomethane. We consider this approach hazardous for large scale operations and therefore adopted a different approach involving alkylation of the carboxylate anion of the acid with an alkyl halide[25].

Thus, hydrolysis of (-)-(27) with 5% aqueous sodium hydroxide in ethanol, followed by the alkylation of the carboxylate anion with 3-phenoxybenzyl bromide, yielded (-)-(28) in 80% yield. Alternatively, (-)-(28) can be formed via the hydrolysis of (-)-(27) with 10% tetra n-butylammonium hydroxide in dichloromethane, and subsequent alkylation with 3-phenoxybenzyl bromide in refluxing dichloromethane. Oxidation of (-)-(28) with Collin's reagent to (1R)-cis-(-)-3'-phenoxybenzyl-3-formyl-2,2-dimethyl-cyclopropane-1-carboxylate (29), followed by Wittig reaction

SCHEME-2

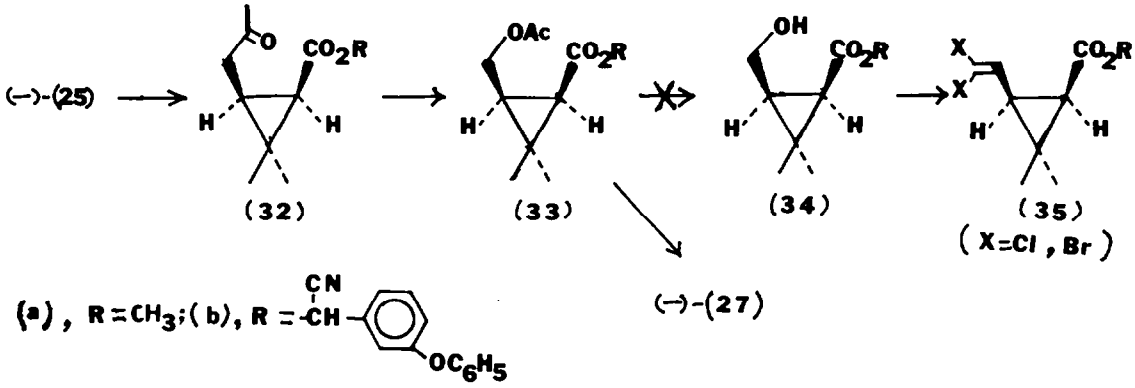


Reagents: (a): $Co(acac)_2/O_2$ or t-butylchromate; (b) 5 $KMnO_4$, AcOH:H_2O, (c) m CPBA, CH_2Cl_2, 25°C, 72 h; (d) 10% aq. HCl, CH_3OH or THF, 25°C, 18h; (e) 5% aq. NaOH, EtOH; m C_6H_5-O-C_6H_4-CH_2Br, Cat. 80°C, 3h; (f) CrO_3·2py, CH_2Cl_2, 25°C, 2h; (g) $P(NMe_2)_3$, CCl_4, 0°C (h) $CHCl_3$, 50% NaOH, PTC, 0°C.

of (-)-(29) with triphenylphosphine/carbon tetrachloride[26] or hexamethyl phosphorus triamide/carbon tetrachloride[27] yielded (1R)-cis-(-)-permethrin (1) in an overall yield of 60% and 70%, respectively.[28]

An important limitation of the above approach is its lack of generality. For example, (1R)-cis-(+)-(2) and (1R)-cis-(+)-(3) could not be prepared through this method, due to the difficulty in preparing the requisite alkyl halide. An alternative

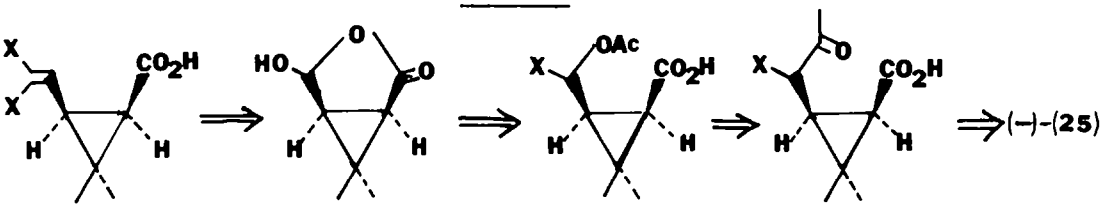
approach involving esterification at the earlier stages of synthesis was therefore considered. The validity of such a scheme was first tested using the readily available methyl ester (32a), prepared by the reaction of (-)-(25) with diazomethane.



Oxidation of (32a) to (33a) proceeded smoothly with mCPBA at 25°C (48 h) in 90% yield. All our attempts to carry out selective hydrolysis of acetate moiety of (33a) to yield (34a) was unsuccessful even with milder bases such as ammonia in methanol[30], potassium carbonate or potassium bicarbonate in methanol[31]. In all cases studied, the reaction led to (-)-(22) in excellent yield.

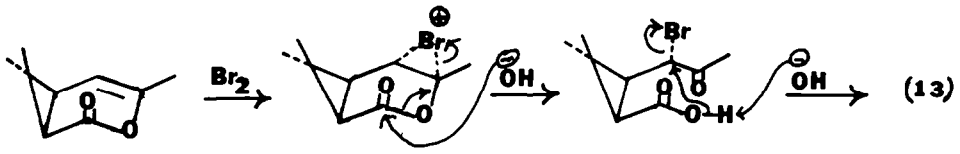
We, therefore, turned our attention to yet another approach which is shown below. It is well established that (1R)-cis-(-)-lactol (16) is an important intermediate for the preparation of the acids, (1R)-cis-(+)-(21) and (1R)-cis-(+)-(22)[18]. Therefore, in planning our synthesis of the above acids, the retrosynthetic pathway, as exemplified in Scheme 3 was viewed with particular attention.

Scheme 3



One notable feature of the pathway is that the intermediate (37) possesses a secondary alkyl substituent α-to the carbonyl group and thus would undergo Bayer-Villiger oxidation more readily (hence shorter reaction time) to yield (36). The intermediate (36) would then possess a masked carbonyl group which could be elaborated to the requisite dihalovinyl functionality.

Synthesis of (37) from the enol-lactone (38) readily obtained from (-)-(25)[32] was attempted using a modified halogenation procedure. Thus, treatment of (-)-(38) with bromine in carbon tetrachloride[33] followed by aqueous work up yielded a mixture of (+)-(13) and presumably, (37) which under prolonged hydrolytic condition was transformed completely to (+)-(13). Thus, a quantitative yield of (+)-(13) was obtained from (-)-(38)[35]. All our attempts to isolate (37), even under anhydrous reaction condition, was unsuccessful and in all the cases, a mixture of (13) and (37) resulted. The above result can be explained as follows :



(38) (39) (37)

addition of bromine to (-)-(38) would likely occur from the bottom plane to yield (39), hydrolysis of which would give rise to (37), subsequent bromolactonization of (37) from the less hindered side would yield (13). It is however, gratifying to note that this novel transformation is general and could be extended to the synthesis of functionally substituted γ-lactones and spiro-γ-lactones[36] (Eqn. 1).

(1)

n = 0 ,1

The elaboration of (+)-(13) to the (1R)-cis-(-)-(1), (1R)-cis-(+)-(2) and (1R)-cis-(+)-(3) has been described earlier. This therefore completes our work on the formal synthesis of optically active (1), (2) and (3) from (+)-(5). To our knowledge this is the only synthesis of optically active (1), (2) and (3) from (+)-3-carene (5) reported so far which totally excludes usage of ozone. The industrial applicability of this route is being evaluated and it appeared that the low yield of (-)-(23) from (+)-(5) and the usage of large excess of potassium permanganate to convert (-)-(23) to (-)-(25) are two limiting steps for such an application. Work to obviate these difficulties are in progress and this would be the subject of our future report.

EXPERIMENTAL :

Melting points and boiling points were uncorrected. NMR spectra were recorded in $CDCl_3$ on a Bruker CW-80 Spectrometer with chemical shift reported in ppm downfield of internal standard tetramethysilane. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. GC-MS were recorded on a Hewlett Packard 5993B spectrometer using, 2% OV-210 on chromosorb WHP 80/100, 2 m x 0.6 cm (Column A), and CP-Sil 5 capillary column, 12 m x 0.2 mm (Column B). The optical rotations were measured on a Jasco DIP-210 automatic polarimeter. GLC analyses were carried out on a Pye-Unicam 204 gas chromatograph using, 6' x 1/4", 3% OV-17 on a diatomaceous earth Q, 100/120. HPLC analyses were carried out on a Water Associates 1440 Chromatograph using, Bondapak C_{18}, particle size 10 micron (30 cm x 3.9 mm ID). The mass spectra were recorded on a Varian MAT 112 spectrometer. In all cases the organic layer after work up was washed with saturated brine solution and then dried over anhydrous sodium sulphate.

(+)-4α-Acetyl-2-carene (6) :

This was prepared[10] from (+)-3-carene ($[\alpha]_D^{25}$ + 17.5° (neat), 97% e.e) in 56% yield

(95% GLC), $[\alpha]_D^{25}$+ 7.91° (C 1, $CHCl_3$); IR (neat) (ν cm^{-1}), 1710, 1660; ^1H nmr (δ), 5.62 (br, 1H, C=C<u>H</u>) 2.8-2.5 (m, 1H, C<u>H</u>-C=O), 2.4-2.0 (m, 1H, bridge C<u>H</u>), 2.13 (s, 3H, <u>CH_3</u>-C=O), 1.88-1.5 (m, 2H, <u>CH_2</u>-), 1.7 (bs, 3H, <u>CH_3</u>-C=), 1.08 (s, 3H, C<u>H_3</u>-C), 1.06-0.88 (m, 1H, bridge), 0.87 (s, 3H, <u>CH_3</u>-C).

(+)-4α-Acetyl-2α, 3α-epoxy-carene (7) :

To a stirred solution of (6) (17.8 g, 0.1 mole) in $CHCl_3$ (60 ml) at 0°C was added dropwise a solution of <u>m</u>CPBA (24.2 g, 0.11 mole) in $CHCl_3$ (120 ml) over a period of 1 h. This was stirred at 0°C for 1 h. The precipitated <u>m</u>-chlorobenzoic acid (mCBA) was filtered, the filtrate washed with 10% Na_2SO_3 and saturated $NaHCO_3$ solution, and evaporated to yield (7) (19.0 g, 98%), as a yellow oil. This was further purified by column chromatography over silica gel (eluent, hexane), (98%, GLC), $[\alpha]_D^{25}$+ 32.7° (C 1, $CHCl_3$); IR (neat), (ν cm^{-1}), 1715; ^1H nmr (δ), 2.92 (s, 1H, C<u>H</u>-O), 2.72 (t, 1H, C<u>H</u>-C=O), 2.4-2.0 (m, 2H, <u>CH_2</u>-), 2.25 (s, 3H, <u>CH_3</u>-C=O), 1.45 (s, 3H, <u>CH_3</u>-C-O), 1.1 (s, 3H, <u>CH_3</u>-C), 1.02 (s, 3H, <u>CH_3</u>-C), 1.05-0.85 (m, 2H, bridge); MS, M^+ 194 (<1), 152 (22), 133 (20, 120 (33), 109 (83), 84 (44), 83 (40), 70 (33), 68 (39), 44 (100), 42 (88), 40 (62).

(+)-4-Acetyl-2α-hydroxy-3-carene (8) :

To a stirred solution of (7) (19.4 g, 0.1 mole) in ethanol (150 ml) at 25°C was added an aqueous solution of 10% NaOH (44 ml) dropwise over a period of 0.5 h. The resulting mixture was stirred for 0.5 h. Ethanol was then removed by distillation and the residue was extracted with CH_2Cl_2 (3x50 ml). Evaporation of the organic layer furnished (7) (17 g, 88%) as a yellow oil, (96% pure, HPLC), $[\alpha]_D^{25}$+ 7.60° (C 1, $CHCl_3$); IR (neat), (ν cm^{-1}), 3420, 1685, 1640; ^1H nmr (δ), 3.95 (brs, 1H, C<u>H</u>-O), 2.88-2.0 (m, 2H, <u>CH_2</u>-CH=), 2.2 (s, 3H, <u>CH_3</u>-C=O), 1.8 (m, 3H, <u>CH_3</u>-C=), 1.0 (s, 3H, <u>CH_3</u>-C), 1.00-0.83 (m, 2H, bridge), 0.87 (s, 3H, C<u>H_3</u>-); MS, M^+ 194 (7), 152 (15), 124 (10), 110 (12), 92 (13), 83 (10), 71 (20), 56 (13), 54 (10), 44 (100), 42 (27), 40 (17).

(-)-4-Acetyl-2α-acetoxy-3-carene (9) :

A mixture of (8) (19.4 g, 0.1 mole), triethylamine (1.1 g, 0.11 mole) and acetic anhydride (12 ml) in dry ether (70 ml) was stirred at 25°C for 24 h. Ether (50 ml) was added and the reaction mixture was washed repeatedly with 10% aq. HCl, saturated $NaHCO_3$ solution, and evaporated to yield (9) as a yellow solid (20.1 g, 85%). Recrystallisation from ether-pentane (4:1) afforded pure (9) (16.5 g, 85%) as a white solid, (98%, GLC), m.p. 51-2°, $[\alpha]_D^{25}$- 52.2° (C 1, $CHCl_3$). The mother liquor was recrystallized to yield more of (9) (2.0 g, 9%); IR ($CHCl_3$), (ν cm^{-1}), 1730, 1690, 1650, ^1H nmr (δ), 5.25 (bs, 1H, C<u>H</u>-O), 3.0-2.25 (m, 2H, <u>CH_2</u>-CH=), 2.25 (s, 3H, <u>CH_3</u>-C=O), 2.1 (s, 3H, <u>CH_3</u>-C=O), 1.7 (m, 3H, <u>CH_3</u>-C=), 1.05 (s, 3H, <u>CH_3</u>-C), 0.95-0.83 (m, 2H, bridge), 0.9 (s, 3H, <u>CH_3</u>-C); MS, M^+ 236 (<1), 193 (8), 178 (46), 162 (62), 133 (72), 124 (60), 92 (46), 44 (100), 42 (88), 40 (60); Anal. calcd. for : C 71.16, H 8.53, Found : C 70.97, H 8.50.

<u>Cis</u>-(+)-3-(1'-acetoxy-2'-oxopropyl)-2,2-dimethyl-1-(2',3'-dioxobutyl)-cyclopropane (10) :

Ozone was bubbled through a stirred solution of (9) (14.16 g, 0.06 mole) in CH_2Cl_2 (75 ml) at -78°C, at a rate of 40 l/hour until the solution attained blue colouration. Oxygen was then purged through the solution to remove excess ozone. To this was added dimethylsulfide (10 ml) and the reaction mixture was stirred at 25°C for 12 h. The CH_2Cl_2 layer was washed once with water, and evaporated to furnish (10) (16 g, 100%) as a pale yellow liquid, $[\alpha]_D^{25}$+ 40.8° (C 1, $CHCl_3$); IR (neat), (ν cm^{-1}),

1740, 1725, 1715; ^{1}H nmr (δ), 4.6 (d, 1H, J=11Hz, C<u>H</u>-O), 2.9(AB,2H,J=9Hz,J=2Hz,C<u>H$_2$</u>-C=O) 2.4 (s, 3H, <u>CH$_3$</u>-C=O), 2.1 (s, 3H, <u>CH$_3$</u>-C=O), 2.05 (s, 3H, <u>CH$_3$</u>-CO$_2$), 1.2-0.88 (m, 2H, bridge), 1.17 (s, 3H, <u>CH$_3$</u>-C), 0.98 (s, 3H, <u>CH$_3$</u>-CO); MS, M$^+$ 268 (<1), 225 (6), 183 (16), 165 (13), 153 (9), 138 (10), 123 (9), 95 (10), 43 (100), 28 (60).

<u>Cis</u>-(+)-3-(1'-acetoxy-2'-oxopropyl)-2,2-dimethyl-1-(2'-acetoxy-3'-oxo-1'-butenyl)-cyclopropane (11) :

A mixture of (10) (16.1 g, 0.06 mole), triethylamine (7.2 g, 0.07 mole) and acetic anhydride (7.0 ml) in dry ether (50 ml) was stirred at 25° for 18 h. Usual work up as described earlier, provided (11) (15.6 g, 84%) as a yellow liquid that solidified on cooling. This was recrystallised from petroleum ether (50-60°) to yield (11) as a white solid (98%, GLC), m.p.71-2°C, $[\alpha]_D^{25}$+ 10.1° (C 0.5, $CHCl_3$); IR (neat) (ν cm^{-1}), 1770, 1750, 1730, 1690 and 1650; ^{1}H nmr (δ), 6.4 (d, 1H, J=11Hz, <u>CH</u>-C=), 4.8 (d, 1H, J=11Hz, C<u>H</u>-O), 2.31 (s, 3H, <u>CH$_3$</u>-C=O), 2.28 (s, 3H, <u>CH$_3$</u>-C=O), 2.16 (s, 6H, 2 <u>CH$_3$</u>-CO$_2$), 1.95-1.0 (m, 2H, 2 bridge <u>H</u>), 1.25 (s, 3H, <u>CH$_3$</u>-C), 1.17 (s, 3H, <u>CH$_3$</u>-C). Anal. Calcd. for:C 61.94, H 7.15. Found : C 61.35, H 7.09.

<u>Cis</u>-(-)-3-(1-acetoxy-2-oxopropyl)-2,2-dimethyl-cyclopropane-1-carbaldehyde (12) :

Ozone was bubbled through a stirred solution of (11) (31 g, 0.2 mole) in CH_2Cl_2 (250 ml) at -78° as described earlier. Usual work up then yielded (12) (19.93 g, 94%) as a pale yellow oil, $[\alpha]_D^{25}$- 16.5° (C 1.1, $CHCl_3$); IR ($CHCl_3$) (νcm^{-1}), 1745, 1730, 1705; ^{1}H nmr (δ), 9.8 (d, 1H, J=3Hz, C<u>H</u>=O), 5.6 (d, 1H, J=11Hz, C<u>H</u>-O), 2.18 (s, 3H, C<u>H$_3$</u>-C=O), 2.15 (s, 3H, C<u>H$_3$</u>-CO$_2$), 1.65-1.0 (m, 2H, bridge, 1.3 (s, 3H, C<u>H$_3$</u>-C), 1.25 (s, 3H, CH$_3$-C).

Cis-(+)-4∝-acetyl-6,6-dimethyl-3-oxo-bicyclo-(3.1.0)-hex-2-one (13) :

To a vigorously stirred solution of (12) (4.24 g, 0.02 mole) in water (150 ml) at 70-80°C was added dropwise a solution of $KMnO_4$ (2.25 g) in water (35 ml). The resulting mixture was stirred for 1 h and then cooled to 10°C. To this was added sodium nitrite (0.5 g) followed by (1:8) aqueous H_2SO_4 dropwise until the reaction mixture became clear. The mixture was stirred at 25°C for4 h and then extracted with CH_2Cl_2 (3x50 ml). Evaporation of the organic layer yielded (13)[36] (2.18 g, 65%) that solidified upon keeping in a refrigerator. Recrystallisation from pentane-ether (4:1) afforded (13) as a colourless crystals (97%, GLC), m.p.64-66°C, $[\alpha]_D^{25}$+ 13.05° (C 1, $CHCl_3$).

(-)-5-Keto-3-carene (23) :

This was prepared either by the oxidation of (+)-3-carene (5), $[\alpha]_D^{25}$+ 17.5° (neat), 97% e.e.[37] with oxygen in presence of a catalyst[22] or by the oxidation of (6)[23] $[\alpha]_D^{25}$- 263° (C 2, $CHCl_3$), 97% e.e[38] with t-butyl chromate.

<u>Cis</u>-(-)-3-(2'-oxopropyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (25) :

To a stirred solution of (-)-(23) (60 g, 0.4 mole) in 1:1 acetic acid-water (1000 ml) at 5°C was added portion-wise finely powdered potassium permanganate (316 g, 2 mole). The resulting mixture was stirred for 1 h at 25°C, and then cooled to 0-5°C. Sulphur dioxide gas was passed through the reaction mixture till the reaction mixture became clear. The supernatent liquid was filtered from the precipitated manganous sulphate and extracted with chloroform (3x150 ml). The solid was washed with chloroform (100 ml), and the washing added to the organic layer that was evaporated. The residue obtained was digested with aqueous sodium bicarbonate solution and extracted with chloroform (100 ml). The aqueous layer was acidified with conc. HCl and then extracted with chloroform (200 ml). Evaporation of the chloroform layer yielded (47.2 g, 70%) that was further purified by column chromatography (eluent, hexane :

chloroform = 9:1) to furnish pure (-)-(25) as a colourless oil, $[\alpha]_D^{25}$-31° (C 3, $CHCl_3$), IR ($CHCl_3$), 1730-1700 (br), 3500-3100; ^1H nmr (δ), 2.9-2.7 (m, 2H, $C\underline{H}_2$), 2.04 's, 3H, $C\underline{H}_3$-C=O), 1.56-1.38 (m, 2H, bridge), 1.16 (s, 3H, $C\underline{H}_3$), 1.1(s,3H,$C\underline{H}_3$).

(-)-6,6-Dimethyl-3-oxabicyclo-(3.1.0)-hex-2-one (27) :

A solution of (-)-(25) (51 g, 0.3 mole) and 85% m-chlorobenzoic acid (73 g, 0.36 mole) in dichloromethane (CH_2Cl_2) (400 ml) was stirred at 25°C in the absence of light for 72 h. The precipitated m-CBA was filtered off and the filtrate distilled to remove CH_2Cl_2 (100 ml). The residue was cooled to precipitate an additional amount of m-CBA that was filtered. The filtrate was concentrated. To this was added methanol (50 ml) and 10% aqueous HCl (50 ml) and the reaction mixture was vigorously stirred at 25°C for 18 h. Evaporation of methanol was followed by extraction of the residue with CH_2Cl_2 (100 ml). The aqueous layer was extracted once with CH_2Cl_2 (20 ml) and the combined organic layer was washed with saturated aqueous sodium bicarbonate solution and evaporated to furnish an oil that on distillation under reduced pressure using a short column yielded (27) as a colourless oil (25.9 g, 69%), b.p. 75-8° (1 mm of Hg). An analytical sample was prepared by thick-layer chromatography (eluent, hexane : $CHCl_3$= 4 : 1) (97%, GLC), $[\alpha]_D^{25}$-34.5° (C 0.6, $CHCl_3$) 94% e.e.[39]; IR (neat), (ν cm^{-1}) 1775, 1730; ^1H nmr (δ), 4.55-4.0 (m, 2H, $C\underline{H}_2$-O), 2.2-1.85 (m, 2H, bridge), 1.18 (s, 6H, 2 $C\underline{H}_3$).

Cis-(-)-(3'-Phenoxybenzyl-2,2-dimethyl-3-hydroxymethyl-cyclopropane carboxylate (28) :

A solution of (-)-(27) (12.6 g, 0.1 mole) in ethanol (30 ml) and 5% aqueous sodium hydroxide (80 ml) was stirred at 25°C for 1 h. Evaporation of this mixture yielded the sodium carboxylate as a pale yellow powder, that was then suspended in ethanol (40 ml). To it was added 3-phenoxybenzyl bromide (26.3 g, 0.1 mole) and triethyl amine (1 g) in ethanol (20 ml) and the resulting mixture was boiled under reflux for 3 h after which ethanol was evaporated. The residue was extracted with dichloromethane (2x50 ml). Evaporation of the organic layer yielded crude (11) (30 g, 93%) that was purified by column chromatography over silica-gel (eluent, hexane : chloroform = 9:1) to afford (28) (26 g, 80%) as a pale yellow viscous oil, (96%, HPLC), $[\alpha]_D^{25}$ - 5.0° (C 2, $CHCl_3$); IR ($CHCl_3$) (ν cm^{-1}), 1725, 3600-3100; ^1H nmr (δ), 7.5-6.8 (m, 9H, aromatic), 5.08 (s, 2H, $C\underline{H}_2$-Ar), 3.85 (d, 2H, J=6Hz), $OC\underline{H}_2$), 1.78-1.3 (m, 2H, bridge), 1.21 (s, 6H, 2 $C\underline{H}_3$). GC-MS (Silylated product with Me_3SiCl) (Column, B); 398 (M^+, weak), 282 (14, 184 (17), 183 (100), 103 (160), 83 (29).

Cis-(-)-3'-Phenoxybenzyl-3-formyl-2,2-dimethyl-cyclopropane carboxylate (29) :

To a slurry of anhydrous chromium trioxide (9 g, 0.09 mole) in CH_2Cl_2 (40 ml) was added pyridine (18 ml) and the mixture was stirred at 25°C for 0.25 h. To this was then added a solution of (-)-(28) (1.63 g, 0.01 mole) in CH_2Cl_2 (5 ml) and the resulting mixture was stirred for 2 h. Ether (50 ml) was added and the organic layer decanted from the black residue, washed with 10% aqueous HCl, and evaporated to furnish (29) (3.1 g, 95%). An analytical sample of (-)-(29) was prepared by thick layer chromatography (eluent, hexane) (96%, GLC), $[\alpha]_D^{25}$- 36° (C 0.8, $CHCl_3$); IR ($CHCl_3$), (ν cm^{-1}), 1725, 1700; ^1H nmr (δ), 9.75 (1H, d, J=6.0Hz, $C\underline{H}O$), 7.5-6.8 (m, 9H, aromatic), 5.1 (s, 2H, $C\underline{H}_2$-Ar), 2.18 (d, 1H, J=8Hz, $C\underline{H}$-CO_2), 1.85 (dd, 1H, J=6Hz, J=2Hz, $C\underline{H}$-CHO).

Cis-(-)-3'-Phenoxybenzyl-3-(2',2'-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylate (1) :

To a stirred mixture of hexamethyl phosphorus triamide (3.26 g, 0.02 mole), carbon tetrachloride (3.08 g, 0.02 mole), and pentane (15 ml) at 0°C, was added dropwise a

a solution of (-)-(29) (3.24 g, 0.01 mole) in pentane (5 ml). The reaction mixture was warmed to 25°C and water (20 ml) was added. The organic layer was thoroughly washed with water and evaporated to afford 3.8 g of crude product that was purified by column chromatography over silica-gel (eluent, hexane) to yield (1) (2.86 g, 74%) as a colourless viscous oil, (99%, HPLC), $[\alpha]_D^{25}$ - 7.8° (C 1, $CHCl_3$), IR ($CHCl_3$), (ν cm^{-1}), 1725; ^{1}H nmr (δ), 7.4-6.9 (m, 9H, aromatic), 6.23 (d, 1H, J=6Hz, C<u>H</u>=), 5.03 (s, 2H, C<u>H</u>$_2$-Ar), 2.04 (t, 1H, J=6Hz, C<u>H</u>-C=), 1.83 (d, 1H, J=6Hz, C<u>H</u>-CO_2), 1.24 (s, 6H, 2C<u>H</u>$_3$); GC-MS (Column B) M^+ 390, 183 (100), 165 (22.6), 163 (24.6).

(-)-4,7,7-Trimethyl-3-Oxabicyclo-(4.1.0)-hept-4-en-2-one (38) :

A mixture of (-)-(25) (170 g, 1 mole), acetetic anhydride (300 ml), p-TsOH.2H_2O (20 g) and benzene (800 ml) was stirred at 0-5°C for 3 h. The reaction mixture was washed thoroughly with saturated aqueous sodium bicarbonate solution. Evaporation of the organic layer followed by distillation yielded (32) (130 g, 85%) as a colourless liquid, b.p. 65.8°/0.6 mm of Hg, that crystallized on standing, m.p. 48°C, lit[32], m.p. 44-45.5°C (100%, GLC), $[\alpha]_D^{25}$-100° (C 1, $CHCl_3$); IR ($CHCl_3$) (ν cm^{-1}), 1745, 1720; ^{1}H nmr (δ), 5.0-5.15 (m, 1H, C<u>H</u>=), 1.88 (s, 3H, C<u>H</u>$_3$-C=), 1.8-1.6 (m, 2H, bridge), 1.22 (s, 3H, C<u>H</u>$_3$), 1.02 (s, 3H, C<u>H</u>$_3$).

(+)-4α-Acetyl-6,6-dimethyl-3-oxabicyclo-(3.1.0)-hex-2-one (13) :

To a stirred solution of (-)-(37) (76 g, 0.5 mole) in carbon tetrachloride (CCl_4) (120 ml) at 0°C was added a solution of liquid bromine (80 g, 0.5 mole) in CCl_4 (70 ml) over a period of 1 h. The resulting mixture was washed with 10% aqueous sodium thiosulphate solution and then stirred with aqueous sodium bicarbonate (100 g) for 16 h. Evaporation of the organic layer yielded (+)-(13) (83 g) that was crystallized from pentane-ether (4:1) to afford (13) (71.5 g, 85%) as colourless crystals, (99.5%, GLC), m.p. 64-65°C, $[\alpha]_D^{25}$+ 13.6° (C 1, $CHCl_3$). The mother liquor on further crystallization yielded 4.2 g of (+)-(13), m.p. 64-65°C. Total yield of pure (+)-(13) is 90%, (GLC, 99%). IR ($CHCl_3$), (ν cm^{-1}), 1780, 1765 and 1725; ^{1}H nmr (δ), 4.45 (s, 1H, C<u>H</u>-O), 2.32 (s, 3H, C<u>H</u>$_3$-C=O), 2.2 (d, 1H, J=7Hz, bridge), 1.2 (s, 6H, 2C<u>H</u>$_3$); GC-MS (Column A) M^+ 168 (5), 153 (10, 125 (10, 125 (55), 111 (12), 97 (28), 79 (28), 79 (25), 69 (20), 53 (22), 43 (100, 41 (65), 39 (35).

(-)4α-Acetoxy-6,6-dimethyl-3-oxabicyclo-(3.1.0)-hex-2-one (15) :

To a solution of (+)-(13) (67.2 g, 0.4 mole) in CH_2Cl_2 (125 ml) was added at 0-5°C a solution of 85% <u>m</u>-CPBA (97.2 g, 0.48 mole) in CH_2Cl_2 (500 ml). The resulting mixture was stirred at 25°C in absence of light for 12 h. The precipitated m-CBA was filtered and the filtrate washed repeatedly with saturated aqueous sodium bicarbonate and 10% aqueous sodium sulphite solution. Evaporation of the organic layer furnished (-)-(15) (70 g, 95%) as a pale yellow solid that was recrystallized from pentane-ether (4:1) to yield (15) (63.6 g, 86.5%), (99%, GLC), m.p. 91-92°C, $[\alpha]_D^{25}$ - 17.0° (C 1, $CHCl_3$); IR ($CHCl_3$) (ν cm^{-1}), 1800, 1780 and 1755; ^{1}H nmr (δ), 6.3 (s, 1H, C<u>H</u>O), 2.13 (s, 3H, C<u>H</u>$_3$-C=O), 2.1 (s, 2H, bridge), 1.25 (s, 3H, C<u>H</u>$_3$), 1.21 (s, 3H, C<u>H</u>$_3$); GC-MS (Column A), 125 (32), 96 (95), 81 (60), 67 (46), 53 (30), 43 (100), 41 (50), 39 (37), 27 (30).

(-)-(15) :

A mixture of (+)-(13) (3.36 g, 0.02 mole), 70% peracetic acid (5 ml) and CH_2Cl_2 (20 ml) was stirred at 40°C for 12 h, diluted with CH_2Cl_2 (25 ml) and worked up as described earlier to afford (15) (2.55 g, 70%) as a white crystalline solid, m.p. 90-92°, $[\alpha]_D^{25}$ - 16.5° (C 2, $CHCl_3$).

Cis-(-)-3-(2',2',2'-Tribromomethyl-1-hydroxyethyl)-2,2-dimethyl cyclopropane-1-carboxylic acid (17) :

In accordance with the procedure[18] for the preparation of (-)-(16), to a solution of (-)-(15) (36.8 g, 0.2 mole) in tetrahydrofuran (THF) (135 ml) and bromoform (27 ml) at -10°C was added dropwise 30% solution of potassium hydroxide in methanol (90 ml) over a period of 1 h. The resulting mixture was stirred for 2 h. Water (200 ml) was added and the resulting mixture was stirred at 25°C for 0-5 h. THF and methanol were removed by distillation under aspirator vacuum and the residue was acidified with 15% aqueous hydrochloric acid to precipitate (17) as a white solid. This was filtered, washed with water and dried to yield (17) (68.5 g, 86%). Recrystallisation from (1:1) isopropanol-water furnished (17), m.p. 177°C, lit[18] m.p. 177°C, $[\alpha]_D^{25}$ - 3.71° (C 1.8, CH_3OH); IR (ν cm^{-1}), 3600-3100, 1700; ^{1}H nmr (δ), 4.32 (d, 1H, J=9Hz), 1.87 (d, 1H, J=9Hz), 1.7 (d, 1H, J=9Hz), 1.43 (s, 3H, $C\underline{H}_3$), 1.25 (s, 3H, $C\underline{H}_3$).

(-)-4α-(1',1',1'-Tribromomethyl)-6,6-dimethyl-3-oxabicyclo-(3.1.0)-hex-2-one (19) :

This was prepared[18] from (-)-(17) (79 g, 0.2 mole) to yield (19) (71.2 g, 95%), m.p. 93°C, lit[18] m.p. 94°C, $[\alpha]_D^{25}$ - 17.8° (C 2, $CHCl_3$); IR ($CHCl_3$), (ν cm^{-1}), 1786-1805; ^{1}H nmr (δ), 4.55 (s, 1H, $C\underline{H}$-O), 2.34 (d, 1H, J=6Hz, $C\underline{H}$-CO_2), 2.17 (d, 1H, J=6Hz, $C\underline{H}$-CH-O), 1.3 (s, 3H, $C\underline{H}_3$), 1.28 (s, 3H, $C\underline{H}_3$).

Cis-(+)-3-(2',2'-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (21) :

To a stirred solution of (-)-(19) (56.6 g, 0.15 mole) in dry ether (400 ml) and acetic acid (330 ml), was added zinc dust (118 g, 1.8 mole) in portions. The resulting mixture was stirred for 2.5 h at 25°C, filtered and the filtrate distilled to remove ether and acetic acid. Water was then added to the residue and the solid that separated was filtered, washed with water and dried to yield (21) (39 g, 88%), as a pale yellow solid. Recrystallisation from isopropanol afforded (21) (36 g, 80%), m.p. 132°, (99%, HPLC), $[\alpha]_D^{25}$+ 16.8 (C 2.5, $CHCl_3$); IR ($CHCl_3$), (ν cm^{-1}), 3500-3100, 1700; ^{1}H nmr (δ), 6.75 (d, 1H, J=8Hz, $C\underline{H}$=), 2.04 (t, 1H, J=8Hz, $C\underline{H}$-C=), 1.83 (d, 1H, J=8Hz, $C\underline{H}$-C=O), 1.28 (s, 6H, $2C\underline{H}_3$).

Cis-(-)-3-(2',2',2'-Trichloromethyl-1-hydroxyethyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (18) :

This was prepared from (-)-(15) according to the procedure[18] for the preparation of (-)-(21) and as described for the preparation of (17). Thus, (-)-(15) (9.2 g, 0.05 mole) yielded (18) (9.12 g, 70%), m.p. 178°C lit[18] m.p. 182°C, $[\alpha]_D^{25}$-26.0° (C 0.5, CH_3OH); IR ($CHCl_3$), (ν cm^{-1}), 1720 (Shoulder), 1690, 3400; ^{1}H nmr (δ), 4.47 (d, 1H, J=9Hz, -$C\underline{H}$-OH), 1.7 (t, 2H, J=9Hz, bridge-$\underline{H}$), 1.38 (s, 3H, $C\underline{H}_3$), 1.25 (s, 3H, $C\underline{H}_3$).

Cis-(+)-3-(2',2'-Dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (22) :

This was prepared from (-)-(19) (4.47 g, 0.02 mole) in dry ether (50 ml) and acetic acid (40 ml) and zinc dust (15.6 g, 0.24 mole) according to the procedure described earlier for the preparation of (+)-(21), to yield (22) (3.3 g, 80%) as colourless crystals m.p. 90-91°C, $[\alpha]_D^{25}$ + 29.7°, 98% e.e.[21]

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