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OPTICALLY ACTIVE 2-VINYLCYCLOBUTANONES

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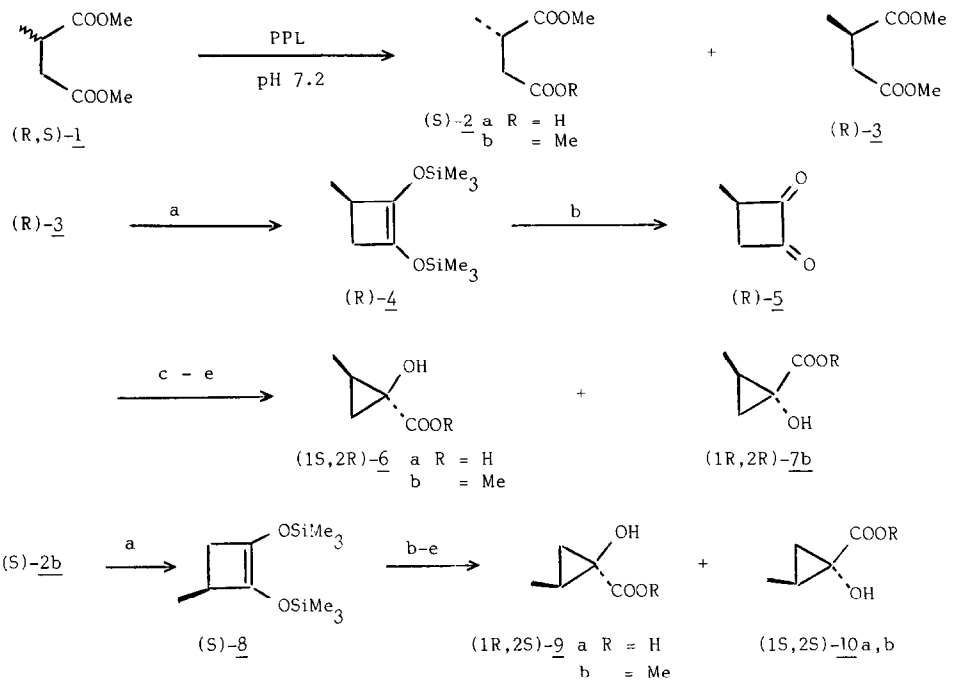
Summary : Enzymatic resolution of dimethyl 2-methylsuccinate, acyloin cyclization and base induced ring contraction provided 1-hydroxycyclopropanecarboxylic acids with high optical purity (>95% e.e). Their derivatives opened a regio- and stereoselective way to optically active 2-vinylcyclobutanones (>84-90% e.e), providing useful building blocks for further ring expansions.

Recent reports have pointed out the synthetic potential of 2-vinylcyclobutanones. Effectively these versatile building blocks can undergo either $C_4 \rightarrow C_5$ (1-5), $C_4 \rightarrow C_6$ (1,6-8) or $C_4 \rightarrow C_8$ (9) ring expansions leading to five, six or eight membered-ring derivatives in acid, base, thermally or photolyticly induced ring rearrangements (10) ; while, ring opening reactions led to functionalized acyclic fragments (1,3,6,11). These challenging synthons are now available from the $C_3 \rightarrow C_4$ acid induced ring expansion of 1-arylthio- (12), 1-alkoxy-(8,13-15) and 1-hydroxycyclopropylvinylcarbinols (12,16) or from the cycloaddition of vinylketenes to simple olefins (6,11). We report in this paper the first preparation of optically active 2-vinylcyclobutanones from the regio- and stereospecific trifluoroborane-etherate (BF_3-Et_2O) induced ring expansion of cyclopropylvinylcarbinols and some subsequent ring rearrangements.

Preparation of (1S,2R) and (1R,2S) methyl 1-hydroxy-2-methylcyclopropanecarboxylates

We have previously shown that methyl 1-hydroxycyclopropanecarboxylate, readily available from methyl succinate, provided a convenient keystone for the construction of naturally occurring cyclopentanoid compounds such as jasmonoïd, spirovetivane, dicranenone and methylenomycin B derivatives (2,16,17). So, it appeared worthwhile to test this approach for the preparation of optically active cyclopropane derivatives. As a matter of fact, it was interesting to check if the chirality was retained or not during the initial cyclization step of optically active succinates such as (S)-2b or (R)-3 and also during the base induced ring contraction of the intermediate 3-methyl 1,2-cyclobutanedione (R)-5, for instance (Scheme I). First of all, this study required chiral succinates with high optical purity. Besides the asymmetric reduction of itaconic acid with cationic rhodium complexes (18), the stereospecific alkylation of either (R) ethyl malate or dimenthyl succinate (19), we found that the enantioselective hydrolysis of racemic diesters by porcine pancreatic lipase (PPL) provided the more convenient and cheap way to both (R) and (S) dimethyl 2-methylsuccinate (20).

Thus on preparative scale, racemic dimethyl 2-methylsuccinate 1 (0.25 mole) upon treatment with PPL (7 g) in buffered water maintained at pH 7.2, underwent regio- and enantioselective hydrolysis to yield the sodium salt of the half-ester (S)-2a and the unhydrolyzed ester (R)-3, which was readily extracted with ether. Acidification of the aqueous phase provided the half-ester 2a which was esterified with methanol ($SOCl_2$, reflux) ; then, a second PPL hydrolysis led, after esterification, to the dimethyl 2-methylsuccinate (S)-2b. The enantiomeric excesses, determined by analysis of the splitting of the methyl ester signals of (S)-2b and (R)-3, comparatively to the racemic succinate 1, on 250 MHz ^1H n.m.r. by using a chiral shift reagent ($Eu(hfc)_3$) (21) was superior to 96%.



Scheme I : Preparation of methyl 1-hydroxy 2-methylcyclopropanecarboxylates (1S,2R)-6b and (1R,2S)-9b.

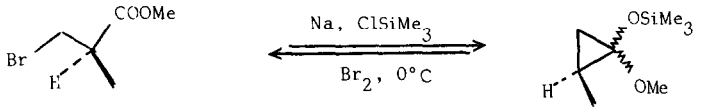
a) $NaClSiMe_3$, toluene, reflux, 78-82% ; b) Br_2, pentane, -50°C ; c) 2M NaOH, 0°C ; d) 10% HCl, ether, 95% ; e) MeOH, $SOCl_2$, reflux 88-92%.

Acyloin type cyclization of (R)-3 by sodium in the presence of trimethylchlorosilane (22) provided the 3-methyl 1,2-disiloxycyclobutene (R)-4 in 78% yield. Bromination of (R)-4 at -20°C in CCl_4 gave the unstable 3-methyl-1,2 cyclobutanedione (R)-5 ; on the other hand, successive addition of bromine (1 equiv.) to a solution of (R)-4 in pentane at -50°C and of a 2M NaOH aqueous solution at 0°C provided, after acidification (2M HCl), directly the (1S,2R) 1-hydroxy-2-methylcyclopropanecarboxylic acid 6a in 95% yield (23).

Esterification (MeOH, $SOCl_2$, reflux) of 6a gave the methyl hydroxyester (1S,2R)-6b in 98% yield, containing $\leq$ 5% of the diastereoisomer (1R,2R)-7b, as evidenced from chromatographic and spectroscopic data (e.g. two methyl ester singlets at δ 3.74 and 3.79 ppm, ratio 95:5) (23). It has been checked that, on heating 6a in acidic methanol ($SOCl_2$, reflux, 5 days) 7b was not a product of isomerization of 6b. Futhermore recrystallization of the acid (1S,2R)-6a led, after esterification, to the stereochemically pure methyl ester 6b .

In the same way, sodium induced cyclization of succinate (S)-2b gave the 3-methyl-1,2-disiloxycyclobutene (S)-8 and after one pot bromination and base induced ring contraction led to a mixture of hydroxyacid (1R,2S)-9a and (1S,2S)-10a (ratio 96:4). Esterification of this mixture (MeOH, $SOCl_2$, reflux) which was not separated by recrystallization, provided the corresponding methyl esters (1R,2S)-9b and (1S,2S)-10b (ratio 96:4). The enantiomeric excesses of (1S,2R)-6b and (1R,2S)-9b, determined by analysis of the splitting of their methyl ester signals on ^1H n.m.r. spectra recorded in the presence of $Eu(hfc)_3$ (21), comparatively to the racemic methyl 1-hydroxy 2-methylcyclopropylcarboxylate analogously prepared from (R,S)-1 was superior to 97 and 95%, respectively.

Therefore, as expected the chirality of the stereocenter was not affected during the sodium induced acyloin cyclization of the enolizable α-methylsuccinates (S)-2b and (R)-3 as well as during the subsequent base induced $C_4 \rightarrow C_3$ ring contraction.



(S)-11 (R or S)-12

Such a comparable stability of the chiral center has been recently observed for the sodium induced cyclization of the methyl β-bromoisobutyrate (S)-11. Thus, the reductive transformation led to a 1:1 diastereoisomeric mixture of cyclopropanols 12 which, upon bromination at 0°C were then transformed back to the starting bromide (S)-11, without loss of optical purity (24).

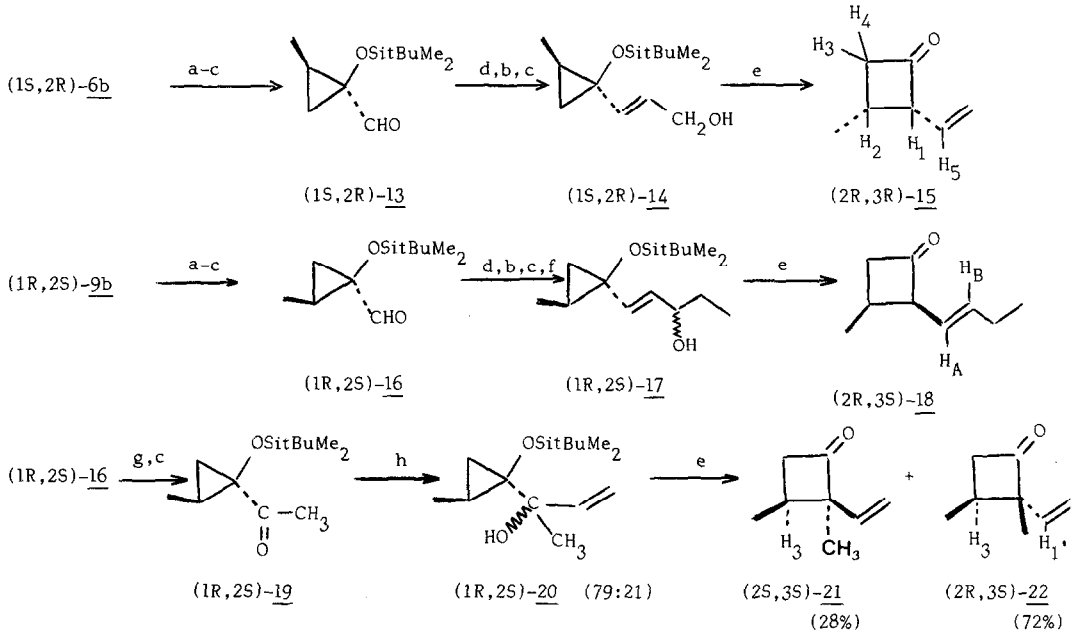
It must be underlined that attempted chemical resolution of the corresponding racemic hydroxyacid with (R) α-methylbenzylamine (25) or enzymatic resolution with PLE as reported for chrysanthemic acids (26) or with PPL (20) did not provide 6a and 9a with such high optical purities.

Regio- and stereospecific trifluoroborane-etherate induced ring expansion of chiral cyclopropylvinylcarbinols

O-silylation of the hydroxyester (1S,2R)-6b with t-butyldimethylchlorosilane in DMF containing imidazole (2 equiv.) (27), then reduction of the ester with diisobutylaluminum hydride (DIBAH) in toluene at -78°C followed by Swern oxidation with oxalyl chloride activated DMSO (28) led to the 1-t-butyldimethylsiloxy-2-methylcyclopropanecarboxaldehyde (1S,2R)-13 in 84% overall yield. Wittig-Horner reaction with methyl dimethoxyphosphonoacetate (n-BuLi, THF) gave, after reduction with DIBAH in toluene at -78°C, the E-cyclopropylvinylcarbinol (1S,2R)-14 in 86% overall yield. Addition of a catalytic amount of trifluoroborane-etherate (BF_3-Et_2O) to a solution of (1S,2R)-14 in CH_2Cl_2 for 60 min. provided mainly the optically active 3-methyl-2-vinylcyclobutanone (2R,3R)-15 ($[\alpha]_D$ = +74° c 1.98, CH_2Cl_2) in 80% yield (Scheme II). The regio- and stereoselectivity of this $C_3 \rightarrow C_4$ ring expansion was evidenced by the geminal coupling constant of the α-methylenic protons (J_{H3H4} = 17.15 Hz) (29) and by the presence of two methyl doublets at δ1.15 and 1.38 ppm (ratio 95:5) in the n.m.r. spectra of crude 15. The cis stereochemistry of pure 15 isolated by g.c., proven by the occurrence of two cis (J_{H2H4} = 9.15 and J_{H2H1} = 9.33 Hz), and one trans (J_{H3H2} = 4.22 Hz) vicinal coupling constants was confirmed by nuclear Overhauser effect ; thus, irradiation of the 3-methyl signal at δ1.15 ppm enhanced the signal area of the H_5 vinylic proton signal at 5.72 ppm by 12.5%.

In the same way, O-silylation of the hydroxyester (1R,2S)-9b (ClSitBuMe$_2$, imidazole, DMF) (27) then reduction of the ester (DIBAH, THF, -78°C) and Swern oxidation (DMSO-$(COCl)_2$, NEt_3) (28) provided in 89% overall yield the 1-t-butyldimethylsiloxy-2-methyl-cyclopropanecarboxaldehyde (1R,2S)-16. Two aldehydic protons at δ 9.0 and 9.4 ppm (ratio 96:4) in the n.m.r. spectra of crude 16 evidenced also the presence of the (1S,2S) stereoisomer. Addition of the methyl dimethoxyphosphonoacetate carbanion in THF to (1R,2S)-16, reduction (DIBAH, toluene, -78°C), oxidation (DMSO-$(COCl)_2$, NEt_3, -60°C) (28) and addition of ethylmagnesium bromide in ether to the resulting allylic aldehyde led to the isomeric E 1-(1-t-butyldimethylsiloxy-2-methylcyclopropyl) pent-1-en-3-ols (1R,2S)-17 in 78% overall yield from 16. On addition of a catalytic amount of BF_3-Et_2O the cyclopropylvinylcarbinols (1R,2S)-17 in CH_2Cl_2 underwent within 5 mn as monitored by t.l.c., total $C_3 \rightarrow C_4$ ring expansion into the optically active E-2-(but-1-enyl)-3-methyl cyclobutanone (2R,3S)-18 (J_{HAHB} = 16 Hz, $[\alpha]_D$ = -62° c 2.0, CCl_4). Two methyl doublets at δ 1.18 and 1.35 ppm (ratio 95:5) as well as gas chromatography and mass spectroscopy analysis evidenced again the formation of one major stereoisomer. The cis stereochemistry of 18, readily isolated by g.c. was, comparatively to the stereochemistry of (2R,3R)-15, determined from the vicinal coupling constants of the four-membered ring protons, and confirmed chemically (vide infra).

On the other hand, addition of methylmagnesium iodide to the aldehyde (1R,2S)-16 in ether and Swern ovidation (DMSO-$(COCl)_2$, NEt_3, -60°C) (28) yielded the cyclopropylmethylketone (1R,2S)-19 which was treated with a 1 M solution of vinylmagnesium-bromide in THF at 65°C for 5 hr to provide in 78% yield the isomeric 3-(1-t-butyldimethylsiloxy-2-methylcyclopropyl) but-1-en-3-ols 20 (ratio 79/21).



Scheme II : Preparation of optically active 2-vinylcyclobutanones.

a) $ClSitBuMe_3$, imidazole, DMF, 35°C, 96% ; b) DIBAH, toluene, -78°C ; c) DMSO-$(COCl)_2$, -60°, NEt_3 ; d) $(MeO)_2P(O)CH_3COOCH_3$, n-BuLi, THF, r.t. ; e) BF_3-Et_2O, CH_2Cl_2, r.t. ; f) EtMgBr, Et_2O, reflux ; g) CH_3MgI, Et_2O, r.t. ; h) CH_2=CHMgBr, THF, 65°C.

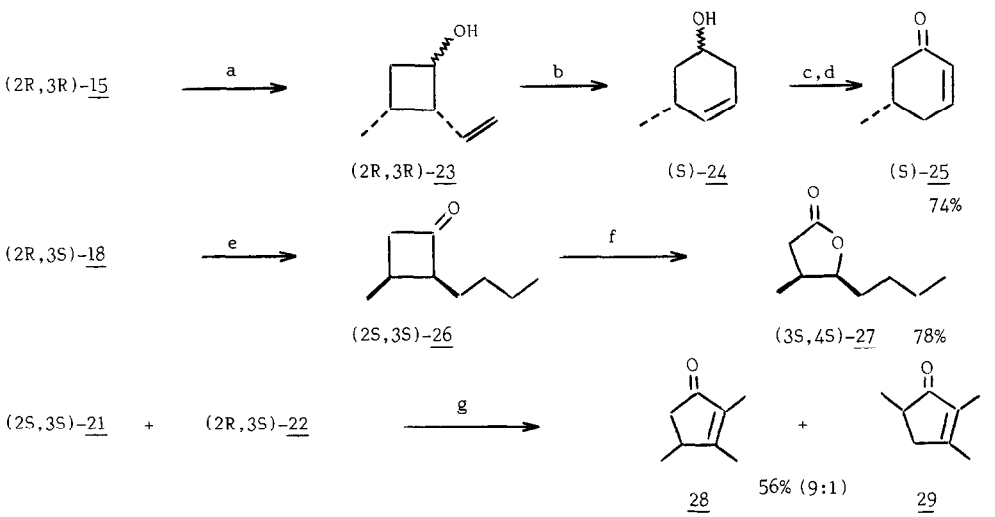
Upon addition of a catalytic amount of BF_3-Et_2O, allylic alcohols 20 in methylenechloride underwent total $C_3 \rightarrow C_4$ ring expansion within 15 mn as monitored by t.l.c. into the stereoisomeric mixture of 2,3-dimethyl-2-vinyl cyclobutanone (2S,3S)-21 and (2R,3S)-22 ($[\alpha]_D$ = +22°, c 1, $HCCl_3$), which have not been isolated. Taking into account the spectroscopic data observed in many other related systems (11), the stereochemistry of the major isomer (72%), characterized by the fact that the ^1H n.m.r. singulet of its α-methyl protons appeared at higher fields ($\Delta\delta$= +0.15 ppm) and the signals of its 3-H and vinylic H-C (1') protons at lower field ($\Delta\delta$= -0.26 and -0.12 ppm, respectively) as compared to the corresponding signals of the minor stereoisomer (28%) was assumed to be trans, i.e., (2R,3S)-22. Moreover, the enantiomeric excesses determined by analysis of the splitting of the α-methyl signals of 21 and 22 on ^1H n.m.r. spectra (250 MHz, Eu(hfc)3), comparatively to the corresponding racemic ketones, was superior to 84%.

Applications to the preparations of (S)-5-methyl cyclohex-2-one, cis 4-butanolide and cyclopentenones

Lithiumaluminum hydride reduction of 3-methyl-2-vinyl cyclobutanone (2R,3R)-15 in ether gave the isomeric cyclobutanols (2R,3R)-23 (ratio 63:37) in 94% yield. Upon treatment with potassium hydride in THF at reflux cyclobutanols (2R,3R)-23 underwent total $C_4 \rightarrow C_6$ ring enlargement (7) into the 5-methyl cyclohex-3-en-1 ols S-24, within one hour as monitored by t.l.c. and g.c. Then, oxidation with Jones reagent in acetone and treatment of the crude resulting enone with basic activity 3 alumina in ether-pentane (5:95) yielded the 5-methyl cyclohex-2-en-1-one (S)-25 ($[\alpha]_D$ = +81°, c 1.04, $HCCl_3$) in 74% yield from 23. Comparison with the enantiomeric (R)(-)-5-methyl cyclohex-2-en-1-one ($[\alpha]_D$ = -90°, c 2.55, $HCCl_3$) prepared from (R) (+) Pulegone (30) has confirmed the configuration and optical purity (90% ee) of (S)-25 and therefore of the cyclobutanone (2R,3R)-15 (31).

Reduction of pure 2-vinylcyclobutanone (2R,3S)-18 catalyzed by palladium on charcoal in ethyl acetate led with partial isomerization to a mixture of 2-butyl-3-methyl cyclobutanone (2S,3S)-26 and its (2R,3S)-diastereoisomer (ratio 90:10) in 89% yield ; while attempted reduction of 18 catalyzed by platine

oxide yielded, besides the expected cyclobutanone 26 (γC=O 1775 cm^{-1}), rearranged product (γC=O = 1715 cm^{-1}) (ratio 63:37). Then, ketone (2S,3S)-26 purified by gas chromatography, underwent Baeyer-Villiger oxidation (MCPBA, CH_2Cl_2, 0°C) to provide the 4-butyl-3-methyl butanolide (3S,4S)-27 (Quercus lactone b) exclusively, as clearly evidenced from the n.m.r. spectra of the crude product characterized by a methyl doublet at δ 1.01 ppm and a C_4 proton multiplet at 4.44 ppm (32). As a matter of fact, the (3S,4R) stereoisomer of 27 (Quercus lactone a), recently prepared from the trans 1,4-addition of lithium dimethyl cuprate to (R)-4-alkylbut-2-enolides (33), showed a methyl doublet at δ 1.14 and a C_4 proton multiplet at 4.01 ppm (32). The Baeyer-Villiger oxidation of 2-alkylcyclobutanones is known to occur with retention of configuration (34), therefore the exclusive formation of the γ-lactone (3S,4S)-27 confirmed the cis stereochemistry of the cyclobutanone 26. The optical rotation of 27 ($[\alpha]_D$ = -78°, c 1, MeOH) comparatively to reported data ($[\alpha]_D$ = -87°) (35) and n.m.r. chemical shift experiments with chiral lanthanide ($Eu(hfc)_3$) proved that the chirality (90% ee) was retained during all these rearrangements. Quercus lactones a and b, found in wines and spirits kept in oak barrels for maturing (32) have been isolated from white oak wood with the ratio 6.5:93.5, respectively (35) ; thus this sequence provided the main natural stereoisomer.



Scheme III : Ring expansions of the 2-vinylcyclobutanones.

a) $LiAlH_4$, ether, reflux, 94% ; b) KH, THF, reflux ; c) CrO_3, H_2SO_4, acetone, 98% ; d) Al_2O_3, ether-pentane 10:90 ; e) H_2, Pd/C, AcOEt ; f) MCPBA, CH_2Cl_2, 0°C, 86% ; g) CH_3SO_3H.

On the other hand, upon treatment with 15 mol-equiv. of methanesulfonic acid neat at room temperature or with 30 mol-equiv. of methanesulfonic acid in CH_2Cl_2 the 2,3-dimethyl-2-vinyl cyclobutanones (2S,3S)-21 and (2R,3S)-22 underwent acid catalysed $C_4 \rightarrow C_5$ ring expansion (1,4,5) into a 90:10 mixture of 2,3,4- and 2,3,5-trimethylcyclopentenones 28 and 29 in 40-56% yields. Unfortunately this rearrangement which required severe acid conditions led to the racemization of the chiral center as shown by the zero value of the optical rotation of cyclopentenones 28 and 29 and by the splitting in two equal signals of the α-methyl singlet on the n.m.r. spectra of cyclopentenone 29 recorded in the presence of 50% $Eu(hfc)_3$ ($\Delta\delta$ = 0.03 ppm).

Discussion

It has been previously reported that 2-methyl-1-vinylcyclopropanol underwent non-regio- and non-stereoselective $C_3 \rightarrow C_4$ ring expansion in sulfuric acid to provide a mixture of 2,4-trans (4%), 2,4-cis (26%), 2,3-trans (24%) and 2,3-cis (46%) dimethylcyclobutanones, while upon treatment with hydrogen bromide in CH_2Cl_2 a 25:75 mixture of cis and trans 2,3-dimethylcyclobutanones was obtained (36). Although preferred migration of the more substituted cyclopropane bond occurred generally in such rearrangements (10), the stereoselectivity of the ring expansion of the cyclopropylvinylcarbinols 14, 17 and 20 was however noteworthy. The conservation of the stereogenic center (>84-90% e.e) strengthened the proposal that in such mild medium (e.g., BF_3-Et_2O in CH_2Cl_2) carbenium ions, i.e., cyclopropylvinylcarbinyl cations were likely not involved. On the other hand, the optically active 2-vinylcyclobutanones 21 and 22 underwent acid induced C_4-C_5 ring expansion, likely as suggested via the intermediacy of reversible cyclopropylvinylcarbinyl cations (5), however the required acidic conditions for the rearrangement entailed, unfortunately, complete racemization of the stereogenic center.

EXPERIMENTAL

Dimethyl 2-methylsuccinate (S)-2b and (R)-3

In a 500 ml erlenmeyer fitted with an automatic burette and a pH-meter was stirred at r.t. a suspension of 40 g (250 mmol) of dimethyl 2-methylsuccinate (R,S)-1 in 300 ml of a buffered (pH 7.2) aq. 0.1 M KH_2PO_4 solution containing 7 g of porcine pancreatic lipase (PPL ; E.C. 3.1.1.3). The pH was maintained at 7.2 by the addition of 2 M NaOH ; when 0.55 equiv. of NaOH was consumed, the mixture was filtered through celite and extracted by 3 x 250 ml of ether. The organic phase was dried over Na_2SO_4 and concentrated on a rotary evaporator. The residue was distilled (b.p. 77.5°C (15 mm)) to give 18.6 g (93%) of dimethyl 2-methylsuccinate (R)-3 ($[\alpha]_D$ = +4.75° c 2.9 $CHCl_3$).

The aqueous phase was acidified to pH 2 then continuously extracted with ether for 36 hr. The organic phase, dried over Na_2SO_4, was concentrated and distilled (b.p. 90° (0.05 mm)) to yield 13.8 g (76%) of the half-ester (S)-2a ($[\alpha]_D$ = -7.6° c 2 $HCCl_3$). To a solution of 13 g (89 mmol) of (S)-2a in 120 ml of methanol was added 0.5 ml de $SOCl_2$ and the mixture was refluxed for 20 h. Then, the solution was concentrated on a rotary evaporator, diluted with 100 ml of ether washed with aq. 10% $NaHCO_3$ and saturated NaCl dried over Na_2SO_4 and contracted in vacuum. The residue was distilled (b.p. 90°/20 mmHg) to give 13.6 g (95%) of dimethyl 2-methylsuccinate (S)-2b. A solution of 13 g of this diester (S)-2b in 100 ml of buffered water was hydrolyzed once more with 4 g of PPL to yield after acidification and distillation 10.6 g (90%) the half ester (S)-2a ($[\alpha]_D$ = -10° c 2.5, $HCCl_3$; Litt., $[\alpha]_D$ = -9.3°c 17.5 $HCCl_3$ (37)). Esterification by methanol ($SOCl_2$) in the same way, gave the diester (S)-2b $[\alpha]_D$ = -4.9°c 2.9 $HCCl_3$.

Determination of the enantiomeric excess

On addition of 0.3 equiv. of Eu(hfc)3 to solutions of 10 mg of dimethyl 2-methylsuccinates in $CDCl_3$, downfield shift ($\Delta\delta$ = 1.5 ppm) and splitting ($\Delta\delta$ = 0.07 ppm) occurred on the 250 MHz n.m.r. ^1H methyl ester signals with the ratios 50:50 (for racemic 1), 2.5:97.5 (for (R)-3) and 98.6:1.4 (for (S)-2b).

3-Methyl 1,2-bis(trimethylsiloxy)-1-cyclobutene (R)-4

To a suspension of 8.05 g (0.35 g.atom) of finely pulverized sodium in 70 ml of anhydrous toluene was added dropwise at 100°C a solution of 14 g (87.5 mmol.) of $ClSiMe_3$. The mixture was refluxed for 6 h and then filtered through sintered glass funnel under a stream of dry nitrogen. The colorless filtrate was transferred to a distilling flask and distillered through a 2.5 cm vacuum jacketed vigreux column to yield 17.5 g (82%) of (R)-4 (b.p. 34-36°C (0.1 mm)) $[\alpha]_D$ = +21° c 2.78 CCl_4 ; IR (CCl_4) (cm^{-1}) : 1720 γ(C=C) ; NMR ^1H ($CDCl_3$, 90 MHz) δ(ppm) : 0.20 (s, 18H), 1.07 (d, J = 6.5 Hz, 3H), 1.6 (m, 1H), 2.27 - 2.45 (m, 2H) ; MS: m/e (rel. int.) : 244 (M^+, 35.2), 171 (13), 129 (2), 73 (100). Anal. calcd for $C_{11}H_{24}O_2Si_2$: C 54.04, H 9.89, Si 22.97. Found : C 53.9, H 9.81, Si 23.04.

3-Methyl 1,2-cyclobutanedione (R)-5

To a suspension of 0.5 g (2 mmol.) of (R)-4 in CCl_4 at -20°C was added dropwise a solution of Br_2 (2 mmol.) in CCl_4 (2 ml). The solution was warmed to r.t. and the solvent evaporated under vacuo (0.1 mm) to yield the dione 5 as a viscous orange-yellow instable liquid. IR (CCl_4) (cm^{-1}) : 1800 and 1775 (γ C=O) ; NMR (250 MHz) ^1H (CCl_4) δ (ppm) : 1.25 (d, J = 7.3 Hz, 3H), 2.67 (ddd, J = 17 Hz, J' = 8 Hz, J'' = 3.2 Hz, 2H), 3-5 (m, 1H) ; MS : m/e (rel. int.) : 98 (M^+, 1.3), 70 (10.6), 56 (2.7), 42 (19).

1-Hydroxy-2-methylcyclopropanecarboxylic acid (1S,2R)-6a

To a solution of 41.2 g (168 mmol.) of (R)-4 in 150 ml of pentane at -50°C was added dropwise 27 g (168 mmol) of bromine. When the addition was over, the mixture was stirred at r.t. for 1 hr then was added 200 ml of a 2 M NaOH solution at 0°C. The mixture was extracted with 3 x 150 ml of ether. The aqueous phase was acidified to pH 1 with 2 N HCl and continuously extracted with ether to yield 18.6 g (95%) of hydroxyacid (1S,2R)-6a.

The crude product ($[\alpha]_D$ = -54° c 1.6 $HCCl_3$) was recrystallized in ether-hexane to yield pure (1S,2R)-6a : ($[\alpha]_D$ = -57° m.p. = 75°C (Litt., (23) m.p. racemic : 64-66°C). NMR (250 MHz) ^1H ($CDCl_3$) δ(ppm) : 0.65 - 0.80 (m, 1H), 1.1 (d, J = 6.3 Hz), 1.4 - 1.6 (m, 2H), 7.85 (s, 2H).

Methyl 1-hydroxy-2-methylcyclopropanecarboxylate (1S,2R-6b

To 18 g of hydroxyacid (1S,2R)-6a in 150 ml of methanol was added 0.5 ml of $SOCl_2$ and the solution was refluxed for 18 h. The solvent was removed on a rotary evaporator, and 150 ml of ether were added. The organic phase was washed with 10% HCO_3Na, with saturated NaCl dried over Na_2SO_4 and concentrated. The residue was distillated (b.p. 78°C (13 mm) to yield 17.8 g (88%) of (1S,2R)-6b. $[\alpha]_D$ = -34° c 2.7 CCl_4. IR (CCl_4) (cm^{-1}) : 1730 (γC=O) ; N.M.R. (250 MHz) ^1H ($CDCl_3$) δ ppm : 0.75 (m, 1H), 1.22 (d, J = 6.25 Hz, 3H), 1.48 (m, 2H), 2.90 (m, 1H), 3.74 (s, 3H) ; M.S. : m/e (rel. int.) : 130 (M^+, 29.5), 70 (100), 42 (71). Anal. calcd for $C_6H_{10}O_3$: C 55.35, H 7.75. Found : C 55.47, H 7.69.

Enantiomeric excess : shift ($\Delta\delta$= 1.85 ppm) and splitting ($\Delta\delta$= 0.12 ppm) of the methyl ester signal on ^1H n.m.r. (250 MHz) (recorded in the presence of 0.4 equiv. of Eu(hfc)3 (ratio 98.4 : 1.6).

3-Methyl-1,2-bis(trimethylsiloxy)-1-cyclobutene (S)-8

Analogously to (R)-4, (S)-8 was prepared from 21.6 g (135 mmol.) of 2-methylsuccinate (S)-2b $[\alpha]_D$ = -22° c 2.82 CCl_4.

1-Hydroxy-2-methylcyclopropanecarboxylic acid (1R,2S)-9a

Analogously to 6a, the hydroxyacid (1R,2S)-9a was prepared from 20.2 g (82.8 mmol.) of the cyclobutene (S)-8 (97% yield).

Attempted recrystallizations of 9a have failed $[\alpha]_D$ = +42° c 2.58 $CHCl_3$.

Methyl 1-hydroxy-2-methylcyclopropanecarboxylate (1R,2S)-9b

Analogously to 6a, 7.3 g (63 mmol.) of hydroxyacid (1R,2S)-9a were esterified by methanol ($SOCl_2$) to yield 6 g (74%) of the methyl ester (1R,2S)-9b. $[\alpha]_D$ = +35.5° c 3.42 CCl_4. N.M.R. (250 MHz) ^1H ($CDCl_3$) δ (ppm) : 0.72 - 0.78 (m, 1H), 1.18 (d, J = 6.3 Hz), 1.40 - 1.60 (m, 2H), 2.89 (m, 1H), 3.75 (s, 2.88 H) and 3.80 (s, 0.12 H).

Enantiomeric excess : shift ($\Delta\delta$= 2.45 ppm) and splitting of the methyl ester signal ($\Delta\delta$= 0.13 ppm) (^1H n.m.r. 250 MHz, 0.4 equiv. Eu(hfc)3, ratio 2.9 : 97.1). Anal. calcd for $C_6H_{10}O_3$: C 55.35, H 57.75. Found : C 55.41, H 7.83.

1-t-butyldimethylsiloxy 2-methylcyclopropanecarboxaldehyde (1S,2R)-13

A solution of 5 g (38.5 mmol.) of hydroxyester (1S,2R)-6b, 6.8 g (45 mmol.) of t-butyldimethylsilyl-chloride and 6.35 g (93 mmol.) of imidazole in 50 ml of DMF was stirred at 35°C. When the reaction was over (t.l.c.) the solution was cooled to r.t., 200 ml of ether were added and the organic phase was washed with 3 x 100 ml of saturated NaCl and dried over Na_2SO_4. The solvents were removed on a rotary evaporator and the residue chromatographed on silica (ether/hexane ; 20/80) to yield 9.1 g (97%) of methyl 1-t-butyldimethylsiloxy 2-methylcyclopropylcarboxylate $[\alpha]_D$ = -19.5°, c 2.33, CCl_4. IR (CCl_4) (cm^{-1}) : 1740 (γC=O) ; N.M.R. (90 MHz) ^1H (CCl_4) δ (ppm) : 0 (s, 3H), 0.15 (s, 3H), 0.85 (s, 9H), 1.25 (m, 6H), 3.6 (s, 3H). M.S. m/e (rel. int.) : 244 (M= 1.7), 187 (100), 129 (10). Anal. calcd for $C_{12}H_{18}O_2Si$: C 58.97, H 9.89, Si 11.49. Found : C 59.22, H 9.89, Si 10.90.

To a solution of 8.15 g (33 mol.) of this ester in 80 ml of anhydrous toluene at -70°C were added dropwise 67 ml of 1 M solution of DIBAH in toluene. When the addition was over, the mixture was stirred at -70°C for 1 h., then were added 25 ml of MeOH. The mixture was allowed to warm to r.t., filtered through a sintered glass and concentrated on a rotary evaporator to yield 6.3 g (88%) of 1-t-butyldimethylsiloxy 2-methylcyclopropylcarbinol $[\alpha]_D$ = +23°, c 4, CCl_4. IR (CCl_4) (cm^{-1}) : 3620, 3430 (γOH) ; N.M.R. (250 MHz) ^1H ($CDCl_3$) 0.12 (s, 3H), 0.18 (s, 3H), 0.35 (m, 1H), 0.70 - 0.90 (m, 2H), 0.95 (s, 9H), 1.15 (d, J = 6.5 Hz, 3H), 1.8 (m, 1H), 3.25 (d, J = 12.82 Hz, 1H), 3.80 (d, J = 12.8 Hz, 1H). M.S. m/e (rel. int.) : 201 (0.5), 185 (6), 159 (76), 101 (4).

To a stirred solution of 2.3 ml (25 mmol.) of oxalylchloride in 70 ml CH_2Cl_2 at -60°C was added dropwise of solution of 3.86 ml of DMSO in 10 ml of CH_2Cl_2. The mixture was stirred for 2 mn and a solution of 4.1 g (19 mmol.) of the cyclopropylcarbinol in 30 ml of CH_2Cl_2 was added within 5 mn and stirring was continued for an additional 15 mn. Then 20 ml (142 mmol.) of NEt_3 were added and the reaction mixture was stirred at -60°C for 5 mn and allowed to warm to room temperature. Water (100 ml) was added and the aqueous layer was extracted twice with 100 ml of CH_2Cl_2. The combined organic layers were washed with 100 ml of saturated NaCl and dried over Na_2SO_4. T.l.c. of an aliquot showed the formation of a

single product. The solution was concentrated in vacuo, the residue was filtered on celite to yield 4 g (98%) of the aldehyde (1S,2R)-13. $[\alpha]_D$ = -44°, c 2.1, $CHCl_3$. IR (CCl_4) (cm^{-1}) : 1720 ($\gamma C=O$) ; N.M.R. (250 MHz) ^1H ($CDCl_3$) δ(ppm) : 0.0 (s, 3H), 0.25 (s, 3H), 0.5 (m, 1H), 0.9 (s, 9H), 1.0 (m, 2H), 1.10 (d, J = 6 Hz, 3H), 9.0 (s, 1H).

3-(1-t-Butyldimethylsiloxy-2-methylcyclopropyl) prop-2-en-1-ol (1S,2R)-14

To a solution of 4.55 g (25 mmol.) of methyl dimethoxyphosphonoacetate in 70 ml of THF at 0°C was added 15 ml of 1.6 N solution (24 mmol.) of n-BuLi. The mixture was stirred at r.t. for 1 h. and cooled to -78°C. Then, was added dropwise a solution of 4.06 g (19 mmol.) of the aldehyde (1S,2R)-13 in 20 ml of THF. The mixture was stirred at r.t. overnight, and the solvent removed in vacuo. The residue was chromatographed on silica (hexane-ether : 90/10) to yield 4.9 g (95%) of E methyl 3-(1-t-butyldimethylsiloxy-2 methyl cyclopropyl) prop-2-enoate $[\alpha]_D$ = -24.5°, c 2, CCl_4. IR (CCl_4) (cm^{-1}) : 1725 ($\gamma C=O$), 1650 ($\gamma C=C$) ; N.M.R. (250 MHz) ^1H ($CDCl_3$) δ(ppm) : 0.05 (s, 3H), 0.18 (s, 3H), 0.78 (m, 1H), 0.9 (s, 9H), 1.1 (m, 3H), 1.4 (m, 2H), 3.6 (s, 3H), 5.8 (d, J = 16 Hz), 6.5 (d, J = 16 Hz). M.S. m/e (rel. int.) : 270 (M^+, 1.3), 213 (26), 211 (87), 73 (100), 59 (21). Anal. calcd for $C_{14}H_{26}O_3Si$: C 62.17, H 9.69. Found : C 61.96, H 9.55.

To a solution of 4.8 g (17.7 mmol.) of this ester in 50 ml of toluene at -78°C was added dropwise 53 ml of 1 M DIBAH solution in toluene. When the addition was over, the mixture was stirred at -70°C for 1 h. and then 25 ml of MeOH were added. The mixture was allowed to warm to r.t. Filtration through a sintered glass and concentration in vacuo yield 3.9 g (90%) of the allylic alcohol (1S,2R)-14. $[\alpha]_D$ = -6.3°, c 1.6, CCl_4. IR ($CDCl_3$) (cm^{-1}) : 3630, 3440 (γOH), 1605 ($\gamma C=C$) ; N.M.R. (250 MHz) ^1H ($CDCl_3$) δ(ppm) : 0.1 (s, 3H), 0.15 (s, 3H), 0.55 - 0.7 (m, 1H), 0.92 (s, 9H, 1.15 (d, J = 6 Hz, 3H), 1.15 (m, 2H), 1.6 (s, 1 H), 4.12 (d, J = 7 Hz, 2H), 5.35 - 5.90 (m, 2H) ; M.S. m/e (rel. int.) : 242 (M^+, 1.9), 212 (22), 575 (100).

3-Methyl-2-vinylcyclobutanone (2R,3S)-15

To a solution of 1.08 g (4.46 mmol.) of allylic alcohol (1S,2R)-14 in 5 ml of CH_2Cl_2 was added 50 µl of BF_3-Et_2O. The reaction was over within 1 h. as monitored by t.l.c. Then, the solution was washed with 5% $NaHCO_3$ saturated NaCl and dried over Na_2SO_4. The solvent was removed in vacuo. Analysis of the residue (G.C. + M.S.) showed formation of two isomers (ratio 95:5). The main product was isolated by preparative g.c. (SE 30 20%, 3 m, 80°C) to yield 327 mg (67%) of the cyclobutanone (2R,3R)-15. $[\alpha]_D$ = +74°, c 1.98, CH_2Cl_2. IR ($CDCl_3$) (cm^{-1}) : 1780 ($\gamma C=O$), 1640 ($\gamma C=C$) ; N.M.R. (250 MHz) ^1H ($CDCl_3$) δ(ppm) : 1.15 (d, J = 7 Hz, 3H), 2.50 (ddd, ^2J = 17.15 Hz, ^3J trans = 4.22 Hz, ^4Jtrans 2.2, 1 H), 2.72 (m, 1H), 3.25 (ddd, ^2J = 17.15 Hz, ^3Jcis = 9.15 Hz, ^4Jtrans = 2.8 Hz, 1H), 3.98 (m, 1H), 5.25 (m, 2H), 5.72 (m, 1H). Upon irradiation of the methyl doublet at 1.15 ppm, the multiplet at 2.72 ppm was transformed into a ddd signal (J = 9.33, 9.15 and 4.23 Hz) ; and the area of the signal at 5.72 ppm was enhanced by 12.5% (NOE). NMR ^{13}C ($CDCl_3$, 62 MHz) δ (ppm) : 18 (CH_3), 23.5 (βC), 52.5 (αC), 65.4 (αC), 119.5 and 130 (ethylenic C), 208 (C=O) ; M.S. m/e (rel. int.) : 110 (M^+ 1.6), 82 (7), 68 (100), 42 (10). HRMS : calc. 110.0731 ; found : 110.0728.

1-t-Butyldimethylsiloxy 2-methylcyclopropanecarboxaldehyde (1R,2S)-16

Analogously to the preparation of the aldehyde 13 from hydroxy ester 6b, treatment of 2 g (15.4 mmol.) of hydroxyester 9b with $ClSitBuMe_2$ (18.5 mmol.) and imidazole (38.6 mmol.) in DMF (20 ml) gave 3.56 g (95%) of methyl 1-t-butyldimethylsiloxy 2-methylcyclopropylcarboxylate $[\alpha]_D$ = +19.8°, c 3.25, CCl_4.

A solution of 2.90 g (11.9 mmol.) of this ester in 25 ml of anhydrous toluene at -70°C was treated with 25 ml of 1 M solution of DIBAH to yield 2.28 g (89%) of 1-t-butyldimethylsiloxy 2-methylcyclopropyl-carbinol. $[\alpha]_D$ = -22°, c 4.2, CCl_4. Addition of 1.51 g (7 mmol.) of this alcohol to 1.56 g of DMSO and 1.06 g $(COCl)_2$ in 20 ml of CH_2Cl_2 at -60°, following the procedure reported for 13, gave 1.48 g (98%) of the aldehyde (1R,2S)-16 $[\alpha]_D$ = +43°, c 2, $HCCl_3$, with IR, NMR and MS spectral data similar to those of aldehyde (1S,2R)-13.

E 1-(1-t-Butyldimethylsiloxy 2-methyl) pent-1-en-3-ols 17

To a solution of 1.82 g (10 mmol.) of methyl dimethoxyphosphonoacetate in 25 ml THF were added dropwise at 0°C 5.6 ml of 1.6 M solution (9 mmol.) of n-BuLi. The mixture was stirred at r.t. for 1 hr and cooled to -78°C. Then a solution of 1.45 g (6.95 mmol.) of the aldehyde (1R,2S)-16 in 5 ml of THF was added dropwise, and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed on silica (hexane/ether : 9/1) to yield 1.58 g (86%) of E methyl 3-(1-t-butyldimethylsiloxy-2-methylcyclopropyl) prop-2-enoate. $[\alpha]_D$ = +24.5°C, c 2.95, CCl_4. Anal. calcd for $C_{14}H_{26}O_3Si$: C 62.17, H 9.69. Found : C 62.03, H 9.61.

To a solution of 1.4 g (5.18 mmol.) of this ester in 15 ml of toluene at -70°C was added dropwise 13 ml of 1 M DIBAH solution in toluene. The mixture was stirred at -70°C for 1 h. and then 5 ml of MeOH were added. The mixture was allowed to warm to room temperature, filtration through a sintered glass and concentration in vacuo gave 1.10 g (88%) of 3-(1-t-butyldimethylsiloxy 2-methylcyclopropyl) prop-2-en-1-ol. $[\alpha]_D$ = +6.1°, c 1.57, CCl_4 with IR, NMR and MS spectra data similar to those of the allylic alcohol 14.

To a solution of 0.52 ml (6 mmol.) of oxalyl chloride in 15 ml of CH_2Cl_2 at -60°C was added dropwise a solution of 0.98 ml (15 mmol.) of DMSO in 2.5 ml of CH_2Cl_2. The mixture was stirred for 2 mn and a solution of 1.10 g (4.54 mmol.) of the prop-2-en-1-ol in 8 ml of CH_2Cl_2 was added dropwise. The mixture was stirred at -70°C for 15 mn and then 4 ml of NEt_3 were added. The reaction mixture was allowed to warm to room temperature, and water (15 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 ml). The combined organic layers were washed with 15 ml saturated NaCl solution, dried over Na_2SO_4. Concentration under reduced pressure and filtration through celite yielded 1 g (92% yield) of

3-(1-t-butyldimethylsiloxy 2-methylcyclopropyl) prop-2-en-1-al . $[\alpha]_D$ = +7.4, c 1.77, CCl_4. IR (CCl_4) (cm^{-1}) : 1690 (γC-O), 1640 (γC=C) ; NMR (250 MHz) ^1H ($CDCl_3$ δ(ppm) : 0.0 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.8 (m, 1H), 1.1 (m, 2H), 1.14 (d, J = 6 Hz, 3H), 5.95 (d, J = 16 Hz, 1H), 6.62 (d, J = 16 Hz, 1H), 9.35 (d, J = Hz, 1H) ; MS m/e (rel. int.) : 198 (2.0), 185 (2.0), 83 (6.2), 42 (4.1).

This aldehyde was added at 0°C to a suspension of ethylmagnesium bromide prepared from 0.189 g (7.78 mmol.) of magnesium and 0.849 g (7.8 mmol.) of ethyl bromide in 5 ml of ether. The mixture was allowed to warm to r.t. and stirred overnight. The reaction mixture was quenched with saturated NH_4Cl solution (2 ml). Ether (10 ml) was added, the aqueous phase was extracted with ether (2 x 5 ml). The combined organic layers were washed with saturated NaCl solution (2 x 3 ml), dried over Na_2SO_4. Concentration under reduced pressure gave a crude product which was chromatographed on silica (ether:hexane ; 10:90) to yield 0.950 g (85% yield) of E 1-(1-t-butyldimethylsiloxy 2-methyl) pent-1-en-3-ols 17. $[\alpha]_D$ = +9°, c 3.2, CCl_4. IR (CCl_4 (cm^{-1}) : 1670 (γC=C) ; NMR (250 MHz) ^1H ($CDCl_3$) : 0.05 (s, 3H), 0.12 (s, 3H), 0.55 (m, 1H), 0.90 (s, 9H), 0.70 - 1.15 (m, 5H), 1.10 (d, J = 6 Hz, 2H), 1.15 (m, 1H), 1.55 (m, 2H), 1.75 (m, 1H), 4 (m, 1H), 5.52 (m, 2H). Anal. calcd for $C_{15}H_{30}O_2Si$: C 66.59, H 11.19, Si 10.39. Found : C 66.37, H 11.12, Si 10.17.

E-2-(but-1-enyl)-3-methyl cyclobutanone (2R-3S)-18

To a stirred solution of 475 mg (1.76 mmol.) of the alcohols 17 in 5 ml of CH_2Cl_2 was added at room temperature 10 µl of BF_3-Et_2O. The reaction was over within 5 mn. as monitored by t.l.c. Then, the solution was washed with 5% $NaHCO_3$, with saturated NaCl solution (2 x 1 ml), dried over Na_2SO_4. Concentration under reduced pressure gave a crude product which was chromatographed on silica (pentane/ether : 9/1) to give 185 mg (76% yield) of a cis/trans mixture (ratio 95:5) of cyclobutanones. Preparative gas chromatography (SE 30, 20%, 3 m, 80°C, 0.6 bar) gave pure E 2-(but-1-enyl) 3-methyl cyclobutanone (2R,3S)-18. $[\alpha]_D$ = -62°, c 2, CCl_4. IR ($CDCl_3$) ($cm^{(-1)}$) : 1780 (γC=O) ; NMR (250 MHz) ^1H ($CDCl_3$)δ(ppm) : 0.97 (t, J = 6.9 Hz, 3H), 1.06 (d, J = 7.7, 3H), 2.05 (dq, J = 6.9 and 2 Hz, 2H), 2.45 (ddd, J = 17, 4.62 and 2 Hz, 1 H), 2.65 (m, 1H), 3.25 (ddd, J = 17, 9.34 and 2.78 Hz, 1H), 3.95 (m, 1H), 5.35 (m, 1H), 5.70 (m, 1H). The E stereochemistry of the double bond JAB = 16 Hz) was determined upon irradiation at 3.95 ppm. NMR ^{13}C ($CDCl_3$, 62 MHz)δ (ppm) : 13.43 (CH_3), 16.39 (CH_3), 23.38 (CH_2), 25.88 (βC), 51.91 (αC), 64.67 (α'C), 119.9 and 137.5 (ethylenic C), 209.71 (C=O) ; MS m/e (rel. int.) : 138 (0.2), 96 (64), 81 (100), 67 (22), 53 (20), 41 (10). HRMS : calc. : 138,1406 ; found : 138,1405.

(1-t-Butyldimethylsiloxy 2-methylcyclopropyl) methyl ketone (1R,2S)-19

To 10 mmol of methylmagnesium iodide (prepared from 1.42 g of methyl iodide and 0.242 g of Mg) in 10 ml of anhydrous ether were added at 0°C 1 g (4.7 mmol.) of the aldehyde (1R,2S)-16.

The mixture was allowed to warm to r.t. After stirring for 1 h, the mixture was quenched at 0°C with saturated NH_4Cl solution. Ether (10 ml) was added, the layers were separated and the aqueous phase was extracted with ether (2 x 5 ml). The combined organic layers were washed with saturated NaCl solution (2 x 2 ml) and dried over Na_2SO_4. Concentration under reduced pressure gave 1 g (93% yield) of (1-t-butyldimethylsiloxy 2-methyl cyclopropyl) methyl carbinol. IR (CCl_4) (cm^{-1}) : 3630 (γOH) ; NMR (90 MHz) ^1H (CCl_4)δ (ppm) : 0.0 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 0.95 - 1.15 (m, 9H), 1.9 (s, 1H), 3.5 (q, J = 7.3 Hz, 1H).

To a solution of 0.52 ml (6 mmol.) of oxalyl chloride in 15 ml of CH_2Cl_2 at -60°C was added a solution of 0.98 ml (15 mmol.) of DMSO in 2.5 ml of CH_2Cl_2. The mixture was stirred for 2 mn. at -60°C and a solution of 1 g (4.34 mmol.) of this cyclopropylcarbinol was added dropwise. The mixture was stirred for 15 mn and 4 ml of NEt_3 were added. Worked-up as reported for aldehyde 13 provided a crude product which was purified by chromatography on silica (hexane/ether : 9/1) to give 0.85 g (81% yield) of the cyclopropylmethyl ketone (1R,2S)-19. $[\alpha]_D$ = +32°, c 1, $HCCl_3$; IR (CCl_4) (cm^{-1}) : 1700 (γC=O) ; NMR (250 MHz) ^1H ($CDCl_3$) δ (ppm) : 0.08 (s, 3H), 0.2 (s, 3H), 0.8 (m, 1H), 0.95 (s, 9H), 1.17 (d, J = 6 Hz, 3H), 1.30 (m, 1H), 1.65 (m, 1H) and 2.20 (s, 3H) ; MS m/e (rel. int.) : 228 (M^+, 46), 213 (4), 171 (57), 115 (14), 75 (100).

3-(t-Butyldimethylsiloxy 2-methylcyclopropyl) but-1-en-3-ols 20

To a solution of 0.5 g (2.20 mmol.) of the cyclopropyl methyl ketone 19 in 7 ml of anhydrous THF at 0°C was added dropwise 3 ml of a M solution of vinylmagnesium bromide in THF. Then, the mixture was heated at 65°C for 5 h. to complete the reaction (t.l.c.). The mixture was cooled and quenched with saturated NH_4Cl solution (2 ml). Ether (10 ml) was added and the layers separated. The organic layer, washed with saturated NaCl solution (2 x 2 ml) and dried over Na_2SO_4 was concentrated under reduced pressure to give a crude product which was chromatographed on silica (hexane/ether : 9/1) to give 0.438 g (78% yield) of the butenols 20. IR (CCl_4 (cm^{-1}) : 3610, 3410 (γOH), 1605 (γC=C) ; NMR (90 MHz) (CCl_4) : 0.1 (s, 6H), 1.0 (s, 9H), 1.1 - 1.6 (m, 9H), 2.15 (s, 1H), 5.0 - 5.4 (m, 2H), 5.85 - 6.25 (m, 1H).

2,3-Dimethyl-2-vinylcyclobutanones (2S,3S)-21 and (2R,3S)-22

To a stirred solution of 150 mg (0.586 mmol.) of the alcohols 20 in 1.5 ml of CH_2Cl_2 was added at r.t. 5 µl of BF_3-Et_2O. After 15 mn the reaction was complete as monitored by t.l.c. Work-up as for ketones 15 and 18 provided a crude product which was chromatographed on silica (pentane/ether : 9/1) to yield 60 mg (83% yield) of a stereoisomeric mixture of cyclobutanones (2S,3S)-21 and (2R,2S)-22 (ratio 28:72) $[\alpha]_D$ = +22°, c 1, $HCCl_3$ (of the mixture). IR (CCl_4) (cm^{-1}) : 1780 (γC=O) ; NMR (250 MHz) ^1H ($CDCl_3$) δ (ppm) : 1.15 (d, J = 6 Hz, 3H), 1.15 (s, 2.16 H), 1.30 (s, 0.84 H), 2.23 (dq, 0.28 H), 2.49 (dq, 0.72 H), 2.54 (dd, ^2J = 17 and ^3J = 9 Hz, 1 H) ; MS of 21 m/e (int. rel.) : 124 (M^+, 0.7), 82 (100), 67 (82), 54 (20), 53 (12), 39 (15) ; MS of 22 m/e (int. rel.) : 124 (M^+, 1), 82 (100), 67 (72), 54 (18), 53 (14), 39 (17). HRMS : calc. : 124,0888 ; found : 124,0891.

Enantiomeric excesses : shift ($\Delta\delta$ = 0.33 and 0.20 ppm) and splitting ($\Delta\delta$ = 0.012 and 0.035 ppm) of the α-methyl signals for the (2S,3S)-21 and (2R,3S)-22 respectively, in the presence of 0.15 equiv. of $Eu(hfc)_3$, ratio 92:8.

3-Methyl-2-vinylcyclobutanols (2R,3R)-23

To 76 mg (2 mmol) of $LiAlH_4$ in 2 ml of anhydrous ether was added dropwise 0.243 g (2.21 mmol.) of the cyclobutanone (2R,3R)-15 and the mixture was refluxed for 1 h. Then the cooled mixture was hydrolyzed with wet Na_2SO_4. Filtration of the organic layer, which was dried on anhydrous Na_2SO_4 and concentration under reduced pressure gave a crude product which was chromatographed on silica (hexane/ether : 75/25) to give 0.232 g (94% yield) of the isomeric cyclobutanols (2S,3R)-23 (ration 63:37 determined by g.c.) $[\alpha]_D$ = 6.3°, c 1.11, $HCCl_3$; IR ($CDCl_3$) (cm^{-1}) : 3610 (γOH), 1640 (γC=C) ; NMR (250 MHz) ^1H ($CDCl_3$) δ(ppm) : 0.95 (d, J = 7 Hz, 3H), 1.71 (m, 1H), 2.0 (m, 2H), 2.48 (m, 1H), 2.82 (m, 1H), 3.14 (m, 1H), 4.25 (m, 1H), 5.19 (m, 2H) and 6.0 (m, 1H) ; MS m/e (rel. int. : 112 (M^+, 9), 95 (1.1), 94 (5), 70 (18), 68 (10), 42 (26).

5-Methyl cyclohex-3-en-1-ols (S)-24

To a solution of 227 mg (2.02 mmol.) of 23 in 8 ml of anhydrous THF was added excess KH (pentane washed solid) until the evolution of H_2 ceased. The reaction mixture was heated at reflux for 1 h and was quenched by the slow addition of H_2O. Ether (10 ml) was added and the solution was washed with water (2 x 3 ml). The organic phase was dried on Na_2SO_4 and the solvents were removed in vacuo. Chromatography on silica gel (hexane/ether : 9/1) gave 186 mg (82% yield of 24 as a 45/55 stereoisomeric mixture, as determined by g.c. IR ($CDCl_3$) (cm^{-1}) : 3720, 3420 (γOH), 1650 (γC=C) ; NMR (250 MHz) ^1H ($CDCl_3$) δ(ppm): 1.0 (d, J = 3.3 Hz, 1.35 H) and 1.05 (d, J = 3.3 Hz, 1.65 H), 1.55 (m, 1 H), 1.7 (s, 1 H), 1.88 (m, 1 H), 2.28 (m, 3 H), 3.92 (m, 1 H), 4.10 (m, 1H) and 5.55 (m, 2H).

5-Methyl-cyclohex-2-en-1-one (S)-25

To a solution of 103 mg (0.92 mmol.) of the alcohols 24 in 2 ml of acetone was added Jones reagent dropwise at r.t. until the reaction mixture attained a permanent yellow colour. When the reaction was over as monitored by t.l.c., the mixture was poured into ether and the organic layer was washed with 10% $NaHCO_3$, with water and dried over Na_2SO_4. Concentration in vacuo gave a crude oil : IR ($CDCl_3$)(cm^{-1}) : 1715 (γC=O) and 1600 (γC=C). The unconjugated ketone was then passed through a column of basic activity 3 alumina (5% ether in pentane) ; removal of the solvent in vacuo gave 91 mg (90% yield) of the conjugated ketone 25. $[\alpha]_D$ = +81°, c 1.04, $CHCl_3$ (Lit. $[\alpha]_D$ = -90° for (R)-25 (30)). IR ($CDCl_3$) (cm^{-1}) : 1680 (γC=O), 1650 (γC=C) ; NMR (250 MHz) ($CDCl_3$) δ(ppm) : 1.07 (d, J = 6 Hz, 3H), 2.22 (m, 3H), 2.47 (m, 2H), 6 (m, 1H), 6.98 (m, 1H) ; MS m/e (rel. int.) : 110 (M^+, 25), 68 (100), 42 (5.8) ; Anal. calcd for $C_7H_{10}O$: C 76.31, H 9.16. Found : C 76.11, H 9.22.

2-Butyl-3-methylcyclobutanone (2S,3S)-26

A solution of 94.7 mg (0.69 mmol.) of cyclobutanone 18 in 1.5 ml of ethyl acetate containing 10 mg of Palladium on carbon was hydrogenated under atmospheric pressure. When 15.5 ml of hydrogen were absorbed (2 equiv.) the product was filtered through celite and the solvent was removed under vacuo to give a 9:1 mixture of diastereoisomeric cyclobutanones. The main compound was isolated by g.c. (col. SE 30, 20%, 110°, 0.6 atm.) to give the pure ketone (2S,3S)-26 $[\alpha]_D$ = +37°, c 1, $CHCl_3$. IR (CCl_4) (cm^{-1}) : 1785 (γC=O) ; NMR (250 MHz) ($CDCl_3$) δ (ppm) : 0.90 (t, J = 7.15 Hz, 3H), 1.10 (d, J = 7.27, Hz, 3H), 1.35 (m, 5H), 1.60 (m, 1H), 2.40 (dd, J = 18.75 and 3.95 Hz, 1H), 2.60 (m, 1H) and 3.2 (m, 2H) ; MS m/e (rel. int.) : 140 (M^+, 4), 98 (42), 83 (11), 57 (11.5), 55 (100) and 42 (25).

4-Butyl-3-methyl butanolide (3S,4S)-27 (Quercus lactone b)

To a solution of 50 mg (0.357 mmol.) of ketone (2S,3S)-26 in 1 ml of CH_2Cl_2 at 0°C was added 40 mg (0.470 mmol.) of $NaHCO_3$ and 107 mg (0.620 mmol) of MCPBA (85%). As monitored by g.c. the reaction was complete within 30 mn. Then, the solution was poured into a mixture of 0.8 ml of saturated aqueous sodium bicarbonate and 0.2 ml of saturated sodium sulfite and extracted with ether (3 x 5 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed in vacuo to give a residue which was chromatographed on silica (pentane/ether : 75/25) to yield 45 mg (81% yield) of Quercus lactone b 27 ($[\alpha]_D$ = -78°, c 1, MeOH ; Lit. $[\alpha]_D$ = -87°, c 0.92, MeOH (35)). The IR, NMR and MS spectral data of 27 were identical to those previously reported for this butyrolactone (32).

2,3,4- and 2,3,5-Trimethylcyclopentenones 28 and 29

To 30 mg (0.24 mmol.) of the 28:72 mixture of cyclobutanones 21 and 22 (>84% e.e) was added 0.12 ml of CH_3SO_3H. After stirring for 3 h at r.t. the reaction was complete (t.l.c.). The mixture was diluted with ether (5 ml) and poured on a mixture of ice and saturated $NaHCO_3$ solution, and the mixture extracted with ether (3 x 5 ml). The organic layer was washed with saturated NaCl solution, dried on Na_2SO_4 and evaporated. The residue was chromatographed on silica (pentane/ether : 75/25) to yield 16.8 mg (56% yield) of a 9:1 mixture of cyclopentenones 28 and 29 with spectral data identical to those previously reported (38).

On addition of 0.5 equiv. of $Eu(hfc)_3$ to solutions of 10 mg of cyclopentenone 28 in $CDCl_3$, downfield shift ($\Delta\delta$ = 6.14 ppm) and splitting ($\Delta\delta$ = 0.03 ppm) occurred on the 250 MHz n.m.r. ^1H methyl ester signals with the ratio 50:50, resulting of a complete racemization.

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