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ENZYMATIC HYDROLYSIS OF CYCLOPROPANES. TOTAL SYNTHESIS OF OPTICALLY PURE DICTYOPTERENES A AND C'.

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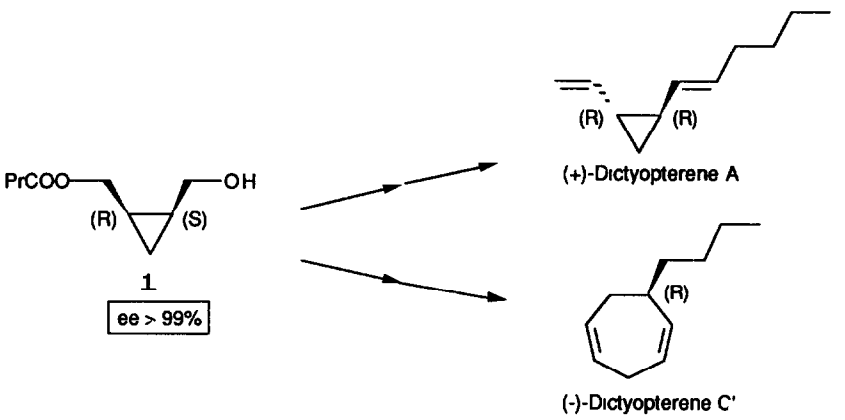
Abstract: Enzymatic hydrolysis of cis-1,2-bis(butyryloxymethyl)cyclopropane 3 under optimized conditions gives, in quantitative yield, optically pure cis-(1S,2R)-1-hydroxymethyl-2-butyryloxymethylcyclopropane 1. This compound is a versatile cyclopropane synthon as exemplified by the total synthesis of optically pure seaweed pheromones Dictyopterenes A and C'

Introduction:

The cyclopropane ring is a common unit in a large number of natural products and compounds of pharmaceutical interest [1] As most of them are optically active, an easy access to optically pure versatile cyclopropane intermediates would be valuable

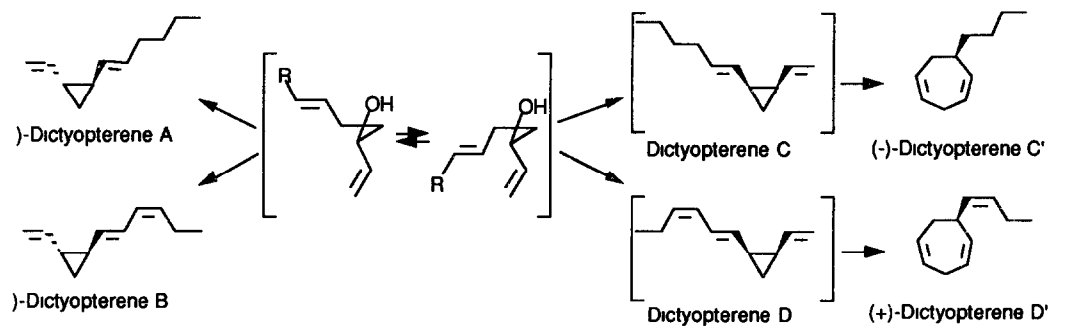
Synthesis of chiral cyclopropanes has been recently reviewed[2] and usually requires either chemical or enzymatic resolution, or diastereoselective or enantioselective cyclopropanation Only tedious chemical resolutions and one enzymic method[3] can afford optically pure cyclopropane derivatives

In this paper, we report a convenient and rapid access to an optically pure cyclopropane synthon, cis-(1R,2S)-1-butyryloxymethyl-2-hydroxymethylcyclopropane 1, via an enzymatic resolution This optically pure functionnalized cyclopropane can be a versatile starting material for the synthesis of biologically interesting cyclopropane compounds In order to demonstrate the usefulness of this chiral cyclopropane synthon, we embarqued on the total synthesis of optically pure Dictyopterenes A and C' (Scheme 1)



Scheme 1

Dictyopterenes constitute a family of sexual pheromones for several brown algae,[4-6] one of which, Dictyopterene A, is responsible for the intense ocean smell of these algae Dictyopterenes are presumably derived[7] from polyunsaturated alcohols which are cyclized into cyclopropanes bearing two unsaturated side chains, vinyl and hexenyl for Dictyopterenes A and C, or vinyl and hexadienyl for Dictyopterenes B and D (Scheme 2) Only the trans cyclopropane isomers, Dictyopterenes A and B, can be isolated The cis isomers, Dictyopterenes C and D, rearrange at sea temperature to the corresponding cycloheptadienes, the actual natural products Dictyopterenes C' and D' (Scheme 2)

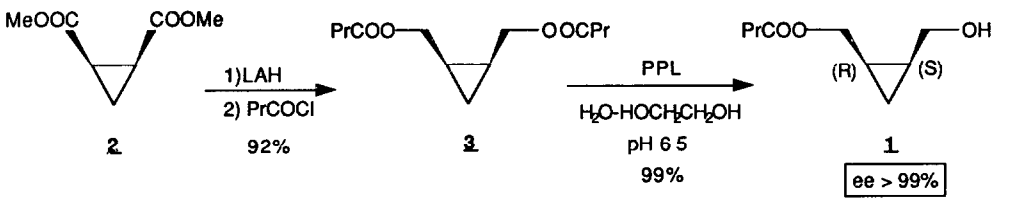


Scheme 2

Among the various reported syntheses[8-17] of Dictyopterenes, only four describe the synthesis of optically active Dictyopterenes Two rely on chemical resolution[14,15] and the two others on intramolecular cyclisation controlled by a chiral auxilliary catalyzed[16] or not[17] by organometallic complexes

Results and discussion:

We recently found that under carefully controlled conditions, the crude lipase extracted from pig pancreas (PPL), is able to catalyze the cleavage of meso diesters of cis-2,3-epoxybutan-1,4-diol with high enantioselectivity and high chemical yields [18] When the following experimental conditions (PPL, water-ethylene glycol, pH 6 5, 3°) are applied to the cyclopropane analogue, cis-1,2-bis(butyryloxymethyl)cyclopropane **3**, the optically pure monoester **1** is isolated in quantitative yield (Scheme 3)



Scheme 3

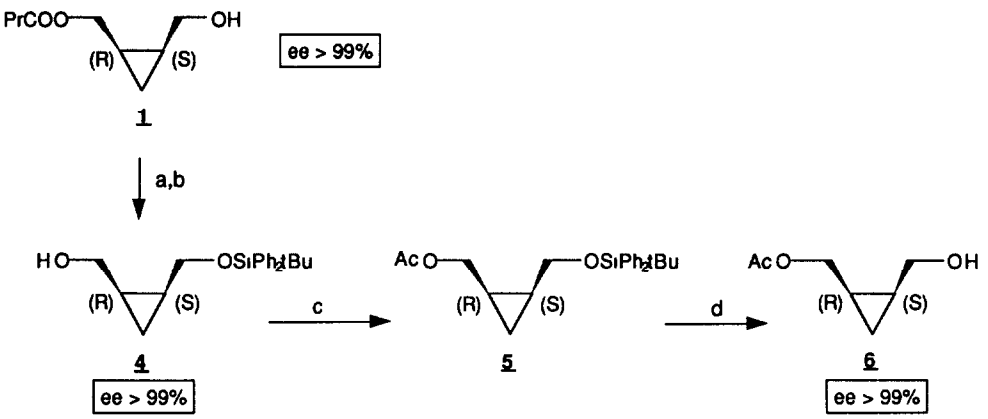
Ester chain length[19] and pH are both determinant for a high level of PPL enantioselectivity since the corresponding diacetate has been hydrolyzed[20] at pH 7 5 by PPL giving the (1S,2R)-monoacetate with a much lower ee (72 %) [21]

The absolute configuration of cis-(1R,2S)-1-butyryloxymethyl-2-hydroxy methylcyclopropane **1** was determined by converting **1** to the known cis-(1R,2S)-1-acetoxymethyl-2-hydroxymethylcyclopropane[20] **6** through a four step sequence (Scheme 4) Ee were best determined at the acetate stage using ^{1}H NMR in the presence of Eu(hfc)$_3$ since the acetate signal of racemic **5** is readily split with increasing amount of Eu(hfc)$_3$ When Eu(hfc)$_3$ was added to a $CDCl_3$ solution of optically active **5** obtained from **1**, only one set of signals could be detected by ^{1}H NMR Althought **4**, formed during the derivatization of **1** toward **5** , is a cristalline compound, no

recristallization was attempted in order to minimize enantiomeric enrichment The optical purity of **1** was later confirmed by the optical rotation of both Dictyopterenes which were synthesized

It is important to note that the formal enantiomer of **1**, that is **4**, is readily available after silylation and hydrolysis of **1** (Scheme 4)

The cyclopropane starting material **3** was easily obtained in two steps and 92% overall yield from the readily commercially available dimethylcyclopropane dicarboxylate **2** (Scheme 3) We were able to scale the enzymatic process up to 20 g of cyclopropane substrate **3**

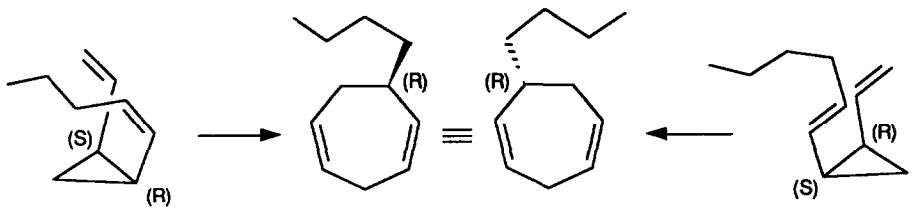


a) $ClSiPh_2tBu$, DMAP, CH_2Cl_2, b) K_2CO_3, MeOH, c) Ac_2O, DMAP, Et_2O, d) $Bu_4NF\ 3H_2O$, THF

Scheme 4

With the synthesis of Dictyopterenes A and C' from optically pure synthon **1**, as our goal, we were faced with two stereochemical problems (i) how can an E double bond be produced in a hydrocarbon chain (ii) how can a trans cyclopropane be produced from a cis cyclopropane ?

An interesting feature of the Cope rearrangement leading to Dictyopterene C' is due to the pseudosymmetric nature of the vinylalkenylcyclopropane The cycloheptadiene Dictyopterene C' can either be obtained from (1S,2R)-1-[(E)-hex-1-enyl]-2-vinylcyclopropane **(E)-9** or (1R,2S)-1-[(Z)-hex-1-enyl]-2-vinylcyclopropane **(Z)-9** (Scheme 5) Therefore the synthesis of Dictyopterene C' can be resolved with a highly cis stereoselective Wittig reaction



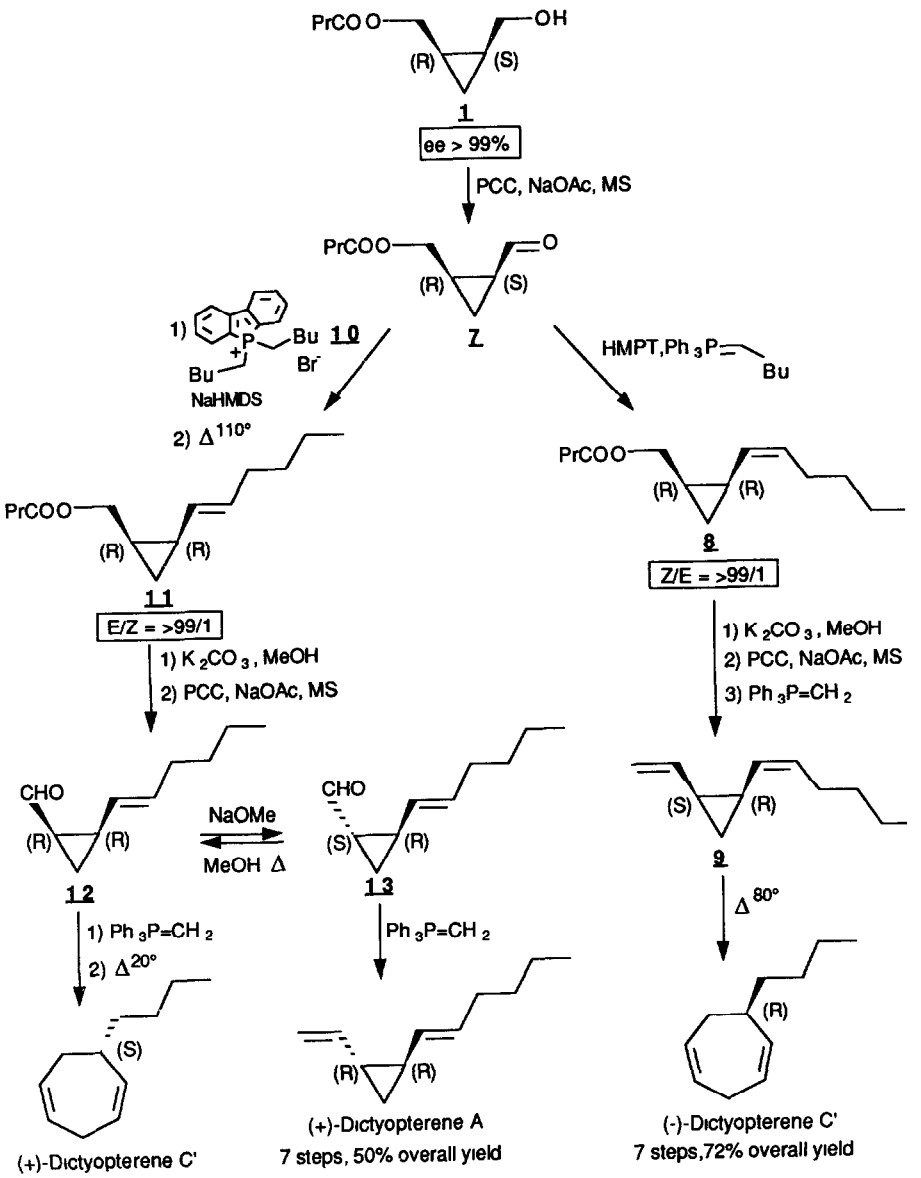
(Z)-9 (E)-9

Scheme 5

We have found the Bestmann conditions[22] suitable for this purpose (Scheme 6) The reaction of the aldehyde **7**, obtained from **1** by mild PCC oxidation[23], with the ylide derived from pentyltriphenylphosphonium bromide gave the expected hexenyl cyclopropane **8** with a Z/E ratio of 99 to 1 The Z/E ratio, determined by integration of the vinylic protons in the NMR at 300 MHz, was 99 to 1 After cleavage of the butyrate group, oxidation[23] to the aldehyde and Wittig methylenation, the cis-(1R,2S)-1-[(Z)-hex-1-enyl]-2-vinylcyclopropane **(Z)-9** was isolated. Heating **(Z)-9** in a sealed tube at 80° in CCl_4 for 6 h provided us with optically pure Dictyopterene C' in quantitative yield ($[\alpha]_D^{22}$ = -16 8°, $CHCl_3$ compared to $[\alpha]_D^{22}$ = -15 5°, $CHCl_3$, reported ee 97%,[14a,14b] and to the natural product $[\alpha]_D^{22}$ = -12 0°, $CHCl_3$, reported ee 75% [4])

For the synthesis of Dictyopterene A, we still required a highly E stereoselective olefination We focused on recent mechanistic investigations of the Wittig reaction[24,25] by Vedejs and his group In our synthesis, we decided to use the dibenzophospholium ylide **10** , readily available in 4 steps[25,26] from tetraphenylphosphonium bromide, and we finally obtained in good yield the expected hexenylcyclopropane **11** with a very high E/Z ratio 99 /1 (Scheme 6) This E/Z ratio was also determined by 300 MHz ^1H NMR

After deprotection of the hydroxyl function and oxidation, the cis cyclopropylaldehyde **12** was epimerized to the trans isomer **13** in basic conditions [27] A 9 to 1 mixture of trans and cis cyclopropanes **13** and **12** was isolated Methylenation of this mixture led to a mixture of Dictyopterene A and cis-(1R,2S)-1-[(E)-hex-1-enyl]-2-vinylcyclopropane, the enantiomer of **(E)-9**, which quantitatively rearranged at room temperature to the unnatural (+)-Dictyopterene C' Repetitive preparative chromato graphy on silica plates impregnated with silver nitrate allowed us


PrCO O
OH
(R)
(S)
1
ee > 99%
PCC, NaOAc, MS
PrCOO
O
(R)
(S)
7
1)
Bu
10
Br
Bu
NaHMDS
2) Δ 110°
HMPT, Ph 3P=
Bu
PrCOO
(R)
(R)
11
E/Z = >99/1
1) K 2CO 3, MeOH
2) PCC, NaOAc, MS
8
Z/E = >99/1
1) K 2CO 3, MeOH
2) PCC, NaOAc, MS
3) Ph 3P=CH 2
CHO
(R)
(R)
12
NaOMe
MeOH Δ
CHO
(S)
(R)
13
(S)
(R)
9
1) Ph 3P=CH 2
2) Δ 20°
Ph 3P=CH 2
Δ 80°
(S)
(R)
(R)
(R)
(+)-Dictyopterene C'
(+)-Dictyopterene A
7 steps, 50% overall yield
(-)-Dictyopterene C'
7 steps,72% overall yield

Scheme 6

to separate the optically pure Dictyopterene A in 85% yield ($[\alpha]_D^{22}$ = +75 3°, $CHCl_3$ compared to $[\alpha]_D^{22}$ = +59 7°, $CHCl_3$, reported ee 83%,[16a,16b] and to the natural product $[\alpha]_D^{22}$ = +72 0°, $CHCl_3$, reported ee 95% [4]) and the optically pure enantiomer of Dictyopterene C' in 10% yield ($[\alpha]_D^{22}$ = +17 1°, $CHCl_3$, compared to $[\alpha]_D^{22}$ = +10 2°, $CHCl_3$, reported ee 85% [16a,16b])

Concluding remarks:

This efficient and highly stereoselective synthesis of optically pure Dictyopterene A and C' has shown the usefulness of cis-(1R,2S)-1-butyryloxymethyl-2-hydroxymethylcyclopropane **1** as an optically pure cyclopropane synthon, easily obtained in preparative scale by enzymatic hydrolysis The other Dictyopterenes can formally be obtained optically pure from **1** As we have demonstrated that cis and trans optically pure cyclopropanes can both be prepared, **1** can be viewed as a valuable precursor to all kinds of optically pure disubstituted cyclopropanes, configured either in a cis or trans relationship

Aknowledgement: We gratefully thank ICI-Pharma, Reims, France, for helping us in material assistance One of us (D G) thanks the "Ministère de la Recherche et de la Technologie" for a doctoral fellowship

Experimental section

General remarks All melting points were uncorrected IR spectra were recorded on Philips SP3-300 infrared spectrophotometer NMR spectra were recorded on Brucker AC-300 spectrometer at 300 MHz for ^1H and 75 5 MHz for ^{13}C Chemical shifts of ^1H NMR were expressed in parts per million downfield relative to internal tetramethylsilane (δ=0) Splitting patterns were assigned as s, singulet, d, doublet, t, triplet, q, quadruplet, sext, sextuplet, m, multiplet ^{13}C NMR were recorded using the central peak of the $CDCl_3$ signal as an internal standard (δ=77 00) Mass spectra were recorded on a JEOL D300 mass spectrometer at 70 ev Optical rotations were measured on a Perkin-Elmer polarimeter at the sodium D line and was reported as follows $[\alpha]_D^{22}$ (concentration in g/100 ml, solvent, ee %) All reactions were monitored by thin-layer chromatography carried out on 0 25-mm E Merck silica gel plates (60 F_{254}) Preparative layer chromatography was performed on 0 5 or 0 25 mm x 20 cm x 20 cm E Merck silica gel plates (60 $P_{F254+366}$) Flash chromatography were performed on silica gel Merck 60 (particle size 0 040-0 063 mm) THF, Et_2O were distillated from sodium/benzophenone, CH_2Cl_2, TEA, diisopropylamine were distillated from calcium hydride, HMPT and MeOH were distillated from sodium All solvents were stored under argon

Cis-1,2-bis(butyryloxymethyl)cyclopropane (3)

To a stirred suspension of LAH (5 88 g, 155 08 mmol, 1 1 eq) in Et_2O (129 ml) at 0°C under argon, was added the cyclopropane diester **2** (20 44 g, 129 23 mmol, 1 eq) in Et_2O (129 ml) After 30 min, the mixture was hydrolysed with H_2O (12 ml) and then filtered The filtered cake was rinced several times with Et_2O and Me_2CO The organic layer was dried and concentrated The crude cyclopropane diol (13 20 g) is directly used in the next step

To a stirred solution of cyclopropane diol (13 20 g, 129 23 mmol, 1 eq) in CH_2Cl_2 (258 ml) under argon, were added DMAP (0 790 g, 6 46 mmol, 0 05 eq) then TEA (39 62 ml, 284 32 mmol, 2 2 eq) After cooling to 0°C, butyryl chloride (29 52 ml, 284 32 mmol, 2 2 eq) was slowly added The mixture was stirred at room temperature for 1 h, then hydrolyzed After extraction with CH_2Cl_2, the organic layer was dried and concentrated Flash chromatography of the crude product yielded **3** (28 80 g, 92 % after 2 steps) as a colorless oil TLC Rf 0 67 (PE-AcOEt 80-20), IR (film) 3080, 3020, 1730, 1365, 1175 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 32-0 39 (1H, m), 0 86-0 95 (1H, m), 0 96 (6H, t, J=7 4), 1 28-1 38 (2H, m), 1 67 (4H, sext, J=7 4), 2 30 (4H, t, J=7 4), 3 91-4 03 (2H, m), 4 19-4 30 (2H, m), ^{13}C NMR ($CDCl_3$) δ 8 56, 13 56, 14 63, 18 37, 36 12, 64 09, 173 48, mass spectrum, m/e (intensity), 155 (M^+-87, 31), 71 (100), 67 (46) Anal Calcd for $C_{13}H_{22}O_4$ C, 64 44, H, 9 15 Found C, 64 74, H, 9 33

(1R,2S)-1-butyryloxymethyl-2-hydroxymethylcyclopropane (1)

A 1 l flask equipped with a mechanical stirring and a combined glass electrode, was charged with water (300 ml) and ethylene glycol (75 ml) After cooling to 3°C, lipase (1 32 g, PPL, type II, crude, SIGMA n° L 3126) was added After adjusting the pH to 6 5 by 1M NaOH, cyclopropane diester **3** (20 40 g, 84 19 mmol, 1eq) was added The pH was kept constant during the hydrolysis by continuous addition of 1M NaOH solution from an autoburette After addition of 79 98 ml (0 95 eq) 1M NaOH (4h20), aqueous $NaHCO_3$ was added (pH=9 2) After neutralisation by NH_4Cl, the product was extracted with Et_2O, then the organic layer was dried and concentrated The crude product was immediately purified by flash chromatography to give **1** (13 63 g, 99 %, conversion 95 %) as a colorless oil TLC Rf 0 38 (PE-AcOEt 60-40), $[\alpha]_D^{22}$ + 18,2° (C=1 58, CH_2Cl_2, ee >99 %), IR (film) 3430, 3080, 3010, 1740, 1730, 1710, 1370, 1180, 1040, 1020 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 21-0 29 (1H, m), 0 81-0 91 (1H, m), 0 96 (3H, t, J=7 4), 1 22-1 40 (2H, m), 1 66 (2H, sext, J=7 4), 2 31 (2H, t, J=7 4), 2 58 (OH), 3 41-3 50 (1H, m), 3 78-3 93 (2H, m), 4 39-4 49 (1H, m), ^{13}C NMR ($CDCl_3$) δ 7 66, 13 42, 14 25, 18 24, 18 37, 36 05, 62 19, 64 30, 173 56, mass spectrum, m/e (intensity), 173 (M^+ +1, 1), 172 (M^+, <1), 155 (25), 141 (6), 131 (3), 89 (13), 85 (7), 84 (11), 83 (11), 71 (100), 67 (25) Anal Calcd for $C_9H_{16}O_3$ C, 62 77, H, 9 36 Found C, 62 93, H, 9 60

(1S,2R)-1-tert-butyldiphenylsilyloxymethyl-2-hydroxymethylcyclopropane (4)

To a solution under argon of monoprotected cyclopropane diol **1** (0 450 g, 2 61 mmol, 1 eq) in CH_2Cl_2 (2 5 ml), were added at room temperature DMAP (0 383 g, 3 13 mmol, 1 2 eq) and TBDPSCl (0 80 ml, 3 13 mmol, 1 2 eq) The mixture was stirred for 30 minutes and H_2O (2 ml) was added After extraction with CH_2Cl_2, drying and solvent evaporation, the product was purified by flash chromatography to afford (1S,2R)-1-tert-butyldiphenylsilyloxymethyl-2-butyryloxymethyl-cyclopropane (0 975 g, 91 %) as a colorless oil TLC Rf 0 77 (PE-AcOEt 90-10), $[\alpha]_D^{22}$ + 6,00° (C=0 9, CH_2Cl_2, ee >99 %), IR (film) 3100, 3080, 3040, 3020, 1975, 1900, 1835, 1740, 1600, 1435, 1185, 1120, 830, 800, 745, 705, 610 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 22-0 29 (1H, m), 0 73-0 83 (1H, m), 0 96 (3H, t, J=7 4), 1 08 (9H, s), 1 22-1 35 (2H, m), 1 67 (2H, sext, J=7 4), 2 30 (2H, t, J=7 4), 3 60-3 70 (1H, m), 3 78-3 87 (1H, m), 4 04-4 13 (1H, m), 4 15-4 24 (1H, m), 7 35-7 49 (6H, m), 7 66-7 77 (4H, m), ^{13}C NMR ($CDCl_3$) δ 8 22, 13 63, 14 48, 18 15, 18 43, 19 16, 26 82, 36 23, 63 62, 64 71, 127 59, 129 57, 133 86, 135 56, 173 74, mass spectrum, m/e (intensity), 353 (M^+-57, 2), 323 (20), 269 (100), 200 (18), 199 (100), 197 (20), 135 (18), 71 (33)

To a stirred solution of the preceding diprotected cyclopropane diol (0 820 g, 2 mmol, 1 eq) in MeOH (10 ml) at room temperature, was added K_2CO_3 (1 g, 7 23 mmol, 3 6 eq) After stirring 10 min, aqueous NH_4Cl was added After extraction with CH_2Cl_2, drying and solvent evaporation, the crude oil was purified by flash chromatography to give **4** (0 635 g, 93 %) as an oil which crystallized as a colorless solid (m p 59°C) TLC Rf 0 75 (PE-AcOEt 60-40), $[\alpha]_D^{22}$ - 10,3° (C=0 73, CH_2Cl_2, ee >99 %), IR (film) 3480, 3100, 3080, 3030, 1975, 1900, 1835, 1785, 1600, 1435, 1120,

1060, 1040, 825, 740, 705, 610 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 10-0 17 (1H, m), 0 65-0 76 (1H, m), 1 06 (9H, s), 1 17-1 31 (1H, m), 1 37-1 51 (1H, m), 3 06 (OH), 3 29-3 40 (2H, m), 3 98-4 13 (2H, m), 7 35-7 49 (6H, m), 7 64-7 77 (4H, m), ^{13}C NMR ($CDCl_3$) δ 8 28, 17 09, 18 37, 19 02, 26 74, 63 22, 64 90, 127 75, 129 83, 132 91, 135 55, mass spectrum, m/e (intensity), 323 (M^+ -17, 1), 283 (5), 265 (3), 239 (4), 225 (3), 200 (37), 199 (100), 197 (14), 181 (18), 139 (37), 105 (14), 77 (24), 67 (10) Anal Calcd for $C_{21}H_{28}O_2Si$ C, 74 07, H, 8 29 Found C, 74 35, H, 8 23

(1R,2S)-1-acetoxymethyl-2-tert-butyldiphenylsilyloxymethylcyclopropane (5)

To a stirred solution of the alcohol **4** (0 494 g, 1 45 mmol, 1 eq) in Et_2O (7 ml), were added at room temperature DMAP (0 195 g, 1 59 mmol, 1 1 eq) and Ac_2O (0 15 ml, 1 59 mmol, 1 1 eq) A solid immediatly formed After 10 min, the mixture was filtered and evaporated The obtained oil was purified by flash chromatography to give **5** (0 555 g, 98 %) as a colorless oil TLC Rf 0 70 (PE-AcOEt 90-10), $[\alpha]_D^{22}$ + 4 4° (C=1 72, CH_2Cl_2, ee >99 %), IR (film) 3100, 3080, 3040, 3020, 1980, 1900, 1835, 1750, 1600, 1435, 1375, 1245, 1120, 830, 805, 745, 705, 610 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 18-0 26 (1H, m), 0 70-0 80 (1H, m), 1 05 (9H, s), 1 20-1 31 (2H, m), 2 03 (3H, s), 3 54-3 64 (1H, m), 3 77-3 87 (1H, m), 4 00-4 10 (1H, m), 4 10-4 21 (1H, m), 7 33-7 47 (6H, m), 7 63-7 73 (4H, m), ^{13}C NMR ($CDCl_3$) δ 8 10, 14 42, 18 15, 19 17, 21 07, 26 80, 63 53, 64 96, 127 63, 129 59, 133 71, 133 83, 135 56, 171 19, mass spectrum, m/e (intensity), 325 (M^+ -57, <1), 285 (2), 279 (1), 242 (22), 241 (100), 200 (12), 199 (59), 149 (12)

(1R,2S)-1-acetoxymethyl-2-hydroxymethylcyclopropane (6)

To a stirred solution of diprotected cyclopropane diol **5** (0 490 g, 1 28 mmol, 1 eq) in THF (6 5 ml) at room temperature, was added TBAF (0 445 g, 1 41 mmol, 1 1 eq) After 10 min, the reaction was quenched by H_2O (2 ml) After extraction with Et_2O, drying and solvent evaporation, the crude product was purified by flash chromatography to afford **6** (0 165 g, 90 %) as a colorless oil TLC Rf 0 31 (PE-AcOEt 60-40), $[\alpha]_D^{22}$ + 2 9° (C=1 58, CH_2Cl_2, ee >99 %), IR (film) 3440, 3080, 3010, 1740, 1730, 1715, 1370, 1240, 1030 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 19-0 27 (1H, m), 0 80-0 90 (1H, m), 1 22-1 42 (2H, m), 2 06 (OH), 2 09 (3H, s), 3 36-3 45 (1H, m), 3 79-3 89 (2H, m), 4 37-4 46 (1H, m), ^{13}C NMR ($CDCl_3$) δ 7 70, 14 32, 18 58, 21 04, 62 48, 64 65, 171 09, mass spectrum, m/e (intensity), 145 (M^+ +1, 3), 127 (67), 113 (26), 103 (65), 86 (25), 85 (42), 84 (57), 83 (55), 67 (95), 61 (39), 57 (34), 56 (42), 55 (100), 54 (62) Anal Calcd for $C_7H_{12}O_3$ C, 58 32, H, 8 39 Found C, 58 50, H, 8 21

(1S,2R)-2-butyryloxymethyl-1-formylcyclopropane (7)

In a 100 ml flask, were introduced under argon PCC (6 26 g, 29 mmol, 2 eq), NaOAc (0 715 g, 8 7 mmol, 0 6 eq), molecular sieves 3Å (2 5 g) and CH_2Cl_2 (29 ml) then a CH_2Cl_2 (7 ml) solution of the

cyclopropane alcohol 1 (2 5 g, 14 5 mmol, 1 eq) The mixture was stirred at room temperature for 1 h then Et_2O (36 ml) and celite were added The mixture was stirred again for 20 min then filtered on silica gel The silica pad was rinced several times with Et_2O After solvents evaporation and chromatography, 7 was isolated as a colorless oil (94 %, conversion 95 %) TLC Rf 0 41 (PE-AE 80-20), $[\alpha]_D^{22}$ + 59 8° (C=2 68, CH_2Cl_2, ee >99 %), IR ($CHCl_3$) 3100, 3020, 2730, 1730, 1710, 1460, 1370, 1180, 1090, 1055, 980 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 90 (3H, t, J=7 4), 1 21-1 36 (2H, m), 1 60 (2H, sext, J=7 4), 1 77-1 89 (1H, m), 1 99-2 09 (1H, m), 2 24 (2H, t, J=7 4), 3 92 (1H, dd, J=12 0, J=9 1), 4 48 (1H, dd, J=12 0, J=6 1), 9 50 (1H, d, J=4 4), ^{13}C NMR ($CDCl_3$) δ 12 58, 13 48, 18 30, 22 34, 26 55, 35 94, 62 13, 173 27, 199 77

(1R,2R)-1-butyryloxymethyl-2-[(Z)-hex-1-enyl]cyclopropane (8)

In a 1 l flask charged with pentyltriphenylphosphonium bromide (10 25 g, 24 80 mmol, 2 eq) and THF (180 ml) cooled to -30°C, NaHMDS (1M in THF, 24 8 ml, 24 8 mmol, 2 eq) was slowly added The orange mixture was allowed to warm to room temperature within 20 min, then cooled to -30°C, and dry, freshly distilled HMPT (46 ml, 8 eq) was added After cooling to -65°C, the aldehyde 7 (2 11 g, 12 40 mmol, 1 eq) previously dried on molecular sieves in THF (20 ml) was added dropwise over 20 min The orange coloration slowly disappeared The mixture was allowed to warm to room temperature and then partitioned twice between pentane (200 ml) and water (200 ml) The organic layer was washed with brine and dried, concentrated The brown oil so obtained was purified by flash chromatography to afford 8 (2 75 g, 99 %, Z/E >99/1) as a colorless oil TLC Rf 0 69 (PE-AcOEt 95-5), $[\alpha]_D^{22}$ - 95 3° (C=0 70, CH_2Cl_2, ee >99 %), IR (film) 3070, 3010, 1735, 1645, 1460, 1375, 1365, 1300, 1280, 1250, 1180, 1090, 1040, 980 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 35-0 43 (1H, m), 0 91 (3H, t, J=7 0), 0 95 (3H, t, J=7 4), 0 97-1 07 (1H, m), 1 29-1 42 (5H, m), 1 65 (2H, sext, J=7 4), 1 67-1 82 (1H, m), 2 11-2 21 (2H, m), 2 28 (2H, t, J=7 4), 3 97 (1H, dd, J=11 7, J=8 1), 4 15 (1H, dd, J=11 7, J=7 2), 5 04 (1H, ddt, J=10 7, J=9 2, J=1 5), 5 46 (1H, dtd, J=10 7, J=7 4, J=1 0), ^{13}C NMR ($CDCl_3$) δ 12 22, 13 62, 13 95, 14 17, 16 59, 18 46, 22 29, 27 30, 31 74, 36 23, 65 06, 127 36, 132 10, 173 74, mass spectrum, m/e (intensity), 224 (M^+, 7), 136 (12), 107 (8), 93 (36), 81 (22), 80 (78), 79 (100), 71 (92), 67 (28) Anal Calcd for $C_{14}H_{24}O_2$ C, 74 95, H, 10 78 Found C, 74 67, H, 10 79

(1R,2S)-1-[(Z)-hex-1-enyl]-2-vinylcyclopropane (9)

K_2CO_3 (6 10 g, 44 2 mmol, 4 eq) was added at room temperature to a stirred solution of ester 8 (2 48 g, 11 05 mmol, 1 eq) in MeOH (22 ml) After 15 min, the mixture was quenched with aqueous NH_4Cl After extraction with CH_2Cl_2, drying and solvents evaporation, the crude product was purified by flash chromatography to give (1R,2R)-1-[(Z)-hex-1-enyl]-2-hydroxymethylcyclopropane (1 57 g, 92 %) as a colorless oil TLC Rf 0 63 (PE-AcOEt 70-30), $[\alpha]_D^{22}$ - 94 9° (C=1 75, CH_2Cl_2, ee >99 %), IR (film) 3340, 3070, 3010, 1645, 1465, 1035, 1015 cm^{-1}, ^1H NMR ($CDCl_3$) δ

0 33-0 39 (1H, m), 0 91 (3H, t, J=7 0), 0 95-1 04 (1H, m), 1 32-1 49 (5H, m), 1 66-1 78 (1H, m), 2 09 (OH), 2 14-2 29 (2H, m), 3 49 (1H, dd, J=11 6, J=8 5), 3 71 (1H, dd, J=11 6, J=6 6), 5 09 (1H, ddt, J=10 8, J=9 4, J=1 4), 5 47 (1H, dtd, J=10 8, J=7 3, J=1 0), ^{13}C NMR ($CDCl_3$) δ 12 11, 13 76, 13 76, 20 48, 22 19, 27 16, 31 65, 63 35, 127 76, 131 81, mass spectrum, m/e (intensity), 154 (M^+, 6), 123 (6), 93 (17), 81 (51), 80 (17), 79 (37), 77 (16), 69 (19), 68 (31), 67(100)

In 100 ml flask charged with 20 ml CH_2Cl_2, at room temperature, were introduced under argon PCC (3 0 g, 13 92 mmol, 2 14 eq), NaOAc (0 280 g, 3 41 mmol, 0 52 eq) and molecular sieves 3 Å (2 5 g) A solution of (1R,2R)-1-[(Z)-hex-1-enyl]-2-hydroxymethylcyclopropane (1 00 g, 6 48 mmol, 1 eq) in CH_2Cl_2 (14 ml) was added After 30 min, Et_2O (34 ml) and celite were added The mixture was stirred again for 20 min then filtered on silica gel The filter cake was rinced with Et_2O and the organic layer was concentrated The crude product was purified by flash chromatography to afford (1R,2R)-1-formyl-2-[(Z)-hex-1-enyl]cyclopropane (0 835 g, 88 %, conversion 96 %) as a colorless oil TLC Rf 0 76 (PE-AE 80-20), $[\alpha]_D^{22}$ - 244 8° (C=0 62, CH_2Cl_2, ee >99 %), IR (film) 3080, 3020, 2750, 2730, 1705, 1650, 1460, 1450, 1430, 1395, 1370, 1190, 1170, 1050, 965, 940 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 90 (3H, t, J=7 0), 1 25-1 45 (4H, m), 1 37-1 50 (2H, m), 2 03-2 19 (3H, m), 2 23-2 37 (1H, m), 5 30 (1H, ddt, J=10 7, J=8 8, J=1 5), 5 52 (1H, dtd, J=10 7, J=7 4, J=1 2), 9 27 (1H, d, J=5 7), ^{13}C NMR ($CDCl_3$) δ 13 83, 15 27, 21 51, 22 22, 27 27, 30 10, 31 42, 125 23, 133 70, 200 83

To a suspension under argon of methyltriphenylphosphonium bromide (2 91 g, 8 15 mmol, 1 8 eq) in Et_2O (40 ml) vigourously stirred at room temperature, was added dropwise NaHMDS (1M in THF, 8 15 ml, 8 15 mmol, 1 8 eq) A yellow color immediatly formed The ylide was then cooled to -78°C and the aldehyde (1R,2R)-1-formyl-2-[(Z)-hex-1-enyl]cyclopropane (0 690 g, 4 53 mmol, 1 eq), previously dried on molecular sieves in Et_2O (5 ml), was added After 5 min, the mixture was allowed to warm to room temperature, filtered on silica gel then concentrated The crude product was purified by flash chromatography to give **9** (0 660 g, 97 %) as a colorless oil TLC Rf 0 98 (pentane), $[\alpha]_D^{22}$ - 124 8° (C=2 35, CCl_4, ee >99 %), IR (film) 3080, 3010, 1635, 1460, 1420, 1380, 1030, 980, 950, 890, 745 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 50-0 58 (1H, m), 0 90 (3H, t, J=7 0), 1 10-1 18 (1H, m), 1 26-1 44 (4H, m), 1 65-1 77 (1H, m), 1 77-1 88 (1H, m), 2 10-2 22 (2H, m), 4,98 (1H, ddd, J=10 2, J=2 0, J=0 7), 5 05 (1H, ddt, J=10 8, J=9 2, J=1 5), 5 11 (1H, ddd, J=17 0, J=2 0, J=0 7), 5 44 (1H, dtd, J=10 8, J=7 3, J=1 0), 5 55 (1H, ddd, J=17 0, J=10 2, J=8 6), ^{13}C NMR ($CDCl_3$) δ 13 92, 14 67, 17 15, 22 32, 22 32, 27 27, 31 84, 114 23, 128 36, 131 04, 138 09

(6R)-6-butylcyclohepta-1,4-diene: (-)-Dictyopterene C'

The cyclopropane **9** (0 240 g, 1 6 mmol) in CCl_4 (3 2 ml) was introduced in a glass tube which was then sealed under vacuum After 6 h in an oil bath at 80°C and cooling, the tube was opened and CCl_4 evaporated The colorless recovered oil was chromatographically pure (0 240 g, 100%) TLC Rf 0 98 (pentane), $[\alpha]_D^{22}$ - 16 8° (C=0 27, $CHCl_3$, ee >99 %), IR (film) 3020, 1650, 1370 cm^{-1}, ^1H

NMR ($CDCl_3$) δ 0 86-0 95 (3H, m), 1 24-1 45 (6H, m), 2 03-2 28 (2H, m), 2 40-2 53 (1H, m), 2 64-2 77 (1H, m), 2 89-3 02 (1H, m), 5 55-5 76 (4H, m), ^{13}C NMR ($CDCl_3$) δ 14 07, 22 85, 28 35, 29 44, 32 88, 36 03, 37 18, 127 21, 128 10, 129 88, 136 82

5,5-dipentyldibenzophospholium bromide (10)

To a solution of diisopropylamine (22 06 ml, 157 4 mmol, 3 3 eq) in THF (100 ml) at room temperature, was slowly added under argon phenyllithium (2M in cyclohexane-ether (75/25), 78 70 ml, 157 4 mmol, 3 2 eq) After 15 min, dried powdered tetraphenylphosphonium bromide (20 g, 47 7 mmol, 1 eq) was added A gentle evolution of heat occured The mixture was stirred overnight at room temperature, heated under reflux for 3 h, cooled in ice and treated over 45 min with aqueous hydrochloric acid (4M, 80 ml) 10 min after the end of HCl addition, the layers were separated and the aqueous layer was extracted once with Et_2O The organic layer was washed twice with saturated aqueous NaCl, once with saturated aqueous $KHCO_3$ After drying and solvents evaporation, the recovered paste was dessicated in high vacuum The solid was triturated with a mixture of MeOH-pentane (1-1), collected, dried in vacuum, recrystallized from EtOH, and the collected solid finally washed with cold MeOH After drying in vacuum, 5-phenyldibenzophosphole was isolated (9 93 g, 80 %) and had m p 93°C

In a 100 ml flask charged with 5-phenyldibenzophosphole (6 78 g, 26 mmol, 1 eq) and THF (52 ml), was added at room temperature powdered lithium (0 360 g, 52 mmol, 2 eq) After refluxing for 4 h and cooling to room temperature, pentyl bromide (6 45 ml, 52 mmol, 2 eq) was slowly added, the mixture color turned to bright red After stirring for 2 h, the reaction was quenched by aqueous NH_4Cl (20 ml) added through cannula to prevent air oxydation The organic layer was decanted under argon and the aqueous layer was washed with Et_2O (4 x 5 ml) The organic layers were combined, dried and concentrated To the recovered crude oil, was added under argon pentyl bromide (12 90 ml, 104 mmol, 4 eq) After refluxing for 3 h, a precipitate formed, the solid was filtered off, rinced with Et_2O then recristallized in a mixture of THF-CH_2Cl_2 (7-3) **10** was recovered as a white solid (6 30 g, 60 %) and had m p 227 °C ^1H NMR ($CDCl_3$) δ 0 65 (6H, t, J=7 0), 1 02-1 31 (12H, m), 3 65 (4H, m), 7 61 (1H, dddd, J=7 7, J=7 5, J_{H-P}=4 0, J=0 6), 7 77 (1H, dddd, J=8 0, J=7 5, J_{H-P}=1 4, J=1 0), 7 94 (1H, dd, J=7 7, J_{H-P}=2 6, J=1 0), 8 75 (1H, dd, J_{H-P}=8 5, J=8 0), ^{13}C NMR ($CDCl_3$) δ 13 42 (q), 21 32 (dt, J_{C-P}=4 3), 21 93 (dt, J_{C-P}=12 1), 22 59 (t), 31 96 (dt, J_{C-P}=14 5), 120 11 (ds, J_{C-P}=84 5), 122 25 (dd, J_{C-P}= 9 1), 130 52 (dd, J_{C-P}=11 4), 133 53 (dd, J_{C-P}=11 2), 135 17 (d), 144 44 (ds, J_{C-P}=14 87)

(1R,2R)-1-butyryloxymethyl-2-[(E)-hex-1-enyl]cyclopropane (11)

In a 250 ml flask under argon charged with the phospholium salt **10** (6 02 g, 14 8 mmol, 1 1 eq) and THF (130 ml), was added dropwise at room temperature NaHMDS (1M in THF, 14 8 ml, 14 8 mmol, 1 1 eq) The orange ylide was cooled to -78°C then the aldehyde **7** (2 3 g, 13 5 mmol, 1 eq), previously dried by molecular sieves in THF (10 ml), was added After 5 minutes, the mixture was

allowed to warm to room temperature then transfered in glass tubes which were sealed under vacuum After 30 minutes in an oil bath at 110°C, the sealed tubes were cooled and opened After hydrolysis, extraction with pentane and solvent evaporation, the crude product was purified by flash chromatography to afford **11** (2 73 g, 90 %, E/Z >99/1) as a colorless oil TLC Rf 0 69 (PE-AcOEt 95-5), $[\alpha]_D^{22}$ - 6 3° (C=1 27, CH_2Cl_2, ee >99 %), IR (film) 3070, 1730, 1455, 1375, 1360, 1300, 1280, 1250, 1175, 1090, 1040, 980, 960 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 40-0 47 (1H, m), 0 86-0 95 (1H, m), 0 88 (3H, t, J=7 0), 0 95 (3H, t, J=7 4), 1 23-1 38 (5H, m), 1 54-1 67 (1H, m), 1 66 (2H, sext, J=7 4), 1 95-2 04 (2H, m), 2 29 (2H, t, J=7 4), 3 94 (1H, dd, J=11 6, J=8 3), 4 14 (1H, dd, J=11 6, J=7 0), 5 21 (1H, ddt, J=15 3, J=7 8, J=1 3), 5 55 (1H, dt, J=15 3, J=7 0), ^{13}C NMR ($CDCl_3$) δ 10 34, 13 61, 13 89, 16 28, 18 37, 18 49, 22 12, 31 68, 32 24, 36 25, 64 90, 127 31, 132 21, 173 77, mass spectrum, m/e (intensity), 224 (M^+, 12), 136 (16), 107 (7), 93 (37), 81 (27), 80 (76), 79 (100), 71 (88), 67 (33) *Anal Calcd for* $C_{14}H_{24}O_2$ C, 74 71, H, 10 93 *Found* C, 74 95, H, 10 78

cis-(1R,2R)-1-formyl-2-[(E)-hex-1-enyl]cyclopropane (12)

K_2CO_3 (4 62 g, 33 42 mmol, 3 eq) was added, at room temperature, to a vigorously stirred solution of the ester **11** (2 5 g, 11 14 mmol, 1 eq) in MeOH (11 ml) After 25 minutes, the mixture was diluted with aqueous NH_4Cl, extracted with CH_2Cl_2 Solvent evaporation and flash chromatography yielded (1R,2R)-1-[(E)-hex-1-enyl]-2-hydroxymethylcyclopropane (1 55 g, 90 %) TLC Rf 0 63 (PE-AcOEt 70-30), $[\alpha]_D^{22}$ - 7 6° (C=0 75, CH_2Cl_2, ee >99 %), IR (film) 3340, 3070, 3010, 1465, 1035, 1015, 960 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 34-0 41 (1H, m), 0 83-0 93 (1H, m), 0 87 (3H, t, J=7 0), 1 21-1 38 (5H, m), 1 50-1 62 (1H, m), 1 74 (OH), 1 95-2 05 (2H, m), 3 45 (1H, dd, J=11 5, J=8 7), 3 71 (1H, dd, J=11 5, J=6 3), 5 23 (1H, ddt, J=15 2, J=8 2, J=1 3), 5 61 (1H, dt, J=15 2, J=7 0), ^{13}C NMR ($CDCl_3$) δ 10 49, 13 84, 18 06, 20 36, 22 13, 31 69, 32 29, 63 23, 127 64, 132 21, mass spectrum, m/e (intensity), 154 (M^+, 6), 123 (8), 93 (16), 81 (47), 80 (17), 79 (38), 77 (15), 69 (21), 68 (26), 67 (100)

In a 100 ml flask charged at room temperature with CH_2Cl_2 (20 ml), were added under argon PCC (3 35 g, 15 56 mmol, 2 eq), NaOAc (0 510 g, 6 22 mmol, 0 8 eq), molecular sieves 3 Å (1 2 g) and finally (1R,2R)-1-[(E)-hex-1-enyl]-2-hydroxymethylcyclopropane (1 20 g, 7 78 mmol, 1 eq) in CH_2Cl_2 (16 ml) After stirring 30 minutes, Et_2O (32 ml) and celite were added The mixture was stirred again for 20 min then filtered on silica gel and the filter cake rinced with Et_2O Solvents evaporation and flash chromatography yielded (1R,2R)-1-formyl-2-[(E)-hex-1-enyl]cyclopropane **12** (0 976 g, 85 %, conversion 97 %) TLC Rf 0 76 (PE-AcOEt 80-20), $[\alpha]_D^{22}$ + 8 0° (C=0 15, CH_2Cl_2, ee >99 %), IR (film) 3080, 2760, 2720, 1705, 1460, 1435, 1395, 1375, 1360, 1170, 1050, 960, 930 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 88 (3H, t, J=7 0), 1 22-1 36 (4H, m), 1 34-1 41 (1H, m), 1 43-1 51 (1H, m), 1 95-2 07 (3H, m), 2 07-2 21 (1H, m), 5 39 (1H, ddt, J=15 3, J=8 0, J=1 3), 5 68 (1H, dtd, J=15 3, J=7 0, J=0 6), 9 27 (1H, d, J=5 5), ^{13}C NMR ($CDCl_3$) δ 13 82, 14 17, 22 10, 25 94, 29 76, 31 40, 32 05,

125 49, 133 95, 201 08

trans-(1S,2R)-1-formyl-2-[(E)-hex-1-enyl]cyclopropane (13)

To a solution under argon of NaOMe (0 273 g, 5 06 mmol, 1 1 eq) in MeOH (48 ml), was added the cis aldehyde **12** (0 700 g, 4 60 mmol, 1 eq) in MeOH (2 ml) The mixture was refluxed for 48 h and then quenched with aqueous NH_4Cl After extraction with Et_2O, solvents evaporation, flash chromatography yielded a 9 to 1 mixture of trans and cis aldehyde isomers **13** and **12** (0 580 g, 83 %) TLC Rf 0 76 (PE-AcOEt 80-20), $[\alpha]_D^{22}$ + 119 7° (C=0 64, CH_2Cl_2, ee >99 %, trans-cis 90-10), IR (film) 3080, 3010, 2720, 1705,1460, 1435, 1395, 1375, 1190, 1160, 960 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 85-0 97 (3H, t, J=7 0), 1 10-1 18 (1H, m), 1 22-1 40 (4H, m), 1 44-1 51 (1H, m), 1 81-1 89 (1H, m), 1 95-2 05 (2H, m), 2 01-2 13 (1H, m), 5 04 (1H, ddt, J=15 3, J=8 1, J=1 2), 5 62 (1H, dt, J=15 3, J=6 8), 9 15 (1H, d, J=5 4), ^{13}C NMR ($CDCl_3$) δ 13 89, 15 10, 22 16, 25 18, 31 43, 31 68, 32 05, 128 38, 132 37, 199 96

(+)-Dictyopterene A and (+)-Dictyopterene C'

To a suspension under argon of methyltriphenylphosphonium bromide (1 72 g, 4 92 mmol, 1 5 eq) in Et_2O (45 ml) vigorously stirred at room temperature, was added dropwise NaHMDS (1M in THF, 4 92 ml, 4 92 mmol, 1 5 eq) After cooling to -78°C, the 9 to 1 mixture of trans-cis aldehyde **13** and **12** (0 500 g, 3 28 mmol, 1 eq), previously dried by molecular sieves in Et_2O (4 ml), was added After 5 minutes, the mixture was filtered on silica gel, and the solvents evaporated Flash chromatography with pentane yielded a 9 to 1 mixture of (+)-Dictyopterene A and (+)-Dictyopterene C' (0 468 g, 95 %) TLC Rf 0 98 (pentane)

This Dictyopterenes mixture was further separated by repetitive plate chromatography on silica gel impregnated by $AgNO_3$

(1R,2R)-1-[(E)-hex-1-enyl]-2-vinylcyclopropane: Dictyopterene A

$[\alpha]_D^{22}$ + 75 3° (C=0 15, $CHCl_3$, ee >99 %), IR (film) 3070, 3000, 1630, 1460, 980, 960, 900 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 74-0 84 (2H, m), 0 89 (3H, t, J=7 0), 1 25-1 44 (6H, m), 1 94-2 04 (2H, m), 4 85 (1H, dd, J=10 3, J=1 7), 5 03 (1H, dd, J=17 1, J=1 7), 5 06 (1H, dt, J=15 2, J=1 3), 5 42 (1H, ddd, J=17 1, J=10 3, J=8 0), 5 48 (1H, dt, J=15 2, J=7 0), ^{13}C NMR ($CDCl_3$) δ 13 88, 14 77, 22 19, 23 53, 24 25, 31 80, 32 14, 111 78, 129 14, 131 57, 140 80

(6S)-6-butylcyclohepta-1,4-diene: (+)-Dictyopterene C'

$[\alpha]_D^{22}$ + 17 1° (C=0 32, $CHCl_3$, ee >99 %) All spectral data were identical to those of (-)-Dictyopterene C'

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A cyclopropane compound of reported high optical purity was also obtained using the cheaper enzyme PLE (3$ / 10 mmol of substrate) PLE catalyzed hydrolysis of dimethyl cis-cyclopropane-1,2-dicarboxylate yielded the corresponding monoester with reported 94% ee and even 97% ee Schneider, M , Engel, N , Boensmann, H *Angew Chem Int Ed Engl* **1984**, *23* , 67 Sabbioni, G , Jones, J B *J Org Chem* **1987**, *52*, 4565 However the Schneider's group described an acid ester having an optical rotation of - 15° (C 1, $CHCl_3$) for a reported 94% ee (determined directly on the acid ester) The same compound was described by the Jones's group with an optical rotation of - 13 4° (C 0 97, $CHCl_3$) for a reported 97% ee (determined after a 2 step derivatization) Moreover opposite absolute configurations are reported for the same acid ester
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