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Regioselective Synthesis of α,α-Dialkylcyclopentanones from 1-Hydroxycyclobutanecarboxylic Acid or from O-Protected Cyclobutanone Cyanohydrin.

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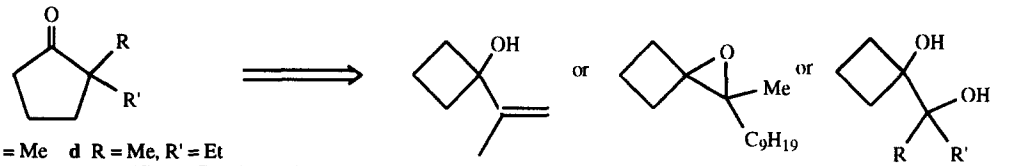
Abstract: 1-(1-Hydroxyalkyl)cylobutanols **4a-f**, readily available either from 1-hydroxycyclobutane carboxylic acid or from O-protected cyclobutanone cyanohydrin, appeared the most suitable precursors for a regioselective synthesis of cyclopentanones α,α–disubstituted with various similar or different alkyl, alkenyl, aryl or cycloalkyl groups. The key steps consist of acid or Grignard reagent induced $C_4 \rightarrow C_5$ ring expansions.

The synthesis of cyclopentanoid compounds is still a subject of current interest because of the discovery of a growing number of biologically active natural and non natural substances that contain the five-membered ring moiety. As the α-alkylation of cyclopentanones is often beset by side reactions including aldol condensation, regioisomer formation due to the ready equilibration among 2-alkylcyclopentanone enolates and polyalkylation, this method is not efficiently amenable to large scale preparation of α,α-dialkylcyclopentanones **1**.[1] However, the Bronsted and Lewis acids induced $C_4 \rightarrow C_5$ ring expansions of the 1-(prop-2-enyl)cyclobutanol **2**,[2] of the oxaspiro[2.3]hexane **3**[3] and of the 1-hydroxycyclobutylcarbinols **4a,b**[4] appeared able to overcome this synthetic problem (Scheme 1).



1a R,R' = Me **d** R = Me, R' = Et
b R,R' = Ph **e** R = $(CH_2)_2$-CH=CH_2, R' = CH=CH_2
c R,R' = Et **f** R = c-C_5H_9, R' = CH=CH_2

2 **3** **4a-f**

Scheme 1

The synthons **2-4a,b** have been previously prepared from cyclobutanone,[5] available from $C_3 \rightarrow C_4$ ring expansion of oxaspiropentane[6] or of cyclopropylcarbinol,[7] for instance.[8] We report here that both 1-hydroxy cyclobutanecarboxylic acid **5** and cyclobutanone cyanohydrin **6** constitute efficient precursors to achieve a general and regioselective synthesis of α,α-dialkylcyclopentanones such as **1a-f**, through the intermediary of the diols **4a-f** (Scheme 2).

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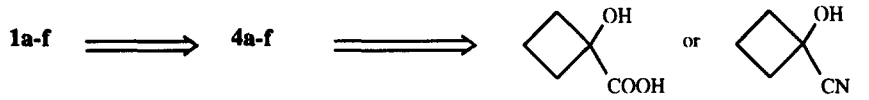
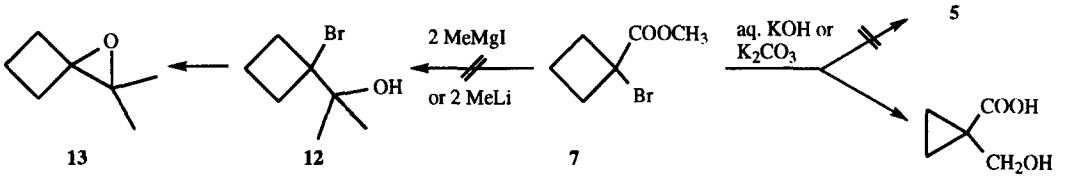


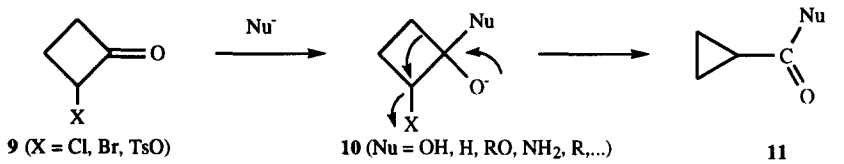
Scheme 2

The preparation of the α-hydroxyacid **5** was also reported from cyclobutanone via the cyanohydrin **6**, in 19[9] and 74% yields;[4] in order to simplify this process, we have investigated more direct accesses to **5** and **6**.



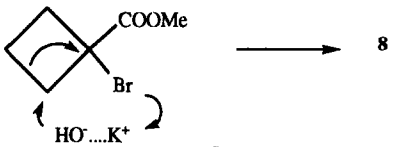
Scheme 3

First of all, cyclobutanecarboxylic acid, a cheap starting material[10] readily available from the thermal decarboxylation of 1,1-cyclobutanedicarboxylic acid resulting from base-induced condensation of diethyl malonate with 1,3-dihalopropanes,[11-13] was brominated in the presence of 10% of red phosphorus to give after the addition of methanol the methyl 1-bromocyclobutanecarboxylate **7** in 90% yield.[14] However, contrary to previous reports, reactions of the α–bromo ester **7** either with refluxing aqueous potassium hydroxide[14] or aqueous potassium carbonate[15] solutions did not provide us the expected 1-hydroxycycylobutanecarboxylic acid **5**, but exclusively the 1-(hydroxymethyl)cyclopropanecarboxylic acid **8**, in 81 and 95% yield, respectively (Scheme 3).[16]



Scheme 4

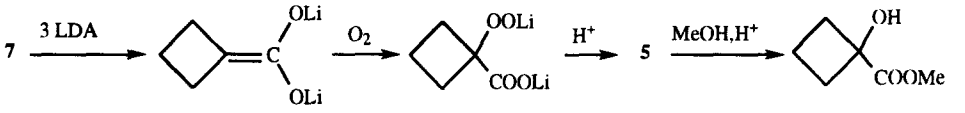
The easy interconversion which occurs among cyclobutane, cyclopropane and open-chain related frameworks have been extensively studied.[17] In particular the stereoselective rearrangement of α-halo- or α-tosyloxycyclobutanones **9** into cyclopropanecarboxylic acid derivatives **11**, has been shown to involve the addition of simple nucleophiles (*e.g.*, H_2O, EtOH, NaOH, EtONa, NH_3, $LiAlH_4$, RMgX, ...) to the carbonyl carbon atom of **9** to produce the intermediary **10**, which then undergo displacement of the α-halide (or tosyloxy) group with concerted 1,2-migration of the C_1-C_4 cyclobutanic bond, thus following the semi-benzilic rearrangement mechanism (Scheme 4).[18]



Scheme 5

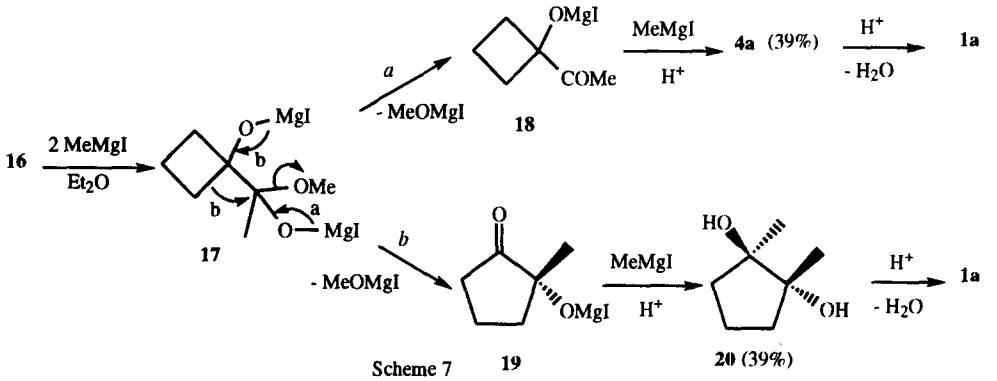
Analogously, displacement of bromine in **7** favoured likely by the presence of potassium cations in the medium should be concerted with the migration of the C_2-C_3 cyclobutanic bond, entailing also a $C_4 \rightarrow C_3$ ring contraction and formation of **8** after saponification (Scheme 5).[19] These two rearrangements, of **7** into **8** and of **9** into **11**, are in fact particular cases of the $S_{N}2'$ reaction mechanism because, as for allylic substrates, simultaneous movement of three pairs of electrons are involved.[20]

The β-hydroxy acid **8** which constitutes a useful synthon, was previously obtained in 43% yield from the partial oxidation of 1,1-bis(hydroxymethyl)cyclopropane;[21] otherwise, it has been reported that solvolysis of the bromoester **7** in refluxing glacial acetic acid containing 1.1 equiv of silver acetate led in 43% yield to the methyl ester derivative of **8**, besides 12% of a homoallylic isomer,[22] arising likely from the ring opening of an intermediate cyclobutyl cation.[17] It must be underlined that the formation of 1-cyclobutenecarboxylic acid, resulting of simple base-induced dehydrobromination of **7** was not observed under these conditions. On the other hand, reaction of the bromoester **7** with either 2 equiv of methylmagnesium bromide or methyllithium provided neither the bromohydrin **12**, nor the expected 2,2-dimethyloxa[2.3]spirohexane **13**; but the formation of several non identified compounds was observed when this reaction was attempted under various conditions (Scheme 3).



Scheme 6

Adaptation of the procedure published for the synthesis of 1-methoxycyclobutanecarboxylic acid,[23]offered then a suitable access to the required α-hydroxy acid **5**;[10,24] thus, simple oxygen bubbling at ambient temperature in a solution of the lithium enolate dianion **14** in tetrahydrofuran , obtained upon treatment of **7** with an excess of lithium diisopropylamine (3 equiv in THF at 0°C), led to the dilithium 2-peroxycarboxylate dianion **15**. Then, hydrolysis with hydrochloric acid provided **5** and esterification by acidic methanol the methyl 1-hydroxycyclobutanecarboxylate **16** in 85% overall yield (Scheme 6).



Scheme 7

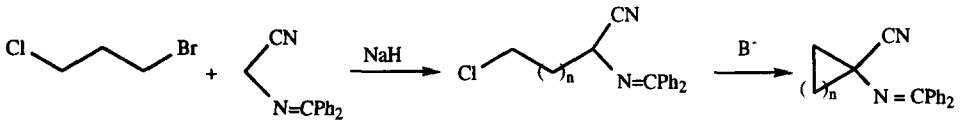
Contrary to the previous report[4], addition of 3.3 equiv of methylmagnesium iodide to **16** in diethyl ether gave in 78% yield a 1:1 mixture of 1-(2-hydroxyprop-2-yl)cyclobutanol **4a**[25] and of *trans* 1,2-dihydroxy-1,2-

dimethylcyclopentane **20**.[26] Therefore the diiodomagnesium glycolate **17** resulting from the reaction of the hydroxyester **16** with 2 equiv of MeMgI, underwent equally elimination of one equiv of MeOMgI either from the iodomagnesium cyclobutylcarbinolate moiety to form the methyl ketone **18** (*way a*) or from the iodomagnesium cyclobutanolate to form the cyclopentanone derivative **19** (*way b*). The formation of this five-membered ring **19** involved therefore the expected $C_4 \rightarrow C_5$ ring expansion, however in this case this rearrangement was obtained under basic conditions. Then, reaction of **18** and **19** with the third equiv of MeMgI gave, after acidic hydrolysis, the diols **4a** and *trans*-**20** respectively. These diols were inseparable by liquid chromatography, but the configuration of **20** is likely *trans* because addition of Grignard reagents to 2-hydroxy-2-alkylcyclopentanone derivatives resulting from the stepwise reaction of 1,2-cyclopentanedione with vinylmagnesium bromide has been reported to provide *trans* 1,2-dialkyl-1,2-cyclopentanediols, exclusively.[27] Finally, both these isomeric diols underwent rearrangement upon treatment either with freshly prepared anhydrous polyphosphoric acid (from H_3PO_4/P_2O_5),[4] or with trifluoroacetic acid in CH_2Cl_2 at room temperature to yield the 2,2-dimethyl cyclopentanone **1a**[28] in 66 % and 92% yields, respectively (Scheme 7, Table 1).[29]

Otherwise, reaction of the α-hydroxy ester **16** with 4 equiv of phenylmagnesium iodide in diethyl ether provided exclusively the diphenylcarbinol **4b** in 87% yield after recrystallization, which upon treatment with a 10 fold excess of polyphosphoric acid, was rearranged as previously reported into the 2,2-diphenyl cyclopentanone **1b** with 84% overall yield (Table 1).[4]

In conclusion the 2,2-dimethyl- **1a**[28] and 2,2-diphenylcyclopentanone **1b**[4] can be obtained regioselectively from cheap cyclobutanecarboxylic acid[10] with 61 and 72% overall yields, respectively.

Alternatively, the cyclobutanone cyanohydrin **6** can be also considered as suitable precursor of diols **4a-f**; however, in spite of its high synthetic potential the use of **6** as synthetic intermediary has, surprisingly, only been reported twice in the literature, *i.e.*, for the patented preparation of 2-amino-5-spirooxazoline-4-one derivatives,[9] which exhibit central nervous system activity and are active as either stimulants or depressants, and for the preparation of 2-amino- and 2-hydroxycyclopentanones.[30] We have then investigated a new and more convenient preparation of the cyanohydrin **6**, previously prepared from cyclobutanone.[4,9]

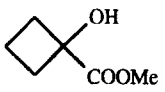
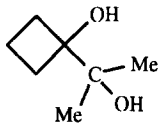
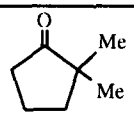
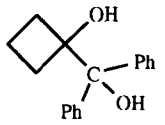
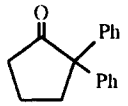
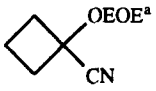
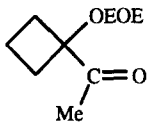
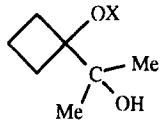
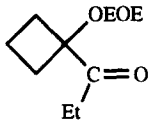
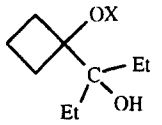
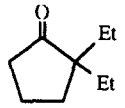
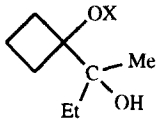
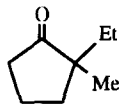
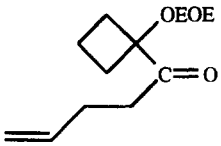
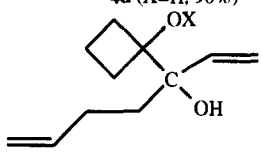
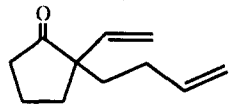
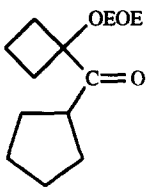
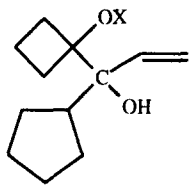
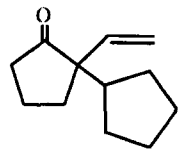


21 **22** **23a** (n=1) **b** (n=2, 93.5%) **24a** (100%) **b** (0%)

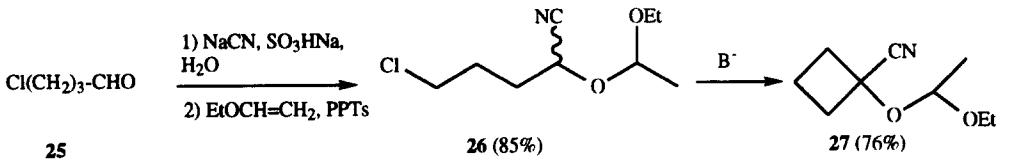
Scheme 8

For this purpose, 1-bromo-3-chloropropane **21** was first reacted with the anion formed upon treatment of the Schiff base **22**[31] with one equiv of NaH to provide the 5-chloro-2[*N*-(diphenylmethylene)amino] pentanenitrile **23b** in 93.5% yield. However, while the benzophenone imine of 2-amino-4-chlorobutyronitrile **23a**, readily available from acrolein, underwent readily base-induced (K_2CO_3, KOH, MeONa, NEt_3,...) quantitative cyclization to give the 1-aminocyclopropanecarbonitrile **24a**, which is a suitable precursor of 2,3-methanoaminoacid (ACC),[32] unfortunately treatment of **23b** under various basic conditions did not produce the expected 1-aminocyclobutanecarbonitrile **24b**, but led only to tarry residue; although basic treatment of δ-chloro ketimines related to **23b**, have been recently reported to offer cyclobutane derivatives (Scheme 8).[33]

Table 1: *Synthesis of α,α-disubstituted cyclopentanones from methyl 1-hydroxycyclobutanecarboxylate* ***16*** *and from O-protected cyclobutanone cyanhydrin* ***27****, via the diols* ***4a-f*** *and* ***20****.*

Precursors	Cyclobutyl ketones	Hydroxycyclobutyl carbinols	Cyclopentanones
		**20**[26](39%) + 	
16		**4a**[25] (39%)	**1a**[28] (92%)
16			
		4b[4] (87%)	**1b**[4] (96.5%)
			**1a**[28] (93%)
27	**30a** (92%)	**31a** (X=EOE, 91%) **4a**[25] (X=H, 86%)	
27			
	30c (87%)	**31c** (X=EOE, 81%) **4c** (X=H, 91%)	**1c**[37] (92%)
	30a or **30c**		
		31d (X=EOE, 90-94%) **4d** (X=H, 90%)	**1d**[38] (89%)
27			
	30e (65%)	**31e** (X=EOE, 91%) **4e** (X=H, 95%)	**1e** (89%)
27			
	30f (95%)	**31f** (X=EOE, 91%) **4f** (X=H, 100%)	**1f** (98%)

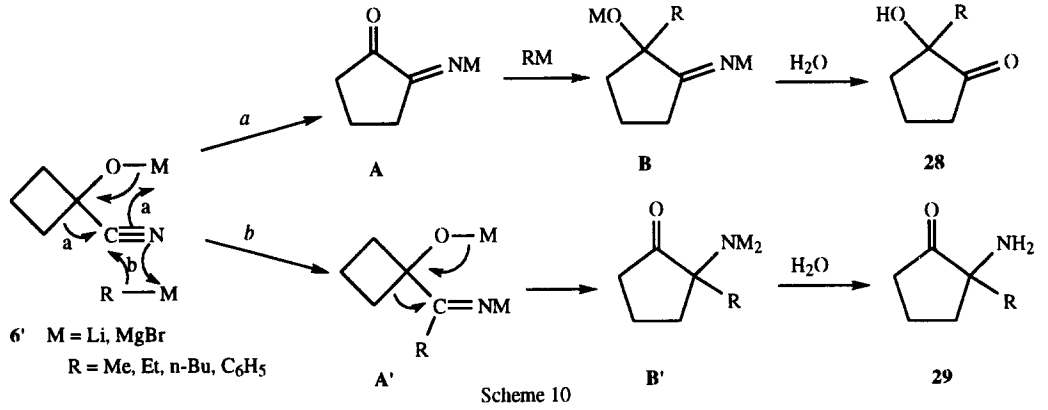
a) EOE is used for the 1-ethoxyethyl protective group.



25 26 (85%) 27 (76%)

Scheme 9

These results led us to consider that the cyanohydrin of the chloroaldehyde **25** should provide an effective precursor of the expected four-membered ring **6**. On that account we have then rediscovered the previous synthesis of small rings involving the Stork protected cyanohydrin method; as a matter of fact, this useful method has not received the attention and devolpment it really deserves.[34] Effectively, addition of sodium cyanide to a solution of 4-chlorobutyraldehyde **25**,[35] (readily available from partial oxidation of very cheap 4-chloro-1-butanol[36]) in water containing sodium bisulfite gave in 85% yield, after hydroxyl protection by ethyl vinyl ether, a 1:1 diastereomeric mixture of the cyanohydrins **26**, which underwent base-induced cyclization by the sodium salt of hexamethyldisilazane in refluxing benzene, to produce the O-protected cyclobutanone cyanohydrin **27** in 76% yield (Scheme 9).[34]



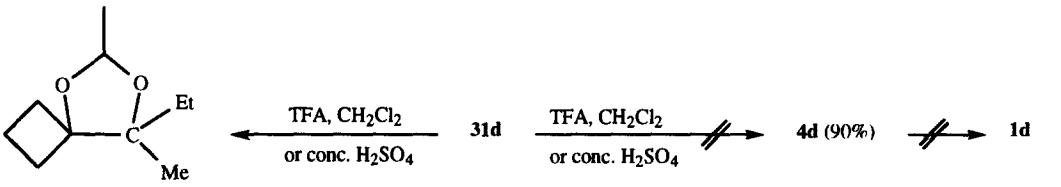
Scheme 10

It had been reported that the cyclobutanone cyanohydrin **6** reacts with an excess (2.5 equiv.) of organometallic reagents RM (MeLi, MeMgBr, EtMgBr, *n*-BuLi, C_6H_5MgBr) to give the 2-alkyl-2-hydroxy cyclopentanones **28** and/or the 2-alkyl-2-aminocyclopentanones **29**.[30] Two competitive pathways were then considered, involving :

- either $C_4 \rightarrow C_5$ ring expansion of the lithium or magnesium salts **6'** into the 1,2-cyclopentanedione monoimines **A**, followed by the addition of the organometallic reagents on the carbonyl moiety to give the cyclopentanol imines **B**, which after hydrolysis provided the α-hydroxyketones **28** (100% when RM = MeMgBr, *way a*)
- or addition of the organometallic reagents RM on the nitrile moiety of **6'** to give the (1-hydroxy cyclobutyl)carboimine salts **A'**, which underwent $C_4 \rightarrow C_5$ ring expansion into the α-aminocyclopentanone derivatives **B'**; then hydrolysis led to the α-aminoketones **29** (100% when RM = C_6H_5MgBr or n-BuLi, *way b*). A 1:1 mixture of the five-membered rings **28** and **29** was obtained when RM = MeLi or EtMgBr (Scheme 10).[30]

On the other hand, we have now found that the O-protected cyanohydrin **27** reacts directly with one equivalent of MeMgI to produce, after hydrolysis with an aqueous solution of ammonium chloride the cyclobutylmethyl ketone **30a** in 92% yield. Then, addition of a second equiv of Grignard reagent (CH_3MgI) to **30a** gave the dimethylcarbinol **31a** (91%) and after acidic hydrolysis (0.2M H_2SO_4) the wanted diol **4a**[25] in 86% yield. Finally treatment of **4a** with a catalytic amount of trifluoroacetic acid in CH_2Cl_2 at room temperature provided in 93% yield exclusively the expected 2,2-dimethylcyclopentanone **1a**,[28] which was therefore obtained in four steps from the O-protected cyclobutanone cyanohydrin **27** with 72% overall yield (Table 1).

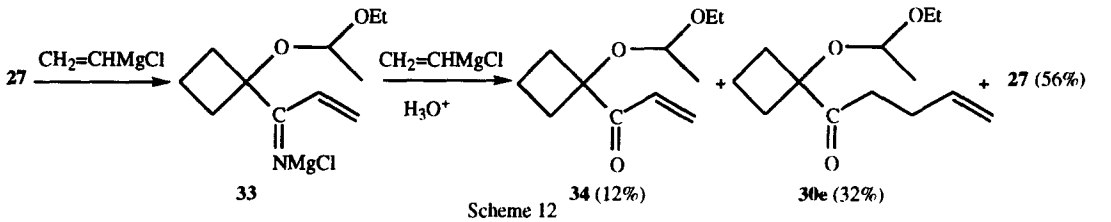
Likewise, reaction of **27** with one equiv of EtMgBr gave after hydrolysis (aq. NH_4Cl) the ethylketone **30c** in 87% yield, and after addition of one second equiv of EtMgBr the corresponding diethylcarbinol **31c** (81%). Deprotection with 0.2M H_2SO_4 provided in 91% yield the (1-hydroxycyclobutyl)diethylcarbinol **4c** and after the same treatment with trifluoroacetic acid in CH_2Cl_2 the 2,2-diethylcyclopentanone **1c**[37] in 92% yield, thus in 59% overall yield from **27** (Table 1). Moreover, addition of one equivalent of EtMgBr to the methylketone **30a** or addition of MeMgI to the ethylketone **30c**, produced the ethylmethylcarbinol derivative **31d** in 90 and 94% yields, respectively. Deprotection of **31d** (0.2M H_2SO_4) and treatment of the corresponding diol **4d** isolated in 90% yield, with trifluoroacetic acid (CH_2Cl_2) offered the 2-ethyl-2-methylcyclopentanone **1d**[38] in 89% yield (Table 1).



32 (95%)

Scheme 11

It must be underlined that treatment of the monoprotected diol **31d** with trifluoroacetic acid (or concentrated sulfuric acid) in CH_2Cl_2 did not lead directly to the ketone **1d**, via the diol **4d**, but differently to the acetal **32** in 95% yield, resulting from an intramolecular transacetalisation (Scheme 11).



33 34 (12%) 30e (32%)

Scheme 12

Reaction of the cyclobutanecarbonitrile **27** with one equiv of vinylmagnesium chloride gave after hydrolysis (aq. NH_4Cl) a 12:32:56 mixture of the vinylketone **34**, of but-3-enylketone **30e** and of **27**; while reaction of **27** with 3 equivalents of CH_2=CHMgCl led exclusively to **30e** in 85% yield. Likely **30e** arose from Michaël addition of the vinylic Grignard reagent to the intermediate cyclobutylvinylcarboimine chloromagnesium salt **33**; and the reaction of **33** appeared therefore faster than the reaction of **27** with CH_2=CHMgCl (Scheme 12, Table 1). Then reaction of the ketone **30e** with one equiv of vinylmagnesium

chloride produced the 3-cyclobutylhepta-1,6-dien-3-ol **31e** in 91 % yield, and after acidic hydrolysis (0.2 M H_2SO_4) the diol **4e** (95%), which underwent the expected ring expansion upon treatment with trifluoroacetic acid in CH_2Cl_2 at reflux, to provide exclusively the 2-(but-3-enyl)-2-vinylcyclopentanone **1e** in 89 % overall yield (Table 1).

Reaction of **27** with one equiv of cyclopentylmagnesium chloride provided after hydrolysis (aq. NH_4Cl) in 95 % yield the cyclobutyl cyclopentyl ketone **30f**, and after addition of one equiv of vinylmagnesium cloride the quaternary carbinol **31f** (97% yield). Then O-deprotection with 0.2 M H_2SO_4 led quantatively to the diol **4f**, which underwent finally the trifluoroacetic acid induced $C_4 \rightarrow C_5$ ring expansion in CH_2Cl_2 at room temperature into the 2-cyclopentyl-2-vinylcyclopentanone **1f** in 98% yield (Table 1).

In conclusion, the readily available O-protected cyclobutanone cyanohydrin **27** can also provide in four steps α,α-dialkylcyclopentanones such as **1a,c-f** in 59-90% overall yields. Moreover contrary to the hydroxy ester **16**, this second precursor allows the preparation of cyclopentanone derivatives α,α-disubstituted with various similar (e.g., **1a,c**) or different (e.g., **1d-f**) groups. The key steps consist of either acid induced $C_4 \rightarrow C_5$ ring expansion of 1-(1-hydroxyalkyl)cyclobutanols **4a-f** arising from both methyl α-hydroxy cyclobutanecarboxylic ester **16** and O-protected cyclobutanone cyanohydrin **27**, or of $C_4 \rightarrow C_5$ ring expansion induced by Grignard reagents of the α–hydroxyester **16** into α-alkyl-α-hydroxycyclopentanone derivatives, such as **19**, which on addition of a second equivalent of Grignard reagent led to 1,2-dihydroxy-1,2-dialkyl cyclopentanols **20**, precursor of **1a** by simple acid induced methyl migration.

EXPERIMENTAL

General: IR spectra were recorded on a Perkin Elmer 682 spectrophotometer. NMR spectra were recorded on a Bruker AM 250 or AC 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC/MS R.10-10 spectrometer. All reactions were carried out under an inert atmosphere of argon and monitored by thin-layer chromatography (TLC). TLC was performed on Merck silica gel 60F-254 precoated on glass.

1-(Hydroxymethyl)cyclopropanecarboxylic acid 8

a) From treatment with potassium carbonate : A mixture of 3.29 g (17 mmol) of methyl 1-bromocyclobutanecarboxylate **7** in 25 mL of water containing 4.72 g (34 mmol) of potassium carbonate was heated at reflux for 5 h. After concentration in vacuum, the residual liquid was treated by a 1M HCl solution and then extracted by 3x50 mL of CH_2Cl_2. The combined organic layers were concentrated in vacuum and the residual liquid was submitted to flash chromatography (silica gel, CH_2Cl_2/MeOH : 80/20) to give 1.6 g (81%) of β-hydroxacid **8** as a white solid.[21]

b) From treatment with potassium hydroxide : A mixture of 3.29 g (17 mmol) of α-bromo ester **7**[14] in 50 mL of a 0.1M solution of KOH in water was stirred at room temperature for 18 h. Identical work-up procedure gave 1.87 g (95%) of the β-hydroxy acid **8**.[21]

1-Hydroxycyclobutanecarboxylic acid 5: To a solution of 23.38 mL (0.202 mol) of diisopropylamine in 400 mL of THF at 0°C, was added dropwise within 45 mn 150 mL of a 1.6M solution of *n*-butyllithium (0.24 mol) in hexane. Then was added a solution of 6.64 g (66.4 mmol) of cyclobutanecarboxylic acid[10-13] in 100 mL of anhydrous THF. The reacting mixture was stirred at 0°C for 30 min and at room temperature for 18 h; then

gazeous oxygen was bubbled through the mixture for 18 h. After addition of 800 mL of water, the aqueous layer was extracted twice by 200 mL of diethyl ether and acidified by concentrated HCl. The acidic aqueous layer was then extracted by 3x300 mL of diethyl ether; the combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to provide 7.7 g (100%) of α-hydroxyacid **5** as a pale yellow oil. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.85-2.15 (2H, m), 2.25-2.45 (2H, m), 2.55-2.70 (2H, m), 5.60 (2H, broad s). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 12.7, 34.4, 67.7 (C-OH), 180.2 (COOH). IR ($CDCl_3$): 3700 cm^{-1} (ν_{OH}), 1705 cm^{-1} ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 116 (0.7, M^+), 88 (43.89), 60 (30.12), 42 (100).

Methyl 1-hydroxycyclobutanecarboxylate 16 : To a solution of 2.49 g (21.5 mmol) of α-hydroxyacid **5** in 50 mL of methanol was added 5 drops of thionyl chloride. The reacting solution was heated at reflux for 4 h. Then evaporation of the solvent under vacuum and flash chromatography (silica gel, CH_2Cl_2/MeOH : 98/2) of the residual liquid gave 1.93 g (69%) of α-hydroxy ester **16** as a pale yellow oil. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.85-2.05 (2H, m), 2.25-2.40 (2H, m), 2.45-2.60 (2H, m), 3.40 (1H, broad s, OH), 3.85 (3H, s, $COOCH_3$). ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 12.6, 34.4, 52.5, 74.2 (C-OH), 176.5 ($COOCH_3$). IR ($CDCl_3$): 3530 cm^{-1} (ν_{OH}), 1735 ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 130 (1.56, M^+), 102 (85.13), 71 (32.13), 42 (100).

1-(2-Hydroxyprop-2-yl)cyclobutanol 4a and *trans* 1,2-dimethylcyclopentan-1,2-diol 20: To a solution of 390 mg (3 mmol) of α-hydroxy ester **16** in 20 mL of diethyl ether were added dropwise under argon atmosphere, 20 mL (10 mmol) of a 0.5M solution of MeMgI in Et_2O. The reacting mixture was stirred at room temperature for 1 h; then 20 mL of Et_2O were added, followed by 5 mL of saturated aqueous NH_4Cl solution. The aqueous layer was extracted continously for 24 h by Et_2O, and the combined organic layers were dried on $MgSO_4$. Evaporation of the solvent under vacuum and flash chromatography (silica gel, CH_2Cl_2/MeOH : 98/2) of the residual oil liquid gave 304 mg (78%) of a 1:1 mixture of isomeric diols **4a**[25] and **20**[26] separable only by gas chromatography, as a colorless oil.

2,2-Dimethylcyclopentanone 1a from diols 4a and *trans*-20 : A mixture of 523.9 µl (9 mmol) of anhydrous phosphoric acid and 523.9 mg (3.6 mmol) of phosphorus pentoxide was heated at 100°C for 15 min.[39] (Use of commercial polyphosphoric acid, as reported[4] gave us lower yield of dehydration product). To this polyphosphoric acid cooled at 45°C, 38 mg (0.29 mmol) of the 1:1 mixture of diols **4a** and *trans*-**20** was added and the reacting mixture was stirred at 45°C for 10 min. The mixture was poured over crushed ice and the aqueous layer was extracted twice by 10 mL of Et_2O. The ether extracts were combined, dried over Na_2SO_4, filtered and evaporated to yield 22 mg (66%) of ketone **1a**.[28]

5-Chloro-2-[*N*-(diphenylmethylene)amino]pentanenitrile 23b : To a suspension of 330.8 mg (8.3 ml) of sodium hydride in oil, washed under argon 3 times by 10 mL of anhydrous pentane, was added a solution of 1.46 g (6.6 mmol) of (*N*-diphenylmethylene)aminoacetonirile **22**[31] in 20 mL of anhydrous THF. The reacting mixture turned to brown colour, then was added dropwise a solution of 1.02 g (6.5 mmol) of 1-bromo-3-chloropropane in 10 ml of anhydrous THF. The solution was stirred at room temperature for 1 h. The solvent was removed under vacuum and 30 mL of diethyl ether was added to the residue. The organic layer was washed twice by 10 mL of water, dried over Na_2SO_4 and concentrated under vacuum ; the residual liquid was submitted to flash chromatography (silica gel, pentane/ether : 95/5) to give 1.83 g (93.5%) of pentanenitrile **23b** as a pale yellow oil. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.90-2.05 (2H, m), 2.05-2.20 (2H, m), 3.55 (2H, t, J = 6.01 Hz), 4.30 (1H, t, J = 6.10 Hz), 7.20 - 7.25 (2H, m), 7.35-7.55 (6H, m), 7.65-7.70 (2H, m). ^{13}C NMR

($CDCl_3$, 50.3 MHz) δ (ppm): 28.43, 32.10, 44.06, 52.30, 127.30, 128.20, 128.90, 129.07, 129.40, 131.30. IR ($CDCl_3$): 2250 cm^{-1} ($\nu_{C\equiv N}$), 1640 ($\nu_{N=C}$). Mass spectrum (EI) m/z (rel. intensity) : 298 (11.48, M^+), 296 (32.91, M^+), 295 (60.71), 261 (26.28, $[M\text{-}Cl]^+$), 233 (13.01), 219 (23.47), 208 (96.94), 180 (18.88), 166 (6.12), 116 (94.39), 104 (55.36), 77 (100). Elemental analysis: Calcd: C, 72.64; H, 5.91; N, 9.21; Cl, 12.13. Found : C, 72.84; H, 5.77; N, 9.44; Cl, 11.94.

5-Chloro-2-(1,3-dioxa-2-methylpentyl)pentanenitrile 26: To a solution of 5.16 g (48 mmol) of sodium bisulfite in 35 mL of water, cooled at -50°C were added dropwise 3 g (28.16 mmol) of 4-chloro butyraldehyde **25**[32]; the stirred reacting mixture was allowed to reach room temperature. The aqueous layer was extracted twice by 30 mL of diethyl ether and then was added a solution of 2.55 g (52 mmol) of sodium cyanide in 8 mL of water. The reacting mixture was stirred for 1 h and then acidified to pH = 1 by concentrated HCl. The aqueous layer was extracted by 100 mL of dichloromethane. The organic layer was treated with 7.6 mL (80 mmol) of ethyl vinyl ether containing 704.4 mg (2.8 mmol) of pyridinium *para*-toluenesulfonic acid salt (PTTS). The reacting mixture was then stirred for 1 h and the organic layer was washed by 20 mL of brine. The organic layer was dried over Na_2SO_4 and concentrated under vacuum; flash chromatography of the residual liquid (silica gel, pentane/ethyl acetate: 90/10) gave 4.91 g (85%) of a 53:47 diastereomeric mixture of O-protected cyanohydrins **26**[34], separable by preparative gas chromatography.

First diastereomer: ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.25 (3H, t, J = 7 Hz), 1.36 (3H, d, J = 5.3 Hz), 2.00-2.05 (4H, m), 3.45-3.75 (4H, m), 4.55-4.60 (1H, m), 4.92 (1H, q, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 14.9, 19.3, 27.5, 30.7, 43.8, 60.9, 61.9, 98.7, 118.25 (C≡N). IR ($CDCl_3$): 2980-2880 cm^{-1} (ν_{CH}). Mass spectrum (EI) m/z (rel. intensity) : 190 (12.86, $[M\text{-}CH_3]^+$), 118 (32.62), 116 (100), 80 (37.5), 73 (92.86), 45 (50). Mass spectrum (CI, NH_3) m/z (rel. intensity) : 225 (100, $[M+ 18]^+$), 223 ($M+ 18]^+$).

Second diastereomer: ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.2 (3H, t, J = 6.8 Hz), 1.4 (3H, d, J = 5.3 Hz), 2.00-2.05 (4H, m), 3.45-3.75 (4H, m), 4.35-4.45 (1H, m), 4.80-4.90 (1H, q, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 14.7, 19.3, 27.5, 31.2, 43.8, 61.4, 62, 100.3, 118.9 (C≡N). Mass spectrum (EI) m/z (rel. intensity) : 190 (12.65), 118 (30.24), 116 (86.23), 80 (33.82), 73 (100), 45 (54.09).

[1-(1,3-Dioxa-2-methylpentyl)cyclobutane]carbonitrile 27[31] : To a solution of 3.25 g (15.8 mmol) of chlorocyanohydrins **26** in 16 mL of anhydrous benzene were added dropwise, under argon, a solution of 9 mL (17.38 mmol) of a 2M solution of sodium hexamethyldisilazane (HMDS) in THF. The reacting mixture was stirred for 2 h at room temperature and then the solvent was removed under vacuum to give a residual liquid, which was stirred overnight in 70 mL of petrol ether. The organic layer was washed by 10 ml of half-saturated brine and dried over Na_2SO_4. Removal of the solvent under vacuum and distillation gave 2 g (76%) of cyclobutanone cyanohydrin **27**.[34]

1-(1,3-Dioxa-2-methylpentyl)cyclobutyl methyl ketone 30a: To 6 mL of a 0.5M (3 mmol) solution of MeMgBr in Et_2O was added dropwise, under argon, a solution of 507 mg (3 mmol) of O-protected cyclobutanone cyanohydrin **27**. The reacting mixture was stirred at room temperature for 3 h; then were added 20 mL of Et_2O and 2 mL of a saturated aqueous solution of NH_4Cl. The mixture was stirred in order to get a clear organic layer. The aqueous layer was extracted twice with 3 mL of diethyl ether and the combined organic layer was dried over Na_2SO_4. Removal of solvent under vacuum and flash chromatography of the residual liquid (silica gel, pentane/diethyl ether : 90/10) provided 513.4 mg (92%) of the methyl ketone **30a**. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.1 (3H, t, J = 6.7 Hz), 1.32 (3H, d, J = 4.4 Hz), 1.50-2.30 (5H, m), 2.19 (3H, s), 2.55

(1H, m), 3.35 (2H, m), 4.53 (1H, q, J = 5.40 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 12.19, 14.69, 20.87, 23.27, 26.50, 31.15, 62.66, 82.48, 96.72, 208.62 (C=O). IR ($CDCl_3$): 1710 cm^{-1} ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 97 (21.41), 73 (100), 45 (54.47). Mass spectrum (CI, NH_3) m/z (rel. intensity) : 187 (100, $[M+1]^+$). Elemental analysis: Calcd: C, 64.49; H, 9.74. Found : C, 64.44; H, 9.91.

2-[1-(1,3-Dioxa-2-methylpentyl)cyclobutyl]propan-2-ol 31a : To 0.8 mL of a 0.5M (0.4 mmol) solution of MeMgBr in Et_2O were added dropwise, under argon, a solution of 55.8 mg (0.3 mmol) of methyl ketone **30a** in 5 mL of Et_2O. After stirring the reacting mixture at room temperature for 2 h, 10 mL of Et_2O and 2 mL of a saturated aqueous solution of NH_4Cl were added. The aqueous layer was extracted twice with 2 mL of Et_2O and the combined organic layer was dried over Na_2SO_4. Removal of the solvent under vacuum and flash chromatography of the residual oil (silica gel, pentane/diethyl ether : 75/25) yielded 55.14 mg (91%) of the dimethyl carbinol **31a**, as a colourless liquid. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.20 (3H, s), 1.20 (3H, t, J = 5.0 Hz), 1.28 (3H, s), 1.37 (3H, d, J = 5.2 Hz), 1.45-1.90 (2H, m), 2.05-2.40 (4H, m), 3.55 (2H, q), 4.00 (1H, broad s), 5.00 (1H, q, J = 5.2 Hz). Elemental analysis: Calcd: C, 65.31; H, 10.96. Found : C, 65.09; H, 10.76.

1-(2-Hydroxyprop-2-yl)cyclobutanol 4a : A solution of 34.34 mg (0.17 mmol) of the ketal **31a** in 5 mL of a 0.5M sulfuric acid solution in methanol was stirred at room temperature for 5 mn. Then were added 20 mL of Et_2O and sufficiently saturated aqueous $NaHCO_3$ solution to neutralize the reacting mixture. The aqueous layer was extracted twice by 10 mL of Et_2O; the combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography of the residual liquid (silica gel, CH_2Cl_2/MeOH: 95/5) gave 19 mg (86%) of diol **4a**[25] as a white solid. Mp.: 85.4°C.

2,2-Dimethylcyclopentanone 1a from O-protected cyclobutanone cyanohydrin 27: To a solution of 41.6mg (0.32 mmol) of the diol **4a** in 5 mL of dichloromethane was added 2.5 µl (0.032 mmol) of trifluoroacetic acid. The reacting mixture was stirred at room temperature, and the reaction was completed within 1 h, as monitored by thin layer chromatography. Filtration through a 1 cm long silica gel column and removal of the solvent under vacuum gave in 93% yield the pure ketone **1a**, as a colourless liquid.[26]

1-(1,3-Dioxa-2-methylpentyl)cyclobutyl ethyl ketone 30c: Following the procedure used to obtain the methyl ketone **30a**, the ethyl ketone **30c** was prepared from reaction of the O-protected cyclobutanone cyanohydrin **27** with one equiv of EtMgBr. Flash chromatography of the residual liquid (silica gel, pentane/diethyl ether : 90/10) obtained after usual work-up gave **30c** in 87% yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.83 (3H, t, J = 6.3 Hz), 0.85 (3H, t, J = 7.4 Hz), 1.28 (3H, d, J = 5.2 Hz), 1.50-1.80 (2H, m), 1.90-2.30 (3H, m), 2.40-2.65 (2H, m), 2.85 (1H, dq, J = 18.0 and 7.4 Hz), 3.30 (2H, m), 4.50 (1H, q, J = 5.16 Hz). ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 7.76, 12.37, 14.87, 20.98, 26.84, 27.86, 31.52, 62.63, 82.40, 96.74, 211.37 (C=O). IR ($CDCl_3$): 1710 cm^{-1} ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 111 (20.76), 73 (100), 45 (44.72). Mass spectrum (CI, NH_3) m/z (rel. intensity) : 201 (0.54, $[M+1]^+$). Elemental analysis: Calcd: C, 66.02; H, 9.99. Found : C, 65.79; H, 10.07.

3-[1-(1,3-Dioxa-2-methylpentyl)cyclobutyl]pentan-3-ol 31c : Following the procedure used to obtain the dimethylcarbinol **31a**, reaction of the ethyl ketone **30c** with one equiv of EtMgBr provided, after usual work-up and flash chromatography (silica gel, pentane/diethyl ether : 50:50) the diethylcarbinol **31c** in 80% yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.89 (3H, t, J = 7.5 Hz), 0.95 (3H, t, J = 7.5 Hz), 1.20 (3H, t, J = 7.0 Hz), 1.35 (3H, d, J = 5.3 Hz), 1.50-1.90 (6H, m), 2.00-2.50 (4H, m), 3.53 (2H, q, J =

7.0 Hz), 4.15 (1H, broad s), 5.03 (1H, q, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 8.42, 8.87, 13.51, 15.24, 19.77, 21.18, 25.86, 26.17, 27.30, 27.62, 29.53, 29.81, 58.75, 86.82, 94.70, 99.5. IR ($CDCl_3$): 3620 cm^{-1} (ν_{OH}). Mass spectrum (EI) m/z (rel. intensity) : 156 (18.23), 127 (67.05), 111 (76.47), 97 (67.90), 83 (60.39), 70 (82.51), 57 (60.82), 42 (100). Elemental analysis: Calcd: C, 67.79; H, 11.38. Found : C, 67.56; H, 11.31.

1-(3-Hydroxypent-3-yl)cyclobutanol 4c : Following the procedure used to obtain the diol **4a** from ketal **31a**, the 3-pentanol **31b** underwent deketalization upon treatment with a 0.2M H_2SO_4 solution to yield the diol **4c**. Flash chromatography of the residual liquid (silica gel, CH_2Cl_2/MeOH: 95/5) provided **4c** in 91% yield as a white solid. Mp.: 36.6°C. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.92 (6H, t, J = 7.9 Hz), 1.28 (1H, broad s), 1.50-1.80 (6H, m), 1.82-2.10 (2H, m), 2.20 (1H, broad s), 2.35-2.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 8.44, 13.68, 26.09, 31.89, 67.06, 81.83. IR ($CDCl_3$): 3700 and 3610 cm^{-1} (ν_{OH}). Mass spectrum (EI) m/z (rel. intensity) : 101 (25.18), 87 (100), 83 (29.28), 69 (32.53), 57 (26.99), 43 (43.37). Mass spectrum (CI, NH_3) m/z (rel. intensity) : 159 (7.39, $[M+1]^+$), 176 (100, $[M+18]^+$).

2,2-Diethylcyclopentanone 1c: Following the procedure to obtain the cyclopentanone **1a** from the diol **4a**, the cyclobutanol **4c** underwent dehydratation and ring expension upon treatment with trifluoroacetic acid in CH_2Cl_2 at room temperature. Simple filtration through silica gel and removal of the solvent under vacuum gave the pure cyclopentanone **1c**[37] in 92% yield, as a colourless liquid.

2-[1-(1,3-Dioxa-2-methyl)pentylcyclobutyl]butan-2-ol 31d

a) From methyl ketone 30a: Following the procedure to obtain the dimethylcarbinol **31a**, reaction of the methyl ketone **30a** with one equiv of EtMgBr provided, after usual work-up and flash chromatography (silica gel, pentane/diethyl ether : 75/25) the pure cyclobutylcarbinol **31d** in 90% yield, as a colourless liquid.

***b) From ethyl ketone 30c*:** Following the procedure to obtain the diethylcarbinol **31c**, reaction of the ethyl ketone **30c** with one equiv of MeMgBr provided, after usual work-up and flash chromatography (silica gel, pentane/diethyl ether : 75/25) also the pure cyclobutylcarbinol **31d** in 94% yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.98 (3H, t, J = 7.5 Hz), 1.13 (3H, s), 1.19 (3H, t, J = 6.90 Hz), 1.34 (3H, d, J = 5 Hz), 1.40-1.90 (4H, m), 2.10-2.40 (4H, m), 3.54 (2H, q, J = 7 Hz), 4.20 (1H, broad s), 5.06 (1H, q, J = 5.34 Hz). ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 7.71, 7.78, 12.66, 12.93, 15.11, 15.26, 18.64, 19.55, 21.07, 21.31, 26.81, 27.08, 27.31, 27.52, 29, 30.17, 58.60, 58.73, 85.48, 94.61, 94.65. IR ($CDCl_3$): 3620 cm^{-1} (ν_{OH}). Mass spectrum (EI) m/z (rel. intensity) : 142 (34.22), 113 (65.69), 98 (85.54), 83 (75.98), 70 (64.28), 56 (61.02), 43 (100). Elemental analysis: Calcd: C, 66.63; H, 11.18. Found : C, 66.71; H, 11.01.

1-(2-Hydroxybut-2-yl)cyclobutanol 4d : Following the procedure used to obtain the diols **4a,c** from acetals **31a,c**, the butan-2-ol **31d** was treated with 0.2M H_2SO_4 solution to yield, after usual work-up and flash chromatography (silica gel, CH_2Cl_2/MeOH: 95/5) the pure diol **4d** (90%) as a white solid. Mp.: 82°C. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.96 (3H, t, J = 7.5 Hz), 1.16 (3H, s), 1.44-1.71 (4H, m), 1.86-1.99 (3H, m), 2.26-2.40 (3H, s). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 7.74, 12.50, 19.27, 27.47, 31.24, 31.33, 75.45, 80.64. IR ($CDCl_3$): 3700 and 3610 cm^{-1} (ν_{OH}). Mass spectrum (EI) m/z (rel. intensity) : 87 (40.73), 73 (100), 56 (39.01), 43 (37.97). Mass spectrum (CI, NH_3) m/z (rel. intensity) : 162 (100, $[M+18]^+$). Elemental analysis: Calcd: C, 66.63; H, 11.18. Found : C, 66.61; H, 11.35.

2-Ethyl-2-methylcyclopentanone 1d[38]: Following the procedure used to obtain the cyclopentanones **1a,c** from diols **4a,c**, the cyclobutanol **4d** was treated with trifluoroacetic acid in CH_2Cl_2 at room temperature to

provide in 89% yield, after simple filtration through silica gel and removal of the solvent under vacuum, the pure cyclopentanone **1d**[38] as a colourless liquid.

2,4-Dimethyl-4-ethyl-1,3-dioxa[3.4]spirooctane 32: To a solution of 70 mg (0.32 mmol) of cyclobutylcarbinol **31d** in 5 mL of dichloromethane was added 2.5 µl of trifluoroacetic acid (or of concentrate sulfuric acid). The reacting mixture was stirred for 1 h at room temperature, until completion of the reaction as monitored by thin layer chromatography; then the mixture was neutralized by addition of aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and concentrated under vacuum; flash chromatography of the residual oil (silica gel, CH_2Cl_2) gave 60 mg (95%) of dioxaspirooctane **32**, as a colourless liquid. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.90-1.00 (3H, m), 1.16 (3H, s), 1.33 (3H, d, J = 4.8 Hz), 1.40-1.70 (4H, m), 2.00-2.40 (4H, m), 5.00-5.15 (1H, m). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 8.13, 8.31, 14.34, 14.54, 19.46, 20.52, 20.95, 21.42, 27.91, 29.27, 29.90, 30.10, 30.27, 31.04, 96.81. Mass spectrum (EI) m/z (rel. intensity) : 170 (0.16, M^+), 142 (15.72), 113 (25.10), 98 (37.27), 83 (75.29), 70 (89.11), 56 (99), 43 (100). HMRS calcd for $C_{10}H_{18}O_2$, m/z 170.1306. Found, 170.1274.

But-3-enyl 1-(1,3-Dioxa-2-methylpentyl)cyclobutyl ketone 30e: Following the procedure used to obtain the ketones **30a,c** reaction of the O-protected cyclobutanone cyanohydrin **27** with three equiv of vinylmagnesium chloride, led after usual work-up and flash chromatography of the residual liquid (silica gel, CH_2Cl_2) to **30e** in 85 % yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.07 (3H, t, J = 7.0 Hz), 1.31 (3H, d, J = 5.2 Hz), 1.50-1.80 (4H, m), 1.90-2.30 (3H, m), 2.45-2.65 (2H, m), 2.90 (1H, dq, J = 18.0 and 7.4 Hz), 3.30 (2H, m), 4.54 (1H, q, J = 5.2 Hz), 5.0 (2H, m), 5.85 (2H, m) . ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 12.28, 14.99, 20.94, 26.66, 27.73, 31.28, 34.20, 62.56, 82.35, 96.73, 114.67, 137.89, 209.70. IR ($CDCl_3$): 1715 cm^{-1} ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 226 (0.11, M^+), 143 (6.76), 73 (100), 55 (11.13), 45 (44.72). Mass spectrum (CI, NH_3) m/z (rel. intensity): 227 (1.3, $[M+1]^+$), 244 (19, $[M+18]^+$).

3-[(1,3-Dioxa-2-methylpentyl)cyclobutyl]-hepta-1,6-dien-3-ol 31e : Following the procedure used to obtain the cyclobutylcarbinols **31a,c**, reaction of the ethyl ketone **30e** with one equiv of CH_2=CHMgCl provided, after usual work-up and flash chromatography (silica gel, pentane/diethyl ether: 80:20) the dienol **31e** in 91 % yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.19 (3H, t, J = 7.3 Hz), 1.33 (3H, d, J = 5.4Hz), 1.50-1.70 (2H, m), 1.80-1.90 (2H, m), 2.0-2.40 (7H, m), 3.55 (2H, q, J = 7.3 Hz), 5.0 (3H, broad s), 5.28 (1H, dd, J = 10.7 and 1.95 Hz), 5.38 (1H, dd, J = 17.1 and 1.95 Hz), 5.85 (1H, m), 5.91 (1H, dd, J = 17.1 and 10.7 Hz). ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 12.60, 15.23, 21.17, 27.81, 27.94, 28.38, 32.25, 58.57, 78.45, 84.28, 94.8, 114.03, 115.05, 138,57, 139.51. Mass spectrum (EI) m/z (rel. intensity) : 156 (18.23), 127 (67.05), 111 (76.47), 97 (67.90), 83 (60.39), 70 (82.51), 57 (60.82), 42 (100).

1-(3-Hydroxyhepta-1,6-dien-3-yl)cyclobutanol 4e : Following the procedure used to obtain the diols **4a,c**, the hepta-1,6-dien-3-ol **31e** underwent deketalization upon treatment with a 0.2M H_2SO_4 solution to yield the diol **4e**. Flash chromatography of the residual liquid (silica gel, AcOEt/CH_2Cl_2: 50/50) provided **4e** in 95 % yield as a white solid. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.50-2.20 (9H, m), 2.30 (3H, m), 4.98 (2H, m), 5.33 (1H, dd, J = 8.87 and 1.54 Hz), 5.40 (1H, dd, J = 15.57 and 1.49 Hz), 5.90 (2H, m). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm):12.34, 27.87, 30.48, 31.56, 32.05, 78.77, 79.16, 114.59, 115.92, 138.63, 139.09. Mass spectrum (EI) m/z (rel. intensity) : 136(6), 112(23), 110(15), 55(100), 54(37), 53(50), 42(29), 41(54). Mass

spectrum (CI, NH_3) m/z (rel. intensity) : 183 (7, $[M+1]^+$), 200 (2, $[M+18]^+$). Elemental analysis: Calcd: C, 72.49; H, 9.95. Found : C, 72.31; H, 9.76.

2-(But-3-enyl)-2-vinylcyclopentanone 1e: Following the procedure to obtain the cyclopentanones **1a,c** from the diols **4a,c**, the cyclobutanol **4e** underwent dehydratation and ring expansion upon treatment with trifluoroacetic acid in CH_2Cl_2 at reflux. Simple filtration through silica gel and removal of the solvent under vacuum gave the pure cyclopentanone **1e** in 89 % yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.08 (2H, m), 1.50-2.35 (10H, m), 5.05 (4H, m), 5.75 (2H, m). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 18.77, 28.64, 32.59, 35.19, 37.51, 55.85, 114.59, 115.49, 138.33, 138.80, 219.84. IR ($CDCl_3$): 1740 cm^{-1} ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 164 (5.58, M^+), 137 (3.7, M^+-C_2H_3), 111 (18.6), 110 (82.8), 109 (12.183 M^+-C_4H_7), 95(48.4), 70 (82.51), 55 (73.5), 41 (100). HMRS calcd for $C_{11}H_{16}O$, m/z 164.120115. Found, 164.1214.

Cyclopentyl 1-(1,3-dioxa-2-methylpentyl)cyclobutyl ketone 30f: Following the procedure used to obtain the ketones **30a,c,e** reaction of **27** with one equiv of cyclopentylmagnesium chloride, led after usual work-up and flash chromatography (silica gel, pentane/diethyl ether : 95:5) to **30f** in 95 % yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.08 (3H, t, J = 7.0 Hz), 1.28 (3H, d, J = 5.17 Hz), 1.50-1.90 (9H, m), 2.08 (1H, m), 2.25 (2H, m), 2.55 (1H, m), 3.35 (2H, q, J = 7.06 Hz), 4.55 (1H, q, J = 5.17 Hz). ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 12.44, 15.05, 21.08, 25.93, 26.70, 27.53, 30.98, 31.25, 32.67, 44.78, 62.28, 82.83, 96.74, 214.38. IR ($CDCl_3$): 1720 cm^{-1} ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 196 (0.45, M^+- 44), 168 (2.12), 143 (3.81), 74 (48) ,73 (100), 44 (13). Mass spectrum (CI, NH_3) m/z (rel. intensity): 258 $[6, M+18]^+$, 241 $[8, M+1]^+$, 240 $[0.5, M+1]^+$.

1-Cyclopentyl-1-[(1,3-Dioxa-2-methylpentyl)cyclobutyl]prop-2-en-1-ol 31f: Following the procedure used to obtain the cyclobutylcarbinols **31a,c, e** reaction of the ketone **30f** with one equiv of CH_2=CHMgCl provided, after usual work-up and flash chromatography (silica gel, pentane/diethyl ether : 95:5) the cyclobutylcarbinol **31f** in 97 % yield, as a colourless liquid. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.22 (3H, t, J = 7.1 Hz), 1.38 (3H, d, J = 5.3 Hz), 1.30-1.85 (12H, m), 2.05-2.45 (3H, m), 3.55 (2H, m), 5.14 (1H, q, J = 5.3 Hz), 5.24 (1H, dd, J = 10.8 and 2 Hz), 5.35 (2H, dd, J = 17.3 and 2 Hz), 6.05 (1H, dd, J = 17.3 and 10.8 Hz), . ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 13.07, 15.34, 21.53, 24.85, 25.16, 27.16, 28.16, 28.54,29.28, 44.68, 58.58, 79.08, 84.94, 94.89, 114.34, 138,26. Mass spectrum (EI) m/z (rel. intensity) : 223 (0.43, M^+- 45), 126 (21), 125 (25), 109 (97), 97 (38), 85 (27), 73(100), 70 (15), 69 (34), 69(34), 45 (69). Mass spectrum (CI, NH_3) m/z (rel. intensity): 286 $[6, M+18]^+$, 269 $[2, M+1]^+$, 268 $[1, M+1]^+$.

1-Cyclopentyl-1-(1-hydroxycyclobutyl)prop-2-en-1-ol 4f: Following the procedure used to obtain the diols **4a,c,e** the ketal **31f** underwent deketalization upon treatment with a 0.2M H_2SO_4 solution to yield the diol **4f**. Flash chromatography of the residual liquid (silica gel, AcOEt/CH_2Cl_2: 50/50) provided quantitatively **4f**.

^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.40-1.80 (8H, m), 1.80-2.10 (5H, m), 2.30-2.50 (4H, m), 5.40 (2H, dd, J = 17.2 and 1.77 Hz), 6.05 (1H, dd, J = 17.2 and 10.8 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm):13.29, 25.01, 25.23, 26.95, 28.19, 31.36, 32.11, 44.17, 79.22, 114.87, 138.38. Mass spectrum (EI) m/z (rel. intensity) : 178 (0.44, M^+- 18), 127(6), 126(26), 125(14), 109(22), 100(16), 85(100), 70(36),56(32),55(80). Mass spectrum (CI, NH_3) m/z (rel. intensity): 214 $[100, M+18]^+$, 197 $[3, M+1]^+$, 2196 $[11, M+1]^+$.

2-Cyclopentyl-2-vinylcyclopentanone 1f: Following the procedure to obtain the cyclopentanones **1a,c,e** from the diols **4a,c, e** the cyclobutanol **4f** was treated with trifluoroacetic acid in CH_2Cl_2 at room temperature.

Simple filtration through silica gel and removal of the solvent under vacuum gave the pure cyclopentanone **1f** in 98% yield, as a colourless liquid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.05-1.40(2H, m), 1.40-1.80 (6H, m), 1.80-2.60 (7H, m),5.08 (1H, d, J = 17.57 Hz), 5.20 (1H, d, J = 10.68 Hz), 5.72 (1H, dd, J = 17.57 and 10.68 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm):.18.76, 25.35, 27.22, 27.75, 29.95, 38.72, 44.84, 59.53, 116.66, 117.29, 137.98, 220.12. IR ($CDCl_3$): 1738 cm^{-1} ($\nu_{C=O}$). Mass spectrum (EI) m/z (rel. intensity) : 180 (0.5, M^+), 121 (5), 111 (76, M^+- C_5H_9), 110 (100), 69 (13, C_5H_9), 55 (17), 53 (19). Mass spectrum (CI, NH_3) m/z (rel. intensity): 196 [100, M+18]$^+$, 179 [13, M+1]$^+$, 178 [2, M]$^+$. Elemental analysis: Calcd: C, 80.85; H, 10.18. Found : C, 80.43; H, 10.01.

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