*Tetrahedron* Vol. 45, No. 18, pp. 5853 to 5866, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00


# A NEW CHIRAL ROUTE TOWARD TERPENOIDS. ANNULATION OF CARVONE TO TRANS- AND CIS-FUSED BICYCLIC SYNTHONS

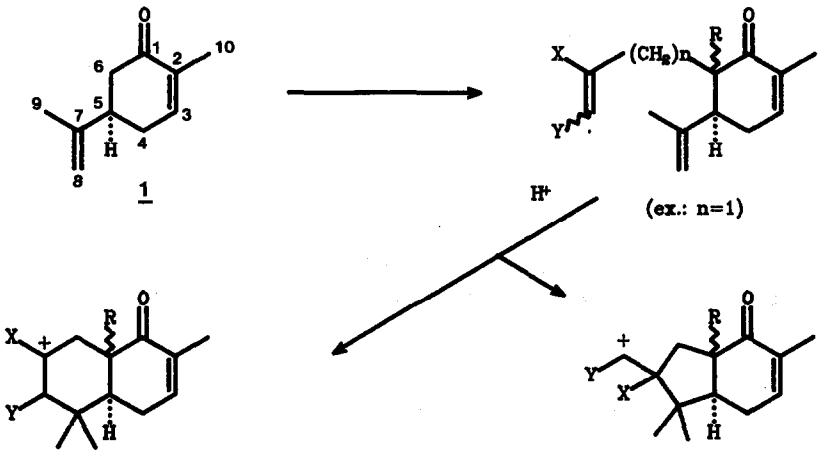
**Jean-Pierre GESSON*, Jean-Claude JACQUESY and Brigitte RENOUX**
Laboratoire de Chimie XII - UA CNRS 489
40,Avenue du Recteur Pineau, 86022 POITIERS (FRANCE)

(*Received in Belgium* 8 *June* 1989)

**ABSTRACT.** Starting from carvone, 1 two consecutive alkylations at C-6 followed by an acid-catalyzed cyclization give new bicyclic ketones which are potentially useful chirons for synthesis of terpenes such as drimanes, labdanes and triterpenes. The stereoselectivity of the second alkylation step which determines the stereochemistry of the ring junction has been studied and the results explained by the model of Tomioka. Several types of products may be formed depending on the acid used and a rearrangement has been observed in one case.

**INTRODUCTION.** The use of a simple chiral natural product for the enantioselective synthesis of more complex structures is presently an area of intense interest.[1] In this respect carvone 1, which is commercially available both in the R and S series, is an attractive chiron for the preparation of various terpenes and related natural compounds.[2]
Taking in consideration the vast array of structures already known for terpenoids it appeared to us that many of these do have a (functionnalized or not) cyclohexane ring bearing a gem-dimethyl group and that this feature makes especially worthwhile the development of a methodology to create a new carbocycle between C-6 and C-8 of carvone.[3] Terpenes such as drimanes, labdanes, stemodanes, abietanes and a large amount of triterpenes ( many of these compounds demonstrating interesting various biological activities)[4] will thus be enantioselectively accessible in either optically active forms.
For this purpose two consecutive alkylations at C-6 of carvone followed by an acid-catalyzed cyclization are considered, the stereochemistry of the newly created ring junction being controlled by the stereoselectivity of the second alkylation step. For such a planned synthesis of terpenes the R group may be methyl (although this is not always the case), the newly created ring may be 6 membered and the ring junction may be either trans or cis. Finally it should be noted that protonation should occur first on the isopropenyl group and therefore a Lansbury[5] type cyclization of an halo-olefin (X,Y=Cl,Br) appears to be the

method of choice (depending on the X and Y substituents two types of cyclization may be anticipated).




The stereochemistry of alkylation of carvone and the acid-catalyzed cyclization will be successively discussed.

**ALKYLATION OF CARVONE.** The kinetic enolate of 1 (LDA-THF) has been previously prepared and methylated by Cory[6] to give a 75% yield of an undetermined mixture of the two possible epimers **2a** and **2b** which could be converted without incident to the expected $\alpha'$ enolate under the same conditions.

In our hands this reaction affords, as reported, a mixture of **2a** and **2b** in a 1.3 ratio easily characterized in the $^1$H-NMR spectrum by the presence of two doublets (J=6.5 Hz) at 1.07 and 0.92 ppm respectively. Base-catalyzed equilibration (MeONa-MeOH, room temperature, 16 h) results in an increase of the 1.07 doublet (ratio: 2.8) confirming the equatorial orientation of the methyl group in **2a**.

Treatment of the above mixture cleanly gives the expected enolate which reacts diastereoselectively with several alkyl halides to afford compounds **3a-g** in good yield. The stereochemistry at the newly created quaternary carbon is anticipated to be as shown as a consequence of steric hindrance by the isopropenyl group on one side of the dienolate.[7] In order to prepare the corresponding C-6 isomers the two steps of alkylation are inverted: the intermediate mixtures of monoalkylated products **4a-e** are deprotonated and treated with $CH_3I$.

Apart from **4b**, a mixture of **3a-e** and **5a-e** is always obtained (Table I): when an ethyl or benzyl group is introduced first the methyl group enters mainly trans to the isopropenyl group (see **a** and **e**), however when a 2-halo allyl group is present the methylation is unselective giving a slight excess of attack cis to the isopropenyl group.

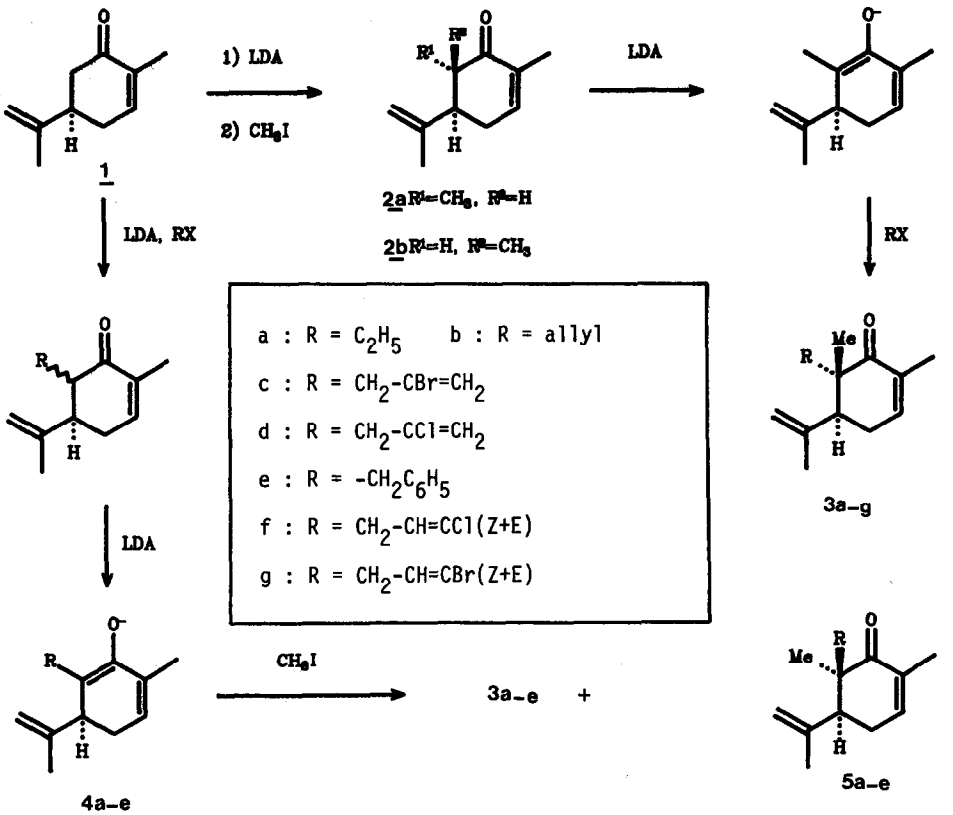
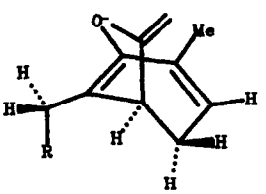


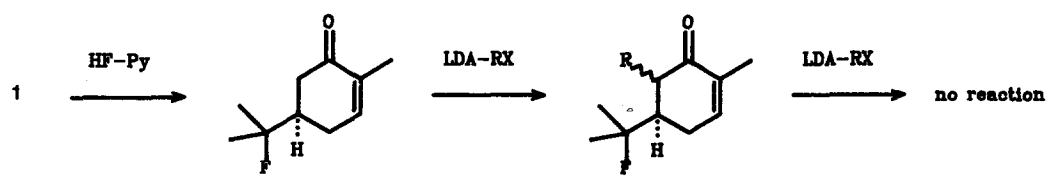

TABLE I

ALKYLATION OF DERIVATIVES 4 WITH METHYL IODIDE

| *Starting material* | *Yield* | *Products* |
|---|---|---|
| 4a: R= ethyl | 60% | 5a(95) + 3a(5) |
| 4b: R= allyl | 81% | 5b(100) |
| 4c: R= 2-bromo allyl | 76% | 5c(45) + 3c(55) |
| 4d: R= 2-chloro allyl | 65% | 5d(44) + 3d(56) |
| 4e: B= benzyl | 72% | 5e(75) + 3e(25) |



Tomioka model of derivatives 4



These results may be explained by the model of Tomioka[8]: the preferred transition state is such that the isopropenyl and the R residue are in a trans quasi-diaxial relationship and thus the relative bulkiness of these groups determines the diastereoselectivity. According to this model the lack of selectivity in the alkylation of **4c** and **4d** is obvious. As a consequence the formation of compounds resulting from alkylation trans to the isopropenyl group can only be favored by an increase in its bulk which may be realized by adding a leaving group on the double bond in order to later induce cyclization. Treatment of carvone with HF-pyridin is known to give the fluoro derivative **6** (95%)[9] which is then deprotonated and monoalkylated to **7** in 53% yield. However a second alkylation with $CH_3I$ using various conditions could not be carried out. The stereospecific synthesis of compounds such as **5c** clearly awaits further studies.

**CYCLIZATION.** The chloro olefin annelations reported earlier by Lansbury[5] were usually carried out using either cold 90% $H_2SO_4$ or formic acid. These conditions have been first studied but other anhydrous acids ($CF_3COOH$, HF, HF-Pyridin) capable to promote cyclization have also been used.

**Cyclization studies with $H_2SO_4$:**

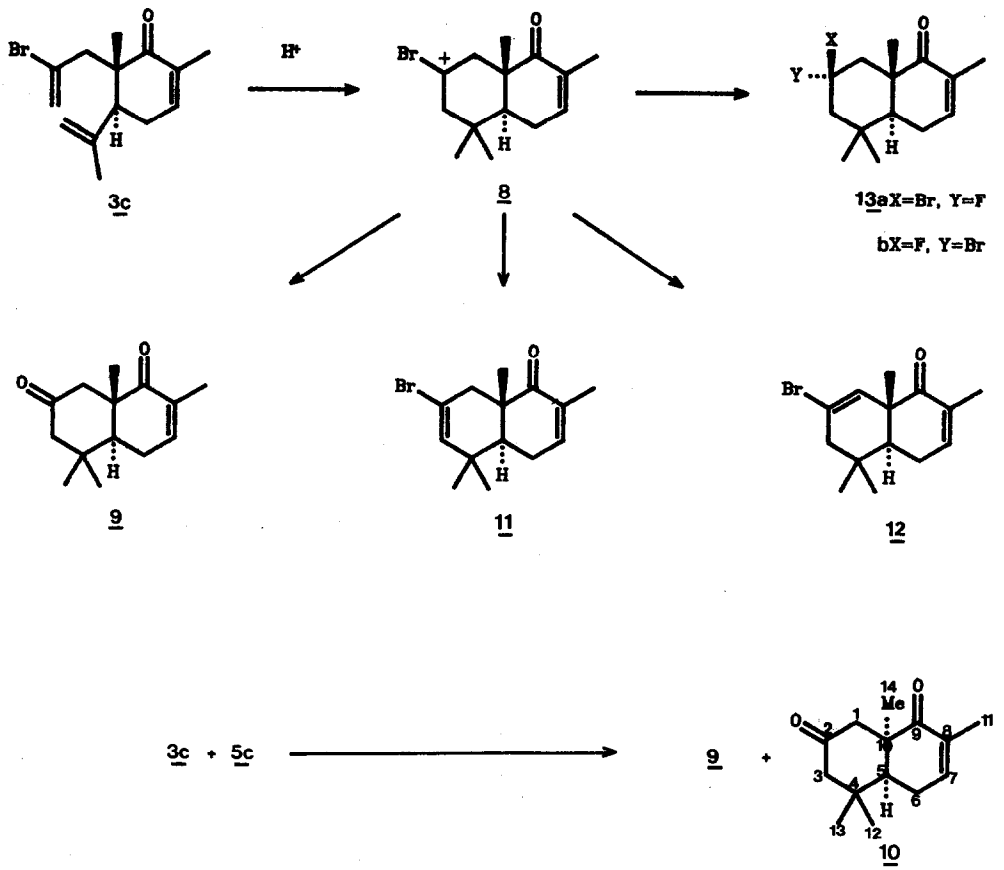
Starting from **3c** and in presence of 80% $H_2SO_4$ a single compound, **9**, is isolated (52%) after 24 h at room temperature. The proposed structure is consistent with $^1H$ and $^{13}C$ NMR spectra and particularly with the presence of a saturated carbonyl (210.58 ppm) and three methyl singlets at 1.01, 1.04 and 1.09 ppm.

Under the same conditions the aforementioned mixture of **3c** and **5c** (55/45 ratio) gives two easily separable diketones **9** (36.7%) and **10** (29.7%) in the same 55/45 ratio. Thus **10** clearly arises from **5c** and may be the cis-fused isomer. The corresponding $^1H$ NMR spectrum is well resolved (see experimental part) and shows three methyl singlets at 0.66, 1.08 and 1.34 ppm. Molecular model examination reveals a conformation in which one of the methyl group is clearly located above the plane of the enone double bond and this explains the high shielding experienced by one methyl (0.66 ppm). This assumption is confirmed by a NOEDIFF experiment which also allows attribution of all signals.

**Cyclization studies with anhydrous acids:**

Treatment of **3c** with $CF_3COOH$ at room temperature for 24 hrs affords an unseparable mixture of two isomeric vinylic bromides **11** and **12** (77%) in a 70/30 ratio as found by HPLC. The presence of two singlets at 5.80 and 6.54 ppm, in a similar (7/3) relative intensity ($^1H$ NMR), allows to locate the double bond in each isomer since deshielding of the vinylic hydrogen by the carbonyl group is expected in **12**. This **11** + **12** mixture is converted with 80% $H_2SO_4$ to **9** in 62% overall yield from **3c**.

However only **11** is isolated in 87% yield when the reaction is conducted in HF (-40°C to +20°C, 2 h). These different results (depending on the acid used) appear to be the consequence of an irreversible deprotonation since the mixture **11** + **12** does no give **11** in HF and **12** is not converted to the mixture **11** + **12** in $CF_3COOH$.

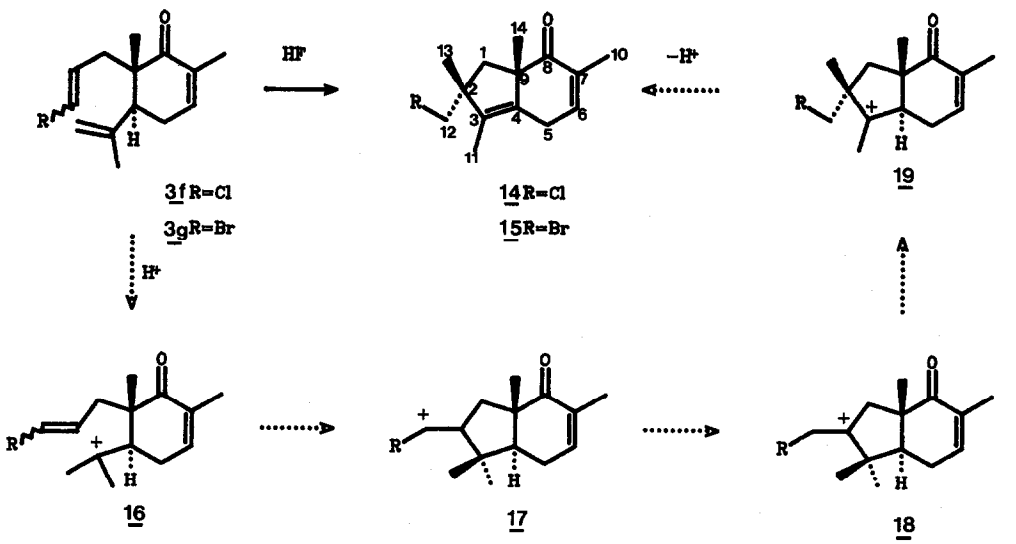



The use of HF-pyridin (70/30, w/w) to promote cyclization of **3c** appears to be possible since this fluorinating agent[10] does react with carvone to give **6** and therefore the intermediate ion which is formed in this process (or from **6** through a probable reversible step) may be trapped by the haloolefin. This assumption is fully confirmed since, at -20°C (3h), **3c** affords a mixture of **11** and **12** (20%) in about a 5/1 ratio as judged by NMR and **13a** (40%). The presence of a geminal fluorine atom (with respect to bromine) is corroborated by molecular ions at 302 and 304 (M.S.) and by a doublet (J=249 Hz) at 107.5 ppm in $^{13}C$ NMR. Two possible epimers **13a** and **13b** are to be considered: examination of the conformation of the intermediate carbenium ion **8** seems to favor attack by fluoride ion from the less hindered α face to give **13a**. However in this case a chair-like conformation of the newly created ring is not expected by analogy with the situation for 2-bromo 4,4-dimethyl steroids: the severe double 1,3 diaxial repulsion between bromine and two methyl groups has been shown to favor boat or twisted conformations.[11] Further examination of the already quoted $^{13}C$ NMR spectra reveals two doublets (J=18 and 21 Hz respectively) at 54.2 and 47.9

ppm for the two methylene carbons (C-1 and C-2 (steroïd numbering)) and two smaller doublets (J=7 Hz) at 46.3 and 35.15 ppm for the two quaternary carbons (C-4 and C-10). This $^3J_{CF}$ which depends on the dihedral angle[12] is in agreement with a pseudo-axial orientation of fluorine, a situation which is expected for a boat-like conformation. This assumption is corroborated by the values of the H-F coupling constants for the C-1 and C-3 protons (which rule out isomer **13b** for which large $^3J_{HF}$ (40-45 Hz)[13] are expected for the axial protons) and by the observed solvent effect on replacement of $CDCl_3$ by pyridin.

**Cyclization of 3f and 3g:**

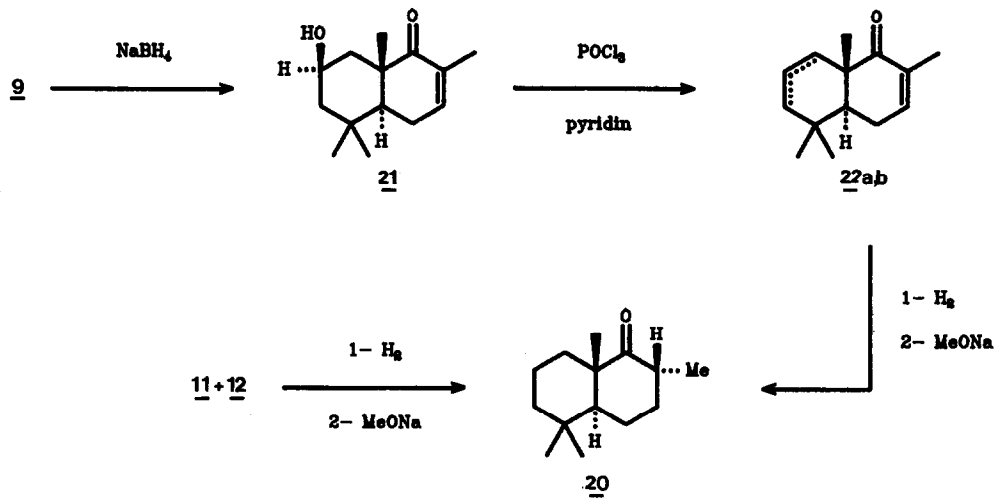
A preliminary investigation on the behavior of **3f** and **3g** in acidic conditions has been undertaken in order to determine the preferred mode of cyclization (formation of either a 5- or 6-membered ring) and evolution of the intermediate carbenium ions. The reaction proceeds cleanly only with HF to afford respectively **14** and **15** in similar yields (40%), decomposition is observed in 80% $H_2SO_4$ and a complex mixture is formed in $CF_3COOH$. The proposed structures are consistent with their MS, $^1H$ and $^{13}C$ NMR spectra and the stereochemistry of the chloromethyl (or bromomethyl) group is confirmed by NOEDIFF spectroscopy. The formation of these compounds may be explained by cyclization of the incipient ion **16** to **17**, rearrangement to the tertiary carbenium ion **18** (which may be further stabilized as a halonium ion), migration of the methyl group and finally deprotonation of **19** to give **14** (or **15**).




**Transformation of bicyclic enones:**

The conversion of some of the bifunctional bicyclic enones prepared by this method to known terpenes may be considered but if compounds bearing an oxygenated function at C-2 are relatively rare[4] the most common ones do not have any functional group in ring A. Therefore the preparation of ketone **20**, a compound already obtained in several steps by degradation of

sclareol[14] and a potential useful chiron for terpenes, has been carried out from **9** and from the mixture **11** + **12** (this will also serve as a chemical correlation for these compounds). Selective reduction of **9** at C-2 ($NaBH_4$, 0.35 molar eq., 0°C) gives the axial alcohol **21** resulting from the expected hydride approach by the α face.[15] Dehydration ($POCl_3$, pyridin) affords an unseparable mixture of the two possible olefins **22a,b** in a 1.5 to 1 ratio as judged by $^1H$ NMR. Hydrogenation (H2, Pd/C) followed by base-catalyzed equilibration (cat. MeONa, MeOH) finally leads to **20** in 65% overall yield from **21**. Our synthetic material exhibits similar physical (m.p. and $[\alpha]_D$) and spectral data as those reported by Adinolfi.[14] However the best method to prepare **20** appears to be the hydrogenation-base-catalyzed equilibration of the mixture **11** + **12** which proceeds in 76% overall yield.




**CONCLUSION.** This work demonstrates that double alkylation of carvone at C-6 followed by acid-catalyzed cyclization leads to bicyclic compounds which will be certainly useful for the preparation of various terpenes. The use of anhydrous acids gives generally better yields than the standard conditions (sulfuric acid) reported for the Lansbury-type cyclization, HF being more selective than $CF_3COOH$. In one case the use of HF-pyridin has permitted the isolation of an interesting fluoro derivative but a more general study to precise the scope of the acid-catalyzed cyclizations using this medium (or related HF-amine complex) is needed.

Finally it must be pointed out that this methodology is not restricted to the exemples described in this paper: studies on other haloolefins or cyclization conditions will be reported on due course as well as synthesis of naturally occurring terpenes from the bicyclic ketones available by this new type of annulation of carvone.

**ACKNOWLEDGEMENTS.** We thank Dr. C. Berrier (this laboratory) for NOEDIFF experiments, Prof. J.D. Connolly (Glasgow U., Scotland) for helpful discussions and CNRS for financial support.

## EXPERIMENTAL

Melting points were determined on a Tottoli Büchi 510 apparatus and are uncorrected. $^1H$ (200 Mz) and $^{13}C$ (50.327 MHz) NMR spectra were recorded on a Brücker WP200SY, using $CDCl_3$ as the solvent (unless stated otherwise) and TMS as an internal standard. Mass spectra (MS) were measured on a Kratos MS25 spectrometer (E.I. 70 eV) and relative peak heights are given in brackets. IR spectra (solvent: $CCl_4$) were recorded on a Beckman Acculab 2. High resolution mass spectra (HRMS) and microanalyses were obtained from the "Service Central de Microanalyse" (CNRS,Lyon). Optical rotations were mesured on a Perkin-Elmer 141 polarimeter. All reactions were run under an inert atmosphere ($N_2$) except for HF and HF-pyridin media (Teflon flasks were used in these cases). Separations and purifications were carried out by column chromatography over $SiO_2$ (Merck Kieselgel 60 (0.063-0.2 mm) or by preparative TLC using silica gel coated plates (60 F254, 1mm). HPLC analyses were carried out, using a Waters 6000A pump and a differential refractometer R401 as detector, on a Merck Lichrosorb Si60 (5 ) column (250x4.6mm). GC analyses were performed on an Intersmat IGC 120FL model (column: 10% SE 30 on chromosorb, 1m50).

**General Procedure for the Alkylation of Carvone Derivatives. Preparation of (5R,6R)-6-methyl carvone 2a and (5R,6S)-6-methyl carvone 2b.**
To a solution of diisopropylamine (5.85 mL, 41.6 mmol) in anhydrous THF (30 mL), kept at -10°C under nitrogen, was slowly added nBuLi (26 mL of a 1.6 M solution in hexane). After stirring the resulting colorless mixture at -10°C for 15 min, a solution of (-)carvone **1** (4.8 g, 31.9 mmol) in anhydrous THF (45 mL) was added dropwise and stirring was then continued for 2 h at -10°C. The enolate was then treated at this temperature by an excess of methyl iodide (10 mL, 5 eq.) and the resulting mixture stirred overnight while slowly warming to room temperature. After hydrolysis (1N HCl) and extraction with ether, the combined extracts were dried over $Na_2SO_4$. Evaporation of the solvent gave a residue which was rapidly chromatographied over silica (Eluent: hexane-AcOEt 90/10 (V/V)) to give **2a,b** (4.2 g, 83%) as an oil. *$^1H$ NMR:* 0.92 and 1.07 (2d,J=6.5Hz,3H), 1.71 (s,3H), 1.78 (s,3H), 2.46 (m,4H), 4.80 (s,2H), 6.70 (broad s,1H) ppm.
A sample of **2b** has been obtained by partial crystallization from hexane. mp 38°C; *$^1H$ NMR:* 1.07 (d,J=6.5Hz,3H), 1.70 (s,3H), 4.80 (s,2H), 6.69 (broad s($W_H$=12 Hz),1H) ppm.

**Preparation of (5S,6S)-6-ethyl-6-methyl carvone 3a.** Alkylation of **2a,b** (LDA: 1.3 eq.; EtI: 10 eq.).
**3a**: oil (81 %); $[\alpha]_D$ -24.85° (c 1.36, chloroform); *$^1H$ NMR*: 0.81 (t,J=7Hz,3H), 0.99 (s,3H), 1.63 (s,3H), 1.77 (s,3H), 2.28 (d($W_H$=9Hz),J=18Hz,1H), 2.64 (partly hindered d,J=18Hz,1H), 2.70 (m,1H), 4.72 (s,1H), 4.76 (s,1H), 6.55 (broad s($W_H$=9Hz),1H) ppm; *IR*: 3080, 2980, 2930, 1670, 1450, 1380,1050, 1010, 900 $cm^{-1}$; *MS*: 192(8), 177(6), 164(13), 163(8), 149(5), 135(10), 124(16), 110(48), 95(55), 82(87), 40(100). *Anal.* Calcd for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 80.89; 10.52.

**Preparation of (5S,6S)-6-allyl-6-methyl carvone 3b.** Alkylation of **2a,b** (LDA: 1.3 eq.; allyl bromide: 1.2 eq.).
**3b**: oil (81 %); $[\alpha]_D$ -60.9° (c 1.6, chloroform); *$^1H$ NMR:* 1.04 (s,3H), 1.61 (s,3H), 1.77 (s,3H), 2.32 (m,3H), 2.66 (m,2H), 4.72 (s,1H), 4.76 (s,1H), 5.02 (m,2H), 5.71 (m,1H), 6.58 (s($W_H$=9Hz),1H) ppm; *IR:* 3120, 2980, 2940, 1660, 1450, 1380, 1235, 1110, 1080, 1000, 900 $cm^{-1}$. *HRMS:* Calcd. for $C_{14}H_{20}O$: 204.15141. Found: 204.1528.

**Preparation of (5S,6S)-6-(2-bromo allyl)-6-methyl carvone 3c.** Alkylation of **2a,b** (LDA: 1.3 eq., 2,3-dibromo propene: 1.2 eq.).
**3c**: oil (84 %); $[\alpha]_D$ +3.7° (c 0.54, chloroform); *$^1H$ NMR:* 1.11 (s,3H), 1.61 (s,3H), 2.31 (d($W_H$=9Hz),J=20Hz,1H), 2.73 (partly hindered d($W_H$=9Hz),J=20Hz,1H), 2.77 (s,1H), 2.82 (s,1H), 2.90 (m,1H), 4.75 (s,1H), 4.78 (s,1H), 5.49 (s,1H), 5.58 (s,1H), 6.60 (broad s($W_H$=9Hz),1H) ppm; *IR:* 3100, 2990, 1670, 1450, 1380, 900 $cm^{-1}$; *MS:* 284(1), 282(1), 204(19), 203(100), 161(16), 145(34), 121(21), 105(26), 91(34), 82(76). *Anal.* Calcd for $C_{14}H_{19}BrO$: C, 59.37; H, 6.76. Found: C, 59.47; H, 6.94.

**Preparation of (5S,6S)-6-(2-chloro allyl)-6-methyl carvone 3d.** Alkylation of **2a,b** (LDA: 1.3 eq., 2-chloro 3-iodo propene: 1.2 eq.).
**3d**: oil (88 %); $[\alpha]_D$ -7.48° (c 1, chloroform); *$^1H$ NMR:* 1.11 (s,1H), 1.61 (s,3H), 1.80 (s,3H), 2.29 (d($W_H$=9Hz),J=20Hz,1H), 2.63 (AB q,J=16Hz,2H), 2.86 (m,2H), 4.75 (s,1H), 4.78 (s,1H), 5.08 (s,1H), 5.32 (s,1H), 6.59 (broad s($W_H$=9Hz),1H) ppm; *IR:* 3000, 2940, 1670, 1630, 1450, 1380, 1200, 1180, 1020, 900, 890 $cm^{-1}$; *MS:* 240(0.6), 238(1.5), 225(1.3), 223(3), 204(48), 203(100), 161(22), 145(47), 121(53), 107(12), 105(42), 91(51), 82(85). *Anal.* Calcd for $C_{14}H_{19}ClO$: C, 70.43; H, 8.02. Found: C, 70.53; H, 8.20.

**Preparation of (5S,6S)-6-benzyl-6-methyl carvone 3e.** Alkylation of **2a,b** (LDA: 1.3 eq., benzyl bromide: 1.2 eq.).
**3e**: oil (95 %); $[\alpha]_D$ -64.1° (c 1.2, chloroform); *$^1H$ NMR:* 0.97 (s,3H), 1.51 (s,3H), 1.82 (s,3H), 2.22 (d($W_H$=9Hz),J=20Hz,1H), 2.68 (d,J=7.5Hz,1H), 2.83 (ABq,J=18Hz,2H), 2.95 (partly hindered d($W_H$=9Hz),J=20Hz,1H), 4.57 (s,1H), 4.64 (s,1H), 6.55 (broad s($W_H$=9Hz),1H), 7.04 (d,J=8Hz,2H), 7.19 (m,3H) ppm; *IR:* 3080, 3040, 2990, 1670, 1500, 1450, 1380, 1200, 1170, 1120, 1100, 900, 700 $cm^{-1}$; *MS:* 254(17), 239(3), 199(12), 186(100), 163(29), 157(35), 135(9), 107(42), 91(56). *Anal.* Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.69; H, 8.73.

**Preparation of (5S,6S)-6-(3-chloro allyl)-6-methyl carvone 3f.** Alkylation of **2a,b** (LDA: 1.1 eq., 1,3-dichloro propene (Z+E): 1.2 eq., HMPA: 1 eq.).
**3f**: oil (87 %); $[\alpha]_D$ -39.57° (c 1.73, chloroform); *$^1H$ NMR:* 1.03 (s,3H), 1.67 (s,3H), 1.77 (s,3H), 2.18 (dd,J=14 and 7Hz,1H), 2.43 (m,3H), 2.70 (m,1H), 4.80 (m,2H), 5.88 (m,2H), 6.61 (broad s($W_H$=9Hz),1H) ppm; *IR:* 3070, 2960, 2920, 1665, 1445, 1420, 1380, 890 $cm^{-1}$; *MS:* 240(17.5), 238(35), 225(14), 223(28), 203(85), 170(47), 135(29), 121(50), 107(46), 91(44), 82(100). *Anal.* Calcd for $C_{14}H_{19}ClO$: C, 70.43; H, 8.02. Found: C, 70.39; H, 8.29.

**Preparation of (5S,6S)-6-(3-bromo allyl)-6-methyl carvone 3g.** Alkylation of **2a,b** (LDA: 1.3 eq., 1,3-dibromo propene (Z+E): 1.2 eq.).
**3g**: oil (85 %); $[\alpha]_D$ -39.55° (c 0.89, chloroform); *$^1H$ NMR:* 1.03 (s,3H), 1.64 (s,3H), 1.78 (s,3H), 2.42 (m,4H), 2.69 (m,1H), 4.78 (m,2H), 6.07 (m,1H), 6.21 (m,1H), 6.62 (broad s($W_H$=9Hz),1H) ppm; *IR:* 3080, 2980, 2930, 1670, 1450, 1380, 950, 900, 690, 670 $cm^{-1}$; *MS:* 284(3.5), 282(3.5), 269(7), 267(7), 241(5), 239(5), 216(33), 214(41), 203(100). *HRMS:* Calcd for $C_{14}H_{19}BrO$: 282.06191. Found: 282.05992.

**Preparation of (5R,6S) and (5R,6R)-6-ethyl carvone 4a.** Alkylation of **1** (LDA : 1.3 eq., EtI : 10 eq.).
**4a** : oil (67%); $[\alpha]_D$ 9.95 (c = 0.46, chloroform); *$^1H$ NMR:* 0.87 (t,J=7Hz,3H); 1.45 (m,2H); 1.73 (s,3H); 1.77 (s,3H); 2.35 (m,3H); 2.70 (m,1H); 4.8 (s,2H); 6.66 (broad s($W_H$=9Hz,1H) ppm; *I.R:* 3100, 2990, 2940, 1675, 1460, 1380, 1370, 900 $cm^{-1}$. *MS:* 178(100), 163(58), 149(72), 137(60), 121(35), 109(41). *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.17. Found : C, 80.75; H, 10.33.

**Preparation of (5R,6S) and (5R,6R)-6-allyl carvone 4b.** Alkylation of 1 (LDA : 1.3 eq.; allyl bromide : 10 eq.)
**4b**: oil (74%); $[\alpha]_D$ 56,3 (c 1.4, chloroform); *$^1H$ NMR:* 1.71 (s,3H), 1.77 (s,3H), 2.4 (m,6H), 4.79 (s,1H), 4.85 (s,1H), 4.97 (m,2H), 5.78 (m,1H), 6.67 (s($W_H$=9Hz),1H) ppm; *IR:* 3090, 2990, 2980, 1675, 1665, 1450, 1430, 1380, 1365, 915, 900 $cm^{-1}$. *MS:* 190(16), 175(12), 161(6), 149(14), 147(17), 133(9), 122(16), 121(14), 109(17), 108(19), 93(36), 91(27), 82(100). *HRMS:* Calcd for $C_{13}H_{18}O$ : 190.13576. Found : 190.13559.

**Preparation of (5R,6S) and (5R,6R)-6-(2-bromo allyl) carvone 4c.** Alkylation of 1 (LDA: 1.3 eq.; 2,3-dibromo propene: 1.2 eq.).
**4c**: oil (54%); $[\alpha]_D$ 34° (c 1.8, chloroform); *1H NMR:* 1.76 (s,6H), 4.82 (s,2H), 5.47 (s,1H), 5.71 (s,1H), 6.66 (broad s($W_H$=11Hz),1H) ppm; *IR:* 3050, 3000, 2940, 1680, 1640, 1630, 1450, 1440, 1385, 1370, 900, 890 $cm^{-1}$; *MS:* 270(1), 268(1), 190(32), 189(100), 156(9), 147(42). *Anal.* Calcd for $C_{13}H_{17}BrO$: C, 58.00; H, 6.36. Found: C,57.70; H, 6.41.

**Preparation of (5R,6S) and (5R,6R)-6-(2-chloro allyl) carvone 4d.** Alkylation of 1 (LDA: 1.3 eq., 2-chloro 3-iodo propene: 1.2eq.).
**4d**: oil (85%); $[\alpha]_D$ 49.6 (c 1.27, chloroform); *$^1H$ NMR:* 1.75 (s,3H), 1.79 (s,3H), 2.43 (m,3H), 2.74 (m,3H), 4.82 (s,1H), 4.86 (s,1H), 5.23 (s,1H), 5.27 (s,1H), 6.67 (broad s($W_H$=11Hz),1H; *IR:* 3090, 2980, 1675, 1640, 1450, 1430, 1380, 1365, 1130, 1090, 900 $cm^{-1}$; *MS:* 226(1), 224(3), 190(33), 189(100), 173(6), 147(24), 91(29), 82(55). *Anal.* Calcd for $C_{13}H_{17}ClO$: C, 69.48; H, 7.62. Found: C, 69.58; H, 7.78.

**Preparation of (5R,6S) and (5R,6R)-6-benzyl carvone 4e.** Alkylation of 1 (LDA: 1.3 eq., benzyl bromide: 1.3 eq.).
**4e**: oil (95%); *$^1H$ NMR:* 1.65 (s,3H), 1.77 (s,3H), 2.39 (broad s($W_H$=15Hz),2H), 2.58 (m,1H), 2.68 (m,1H), 2.92 (m,2H), 4.78 (s,1H), 4.87 (s,1H), 6.62 (broad s($W_H$=10Hz),1H), 7.22 (m,5H) ppm; *IR:* 3080, 3040, 2980, 2930, 1670, 1600, 1490, 1480, 1380, 1360, 1090, 1070, 1030, 900, 690 $cm^{-1}$; *MS:* 240(52), 225(6), 185(11), 172(26), 149(21), 131(13), 107(16), 92(72), 91(100). *Anal.* Calcd for $C_{17}H_{20}O$: C,84.95; H, 8.38. Found: C, 84.66; H, 8.14.

**Preparation of (5S,6R)-6-ethyl-6-methyl carvone 5a and of 3a.** Alkylation of 4a (LDA: 1.3 eq., methyl iodide: 10 eq.).
**5a + 3a**: oil (60%); ratio: 95/5 (HPLC, GC); *$^1H$ NMR:* 0.73 (t,J=7Hz,3H), 1.08 (s,3H), 1.43 (m,2H), 1.74 (s,3H), 1.77 (s,3H), 2.43 (broad s($W_H$=16Hz),2H), 4.76 (s,1H), 4.88 (s,1H), 6.58 (broad s($W_H$=9Hz),1H) ppm.

**Preparation of (5S,6R)-6-allyl-6-methyl carvone 5b.** Alkylation of 4b (LDA: 1.3 eq., methyl iodide: 10 eq.).
**5b**: oil (81%); $[\alpha]_D$ -60.65° (c 0.92, chloroform); *$^1H$ NMR:* 1.11 (s,3H), 1.71 (s,3H), 1.77 (s,3H), 2.20 (m,1H), 2.52 (m,4H), 4.74 (s,1H), 4.89 (s,1H), 5.00 (m,2H), 5.68 (m,1H), 6.57 (broad s($W_H$=13Hz),1H) ppm; *IR:* 3035, 3010, 2980, 2940, 1665, 1450, 1440, 1375, 1230, 1025, 995, 915, 900 $cm^{-1}$; *MS:* 204(12), 189(23), 176(13), 163(14), 161(27), 147(23), 136(28), 123(35), 109(49), 108(89), 107(100), 91(67), 82(98). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.86. Found: C, 82.41; H, 10.04.

**Preparation of (5S,6R)-6-(2-bromo allyl)-6-methyl carvone 5c and of 3c.** Alkylation of 4c (LDA: 1.3 eq., methyl iodide: 10 eq., HMPA: 1 eq.).
**5c + 3c**: oil (82%), ratio: 45/55 (HPLC, GC); *$^1H$ NMR:* 1.11 (s,3H,3c), 1.25 (s,3H,5c), 1.61 (s,3H,3c), 1.76 (s,3H,5c), 1.80 (s,6H,3c + 5c), 4.73 (s,1H,5c), 4.75 (s,1H,3c), 4.78 (s,1H,3c), 4.96 (s,1H,5c), 5.49 (s,1H,3c), 5.52 (s,2H,5c), 5.58 (s,1H,3c), 6.59 (broad s($W_H$= 18 Hz),2H,3c + 5c) ppm (relative intensities for signals: 50% for 3c and 50% for 5c).

**Preparation of (5S,6R)-6-(2-chloro allyl)-6-methyl carvone 5d and of 3d.** Alkylation of **4d** (LDA: 1.3 eq;, methyl iodide: 10 eq.).

**5d + 3d**: oil (65%), ratio: 45/55 (HPLC, GC); *$^1$H NMR:* 1.10 (s,3H,**3d**), 1.23 (s,3H,**5d**), 1.60 (s,3H,**3d**), 1.76 (s,3H,**5d**), 1.80 (s,6H,**3d + 5d**), 2.29 (d($W_H$=9Hz),J=20Hz,1H,**3d**), 2.46 (broad s($W_H$=15Hz),1H,**5d**), 2.65 (ABq,J=15Hz,4H,**3d + 5d**), 4.73 (s,1H,**5d**), 4.76 (s,1H,**3d**), 4.78 (s,1H,**3d**), 4.96 (s,1H,**5d**), 5.08 (s,2H,**5d**), 5.26 (s,1H,**5d**), 5.32 (s,1H,**3d**), 6.56 (broad s($W_H$=16Hz),2H,**3d + 5d**) ppm (relative intensities of signals: 50% for **3d** and **5d**).

**Preparation of (5S,6R)-6-benzyl-6-methyl carvone 5e and of 3e.** Alkylation of **4e** (LDA: 1.3 eq., methyl iodide: 10 eq.).

**5e + 3e**: oil (72%), ratio: 75/25 (HPLC, GC); *$^1$H NMR:* 0.96 (s,3H), 1.53 (s,3H,**3e**), 1.81 (s,3H), 4.56 and 4.64 (2s,2H), 6.59 (broad s,1H), 6.99 (m,2H), 7.18 (m,3H) ppm for **3e** and 1.04 (s,3H), 1.81 (s,6H), 4.81 and 5.08 (2s,2H), 6.59 (broad s,1H), 6.99 (m,2H), 7.18 (m, 3H) ppm for **5e** (relative intensities of signals: 25% for **3e** and 75% for **5e**).

**Cyclization of 3c in $H_2SO_4$: preparation of trans diketone 9.**

**3c** (1.47 g; 5.18 mmol) was added slowly to 80% H2SO4 (28 mL) and the resulting solution stirred for 24 h at room remperature. After dilution with water, neutralization with a sat. $NaHCO_3$ solution and extraction with $CH_2Cl_2$, chromatography over silica (eluent: hexane-ethyl acetate 10/90) afforded **9** (0.59 g, 52%).

**9**: mp 61-62°C; $[\alpha]_D$ -49.3° (c 1.18, chloroform); *$^1$H NMR:* 1.01 (s,3H), 1.04 (s,3H), 1.09 (s,3H), 1.75 (s,3H), 6.74 (broad s($W_H$=9Hz),1H) ppm; *13C NMR (J Resolved):* 16.22(q), 18.17(q), 22.99(q), 24.74(t), 31.17(q), 39.50(s), 48.95(s + d + t), 56.01(t), 133.16(s), 143.10(d), 202.60(s), 210.58(s) ppm; *MS:* 220(36), 205(4.5), 187(5), 177(6), 163(11), 136(23), 121(20), 107(16), 91(31), 82(100). *Anal.* Calcd for $C_{14}H_{20}O_2$: C,76.32; H, 9.13. Found: C, 76.26; H, 9.38.

**Cyclization of 3c + 5c in $H_2SO_4$: preparation of 9 and cis diketone 10.**

Starting from the mixture **3c + 5c** obtained from **4c** (see above) and using the same protocol as for **3c** there is obtained after chromatography **10** (29.7%) and **9** (36.7%).

**10**: mp 112-113°C; $[\alpha]_D$ 54.4° (c 1, chloroform); *$^1$H NMR:* 0.66 (s,3H,H-13), 1.08 (s,3H,H-12), 1.34 (s,3H,H-14), 1.75 (pentuplet,J=1Hz,3H,H-11), 1.98 (d,J=14Hz,1H,H-1), 2.05 (dd,J=14 and 2.4Hz,1H,H-3), 2.20 (d,J=6.5Hz,1H,H-5), 2.30 (d,J=14Hz,1H,H-3), 2.54 (dd,J=20 and 5.5Hz,1H,H-6 ), 2.72 (dddq,J=20,6.5,3 and 1Hz respectively,1H,H-6 ), 3.29 (dd,J=14 and 2.4Hz,1H,H-1), 6.52 (broad s,1H,H-7) ppm. *NOEDIFF (nOe's observed after irradiation of the specified proton(s)):* H-7 (H-1:4%,H-6:5%,H-6:5%,H-11:10%), H-12 (H-3:7%,H-5:8%,H-3:7%,H-6:13%), H-14 (H-1:3.5%,H-6:10%,H-5:2%,H-1:1%), H-13 (H-3:7%,H-12:0.5%); *$^{13}$C NMR (J Resolved):* 15.93(q), 23.65(t + q), 28.33(q), 30.70(q), 39.25(s), 47.50(t), 48.70(s), 51.00(d), 56.26(t), 134.00(s), 141.00(d), 200.50(s), 208.00(s) ppm. *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.27; H, 9.20.

**Cyclization of 3c in $CF_3COOH$: preparation of 11 and 12.**

A solution of **3c** (0.58 g, 2 mmol) in $CF_3COOH$ (14.5 mL) was stirred for 24 h at room temperature and then neutralized using a sat. solution of $NaHCO_3$. After extraction with ether an unseparable mixture of **11** and **12** (ratio: 70/30 as judged by HPLC) is obtained as an oil (77%).

**11 + 12**: *$^1$H NMR:* 1.05 (s,3H), 1.07 (s,3H), 1.13 (s,3H), 1.77 (s,3H), 5.80 and 6.54 (2s,1H), 6.80 (s($W_H$=10Hz),1H) ppm.

**Cyclization of 3c in anhydrous HF: preparation of 11.**

**3c** (0.127 g, 0.448 mmol) is slowly added to a solution of anhydrous HF (3 mL) maintained at -40°C in a Teflon bottle. The resulting mixture is stirred for 2 h (-40 to 20°C) and then poured over an iced sat. $NaHCO_3$ solution and extracted with ether. Chromatography over $SiO_2$ afforded **11** as an oil (0.11 g, 87%).

**11**: *$^1$H NMR:* 1.05 (s,3H), 1.07 (s,3H), 1.13 (s,3H), 1.77 (s,3H), 5.80 (s,1H), 6.78 (s($W_H$=10Hz),1H).

**Cyclization of 3c in HF-pyridin: preparation of 13a.**
**3c** (0.31 g, 1.1 mmol) is slowly added to a solution of HF-pyridin (70%, 5 mL) maintened at -20°C in a Teflon bottle. After 2 h at this temperature, the reaction mixture is treated as above. There is obtained after chromatography a mixture of **11** and **12** (20%) and **13a** (0.13 g, 40%).

**13a**: oil; $[\alpha]_D$ -23.3° (c 0.68, chloroform); *$^1$H NMR:* 1.02 (s,3H), 1.25 (s,3H), 1.33 (s,3H), 1.76 (s,3H), 2.05 (t,J=15Hz,1H), 2.40 (m,5H), 2.80 (ddd,J=15,9 and 1.5Hz,1H), 6.72 (broad s($W_H$=10Hz),1H) ppm; *$^1$H NMR ($C_6D_6$):* 0.65 (s,3H), 1.01 (s,3H), 1.22 (s,3H), 1.86 (s,3H), 2.30 (ddd,J=15,9 and 1.5Hz,1H), 2.55 (t,J=15Hz,1H), 3.07 (ddd,J=15,9 and 1.5Hz,1H), 6.14 (broad s($W_H$=11Hz),1H) ppm; *$^{13}$C NMR (J Resolved):* 16.28($CH_3$), 18.25($CH_3$), 23.76($CH_2$), 24.12($CH_3$), 32.90($CH_3$), 35.15(C,d,$J_{CF}$=7Hz), 46.30(C,$J_{CF}$=7Hz), 46.80(CH), 47.90($CH_2$, d,$J_{CF}$=21Hz), 54.20 ($CH_2$,d,$J_{CF}$=18Hz), 107.50(C,d,$J_{CF}$=249Hz), 132.50(C), 143.00(CH), 202.90(C) ppm; *IR:* 2960, 2930, 1670, 1460, 1430, 1000, 940 cm-1; MS: 304(18), 302(18), 261(4), 259(4), 241(2), 239(2), 223(13), 207(9), 203(5), 179(15), 165(5), 151(10), 135(22), 82(100), 43(47). *HRMS:* Calcd for $C_{14}H_{20}BrFO$: 302.06816. Found: 302.07255.

**Cyclization of 3f in anhydrous HF: preparation of 14.**
**3f** (0.133 g, 0.55 mmol) was dissolved in HF (3 mL) at -40°C and the resulting mixture stirred until the temperature reached -20°C (about 3 h). After neutralization and extraction as usual with ether, chromatography over silica (eluent: hexane-ethyl acetate 50/50) afforded **14** as an oil (0.053 g, 40%).

**14**: $[\alpha]_D$ 160.7° (c 1.45, chloroform); *$^1$H NMR:* 1.19 (s,3H), 1.24 (s,3H), 1.54 (s,3H), 1.57 (d,J=14Hz,1H), 1.79 (s,3H), 2.67 (d,J=14Hz,1H), 3.02 (broad s($W_H$=18Hz),2H), 3.37 (s,2H), 6.62 (broad s($W_H$=9Hz),1H) ppm; *NOEDIFF (nOe's observed after irradiation of the specified proton(s)):* H-1 and H-11 (H-6:2%), H-12(H-1:2%,H-11:2.5%,H-13:2%), H-13 (H-11:1%,H-12:1%), H-5 and (H-6:7%,H-11:5%), H-6 (H-5 and :7%,H-10:3.5%); *$^{13}$C NMR (J Resolved):* 9.3(q), 16.3(q), 24.6(q), 25.6(t + q), 43.1(t), 50.8(s), 52.9(t), 56.5(s), 133.8(s), 134.5(s), 135.8(s), 140.5(d), 203.6(s) ppm; *IR:* 2980, 2940, 1690, 1680, 1450, 1370 cm-1; *MS:* 240(6.5), 238(16), 203(18), 189(100), 161(27). *HRMS:* Calcd for $C_{14}H_{19}ClO$: 238.11243. Found: 238.11083.

**Cyclization of 3g in anhydrous HF: preparation of 15.**
The reaction is performed as above for **3f**.

**15**: oil (40%); $[\alpha]_D$ 129.5° (c 0.78, chloroform); *$^1$H NMR:* 1.24 (s,3H), 1.26 (s,3H), 1.54 (s,3H), 1.57 (partly hindered d,J=14Hz,1H), 1.80(s,3H), 2.65 (d,J=14Hz,1H), 3.02 (broad s($W_H$=18Hz),2H), 3.31 (ABq,J=1Hz,1H), 6.62 (broad s($W_H$=9Hz),1H) ppm; *IR:* 2970, 2940, 1690, 1680, 1450, 1370 $cm^{-1}$; *MS:* 284(9), 282(9), 241(11), 239(11), 203(21), 189(100), 187(42), 161(22). *HRMS:* Calcd for $C_{14}H_{19}BrO$: 282.06191. Found: 282.05876.

**Reduction of 9 to 21.**
To a solution of **9** (1.1 g, 5.02 mmol) in methanol (22 mL) was added slowly $NaBH_4$ (0.35 molar eq.) at 0°C. The reaction was followed by TLC and after total consumption of starting material (about 3h) the mixture was hydrolyzed and extracted with ether. Chromatography over $SiO_2$ afforded the axial alcohol **21** (0.82 g, 74%).

**21**: mp 105-107°C; $[\alpha]_D$ -41.6° (c 1, chloroform); *$^1$H NMR:* 0.93 (s,3H), 1.25 (s,3H), 1.33 (s,3H), 1.75 (s,3H), 4.32 (t,J=2.5Hz,1H), 6.70 (broad s($W_H$=9Hz,1H); *$^{13}$C NMR (J Resolved):* 16.4(q), 19.1(q), 24.3(t + q), 33.01(s + q), 38.85(t), 44.6(s), 46.4(t), 49.1(d), 67.8(d), 132.5(s), 143.45(d), 205.4(s) ppm; *MS:* 222(22), 204(6), 189(11), 163(14), 148(11), 147(10), 137(10), 135(20), 123(19), 122(12), 109(15), 107(11), 96(17), 82(100). *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.57; H, 9.71.

**Dehydration of 21 to 22a,b.**
To a solution of **21** (0.23 g, 1.04 mmol) in dry ether (4.5 mL) and pyridin (4.5 mL) was added a solution of $POCl_3$ (0.21 mL) in petroleum ether (4.5 mL). The reaction mixture was refluxed for 3 h and after hydrolysis and extraction as usual the crude product was chromatographied over $SiO_2$ (eluent: hexane-ethyl acetate 2/98) to gave a mixture of **22a** and **22b** (0.18 g, 85%).
**22a,b**: *$^1H$ NMR:* 0.95 (s,3H), 1.00 (s,3H), 1.06 (s,3H), 1.77 (s,3H), 5.40 (dd,J=11 and 1.5Hz,1H), 6.06 (dd,J=10 and 1.5Hz,1H), 6.69 and 6.78 (2s,1H).

**Preparation of 20.**
To a solution of **22a,b** (0.18 g, 0.88 mmol) in ethyl acetate (5 mL) was added Pd/C (about 50 mg) and the resulting suspension was stirred under hydrogen (atmospheric pressure) for 12 h. After filtration of the catalyst and removal of the solvent (rotavapor), the crude reaction mixture was dissolved in methanol (2 mL) and treated with a 10% solution of MeONa in MeOH (1.38 mL). After stiring for 6 h at room temperature, work-up as usual afforded **20** as a white powder (0.137 g, 65%).
**20**: mp 46-49°C; $mp_{Litt}$ 49-50°C; $[\alpha]_D$ -38.47° (c 1, chloroform); $[\alpha]_D$Litt -36.9° (c 1, chloroform); *$^1H$ NMR:* 0.89 (s,3H), 0.93 (s,3H), 0.98 (d,J=6Hz,3H), 1.14 (s,3H) ppm.

## REFERENCES


1.Hanessian S.*Total Synthesis of Natural Products : The Chiron Approach*,Pergamon Press,**1984**.

2.For a recent reference on the use of (-)carvone in natural product synthesis see:
Ireland,R.E.;Maienfisch,P.,*J.Org.Chem.***1988**,*53*,640 and references cited therein.
For other references on the use of carvone for the synthesis of terpenoids see:
ApSimon,J.*The Total Synthesis of Natural Products*,J.Wiley and Sons Ed.,**1973**,Vol.2 and **1983**,Vol.5.

3.For a preliminary communication see: Gesson,J.-P.;Jacquesy,J.-C.;Renoux,B.*Tetrahedron Lett.***1986**,*27*,4461.

4.For recent reviews on sesquiterpenoids see:
Roberts,J.S.;Bryson,I.*Nat.Prod.Rep.***1984**,*1*,105.
Roberts,J.S.*ibid.***1985**,*2*,97.
Fraga,B.M.*ibid.***1985**,*2*,147;*ibid.***1986**,*3*,273;*ibid.***1987**,*4*,473;*ibid.*,**1988**,*5*,497.
For recent reviews on diterpenoids see:
Hanson,J.R.*ibid.***1984**,*1*,171,339,533;*ibid.***1986**,*3*,307;*ibid.***1987**,*4*,399;*ibid.***1988**,*5*,211.
For recent reviews on triterpenoids see:
Boar,R.B.*ibid.***1984**,*1*,53.
Connolly,J.D.;Hill,R.A.*ibid.***1985**,*2*,1;*ibid.***1986**,*3*,421.
For recent reviews on sesterterpenoids see:
Hanson,J.R.*ibid.***1986**,*3*,123.

5.Lansbury,P.T.*Acc.Chem.Res.***1972**,*5*,311.

6.Cory,R.M.;Renneboog,R.M.*J.Org.Chem.***1984**,*49*,3898.

7.Stork,G.;Danheiser,R.L.;Ganem,B.*J.Am.Chem.Soc.***1973**,*95*,3414.

8.Tomioka,K.;Yasuda,K.;Kawasaki,H.;Koga,K.*Tetrahedron Lett.***1986**,*27*,3247.

9.Maas,D.D.;Blagg,M.;Wiemer,D.F.*J.Org.Chem.***1984**,*49*,853.

10.Olah,G.A.;Welch,J.T.;Vankar,Y.D.;Nojime,N.;Kerekes,I.;Olah,J.A.*J.Org.Chem.***1979**,*44*,3872.
11.Francois,P.;Lablache-Combier,A.;Levisalles,J.*Bull.Soc.Chim.***1965**,2588.
Lablache-Combier,A.;Lacoume,B.;Levisalles,J.*Bull.Soc.Chim.***1965**,2595.
12.Schneider,H.J.;Gschwendtner,W.;Heiske,D.;Hoppen,V.;Thomas,F.*Tetrahedron*,**1977**,*33*,1769.
13.Jones,K;Mooney,E.F.*Annual Reports on NMR Spectroscopy*,Mooney,E.F.Ed.Academic Press,London,**1970**,261.
14.Adinolfi,M.;Laonigro,G.;Mangoni,L.*Gazz.Chim.Ital.***1968**,*98*,107.