Available online at www.sciencedirect.com
ScienceDirect
C. R. Chimie 10 (2007) 259–267
COMPTES RENDUS CHIMIE
http://france.elsevier.com/direct/CRAS2C/

Full paper / Mémoire

Synthesis of 2,4-dimethyl-cyclohex-3-ene carboxaldehyde derivatives with olfactory properties

Patricia Monnier-Benoit [b], Ivan Jabin [a], Jean-Noël Jaubert [a], Pierre Netchitaïlo [a,*], Bernard Goyau [b]

[a] *URCOM, EA 3221, UFR des sciences and techniques, université du Havre, 25, rue Philippe-Lebon, BP 540, 76058 Le Havre cedex, France*
[b] *PCAS, BP 181, 91161 Longjumeau cedex, France*

Received 7 July 2006; accepted after revision 20 October 2006
Available online 9 January 2007

Abstract

Oxidation of the starting aldehyde **1** led to the acid **6** which was esterified in neutral conditions to give the esters **7**–**11**. A Wittig reaction with **1** and various phosphoranes led to compounds **12**–**15** bearing a functionalized unsaturated side chain. Acidic hydrolysis of **15** gave the aldehyde **16** homologue of **1**. Ketone **19** was obtained by Grignard reaction between **1** and the bromoacetal **17** followed by oxidation of the alcohol **18**. Intramolecular cyclization of **18** and **19** gave the lactone **22** and the pentenone **20**, respectively. Analysis of the olfactory properties of all these compounds revealed that esters **7**, **9**, ether **15** and aldehyde **16** could be used in the formulation of flowery or fruity compositions. ***To cite this article: P. Monnier-Benoit et al., C. R. Chimie 10 (2007).***

Résumé

L'oxydation de l'aldéhyde de départ **1** conduit à l'acide carboxylique **6**, qui a été estérifié en milieu neutre pour donner les esters **7**–**11**. Une réaction de Wittig entre le composé **1** et différents phosphoranes a conduit aux composés **12**–**15**, qui possèdent une chaîne latérale insaturée. L'hydrolyse acide du composé **15** donne l'aldéhyde **16**, qui constitue l'homologue du composé **1**. La cétone **19** a été synthétisée par une réaction de Grignard entre le composé **1** et le bromoacétal **17**, suivie d'une oxydation de l'alcool **18**. La cyclisation intramoléculaire des composés **18** et **19** conduit à la lactone **22** et à la cyclopentenone **20**, respectivement. L'analyse olfactive de l'ensemble des composés obtenus montre que les esters **7**, **9**, l'éther **15** et l'aldéhyde **16** pourraient être utilisés dans la formulation de compositions florales ou fruitées. ***Pour citer cet article : P. Monnier-Benoit et al., C. R. Chimie 10 (2007).***

Keywords: 2,4-Dimethyl-cyclohex-3-ene carboxaldehyde; Esters; Olfactory properties

Mots-clés : 2,4-Diméthyl-cyclohex-3-ène carboxaldéhyde ; Esters ; Propriétés olfactives

* Corresponding author.
E-mail address: pierre.netchitailo@univ-lehavre.fr (P. Netchitaïlo).

1631-0748/$ - see front matter © 2006 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.crci.2006.10.006

1. Introduction

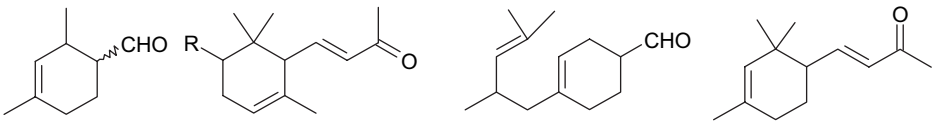
Numerous compounds bearing a polyalkyl-substituted cyclohexane backbone have been developed for their applications in flavour chemistry and perfume industry. Among them are important fragrant compounds such as menthols [1], carvones [2], ionones [3] and damascones [4]. Various substances show a combination of conjugate or non-conjugate double bonds with a carbonyl group in correlation with the natural pattern of the 2,6,6-trimethyl or 1-methyl-4-isopropyl substituents. In the group of ionones, structure–odour relationship has shown that the position of the double bond in the nucleus affects the quality but not the type of odour, while the introduction of a second double bond destroys the violet odour [5]. Furthermore, ionone derivatives having a *gem*-dimethyl group *ortho* and a methyl group *para* to the side chain exhale a closed violet-odour. Among the numerous syntheses of both natural and synthetic cyclohexane derivatives, we took notice of 2,4-dimethyl-cyclohex-3-ene carboxaldehyde **1** [6] as an attractive starting substrate for syntheses of more elaborate derivatives with potential olfactory properties. We have chosen compound **1** as the starting synthon for the following reasons: (a) it possesses olfactory properties; (b) it could lead to analogs of both natural and synthetic olfactive compounds such as α-ionone **2**, β-irone **3**, 4-(4-methyl-3-penten-1-yl)-3-cyclohexene carboxaldehyde **4** [7] or 4-(2,2,4-trimethyl-cyclohex-3-enyl)-but-3-en-2-one **5** [5b] (Scheme 1); (c) it constitutes a raw material since it is industrially produced by Diels–Alder reaction starting from acrolein and 2-methylpentadiene and is available in a large scale; (d) our aim was to investigate syntheses of compounds with a high added-value including at least one equivalent of acrolein.

Aldehyde **1** is usually produced in standard conditions of Diels–Alder reaction between acrolein and 2-methylpentadiene as a racemic mixture of *cis*- and *trans*-diastereomer (80:20 ratio) besides a small amount of the regioisomer 2,4-dimethylcyclohex-2-ene carboxaldehyde. The reaction can be conducted in the presence of Lewis acid catalysts or metal transition catalysts to improve the stereoselectivity [8,9].

2. Results and discussion

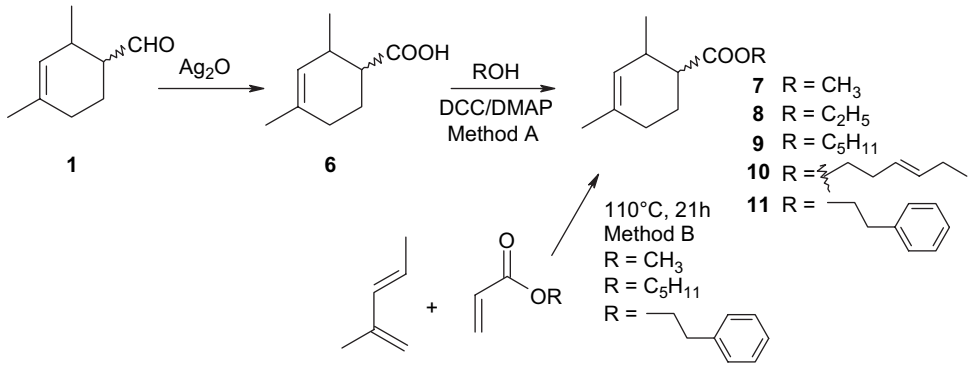
The aim of the study was to synthesize derivatives of compound **1** with functions that are likely to provide a pleasant olfactory note using simple methodology associated, if possible, with low-cost reactives so as to allow possible industrial transfer of the process. First experiments were conducted to synthesize various esters from the acid **6** produced by oxidation of **1** using Ag_2O in basic conditions (Scheme 2).

Esterification of **6** in acidic conditions via the acyl chloride or directly by the action of alcohols failed. Under these conditions, we observed the isomerization of the double bond in position 4 and the formation of numerous by-products resulting from the addition of hydrogen chloride or alcohol on the double bond. Finally, the esterification of **6** was performed (method A), at room temperature, in mild conditions using dicyclohexylcarbodiimide (DCC) as the coupling agent in the presence of the alcohol and dimethylaminopyridine (DMAP). Five esters **7**–**11** were synthesized with moderate yields (55–63%). Among them, the methyl ester **7**, the pentyl ester **9** and the phenylethyl ester **11**, have revealed interesting olfactory characteristics (see Table 1). Therefore, we searched a cheap alternative procedure. As already reported with ethyl acrylate and various dienes [10], Diels–Alder reaction between methyl acrylate and 2-methylpentadiene led to the corresponding adduct **7** with a good yield (74%). The reaction was conducted at 110 °C for 21 h in the presence of a small amount of hydroquinone to avoid acrylate polymerization (method B). Under the same conditions, pentyl acrylate and phenylethyl acrylate conducted to the adducts **9**, **11** in good yields (87 and 83%). The stereoselectivity of the addition was determined by GC–MS analysis of the distillate. As expected, in each case, the major *cis*/*trans*-diastereomers were obtained beside a minor



1 R = H α-I onone **2**; R = CH_3 β-Irone **3** **4** **5**

Scheme 1.



Scheme 2.

regioisomer as described above for the synthesis of **1** (further details are indicated in Section 4).

A Wittig reaction between **1** and substituted-methylenetriphenylphosphoranes led to the syntheses of compounds bearing a functionalized unsaturated lateral chain (Scheme 3).

The reaction conducted for 15 h at reflux in the presence of toluene with carbomethoxy or carboethoxymethylenetriphenylphosphorane yields the expected unsaturated esters **12** and **13** (66 and 83%). Similarly and under the same conditions, the formylmethylenetriphenyl-phosphorane led to the unsaturated aldehyde **14** in a poor yield (12%) accompanied with a large amount of the starting compound **1**. Other protocols, notably using other solvents, prolonged heating or higher temperature, have failed in all cases. Finally, the reaction of **1** with methoxymethylenetriphenylphosphorane at 0 °C for 30 min in toluene led to the enol ether **15**, which was hydrolysed in a mixture of acetic acid–water–THF (3:1:1) at room temperature for 5 days, giving the aldehyde **16**, homologue of the starting compound **1**. ^{1}H NMR analyses indicated that in the structures **12**–**14**, the ethylenic protons display coupling constants characteristic of an *E* double bond. On the other hand, the NMR pattern of compound **15** supported the presence of a mixture of *Z* and *E* stereoisomers (57:43 ratio).

Table 1
Olfactory properties of compounds

Compounds	Quality	Referents [14]
7	Hesperidic-fruity	Isobutylquinoleine/nootkatone
8	Fruity	Ethyl isobutyrate/benzyl acetate
9	Ester-watermelon like	Ethyl isobutyrate/nonanal/decadienal
10	Ester-fruity/green	Ethyl isobutyrate/nonanal/hexenyl acetate
11	Soft rosy odour	Ethyl isobutyrate/phenylethylic alcohol
12	Floral	Benzyl acetate
13	Floral	Benzyl acetate/naphthaline
14	Fatty acidic	Isovaleric acid
15	Green ester/fatty	Cyclopentanone/*cis*-3-hexenol/nonanal
16	Aldehydic/camphor	*cis*-3-Hexenol/camphor
20	Hesperidic-fruity	Nootkatone
21	Angelic-type-terpenic ester	Styralyl acetate

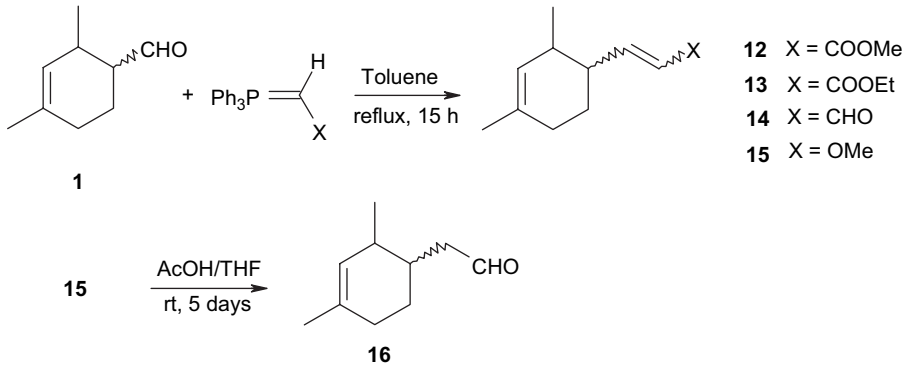
Then, according to the aim of our study, we focused our interest on the Grignard reagent derived from 2-(2-bromoethyl)-[1,3]dioxane **17**, which is directly derived from acrolein. As indicated in Scheme 4, a Grignard reaction between **1** and the bromo derivative **17**, conducted in the conditions described elsewhere [11], gave the alcohol **18** in a very good yield (91%).

Oxidation of the alcohol **18** using pyridinium chlorochromate [12] in methylene chloride at room temperature for 3 h led to the ketone **19** in good yield (84%). The ketone **19** was then reacted with lithium trimethylsilyldiazomethane [13] to give, after hydrolysis in diluted citric acid of the intermediate acetal which was not isolated, the cyclopentenone **20** in a moderate yield (40%). Finally, treatment of the alcohol **18** with *para*-toluene sulfonic acid at reflux in a mixture of acetone–water (3:1) gave the lactol **21**. This latter was not isolated, but oxidized using the Jones reagent in acetone at 0 °C for 1 h, leading to the lactone **22** in a moderate yield (56%).

3. Olfactory evaluations

Table 1 summarizes the olfactive properties of compounds **7**–**16** and **20**, **22**.

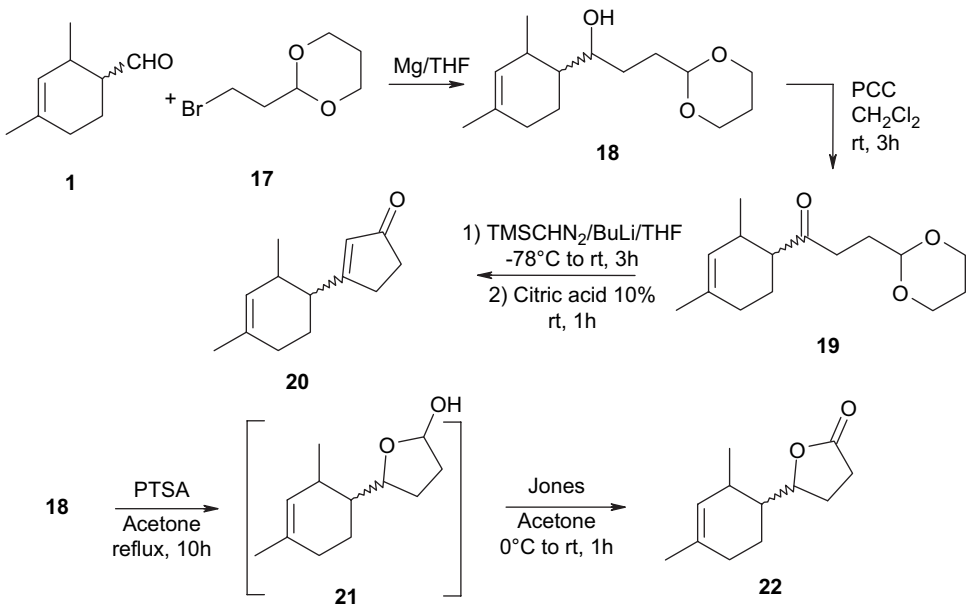
Starting aldehyde **1** exhibits an extremely strong accentuated grassy-green note with a herbal camphor



Scheme 3.

side note. Esters **7** and **8** are hesperidic-fruity odorants with grapefruit notes. Compound **9** possesses typical ester notes with an aldehydic tonality and a watermelon odour which is currently attractive and could well be applied to perfume compositions. Ester **10** is fruity-green with a fatty aldehydic character. In contrast, compound **11** is not very powerful, possessing a rosy odour weaker than phenylethylic alcohol. Esters **12** and **13** which could be considered as vinylic analogs of esters **7** and **8** show, in contrast, a heavy floral note. Compound **12** shows a linear odour with a good tenacity while the floral odour of compound **13** is less interesting than ester **12** because of an unpleasant aromatic undertone. In contrast to compound **1**, aldehyde **14** is characterized by an unpleasant fatty acidic odour similar to isovaleric acid. Olfactory properties of **15** and **16** are interesting since they show two facets. Compound **16** exhibits a green ester and fatty note, while aldehyde **16** shows a typical aldehydic note associated with a terpenic by-note. Acetals **18** and **19** do not present any significative odour. Finally, cyclopentenone **20** possesses a hesperidic-fruity note like nootkatone, but shows weaker tenacity, and the lactone **21** has terpenic odorant with an angelic-type odour like styralyle acetate.

The odour evaluations performed on our samples pointed out that all these compounds had very different odour properties in spite of their common dimethylcyclohexenyl skeleton. Compounds **7**, **9**, **15** and **16** which were selected by the olfactory evaluation panel to possess interesting fragrance could be used in flowery or fruity compositions.



Scheme 4.

4. Experimental section

4.1. General procedure

Analytical thin layer chromatography was performed on precoated plates of silica gel 60F 254 (Merck) and column chromatography on Nacherey Nagel silica gel (230–400 mesh). GC analyses were carried out on GC/MS Hewlett Packard 5890A, detector HP5970, column supelco SPB-1 (polydimethylsiloxane). The infrared spectra were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC 200 instruments using $CDCl_3$ as solvent, and chemical shifts (δ) are expressed in parts per million relative to residual $CHCl_3$ at $\delta = 7.27$ for ^{1}H. All the compounds described herein are obtained as a mixture of diastereoisomers. For each compound we indicated the ^{1}H NMR data of the major and minor diastereoisomers, except for compound **10** which was obtained as a mixture of two diastereoisomers in a proportion not determined by NMR (determined by GC) and compound **15**, which was obtained as a mixture of 4 identified diastereoisomers. In all cases, the ^{13}C NMR spectra are in accordance with the structures.

4.2. 2,4-Dimethylcyclohex-3-ene carboxylic acid (*6*)

An aqueous solution of **1** (20 g, 0.14 mol), Ag_2O (34.8 g, 0.15 mol) and NaOH (27 g, 0.67 mol) was stirred at room temperature for 15 h and then diluted with diethyl ether (100 ml). The aqueous layer was slowly acidified to pH = 2 with 10% aqueous HCl and extracted with diethyl ether. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product (15.9 g, 74% yield) which was obtained as a mixture of two diastereoisomers (80:20 ratio, stereochemistry not determined) was pure enough to be used without further purification in the next step.

mp = 91 °C (lit. mp = 92–93 °C [9]). IR (film) ν (cm^{-1}): 1702 (C=O). ^{1}H NMR δ (ppm): 0.92 (d, $J = 7.0$ Hz, 3H, minor diastereoisomer, 20%), 0.98 (d, $J = 7.0$ Hz, 3H, major diastereoisomer, 80%), 1.55–2.12 (m, 4H), 1.65 (s, 3H), 2.42–2.48 (m, 1H), 2.50–2.72 (m, 1H), 5.17 (s, 1H, major diastereoisomer, 80%), 5.30–5.39 (m, 1H, minor diastereoisomer, 20%).

4.3. General procedure for preparation of esters *7–11* (method A)

A solution of **6** (3 g, 19.4 mmol), alcohol (23 mmol), dicyclohexylcarbodiimide (DCC) (4.42 g, 21.3 mmol), and dimethylaminopyridine (0.2 g, 1.64 mmol) in dichloromethane (30 ml) was stirred at room temperature for one day under inert conditions. The excess of DCC was hydrolysed with 10% aqueous HCl (3 ml). The mixture was stirred for 1 h and extracted with diethyl ether (2 × 50 ml). The organic layer was washed with water (3 × 20 ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by chromatography on silica gel (hexane–ethylacetate 85:15 v/v).

4.3.1. Methyl(2,4-dimethyl-cyclohex-3-ene) carboxylate (*7*)

This compound was obtained using methanol with 59% yield as a colorless liquid and as a mixture of two diastereoisomers (65:35 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1738 (C=O). ^{1}H NMR δ (ppm): 0.82 (d, $J = 7.0$ Hz, 3H, minor diastereoisomer, 35%), 0.91 (d, $J = 7.0$ Hz, 3H, major diastereoisomer, 65%), 1.52–2.12 (m, 4H), 1.62 (s, 3H), 2.18–2.60 (m, 2H), 3.64 (s, 3H), 5.12 (s, 1H, major diastereoisomer, 65%), 5.32 (s, 1H, minor diastereoisomer, 35%). MS (EI): *m/z* 168 (M^+, 15), 137 (7), 136 (7), 125 (5), 121 (4), 109 (41), 108 (100), 93 (92), 77 (18), 67 (47), 55 (19).

4.3.2. Ethyl(2,4-dimethyl-cyclohex-3-ene) carboxylate (*8*)

This compound was obtained using ethanol with 59% yield as a colorless liquid and as a mixture of two diastereoisomers (55:45 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1731 (C=O). ^{1}H NMR δ (ppm): 0.83 (d, $J = 7.0$ Hz, 3H, minor diastereoisomer, 45%), 0.93 (d, $J = 7.0$ Hz, 3H, major diastereoisomer, 55%), 1.23 (t, $J = 7.5$ Hz, 3H), 1.55–2.22 (m, 4H), 1.62 (s, 3H), 2.25–2.68 (m, 2H), 4.11 (q, $J = 7$ Hz, 2H, minor diastereoisomer, 45%), 4.12 (q, $J = 7$ Hz, 2H, major diastereoisomer, 55%), 5.15 (s, 1H, minor diastereoisomer, 45%), 5.25 (s, 1H, major diastereoisomer, 55%). MS (EI): *m/z* 182 (M^+, 11), 153 (6), 137 (10), 125 (5), 121 (4), 109 (43), 108 (100), 107 (41), 93 (57), 91 (15), 79 (15), 77 (15), 67 (32), 55 (15).

4.3.3. Pentyl(2,4-dimethyl-cyclohex-3-ene) carboxylate (*9*)

This compound was obtained using pentyl alcohol with 63% yield as a colorless liquid and as a mixture of two diastereoisomers (55:45 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1732 (C=O). ^{1}H NMR δ (ppm): 0.80–0.97 (m, 6H), 1.18–1.44 (m, 2H), 1.50–2.10 (m, 8H), 1.65 (s, 3H), 2.30–2.60 (m, 2H), 3.75–4.10

(m, 2H), 5.15 (m, 1H, minor diastereoisomer, 45%), 5.31 (m, 1H, major diastereoisomer, 55%). MS (EI): *m/z* 224 (M^+, 13), 153 (19), 137 (10), 136 (15), 109 (41), 108 (100), 93 (28), 67 (22), 55 (16).

*4.3.4. cis-3-Hex-3-enyl(2,4-dimethyl-cyclohex-3-ene)carboxylate (**10**)*

This compound was obtained using *cis*-3-hex-3-enyl alcohol with 55% yield as a colorless liquid and as a mixture of two diastereoisomers (55:45 ratio, determined by gas chromatography).

IR (film) ν (cm^{-1}): 1733 (C=O). ^1H NMR δ (ppm): 0.79–1.01 (m, 6H), 1.55–2.18 (m, 8H), 1.58 (s, 3H), 2.25–2.60 (m, 2H), 3.92–4.11 (m, 2H), 5.12–5.55 (m, 3H). MS (EI): *m/z* 236 (M^+, 2), 154 (15), 153 (36), 136 (8), 109 (35), 108 (47), 107 (100), 93 (30), 83 (38), 67 (53), 55 (95).

*4.3.5. Phenethyl(2,4-dimethyl-cyclohex-3-ene) carboxylate (**11**)*

This compound was obtained using 1-phenylethyl alcohol with 55% yield as a colorless liquid and as a mixture of two diastereoisomers (51:49 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1732 (C=O). ^1H NMR δ (ppm): 0.76 (d, $J = 7$ Hz, 3H, minor stereoisomer, 49%), 0.90 (d, $J = 7$ Hz, 3H, major diastereoisomer, 51%), 1.58–2.22 (m, 4H), 1.63 (s, 3H), 2.25–2.56 (m, 2H), 2.95 (t, $J = 7.0$ Hz, 2H), 4.23–4.38 (m, 2H), 5.18 (m, 1H, minor diastereoisomer, 49%), 5.35 (m, 1H, major diastereoisomer, 51%), 7.12–7.55 (m, 5H). MS (EI): *m/z* 258 (M^+, 7), 153 (25), 108 (22), 107 (31), 105 (100), 91 (19), 79 (20), 67 (16).

*4.4. General procedure for preparation of esters **7**, **9** and **11** (method B)*

A mixture of 2-methyl-1,3-pentadiene (6.9 g, 84 mmol), hydroquinone (0.1 g, 0.084 mmol) and methyl-, pentyl- or phenylethyl acrylate (70 mmol) was stirred at 120 °C for one day in a reactor. After cooling, distillation of the crude product afforded the expected esters as a mixture of two diastereoisomers (75:25).

*4.5. Methyl[3-(2,4-dimethyl-cyclohex-3-enyl)] acrylate (**12**)*

A solution of **1** (3 g, 22.7 mmol) in toluene (30 ml) was slowly added to a solution of carbomethoxymethylenetriphenylphosphorane (7.8 g, 22.7 mmol) in toluene (30 ml) under inert conditions. The solution was refluxed for 15 h and the solvent was removed under reduced pressure. The residue was diluted with diethylic ether (40 ml) and the solution was stirred for 1 h. The solution was filtered and insoluble triphenylphosphine was washed with diethyl ether (3×20 ml). The organic extracts were collected, dried over $MgSO_4$, filtered and concentrated. Purification of the residue by silica gel chromatography (hexane–ethylacetate 80:20) afforded 2.9 g (66% yield) of **12** as a colorless liquid and as a mixture of two diastereoisomers (70:30 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1726 (C=O), 1652 (C=C). ^1H NMR δ (ppm): 0.82 (d, $J = 7$ Hz, 3H, major diastereoisomer, 70%), 0.92 (d, $J = 7$ Hz, 3H, minor diastereoisomer, 30%), 1.63–1.87 (m, 2H), 1.65 (s, 3H), 1.89–2.12 (m, 2H), 2.21–2.57 (m, 2H), 3.70 (s, 3H), 5.18 (s, 1H, minor diastereoisomer, 30%), 5.28 (s, 1H, major diastereoisomer, 70%), 5.82 (dd, $J = 1.7$ Hz, $J = 16.1$ Hz, 1H), 6.87 (dd, $J = 8.6$ Hz, $J = 15.6$ Hz, 1H, minor diastereoisomer, 30%), 6.98 (dd, $J = 8.1$ Hz, $J = 15.6$ Hz, 1H, major diastereoisomer, 70%). MS (EI): *m/z* 194 (M^+, 10), 135 (7), 108 (11), 93 (10), 82 (100), 67 (64), 53 (15).

*4.6. Ethyl[3-(2,4-dimethyl-cyclohex-3-enyl)] acrylate (**13**)*

A procedure similar to that described above for preparation of compound **12** afforded 4.1 g (88% yield) of **13** as a colorless liquid and as a mixture of two diastereoisomers (75:25 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1718 (C=O), 1654 (C=C). ^1H NMR δ (ppm): 0.80 (d, $J = 7.4$ Hz, 3H, major diastereoisomer, 75%), 0.90 (d, $J = 7.4$ Hz, 3H, minor diastereoisomer, 25%), 1.25 (t, $J = 7$ Hz, 3H) 1.58–1.80 (m, 2H), 1.61 (s, 3H), 1.89–2.20 (m, 2H), 2.22–2.55 (m, 2H), 4.13 (q, $J = 7.5$ Hz, 2H), 5.16 (s, 1H, minor diastereoisomer, 25%), 5.24 (s, 1H, major diastereoisomer, 75%), 5.82 (dd, $J = 1.6$ Hz, $J = 15.6$ Hz, 1H), 6.86 (dd, $J = 8.1$ Hz, $J = 15.6$ Hz, 1H, minor diastereoisomer, 25%), 6.98 (dd, $J = 8.1$ Hz, $J = 15.6$ Hz, 1H, major diastereoisomer, 75%). MS (EI): *m/z* 208 (M^+, 8), 135 (8), 108 (10), 82 (100), 67 (53), 53 (12).

*4.7. 3-(2,4-Dimethyl-cyclohex-3-enyl)-propenal (**14**)*

A mixture of **1** (9 g, 6.51 mmol) and triphenylphosphoranylidene acetaldehyde (2 g, 6.57 mmol) in toluene (100 ml) was refluxed for 9 h under inert atmosphere. The mixture was concentrated and the residue was purified by chromatography on silica gel

(cyclohexane–dichloromethane, 70:30) to give **14** (1.28 g, 12% yield) as a colorless liquid and as a mixture of two diastereoisomers (60:40 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1686 (C=O), 1633 (C=C). ^1H NMR δ (ppm): 0.85 (d, $J = 7.1$ Hz, 3H, major diastereoisomer, 60%), 0.93 (d, $J = 7.1$ Hz, 3H, minor diastereoisomer, 40%), 1.25 (t, $J = 7$ Hz, 1H) 1.45–2.10 (m, 4H), 1.55 (s, 3H), 2.10–2.72 (m, 2H), 5.20 (s, 1H, minor diastereoisomer, 40%), 5.38 (s, 1H, major diastereoisomer, 60%), 6.12 (dd, $J = 7$ Hz, $J = 15.6$ Hz, 1H), 6.76 (dd, $J = 7.8$ Hz, $J = 15.6$ Hz, 1H, minor diastereoisomer, 40%), 6.87 (dd, $J = 7.8$ Hz, $J = 15.6$ Hz, 1H, major diastereoisomer, 60%), 9.49 (d, $J = 7.8$ Hz, 1H). MS (EI): *m/z* 164 (M^+, 5), 149 (12), 108 (18), 107 (16), 92 (18), 82 (85), 67 (100), 53 (20).

*4.8. 4-(2-Methoxy-vinyl)-1,3-dimethyl-cyclohex-3-ene (**15**)*

A solution of LDA in THF was prepared as follows: to a solution of THF (50 ml) and distilled diisopropylamine (1.2 ml, 8.6 mmol) was added dropwise a solution of *n*-butyllithium 2.5 M (3.5 ml, 8.7 mmol) at −30 °C under inert atmosphere. The mixture was stirred at this temperature for 30 min and was allowed to react for an additional 30 min at room temperature. The solution of LDA was added dropwise to a mixture of methoxymethyltriphenylphosphonium chloride (2.8 g, 8.2 mmol) in toluene (10 ml) at 0 °C under inert atmosphere. After stirring for 30 min, a solution of **1** (1 g, 7.2 mmol) in toluene (5 ml) was added and the mixture was allowed to react at 0 °C for 30 min and then hydrolysed successively with a saturated aqueous NH_4Cl solution (7 ml) and with water (10 ml) to dissolve precipitated salts. The solution was extracted with diethylic ether (3 × 5 ml) and the organic phase was washed with brine (2 × 5 ml). After drying over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (hexane–ethylacetate, 95:5) to give **15** (0.67 g, 56% yield) as a colorless liquid and as a mixture of four diastereoisomers *Z-cis*, *Z-trans*, *E-cis* and *E-trans* (47:10:30:13 ratio, respectively).

^1H NMR δ (ppm): 0.78–0.94 (m, 3H), 1.52–2.02 (m, 4H), 1.61 (s, 3H), 2.10–2.38 (m, 7H), 2.72–2.88 (m, 1H), 3.52 (s, 3H, *E* diastereoisomers, 43%), 3.57 (s, 3H, *Z* diastereoisomers, 57%), 4.18 (dd, $J = 6.5$ Hz, $J = 9.7$ Hz, 1H, *trans* diastereoisomers, 23%), 4.30 (dd, $J = 6.5$ Hz, $J = 9.7$ Hz, 1H, *cis* diastereoisomers, 77%), 4.58 (dd, $J = 8.1$ Hz, $J = 12.9$ Hz, 1H, *trans* diastereoisomers, 23%), 4.59 (dd, $J = 9.1$ Hz, $J = 13$ Hz, 1H, *cis* diastereoisomers, 77%), 5.12–5.28 (m, 1H), 5.78 (dd, $J = 1.1$ Hz, $J = 6.5$ Hz, 1H, *Z* diastereoisomers, 57%), 6.30 (d, $J = 12.4$ Hz, 1H, *E* diastereoisomers, 43%). MS (EI): *m/z* 166 (M^+, 2), 108 (14), 84 (100), 69 (28).

*4.9. (2,4-Dimethyl-cyclohex-3-enyl)-acetaldehyde (**16**)*

A solution of compound **15** (0.5 g, 3 mmol) in 3 ml of a mixture of acetic acid, THF and water (3:1:1) was stirred under inert atmosphere for 5 days. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (hexane–ethylacetate, 80:20) to give **16** (0.2 g, 44% yield) as a colorless liquid and as a mixture of two diastereoisomers (70:30 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1725 (C=O). ^1H NMR δ (ppm): 0.82 (d, $J = 7.0$ Hz, 3H, minor diastereoisomer, 30%), 0.96 (d, $J = 7$ Hz, 3H, major diastereoisomer, 70%), 1.15–2.42 (m, 7H), 1.60 (s, 3H), 2.52 (ddd, $J = 1.6$ Hz, $J = 4.3$ Hz, $J = 16.1$ Hz, 1H), 5.16 (s, 1H, major diastereoisomer, 70%), 5.25 (s, 1H, minor diastereoisomer, 30%), 9.74 (t, $J = 1.6$ Hz, 1H). MS (EI): *m/z* 152 (M^+, 2), 108 (100), 93 (95), 91 (21), 82 (23), 77 (20), 67 (66), 55 (18).

*4.10. 1-(2,4-Dimethyl-cyclohex-3-enyl)-3-[1,3]dioxan-2-yl-propan-1-ol (**18**)*

To a suspension of magnesium (0.3 g, 12.3 mmol) in anhydrous THF (4 ml) was added dropwise a solution of **17** (2.1 g, 10.8 mmol) in anhydrous THF (15 ml). The temperature was kept at 35 °C during the addition of the halide and the mixture was allowed to react for 30 min at room temperature. A solution of **1** (1 g, 7.2 mmol) in anhydrous THF (6 ml) was then added dropwise at room temperature and the mixture was allowed to react again for 15 min. The reaction was carefully quenched with saturated aqueous NH_4Cl solution (2 ml) and diethylic ether (8 ml) was then added. The precipitate was filtered and washed with diethylic ether. The organic phases were collected, washed with water (3 × 4 ml), dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent and recrystallization of the residue from ethanol–water (40:60) led to compound **18** (1.67 g, 91% yield) as a white solid and as a mixture of two diastereoisomers (75:25 ratio, stereochemistry not determined).

mp = 92 °C. IR (film) ν (cm^{-1}): 3017 (OH). ^1H NMR δ (ppm): 0.75 (d, $J = 7$ Hz, 3H, major diastereoisomer, 75%), 0.88 (d, $J = 7$ Hz, 3H, minor diastereoisomer,

25%), 1.15–2.25 (m, 8H), 1.59 (s, 3H), 1.75 (s, 2H), 1.89 (s, 2H), 2.35 (d, $J = 4.7$ Hz, 1H), 3.30–3.48 (m, 1H), 3.72 (t, $J = 11$ Hz, 2H), 4.05 (dd, $J = 4.7$ Hz, $J = 11$ Hz, 2H), 4.41 (t, $J = 4.7$ Hz, 1H, minor diastereoisomer, 25%), 4.51 (t, $J = 4.7$ Hz, 1H, major diastereoisomer, 75%), 5.14 (d, $J = 4.4$ Hz, 1H, minor diastereoisomer, 25%), 5.26 (d, $J = 4.4$ Hz, 1H, major diastereoisomer, 75%). MS (EI): *m/z* 253 (M^+, 2), 178 (35), 145 (48), 106 (42), 87 (100), 71 (55), 67 (54).

*4.11. 1-(2,4-Dimethyl-cyclohex-3-enyl)-3-[1,3] dioxan-2-yl-propan-1-one (**19**)*

A solution of **18** (3 g, 11.8 mmol) in CH_2Cl_2 (45 ml) was added dropwise to a solution of pyridinium chlorochromate (6.4 g, 29.7 mmol) in CH_2Cl_2 (45 ml) at room temperature. After 3 h reaction at room temperature, the solvent was eliminated under reduced pressure and the residue was diluted with diethylic ether (100 ml). The organic phase was successively washed with saturated $NaHCO_3$ solution (40 ml), water (2 × 20 ml), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (cyclohexane–diethylic ether, 80:20) to give **19** (2.5 g, 84% yield) as a white solid and as a mixture of two diastereoisomers (95:5 ratio, stereochemistry not determined).

mp = 31 °C. IR (film) ν (cm^{-1}): 1710 (C=O), 1377 (C–O–C). ^{1}H NMR δ (ppm): 0.72 (d, $J = 6.3$ Hz, 3H, major stereoisomer, 95%), 0.82 (d, $J = 6.3$ Hz, 3H, minor stereoisomer, 5%), 1.30 (d, $J = 13.3$ Hz, 2H), 1.52–2.18 (m, 6H), 1.61 (s, 3H), 2.34–2.72 (m, 4H), 3.70 (t, $J = 11.4$ Hz, 2H), 3.90 (dd, $J = 3.9$ Hz, $J = 11$ Hz, 2H), 4.48 (t, $J = 5.5$ Hz, 1H), 5.35 (s, 1H). MS (EI): *m/z* 252 (M^+, 5), 251 (5), 176 (55), 143 (22), 132 (25), 109 (60), 100 (85), 87 (58), 85 (100), 67 (58).

*4.12. 3-(2,4-Dimethyl-cyclohex-3-enyl)-cyclopent-2-enone (**20**)*

A 2.2 M solution of *n*-butyllithium in hexane (0.6 ml, 1.32 mmol) was added to a 2 M solution of trimethylsilyldiazomethane (0.6 ml, 1.2 mmol) in hexane diluted with anhydrous THF (2 ml) at −78 °C under inert conditions. After 1 h of reaction, a solution of **19** (0.23 g, 0.91 mmol) in THF (5 ml) was added dropwise at the same temperature. The mixture was allowed to react at −78 °C for 1 h and allowed to reach room temperature over a period of 1 h. The solution was acidified with 10% citric acid solution (10 ml) under stirring for 1 h and extracted with ethylacetate (15 ml). The organic phase was washed with saturated NaCl solution (7 × 5 ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (cyclohexane–ethylacetate, 90:10) to give **20** (70 mg, 40% yield) as a colorless liquid and as a mixture of two diastereoisomers (70:30 ratio, stereochemistry not determined).

IR (film) ν (cm^{-1}): 1711 (C=O), 1679 and 1609 (C=C). ^{1}H NMR δ (ppm): 0.75 (d, $J = 7.1$ Hz, 3H, major diastereoisomer, 70%), 0.84 (d, $J = 7.1$ Hz, 3H, minor diastereoisomer, 30%), 1.52–1.85 (m, 2H), 1.62 (s, 3H), 1.86–2.31 (m, 2H), 2.35–2.75 (m, 6H), 5.21 (s, 1H, minor diastereoisomer, 30%), 5.40 (s, 1H, major diastereoisomer, 70%), 5.90 (d, $J = 1.57$ Hz, 1H, major diastereoisomer, 70%), 5.95 (d, $J = 1.57$ Hz, 1H, minor diastereoisomer, 30%). MS (EI): *m/z* 190 (M^+, 35), 109 (75), 82 (100), 67 (90).

*4.13. 5-(2,4-Dimethyl-cyclohex-3-enyl)-3-[1,3] dihydro-furan-2-one (**22**)*

A solution of **18** (1.5 g, 5.9 mmol) and *para*-toluene sulfonic acid (0.15 g, 0.79 mmol) in acetone (45 ml) and water (22.5 ml) was heated at reflux for 10 h. After addition of saturated $NaHCO_3$ solution (2 ml), the mixture was extracted with ether (4 × 15 ml) and the organic phases were washed with water (2 × 10 ml), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was dissolved in acetone (50 ml), cooled at 0 °C, and Jones reagent (2.2 ml, 5.9 mmol) was added dropwise over a period of 30 min. The reaction mixture was allowed to reach room temperature and was hydrolysed with water (100 ml). After extraction with diethylic ether (3 × 100 ml), the collected organic phases were washed with 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by distillation under reduced pressure ($Eb_{3\ mm\ Hg} = 140$ °C) to give **22** as a white solid which slowly crystallizes (0.65 g, 56% yield) and as a mixture of two diastereoisomers (95:5 ratio, stereochemistry not determined).

mp = 40 °C. IR (film) ν (cm^{-1}): 1770 (C=O), 1377 (C–O–C). ^{1}H NMR δ (ppm): 0.85 (d, $J = 7.1$ Hz, 3H, major stereoisomer, 95%), 0.92 (d, $J = 7.1$ Hz, 3H, minor stereoisomer, 5%), 1.15–2.10 (m, 6H), 1.68 (s, 3H), 2.12–2.40 (m, 2H), 2.55 (dd, $J = 7.1$ Hz, $J = 10.2$ Hz, 2H), 4.30 (ddd, $J = 5.5$ Hz, $J = 8.6$ Hz, $J = 14.9$ Hz, 1H), 5.28–5.39 (m, 1H). MS (EI): *m/z* 194 (25), 109 (50), 107 (52), 85 (100), 67 (60).

Acknowledgements

Patricia Monnier-Benoit was financially supported by a grant from Agence Nationale de la Recherche

Technique and from PCAS SA (Longjumeau, France), a chemical company focused on several expanding markets in fine and specialty chemicals.

References

[1] G. Ohloff, in: D.R. Gottlieb (Ed.), Progress in the Chemistry of Organic Natural Products, Springer, Berlin and New York, 1978, p. 431.
[2] T.J. Leitereg, D.G. Guadagni, J. Harris, T.R. Mon, R. Teranishi, Nature 230 (1971) 455.
[3] (a) Y.R. Naves, Riv. Ital. EPPOS 58 (1976) 505;
(b) Y.R. Naves, Riv. Ital. EPPOS 59 (1977) 507;
(c) F.J. Marner, T. Runge, W.A. Konig, Helv. Chim. Acta 73 (1990) 2165.
[4] E. Demole, P. Enggist, U. Sauberti, M. Stoll, Helv. Chim. Acta 53 (1970) 541.
[5] (a) Y.R. Naves, Parfums de France 12 (1934) 255;
(b) O.N. Jitkow, M.T. Bogert, J. Am. Chem. Soc. 63 (1941) 1979.
[6] A.J. Chalk, J.A. Virgilio, S.A. Givaudan-Roure, EP 952139, Chem. Abstr. 131 (1999) 299148.
[7] J.M. Sanders, W.I. Taylor, I.D. Hill, J.J. Kryschuk, International flavours and fragrances Inc., US 4031161, Chem. Abstr. 87 (1977) 151775.
[8] Z. Zhu, J.H. Stevenson, J. Am. Chem. Soc. 119 (1997) 3507.
[9] K.A. Ahrendt, C.J. Borths, D.W.C. MacMillan, J. Am. Chem. Soc. 122 (2000) 4243.
[10] P.G. Gassman, S.P. Chavan, J. Org. Chem. 53 (1988) 2394.
[11] A. Speicher, T. Eicher, Synthesis (1995) 998.
[12] D.W. Jones, R.J. Marmon, J. Chem. Soc. Perkin Trans 1 (1993) 681.
[13] A. Sakai, A. Aoyama, T. Shiori, Tetrahedron Lett. 41 (2000) 6859.
[14] J.N. Jaubert, C. Tapiero, J.C. Doré, Perfumer Flavorist 20 (1995) 1.