FULL PAPER

New Aldehydes by Catalytic Diene Cycloisomerisations

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The Rh-catalysed hydroformylation of isopropylidenecyclohexane derivatives obtained by intramolecular diene cyclisations affords the corresponding aldehydes in good yields and in a completely chemo- and regioselective manner. Diastereoselectivities of ca. 90 % were achieved for all substrates when a bulky phosphite was used as the Rh ligand. The stereochemical outcomes of the hydroformylation reactions were established by detailed NMR studies. The olfactory evaluation of the different aldehydes is also presented.

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Introduction

The selective functionalisation of isolated C–C double bonds by nucleophiles through catalytic methods is still a challenge in organic synthesis. Highly cationic late transition metal complexes for the enhancement of olefin activation have been reported.[1] We have recently developed a catalytic reaction for the regiocontrolled addition of heteronucleophiles to non-activated olefins by Lewis superacids derived from metal triflates (trifluoromethanesulfonates). Among these catalytic processes, the cycloisomerisation of alcohols to cyclic ethers through the use of Sn^{IV}[2] and Al^{III} triflates has been reported.[3] Lewis acid catalysed regioselective additions of thiols and thioacids to non-activated olefins in the presence of In^{III} triflate have recently been reported; they afford the corresponding sulfur derivatives with Markovnikov-type selectivities,[4,5] in contrast to the classical radical-type addition processes.[6]

The cyclisation of 1,6-dienes catalysed by transition metal complexes generally affords five-membered carbocycles.[7] Only a few examples afford cyclohexane derivatives, and these generally require terminally unsubstituted olefins and catalytic systems associated with reducing agents.[8] In contrast with those results, we have recently reported that the cyclisation of diene **1a** in the presence of $Sn(NTf_2)_4$ (5 mol-%), and in the absence of any added ligand, leads to the highly substituted *gem*-dimethylcyclohexane structure **1b** in 92% yield. Furthermore, under the same conditions, the diprenyl cyanoacetate **2a** produces the corresponding cyclohexene derivative **2b** as a single diastereoisomer in 56% isolated yield, as illustrated in Scheme 1.[9]
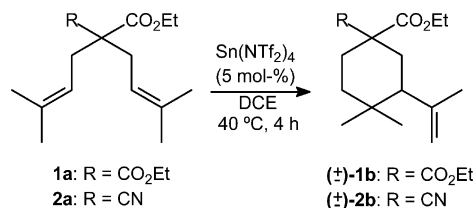
Scheme 1.

The hydroformylation of alkenes is one of the most important reactions for manufacturing aldehydes in industry. More than 6 million tons of aldehydes and alcohols are produced through this reaction annually, the major products being those derived from simple olefins such as propene.[10] More recently, the reaction has been employed for the direct introduction of formyl groups into more elaborate substrates.[11] For this purpose, the use of rhodium catalysts is essential, since they perform under milder conditions than cobalt ones and they achieve better selectivities.[12] The hydroformylation of substrates containing substituted or endocyclic double bonds is troublesome and usually requires harsh reaction conditions.[13] A remarkable exception to this, however, is represented by reactions performed in the presence of rhodium(I) catalysts modified with bulky phosphites, such as tris(*o-tert*-butylphenyl) phosphite [P(O-*o-t*BuC$_6$H$_4$)$_3$].[14] The large cone angle of

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this phosphite prevents the coordination of a second phosphite to the metal centre, even when a large excess of ligand is used. As a consequence, the overall steric hindrance around the Rh atom is low, which favours the coordination of substituted alkenes. On the other hand, the stronger π-acid properties of the phosphite, in relation to those of phosphanes, weaken the Rh–CO bonds, allowing a fast substitution of the carbonyl ligand by the alkene, followed by the alkene insertion into the Rh–H bond, in what is assumed to be the rate-determining step of a hydroformylation of an encumbered alkene in the presence of the Rh/P(O-o-tBuC$_6$H$_4$)$_3$ catalyst.[15] This catalyst is commercially used in hydroformylation of 3-methylbut-3-en-1-ol,[16] while its performance in the hydroformylation of sterically hindered alkenes such as cyclic ethers,[17] glucal derivatives,[18] fatty acids,[19] terpenes,[20] and steroids[21] has also been reported.

Aldehydes often show interesting organoleptic properties, and several aldehyde derivatives are therefore used as commercial fragrances.[22] Furthermore, some of these aldehydes are obtained by hydroformylation.[23]

Here we report the synthesis of differently substituted analogues of **1b**. These *gem*-dimethylcyclohexane derivatives, as well as the unsaturated cyanoacetate derivative **2b**, were further functionalised by Rh-catalysed hydroformylation of their disubstituted double bonds. The reaction allowed regiospecific access to several new aldehyde structures, the stereochemical aspects of which are discussed below. The olfactory evaluation of these compounds is also presented.

Results and Discussion

1. Preparation of Isopropylidenecyclohexane Derivatives

Scheme 2 summarizes the synthesis of the isopropylidenecyclohexane derivatives **3**–**5** prepared from **1b**. Conformational analysis of the diester substrate **1b** by NMR spectroscopy suggested that there is free rotation of the isopropylidene fragment with respect to the cyclohexane through the C^3–C^7(sp^2) bond. Evidence for this was provided by the NOE correlations shown in Figure 1.[24]
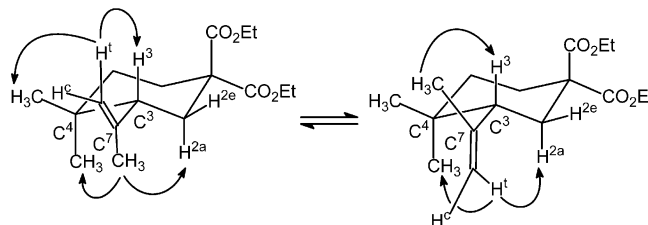

Figure 1. Relevant 2D-NOESY effects showing the free rotation of the isopropylidene fragment in (±)-**1b**.

The direct decarboxyethoxylation of **1b**, catalysed by LiCl in DMSO at reflux, led to a diastereoisomeric mixture of *trans* and *cis* monoesters – (±)-**3b** and (±)-**3c**, respectively – obtained in 68% overall yield (Scheme 2). The *cis* and *trans* isomers were fully characterized by 1D and 2D NMR techniques, the isomeric mixture being found to be slightly enriched in *trans* isomer **3b** (55:45). Stereochemical assignment was assisted by NOESY correlations between the equatorial 1-H atom of the major *trans* isomer **3b** at δ = 2.71 ppm and the two axial and equatorial hydrogen atoms at C-2 and C-6, as shown in Figure 2. For the *cis* isomer **3c**, the most relevant correlations were the 1,3-diaxial contacts between the axial 1-H, 3-H and 5-H hydrogen atoms, as also shown in Figure 2. Integration of the well-isolated 1-H signals of **3b** and **3c** in the purified mixture of the deethoxycarbonylation products allowed the major/
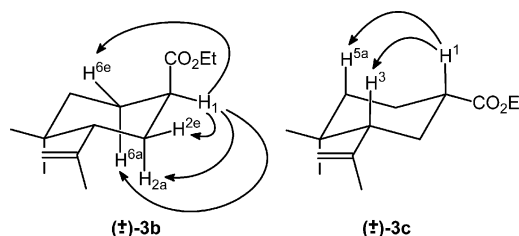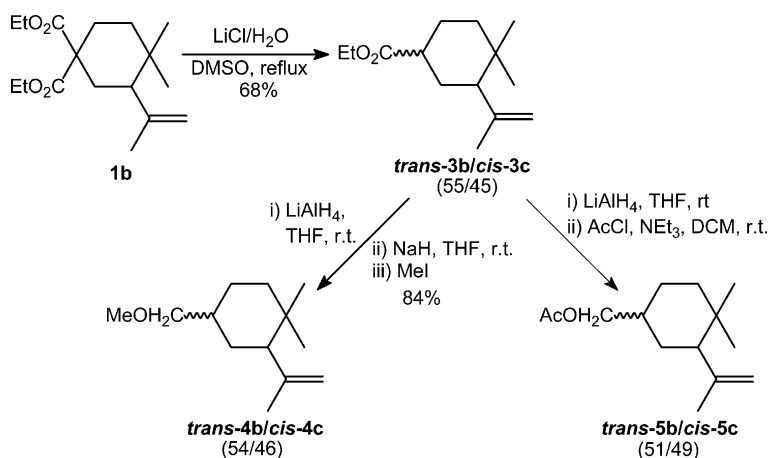

Figure 2. Relevant NOESY correlations for (±)-**3b** and (±)-**3c**.

Scheme 2.

minor isomer ratio to be determined, in good agreement with GC integration. As in the case of **1b**, conformational analysis of the **3b/3c** mixture indicated that there is free rotation of the isopropylidene fragment with respect to the cyclohexane ring, through the C^3–$C^7(sp^2)$ bond, in both isomers.

Reduction of the **3b/3c** ester mixture with LiAlH$_4$, followed by methoxylation, afforded a diastereoisomeric mixture of *trans* and *cis* ethers (**4b/4c**) in 84% yield after chromatographic purification (Scheme 2). Detailed NMR analyses revealed that the mixture of the methyl ethers **4b/4c** was slightly enriched in the *trans* isomer (**4b/4c** 54:46).

Reduction of **3b/3c** followed by acetylation led to the corresponding *trans*- and *cis*-acetates **5b/5c**, as a nearly equimolar mixture in almost quantitative yield.

2. Hydroformylation

The hydroformylation of **1b**, either with Rh/PPh$_3$ or with Rh and P(O-*o*-*t*BuC$_6$H$_4$)$_3$, produced a mixture of the two diastereoisomeric aldehydes **1d** and **1e** with complete chemoselectivity, as shown in Scheme 3. The reaction was fully regioselective towards the linear aldehydes. Although the two stereoisomers could not be separated, complete assignment of the ^{1}H and ^{13}C NMR chemical shifts was achieved for the two products in the purified mixture of the two aldehydes, as discussed below.

The results of several hydroformylation reactions carried out with **1b**, in order to examine the influence of the nature of the ligand, the ligand/metal ratio, the CO/H$_2$ pressure and the temperature, are summarised in Table 1.

The results shown in Table 1 indicate that the hydroformylation of the racemic **1b** catalysed by Rh(acac)(CO)$_2$ precursor and tris(*o-tert*-butylphenyl) phosphite gave a better rate and stereoselectivity than the reaction catalysed by Rh/PPh$_3$ (Entries 1 and 2).

With the Rh/phosphite catalyst, the reaction rate was slightly increased with the concentration of the ligand (Entries 2 and 3). An increase in the P/Rh ratio produced a shift in the equilibrium of substitution of a CO ligand from RhH(CO)$_4$ by the phosphite, favouring the formation of the active species RhH(CO)$_3$[P(O-*o*-*t*BuC$_6$H$_4$)$_3$]. Any further increase in the ligand concentration had no effect on the outcome of the reaction, since only one bulky phosphite ligand can coordinate to the metal centre.[25]

The conversion of **1b** was slightly increased on decreasing the syn gas pressure (compare Entries 3 and 4). The reaction is known to have a negative kinetic order with respect to the CO pressure, because the rate-determining step requires the dissociation of a CO ligand before the alkene coordination to the metal atom.[14] Neither the gas pressure nor the ligand/metal ratio had any significant influence on the selectivity of the hydroformylation, which afforded a **1d/1e** ratio of 88:12. As expected, an increase in the temperature raised the conversion, but involved a small drop in the stereoselectivity (Entry 5). Interestingly, an increase in the concentrations of the catalysts and substrate produced a remarkable increase in the conversion (Entry 6). This effect was associated with the kinetic first order of the reaction both in the reagent and in the catalyst.[15]

In order to determine the stereochemistry of the major and minor aldehydes – **1d** and **1e** – derived from **1b**, a detailed NMR study was undertaken. For this purpose, better signal separation was observed when C$_6$D$_6$ was used instead of CDCl$_3$ as solvent for the NMR experiments. As expected, the main differences in ^{1}H and ^{13}C NMR chemical shifts observed between the two isomeric aldehydes **1d** and **1e** was found in the *sec*-butanal fragment, in particular in
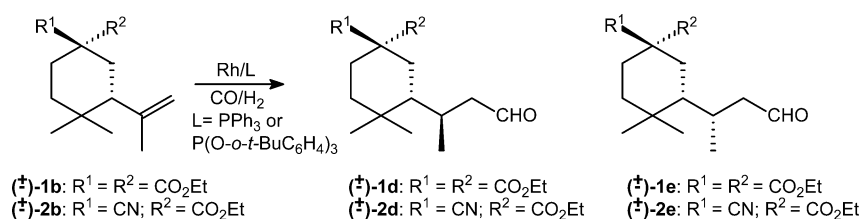
Scheme 3.

Table 1. Hydroformylation of **1b** catalysed by Rh^I modified with PPh$_3$ or tris(*o-tert*-butylphenyl) phosphite ligands.[a]

Entry	P-donor ligand	P[b] [bar]	T [°C]	P/Rh[c]	Conversion of **1b**[d] (%)	Ratio **1d/1e**
1	PPh$_3$	45	80	5	29	79:21
2	P(O-*o*-*t*BuC$_6$H$_4$)$_3$	45	80	5	45	88:12
3	P(O-*o*-*t*BuC$_6$H$_4$)$_3$	45	80	10	48	88:12
4	P(O-*o*-*t*BuC$_6$H$_4$)$_3$	20	80	10	52	88:12
5	P(O-*o*-*t*BuC$_6$H$_4$)$_3$	20	90	10	58	85:15
6[e]	P(O-*o*-*t*BuC$_6$H$_4$)$_3$	20	90	10	84	86:14

[a] Reaction conditions: 4.0×10^{-3} mmol of Rh(acac)(CO)$_2$ and 0.40 mmol of **1b** in 5 mL of toluene; reaction time 24 h. [b] Total pressure of syn gas, P(CO)=P(H$_2$). [c] P-donor ligand/Rh molar ratio. [d] The yield of **1d/1e** closely corresponded to the conversion reached at the indicated time. No other byproducts were formed. [e] The reaction was carried out with 1.0×10^{-2} mmol of Rh(acac)(CO)$_2$ and 1.0 mmol of **1b** in 5 mL of toluene.

the signals for the methyl group at C-7 and the α-carbonyl methylene group of C-8. Smaller differences were also observed in the rest of the carbon signals, as well for some of the signals in the ^{1}H NMR spectra, although the two mentioned ^{13}C NMR signals of the *sec*-butanal moiety were the most conclusive for the assignment of the stereochemistry of the aldehydes obtained from the rest of the substrates (see below). NOESY spectra show that in both isomers there is restricted rotation about the C^3–C^7(sp^2) bond (see Figure 3 for **1d**), probably due to steric interactions between the *gem*-dimethyl system at C-4 and the *sec*-butanal substituent at C^3. Furthermore, the collected data revealed that both **1d** and **1e** were present as single conformers at room temperature. These two facts allowed the stereochemistry of the new asymmetric carbon centre C-7, generated in the hydroformylation of **1b**, to be determined unequivocally. As an example, the NOESY correlations of the major aldehyde of the reaction – **1d** – are illustrated in Figure 3.[26]
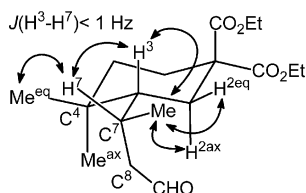

Figure 3. Relevant NOESY correlations for determining the stereochemistry of (±)-**1d**.

The NMR conformational analysis indicated that in the ground-state conformation the two diastereoisomeric aldehydes **1d** and **1e** presented the 7-H atom in a *gauche* position with respect to 3-H. In this way, steric repulsions between the two other substituents at C-7 and the *gem*-dimethyl fragment at C-4 are minimised. In agreement with NMR analysis, MM3 calculations showed conformational minima both for **1d** and **1e**, with 7-H–3-H dihedral angles very close to 90°, as shown in Figure 4.
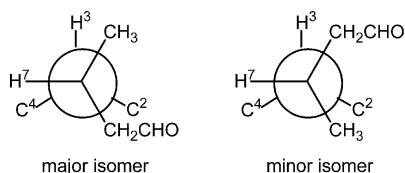

Figure 4. Newman projections showing the preferred conformations about the C^3–C^7 bonds for (±)-**1d** and (±)-**1e**.

The hydroformylation of **1b** under the optimized conditions (Entry 6, Table 1) produced an 86:14 mixture of the aldehydes **1d** and **1e**. Since the olefin moiety of **1b** presents two conformational minima, due to the free rotation of the isopropylidene group about the C^3–C^7 bond, if the catalyst were to attack on conformer **A** of **1b** through the sterically open face of the alkene, the reaction would end in major aldehyde **1d**. In contrast, the reaction through the open face of conformer **B** would result in the minor stereoisomer **1e**, as illustrated in Scheme 4. It should be noted that both con-

formations **A** and **B** experience *syn*-pentane steric repulsion between the methyl group at C-7 and one of the two methyl groups at C-4.
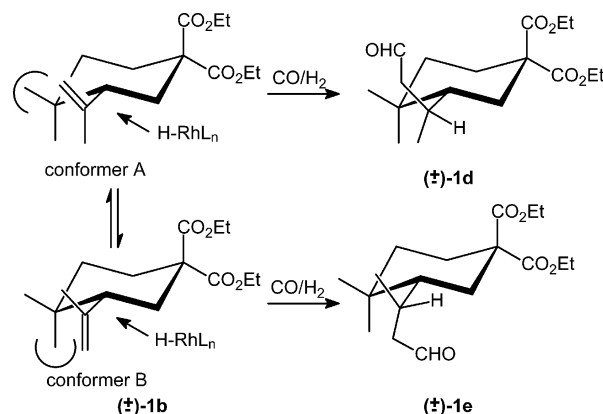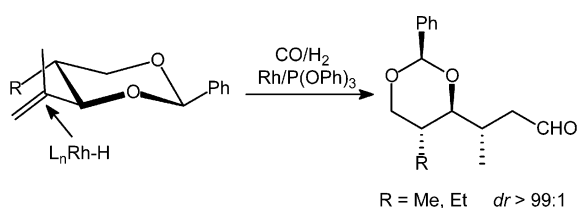

Scheme 4. Conformational equilibrium of (±)-**1b** leading to (±)-**1d** and (±)-**1e**.

In order to evaluate the relative stabilities of the conformers **A** and **B**, MM3 calculations were carried out on **1b** and indicated that the energy of conformer **A** was only 0.7 kJ mol^{-1} below that of conformer **B** (Scheme 4). This energy difference should correspond to a nearly equal distribution (ca. 55:45) of the two conformers **A** and **B**[27] and does not correlate with the experimentally observed **1d**/**1e** product distribution (88:12).

Therefore, the stereochemistry of the hydroformylation of **1b** cannot be interpreted on the grounds of the equilibrium between the most stable conformers of this substrate. For substrates such as **1b**, with high conformational freedom and with low interconversion-energy barriers, it seems likely that in the transition state of the irreversible catalytic step (i.e., the one that determines the selectivity of the process), the conformation of the substrate could differ substantially from that of the ground state. In particular, for **1b** there are several conformations with energies slightly above that of the ground state, but presenting lower steric hindrance about the carbon–carbon double bond that would allow an easier approach of the catalyst than in the ground-state conformations.

The regio- and stereoselective outcome of the hydroformylation of **1b** may be related to the reported hydroformylation of substituted 4-isopropenyl-1,3-dioxanes, as shown in Scheme 5.[28] The stereochemical arrangements of the aldehydes derived from the 1,3-dioxanes could be interpreted by conformational analysis of the unsaturated substrates. Thus, the Rh/P(OPh)$_3$-catalysed hydroformylation of 5-alkyl equatorially substituted 4-(prop-2-enyl)-1,3-dioxanes has been reported to take place with nearly complete stereoselectivity, because the equatorial group at the 5-position prevents the approach of the catalyst through one olefin face. This is supported by NOESY experiments and MM3 calculations, which indicated that the conformation shown in Scheme 5 is populated to almost 90%.[29] The stability of this conformation with respect to that produced by a 180° rotation of the isopropenyl fragment is due to the

F. Grau, J. C. Bayón, P. A. Aguirre, T. Parella, E. Duñach

presence of a *syn*-pentane repulsive interaction in the latter species, which is not produced in the former. Furthermore, 4-(prop-2-enyl)-1,3-dioxanes not substituted at C-5 or with the opposite configuration at this carbon atom gave significantly poorer diastereoselectivities. Therefore, the ground-state conformations of these substrates were reported to be the underlying causes of the stereoselective outcomes of their hydroformylations, in contrast to the results attained in the hydroformylation of **1b**. However, in the hydroformylation of 1,3-dioxanes, P(OPh)$_3$ was used as auxiliary ligand, instead of the bulky phosphite used in the present work. Since P(OPh)$_3$ forms the catalytic active species RhH(CO)$_2$[P(OPh)$_3$]$_2$,[30] in which the metal atom is sterically more encumbered than in the monoligand catalytic species formed by the bulky phosphite ligand,[25] the steric contribution of the catalyst to the reactions outcome cannot be neglected.

(±)-**3b**: R = CO$_2$Et (±)-**3d**: R = CO$_2$Et (±)-**3e**: R = CO$_2$Et
(±)-**4b**: R = CH$_2$OMe (±)-**4d**: R = CH$_2$OMe (±)-**4e**: R = CH$_2$OMe
(±)-**5b**: R = CH$_2$OAc (±)-**5d**: R = CH$_2$OAc (±)-**5e**: R = CH$_2$OAc

(±)-**3c**: R = CO$_2$Et (±)-**3f**: R = CO$_2$Et (±)-**3g**: R = CO$_2$Et
(±)-**4c**: R = CH$_2$OMe (±)-**4f**: R = CH$_2$OMe (±)-**4g**: R = CH$_2$OMe
(±)-**5c**: R = CH$_2$OAc (±)-**5f**: R = CH$_2$OAc (±)-**5g**: R = CH$_2$OAc

Scheme 6.

Scheme 5.

Table 2 collects the results relating to the hydroformylation of the isopropylidenecyclohexane derivatives of **1b**. A new stereogenic centre at C-7 is formed in all cases. The different olefin substrates **2**–**5** differ in the natures of the functional groups at C-1. Substrates **b** correspond either to a single isomer in the case of **1b** and **2b** (Scheme 3), or to the *trans* isomers in the diastereoisomeric mixtures **3** to **5**, whereas substrates **c** correspond to the *cis* diastereoisomers. As in the case of the hydroformylation of **1b**, the corresponding linear aldehydes **d**–**g** were the only products formed in the hydroformylation of substrates **2**–**5**, again indicating complete chemo- and regioselectivity for all these substrates. For aldehyde assignments, the *trans* isomers **b** afforded aldehyde stereoisomers **d** and **e** and the *cis* substrates **c** gave aldehydes **f** and **g**, as illustrated in Scheme 6.
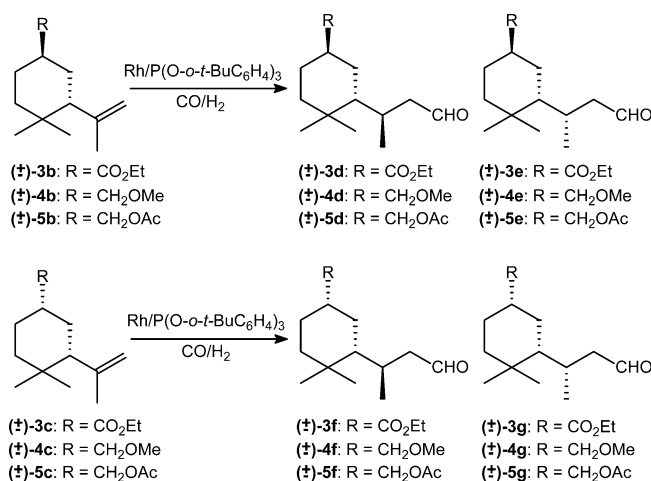
The hydroformylation of the double bond in the cyano derivative **2b** (single diastereoisomer; Entry 2 in Table 2) under the conditions optimised for **1b** (Entry 1) afforded a mixture of isomeric aldehydes **2d**/**2e** in 90% yield and 96:4 ratio (Scheme 3). Complete assignment of the ^{1}H and ^{13}C NMR signals for the major aldehyde **2d** was achieved. However, direct determination of the C-7 stereochemistry through NOESY techniques was too complicated due to the signal overlapping. The stereochemistry of the aldehydes **2d**/**2e** was established by comparison of relevant NMR chemical shifts with those of the major and minor aldehydes **1d** and **1e**, arising from olefin **1b**. For the major aldehyde **2d**, the ^{13}C NMR signals for the methyl group at C-7 appeared at $\delta = 21.6$ ppm ($\delta = 21.8$ ppm for the major isomer **1d**), and for the methylene group C-8 at $\delta = 47.4$ ppm ($\delta = 47.5$ ppm for **1d**). Furthermore, although complete assignment of the NMR signals of the minor aldehyde **2e** was not attempted, HSQC correlations were observed between signals at $\delta = 0.88$ and 16.5 ppm for the methyl group at C-7 ($\delta = 16.6$ ppm for **1e**), and between 2.46–2.38 and 52.0 ppm, corresponding to the methylene group C-8 ($\delta = 52.0$ ppm for **1e**). The nearly perfect match between the four chemical shifts completely corroborated the stereochemistry of the two aldehydes arising from **2b**. As shown in Scheme 3, for **2d** – and therefore for **2b** and

Table 2. Hydroformylation of the isopropylidenecyclohexane derivatives of **1b** with Rh/P(O-*o*-tBuC$_6$H$_4$)$_3$ as the catalyst[a] (see Schemes 3 and 6 for the stereochemistry of the products).

Entry	Olefin substrate (relative ratio)	Yield of RCHO (**d**+**e**/**f**+**g** isomer ratio)	Selectivity obtained from *trans* isomer **b** **d**/**e** ratio	Selectivity obtained from *cis* isomer **c** **f**/**g** ratio
1	**1b**	84%	86:14	–
2	**2b**	90%	96:4	–
3	**3b**/**3c** (55:45)	95% (44:56)	91:9	89:11
4	**4b**/**4c** (54:46)	95% (55:45)	88:12	91:9
5	**5b**/**5c** (51:49)	87% (50:50)	90:10	90:10

[a] Reaction conditions: 1.0×10^{-2} mmol of Rh(acac)(CO)$_2$, 1.0×10^{-1} mmol tris(*o*-*tert*-butylphenyl) phosphite and 1.0 mmol of substrate in 5 mL of toluene. $T = 90$ °C; $P = 20$ bar; P(CO) = P(H$_2$); reaction time 24 h.

2e – the nitrile group occupies the axial position at C-1. This was supported by the expected low-field shift observed for the two axial 3-H (δ = 1.46 ppm) and 5-H (δ = 1.68 ppm) atoms of **2d**, with respect to the corresponding signals in compounds such as **1d** and **1e**, as well as for **3d**, bearing an axial ethyl carboxylate group at C-1 instead of a nitrile, which showed signals in the δ = 1.18–1.25 ppm range for axial 3-H and δ = 1.34–1.38 ppm for axial 5-H.[31] This supports the conjecture that the carboxylate group at C-1 is in an equatorial position, corroborating the stereochemical assignment for the nitrile derivatives **2b**, **2d** and **2e**.

The hydroformylation of the double bonds in a 55:45 mixture of monoesters **3b/3c** led to a mixture of four aldehydes in 95% yield. The major *trans*-olefin **3b** afforded diastereoisomeric *trans*-aldehydes **3d** and **3e** (*trans* configurations between C-1 and C-3) in a 91:9 ratio, the two stereoisomers presenting opposite configurations at the new stereogenic centres at C-7. Similarly, the minor starting monoester *cis*-**3c** afforded a mixture of aldehydes **3f** and **3g** in a 89:11 ratio. Complete assignment of the ¹H and ¹³C NMR signals of the major aldehydes **3d** and **3f** was achieved. However, direct determination of the C-7 stereochemistry through NOESY techniques was not possible, because of some overlap among the signals of the isomers. Thus, the stereochemical configurations of **3d** and **3f**, and therefore those of the minor aldehydes *trans*-**3e** and *cis*-**3g** (Scheme 6), could be established by direct correlation of the chemical shifts of the major isomers with those of the major and minor aldehydes **1d** and **1e** arising from olefin **1b**, as described above for **2d**. For instance, the ¹³C NMR signals of the methyl groups at C-7 in **3d** and **3f** appeared at δ = 21.6 and 21.9 ppm, respectively (δ = 21.8 ppm for the major isomer **1d**, but δ = 16.6 ppm for **1e**), while the signals of the methylene groups C-8 appeared at δ = 47.3 and 47.5 ppm for **3d** and **3f**, respectively (δ = 47.5 ppm for **1d**, but δ = 52.0 ppm for **1e**). This indicated that both major aldehydes **3d** and **3f** presented the same configuration at C-7 as in aldehydes **1d** and **2d**. The rest of the signals, both in the ¹H and ¹³C NMR spectra, fully corroborated the stereochemical assignments for these two major aldehydes. Similar analysis allowed the configurations of the rest of the major aldehyde products to be established, because the chemical shifts of the methyl protons at C-7 and of the methylene protons at C-8 showed characteristic γ-effects independent of the C-1 substitution patterns (see Figure 4).[32] The remarkable similarity of the chemical shifts of the characteristic signals in all major aldehydes (see Experimental Section) indicated that the frozen conformation of the *sec*-butanal fragment was preserved in all these products. This fact made their stereochemical assignment based on the correlation of the chemical shifts fully reliable.

The configuration of the major aldehyde **2d** arising from **2b**, as well as those of the major aldehydes **3d** and **3f** produced from the **3b/3c** mixture, revealed that the hydroformylation reaction took place through the preferential attack of the Rh catalyst through the same face and same conformation of the double bond as in the case of **1b**, leading to

aldehyde **1d** as shown in Scheme 4. The same is true for the major aldehydes obtained by hydroformylation of the methyl ether derivatives **4b** and **4c** and the acetyl derivatives **5b** and **5c**. The **4b/4c** diastereoisomeric mixture afforded a 95% overall yield of a mixture of aldehydes **4d** and **4e** (88:12 ratio) arising from the *trans*-olefin **4b** together with **4f** and **4g** (91:9 ratio) originating from the *cis*-olefin **4c**. On the other hand, the **5b/5c** diastereoisomeric mixture afforded an 87% overall yield of a mixture of aldehydes **5d** and **5e** (90:10 ratio) from *trans*-**5b** and aldehydes **5f** and **5g** (90:10 ratio) from *cis*-**5c** (Scheme 6).

The stereoselectivities obtained in the hydroformylation of substrates **1**–**5** were similar (ca. 90:10), regardless of the substitution or stereochemistry at C-1, indicating that there was no significant interaction between this stereogenic centre and the newly created C-7 centre in the reaction. Therefore, the configuration of C-7 was completely controlled by that of C-3.

3. Olfactory Evaluation

The *gem*-dimethylcyclohexane framework is present in several terpene-derived structures that present interesting properties in the field of fragrances.[33] Thus, natural compounds such as those of the families of ionones, damascenes and irones present *gem*-dimethylcyclohexane structures with carbonyl groups in the side chains. On the other hand, volatile aldehydes often contribute intensively to the organoleptic properties of the corresponding compounds.[22] Therefore, several of the newly prepared derivatives were subject to olfactory tests in 10% ethanol solutions. Diester derivative **1b** presented woody, floral, iris notes, and monoesters **3b** and **3c** had leather and warm notes. Methyl derivatives **4b** and **4c**, as well as their acetyl derivatives **5b** and **5c**, presented woody notes, essentially of pine.

With regard to the aldehyde derivatives, monoester aldehydes **3d**–**3g** presented interesting agar wood and animal notes. The aldehydes derived from the methoxylated and the acetylated substrates, **4d**–**4g** and **5d**–**5g**, respectively, presented woody notes, but of low intensity. The different *gem*-dimethylcyclohexane derivatives prepared and tested in this work presented mainly woody notes.

Conclusions

A series of C-1-functionalized 4,4-dimethylcyclohexane derivatives, each with an isopropylidene group at C-3, were prepared and further subjected to Rh^I-catalysed hydroformylation. The preparation of the starting olefins **1b** and **2b** was effected through the cycloisomerisation of substituted 1,6-dienes. Functional group transformations led to the different substrates. NMR experiments and basic molecular mechanics analysis indicated that the isopropylidene fragment of **1b** could freely rotate with respect to the cyclohexane ring, thus exposing both faces of the double bond nearly equally to catalyst attack. The hydroformylation of all the olefinic substrates in the presence of the Rh^I catalyst

modified with the bulky phosphite P(O-*o*-*t*BuC$_6$H$_4$)$_3$ under mild reaction conditions allowed the corresponding aldehydes to be obtained in high yields with complete chemoselectivity and with the exclusive formation of the linear aldehydes. The diastereoselectivities achieved were in all cases around 90%. All the major aldehydes were the products of the preferential attack of the catalyst on the same face of the double bond, independently of the substitution at the C-1 position and independently of the *trans/cis* configuration of the starting olefins. These results indicated that the stereochemical outcome of the reaction is controlled by the conformation of C-3 and that it could not be inferred from the conformation of the starting alkenes, contrary to what has been described previously in the diastereoselective hydroformylation of related substrates.

The olfactory evaluation revealed iris notes for the diester derivative **1b**, leather notes for **3b/3c**, agar wood and animal notes for aldehydes **3d**–**3g**, and less intense woody notes for the rest of the products.

Experimental Section

General: Toluene and THF were dried by heating at reflux with sodium wire/benzophenone and then distilled under nitrogen. Tris(*o-tert*-butylphenyl) phosphite was prepared as described previously.[14] Catalytic hydroformylations were carried out in a home-made glass-lined stainless steel autoclave with electrical heating. GC analyses were performed with an HP5890 instrument fitted with an HP-5 column and with an HP-5890A fitted with an HP-1 column. GC-MS data were recorded with an HP-G1800A instrument, and GC-TOF experiments were carried out with a Waters GCTOF. Elemental analyses and HRMS were carried out at the Service Central d'Analyse, CNRS, Vernaison, France. ^{1}H and ^{13}C NMR spectra were recorded with Bruker instruments at 250 and 500 MHz, respectively. The NMR stereochemical analyses were carried out with a Bruker AVANCE spectrometer operating at 500.13 MHz for ^{1}H.

Preparation of Starting Olefin Derivatives

Diethyl 4,4-Dimethyl-3-(1-methylethenyl)-1-cyclohexanedicarboxylate (1b): This compound was prepared as described previously.[9] More detailed data: ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 2.10 (2-H$_{eq}$), 1.93 (2-H$_{ax}$), 1.94 (3-H$_{ax}$), 1.34 (5-H$_{eq}$), 1.36 (5-H$_{ax}$), 2.17 (6-H$_{eq}$), 1.86 (6-H$_{ax}$), 1.22 (C*H*$_3$CH$_2$O$_2$C$_{eq}$), 4.14 (CH$_3$C*H*$_2$O$_2$C$_{eq}$), 1.24 (C*H*$_3$CH$_2$O$_2$C$_{ax}$), 4.19–4.22 (CH$_3$C*H*$_2$O$_2$C$_{ax}$), 1.72 (C*H*$_3$–C=), 4.62 [C*H*$_2$=C (*trans* Me)], 4.86 [C*H*$_2$=C (*cis* Me)], 0.86 (C*H*$_3$–C-4$_{eq}$), 0.88 (C*H*$_3$–C-4$_{ax}$) ppm. ^{13}C NMR (CDCl$_3$, 125.7 MHz): δ = 55.7 (C-1), 32.4 (C-2), 49.7 (C-3), 33.0 (C-4), 38.9 (C-5), 27.1 (C-6), 14.2 (*C*H$_3$CH$_2$O$_2$C$_{eq}$), 61.2 (CH$_3$*C*H$_2$O$_2$C$_{eq}$), 172.3 (*C*O$_{2eq}$), 14.2 (*C*H$_3$CH$_2$O$_2$C$_{ax}$), 61.0 (CH$_3$*C*H$_2$O$_2$C$_{ax}$), 171.2 (*C*O$_{2ax}$), 24.3 (*C*H$_3$–C=), 146.8 (*C*=CH$_2$), 112.8 (*C*H$_2$=C), 31.3 (*C*H$_3$–C-4$_{eq}$), 20.5 (*C*H$_3$–C-4$_{ax}$) ppm.

Ethyl 1-Cyano-4,4-dimethyl-3-[(1*Z*)-1-methylethenyl]-1-cyclohexanecarboxylate (2b): This compound was prepared as described previously.[9] ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 2.25 (CH–*H*), 2.07 (CH–*H*), 1.99 (C*H*$_2$), 1.89 (CH–*H*), 1.68 (CH–*H*), 1.51 (CH–*H*), 4.27 (CH$_3$C*H*$_2$O$_2$C), 1.33 (C*H*$_3$CH$_2$O$_2$C), 1.76 (C*H*$_3$–C=), 4.94 [C*H*$_2$=C (*cis* Me)], 4.67 [C*H*$_2$=C (*trans* Me)], 0.98 (C*H*$_3$–C-4), 0.90 (C*H*$_3$–C-4) ppm. ^{13}C NMR (CDCl$_3$, 125.7 MHz): δ = 46.8 (C-1), 34.3 (C-2), 49.6 (C-3), 33.7 (C-4), 38.5 (C-5), 29.2 (C-6), 14.3 (*C*H$_3$CH$_2$O$_2$C), 63.1 (CH$_3$*C*H$_2$O$_2$C), 169.7 (*C*O$_2$), 119.6 (*C*N),

145.4 (*C*=CH$_2$), 24.7 (*C*H$_3$–C=), 114.4 (*C*H$_2$=C), 31.0 (*C*H$_3$–C-4$_{eq}$), 24.7 (*C*H$_3$–C-4$_{ax}$) ppm. MS (70 eV): *m/z* (%) = 249 (6) [M]$^{+}$, 181 (74), 152 (11), 126 (25), 69 (67), 56 (100). HRMS (ES$^+$): calcd. for C$_{15}$H$_{23}$NO$_2$Na [MNa]$^+$ 272.1626, found 272.1613.

Ethyl 4,4-Dimethyl-3-(1-methylethenyl)cyclohexane-1-carboxylate (3b and 3c): Diester **1b** (23.68 g, 80 mmol) in DMSO (200 mL) was heated at reflux in the presence of LiCl (160 mmol) and water (80 mmol) for 4–5 h, the reaction being monitored by GC. The solution was cooled down, hydrolysed with HCl (1 M saturated with NaCl), extracted with diethyl ether, washed with water/NaCl and dried with MgSO$_4$, and the solvent was evaporated. The oily crude reaction product was purified by column chromatography on silica gel with pentane/diethyl ether (95:5) as the eluent. The purified product was obtained in 68% yield (12.19 g) as a 55:45 mixture of *trans/cis* isomers.

3b: ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 2.71 (1-H$_{eq}$), 1.93 (2-H$_{eq}$), 1.77 (2-H$_{ax}$), 1.99 (3-H$_{ax}$), 1.30 (5-H$_{eq}$), 1.39 (5-H$_{ax}$), 1.97 (6-H$_{eq}$), 1.69 (6-H$_{ax}$), 1.27 (C*H*$_3$CH$_2$O$_2$C$_{ax}$), 4.11–4.22 (CH$_3$C*H*$_2$O$_2$C$_{ax}$), 1.73 (C*H*$_3$–C=), 4.64 [C*H*$_2$=C (*trans* Me)], 4.87 [C*H*$_2$=C (*cis* Me)], 0.89 (C*H*$_3$–C-4$_{eq}$), 0.89 (C*H*$_3$–C-4$_{ax}$) ppm. ^{13}C NMR (CDCl$_3$, 125.7 MHz): δ = 39.6 (C-1), 28.7 (C-2), 49.8 (C-3), 33.3 (C-4), 38.4 (C-5), 23.2 (C-6), 14.6 (*C*H$_3$CH$_2$O$_2$C$_{ax}$), 60.1 (CH$_3$*C*H$_2$O$_2$C$_{ax}$), 175.9 (*C*O$_{2ax}$), 24.2 (*C*H$_3$–C=), 147.4 (*C*=CH$_2$), 112.5 (*C*H$_2$=C), 31.1 (*C*H$_3$–C-4$_{eq}$), 20.7 (*C*H$_3$–C-4$_{ax}$) ppm. GC-MS (70 eV): *m/z* (%) = 224 (9) [M]$^{+}$, 181 (15), 156 (63), 109 (46), 101 (100), 81 (66), 69 (59).

(±)-3c: ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 2.31 (1-H$_{ax}$), 1.75 (2-H$_{eq}$), 1.71 (2-H$_{ax}$), 1.87 (3-H$_{ax}$), 1.48 (5-H$_{eq}$), 1.28 (5-H$_{ax}$), 1.76 (6-H$_{eq}$), 1.64 (6-H$_{ax}$), 1.26 (C*H*$_3$CH$_2$O$_2$C$_{eq}$), 4.14 (CH$_3$C*H*$_2$O$_2$C$_{eq}$), 1.73 (C*H*$_3$–C=), 4.64 [C*H*$_2$=C (*trans* Me)], 4.87 [C*H*$_2$=C (*cis* Me)], 0.91 (C*H*$_3$–C-4$_{eq}$), 0.90 (C*H*$_3$–C-4$_{ax}$) ppm. ^{13}C NMR (CDCl$_3$, 125.7 MHz): δ = 44.0 (C-1), 30.3 (C-2), 53.2 (C-3), 33.3 (C-4), 41.8 (C-5), 24.9 (C-6), 14.6 (*C*H$_3$CH$_2$O$_2$C$_{eq}$), 60.1 (CH$_3$*C*H$_2$O$_2$C$_{eq}$), 175.2 (*C*O$_{2eq}$), 24.2 (*C*H$_3$–C=), 146.9 (*C*=CH$_2$), 112.5 (*C*H$_2$=C), 31.1 (*C*H$_3$–C-4$_{eq}$), 20.4 (*C*H$_3$–C-4$_{ax}$) ppm. GC-MS (70 eV): *m/z* (%) = 224 (11) [M]$^{+}$, 209 (9), 181 (14), 168 (18), 165 (26), 135 (27), 109 (51), 101 (100), 81 (77), 69 (59). HRMS (CI$^+$): calcd. for C$_{14}$H$_{26}$O$_2$ [MH]$^+$ 225.1855, found 225.1859.

1-(Methoxymethyl)-4,4-dimethyl-3-(1-methylethenyl)cyclohexane (4b and 4c): A solution containing a 55:45 mixture of **3b/3c** (5.6 g, 25 mmol) in distilled THF (10 mL) was added dropwise to a suspension of LiAlH$_4$ (30 mmol) in THF (30 mL), and the mixture was stirred at room temperature for 1 h. Hydrolysis by slow addition of HCl solution (1 M) was followed by diethyl ether extraction, washing with water/NaCl, drying with MgSO$_4$ and solvent evaporation. The product was slowly added to a suspension of NaH (27 mmol) in THF (50 mL). After hydrogen evolution, MeI (40 mmol) was added and the solution was stirred at room temperature for 1 h. After hydrolysis and diethyl ether extraction, drying with MgSO$_4$ and solvent evaporation, the crude product was purified by column chromatography on silica gel with pentane/diethyl ether mixtures as the eluents. The purified product was obtained in 68% yield (3.33 g) as a 54:46 mixture of *trans/cis* isomers.

4b/4c Isomer Mixture: ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 4.8 (8-H), 4.6 (8-H), 4.5 (8-H), 3.3 (C*H*$_3$O), 3.4–3.2 (C*H*$_2$O), 1.7 (C*H*$_3$–C=), 2.1–0.9 [(C-1 and C-3)*H* and (C-, C-5 and C-6)*H*$_2$], 0.9 (C*H*$_3$–C-4), 0.8 (C*H*$_3$–C-4) ppm. ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 38.8 and 33.1 (C-1), 31.6 and 29.1 (C-2), 53.5 and 48.6 (C-3), 33.7 and 33.6 (C-4), 42.1 and 37.0 (C-5), 25.8 and 23.2 (C-6), 58.8 and 58.7 (*C*H$_3$O), 78.7 and 74.9 (*C*H$_2$O), 24.2 and 23.9 (*C*H$_3$–C=), 147.8 and 147.8 (*C*=CH$_2$), 112.4 and 112.3 (*C*H$_2$=C), 31.3 and 31.1 (*C*H$_3$–C-4$_{eq}$), 21.6 and 20.5 (*C*H$_3$–C-4$_{ax}$) ppm. GC-MS (70 eV): **4b:**

m/z (%) = 196 (21) [M]·+, 164 (53), 149 (76), 121 (90), 108 (91), 95 (100), 81 (99), 67 (98), 55 (99); **4c**: *m/z* (%) = 196 (29) [M]·+, 164 (52), 149 (82), 121 (89), 108 (92), 95 (99), 81 (99), 67 (100), 55 (99). HRMS (EI+): Isomer mixture: calcd. for $C_{13}H_{24}O$ [M+] 196.1827, found 196.1827.

4,4-Dimethyl-3-(1-methylethenyl)cyclohexylmethyl Acetate (5b and 5c): A solution containing a 55:45 mixture of **3b/3c** (1.12 g, 5 mmol) in distilled THF (5 mL) was added dropwise to a suspension of LiAlH₄ (6 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 1 h. Hydrolysis by slow addition of HCl solution (1 M) was followed by diethyl ether extraction, drying with MgSO₄ and solvent evaporation. The product was slowly added to a solution of acetyl chloride (6 mmol) and triethylamine (6 mmol) in dichloromethane (20 mL). After stirring at room temperature for 2 h, the solution was hydrolysed with HCl (1 M), extracted with diethyl ether and dried with MgSO₄, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel with pentane/diethyl ether mixtures as the eluents. The acetate was obtained in 84% yield (940 mg) as a 51:49 mixture of *trans/cis* isomers.

Isomer Mixture 5b/5c: ¹H NMR (CDCl₃, 200 MHz): δ = 2.0–1.1 [(C-1 and C-3)H and (C-2, C-5 and C-6)H₂], 1.0–0.8 (*CH₃*–C-4), 2.1 (*CH₃*–C=), 4.9–4.8 (8-H), 4.7–4.5 (8-H), 4.2–4.0 (8-H), 4.0–3.8 (8-H) ppm. ¹³C NMR (CDCl₃, 50 MHz): δ = 38.2 and 34.0 (C-1), 31.6 and 29.3 (C-2), 53.7 and 48.7 (C-3), 32.7 (C-4), 42.2 and 37.1 (C-5), 25.8 and 24.7 (C-6), 21.4 and 21.3 (*CH₃*CO), 171.7 and 171.6 (*CO*), 69.8 and 66.6 (*CH₂*O), 24.2 and 23.5 (*CH₃*–C=), 147.9 (*C*=CH₂), 112.9 (*CH₂*=C), 31.4 (*CH₃*–C-4ₑq), 21.8 and 20.8 (*CH₃*–C-4ₐx) ppm. GC-MS (70 eV): **5b**: *m/z* (%) = 224 (1) [M]·+, 164 (46), 149 (60), 121 (64), 108 (76), 93 (100), 81 (50), 67 (39), 55 (30), 43 (79); **5c**: *m/z* (%) = 224 (2) [M]·+, 164 (33), 149 (66), 121 (37), 108 (96), 93 (100), 81 (49), 67 (37), 55 (30), 43 (79). HRMS (EI+): calcd. for $C_{14}H_{24}O_2Na$ [MNa]+ 247.1674, found: 247.1681.

Catalytic Hydroformylation. General Procedure: In a typical experiment, an autoclave with a glass liner was purged with three cycles of vacuum and syn gas (CO/H₂, 1:1). With the reactor under vacuum, a solution containing [Rh(acac)(CO)]₂ (1.0×10^{-2} mmol), tris(*o-tert*-butylphenyl) phosphite or PPh₃ (1.0×10^{-1} mmol) as P-donor ligand, and the olefin substrate (1.0 mmol), dissolved in toluene (5 mL), was introduced through an inlet valve. The inlet device was rinsed with solvent (1 mL), then the autoclave was charged with syn gas until about 80% of the working pressure, and the temperature was set to that selected for the experiment. When this temperature was reached (after ca. 5 min) the autoclave was adjusted to the working pressure. The conversion and selectivity were determined during the reaction by gas chromatography analysis of aliquots of the reaction mixture. The mixture of aldehydes was separated from the unreacted substrate and the catalysts by preparative column chromatography (silica; toluene/ethyl acetate, 5:1) to produce a colourless viscous oil in a yield of ca. 80% for a conversion of ca. 80%. The mixtures of aldehydes were then characterized by ¹H and ¹³C NMR spectroscopy (Bruker 250 and 500 MHz), as well as by conventional GC-MS (HP-G1800A instrument). The exact masses of the main fragments were determined in a time-of-flight mass spectrometer (Waters GCTOF, SIDI, Universidad Autónoma de Madrid), with use of the 218.9856 uma peak of perfluorotributylamine as lock mass. Both GC-MS instruments were fitted with HP5 columns. The NMR stereochemical analysis of the products was carried out with a Bruker AVANCE spectrometer operating at 500.13 MHz for ¹H. Complete ¹H and ¹³C NMR chemical shift assignments were performed by two-dimensional COSY, NOESY, HSQC and HMBC experiments at 298 K. When possible,

selective 1D versions of the TOCSY and NOESY were also recorded. The mixing times in the NOESY experiments were always set to 500 ms.

Diethyl 4,4-Dimethyl-3-(1-methyl-3-oxopropyl)cyclohexane-1,1-dicarboxylate (1d and 1e): 86:14 relative ratio.

1d: ¹H NMR (CDCl₃, 500 MHz): δ = 2.17 (2-Hₑq), 1.58 (2-Hₐx), 1.20 (3-Hₐx), 1.30 (5-Hₑq), 1.38 (5-Hₐx), 2.19 (6-Hₑq), 1.79 (6-Hₐx), 1.25 (*CH₃*CH₂O₂Cₐx), 4.17 (CH₃*CH₂*O₂Cₐx), 1.27 (*CH₃*CH₂O₂Cₑq), 4.17–4.26 (CH₃*CH₂*O₂Cₑq), 2.48 (C*H*–CH₃), 0.99 (*CH₃*–CH), 2.18–2.49 (*CH₂*–CHO), 9.77 (d, *J* = 2.8 Hz, C*H*O), 0.98 (*CH₃*–C-4ₑq), 0.90 (*CH₃*–C-4ₐx) ppm. ¹³C NMR (CDCl₃, 125.7 MHz): δ = 55.9 (C-1), 28.1(C-2), 47.7 (C-3), 33.9 (C-4), 39.6 (C-5), 27.5 (C-6), 14.3 (*CH₃*CH₂O₂Cₐx), 61.6 (CH₃*CH₂*O₂Cₐx), 172.8 (*CO*ₐx), 14.3 (*CH₃*CH₂O₂Cₑq), 61.4 (CH₃*CH₂*O₂Cₑq), 171.1 (*CO*ₑq), 21.8 (*CH₃*–CH), 25.7 (*CH*–CH₃), 47.5 (*CH₂*–CHO), 202.3 (*CHO*), 30.7 (*CH₃*–C-4ₑq), 20.5 CH₃–C-4ₐx ppm. GC-MS (70 eV): *m/z* (%) = 283 (5), 209 (8), 107 (67), 69 (80), 41 (95), 29 (100). GC-TOF MS (70 eV): calcd. for [M – CH₂CHO]+ 283.1909, found 283.1906.

1e: ¹H NMR (CDCl₃, 500 MHz): δ = 2.05 (2-Hₑq), 1.68 (2-Hₐx), 1.18 (3-Hₐx), 1.35 (5-Hₑq), 1.35 (5-Hₐx), 2.21 (6-Hₑq), 1.82 (6-Hₐx), 1.26 (*CH₃*CH₂O₂Cₐx), 4.17 (CH₃*CH₂*O₂Cₐx), 1.26 (*CH₃*CH₂O₂Cₑq), 4.17–4.26 (CH₃*CH₂*O₂Cₑq), 2.52 (C*H*–CH₃), 0.89 (*CH₃*–CH), 2.33–2.42 (*CH₂*–CHO), 9.75 (C*H*O), 0.99 (*CH₃*–C-4ₑq), 0.94 (*CH₃*–C-4ₐx) ppm. ¹³C NMR (CDCl₃, 125.7 MHz): δ = 27.8 (C-2), 44.2 (C-3), 39.6 (C-5), 27.5 (C-6), 14.3 (*CH₃*CH₂O₂Cₐx), 61.6 (CH₃*CH₂*O₂Cₐx), 14.3 (*CH₃*CH₂O₂Cₑq), 61.4 (CH₃*CH₂*O₂Cₑq), 16.6 (*CH₃*–CH), 26.4 (*CH*–CH₃), 52.0 (*CH₂*–CHO), 202.3 (*CHO*), 30.7 (*CH₃*–C-4ₑq), 20.8 (*CH₃*–C-4ₐx) ppm. GC-MS (70 eV): *m/z* (%) = 283 (2), 208 (17), 107 (53), 69 (72), 41 (91), 29 (100). GC-TOF MS (70 eV): calcd. for [M – CH₂CHO]+ 283.1909, found 283.1920.

Ethyl *cis*-4,4-Dimethyl-3-(1-methyl-3-oxopropyl)-1-cyanocyclohexane-1-carboxylate (2d and 2e): 96:4 ratio.

2d: ¹H NMR (CDCl₃, 500 MHz): δ = 1.92 (2-Hₑq), 1.70 (2-Hₐx), 1.53 (3-Hₐx), 1.46 (5-Hₑq), 1.68 (5-Hₐx), 1.96 (6-Hₑq), 1.92 (6-Hₐx), 1.08 (*CH₃*CH₂O₂C), 4.30 (CH₃*CH₂*O₂C), 2.55 (C*H*–CH₃), 1.02 (*CH₃*–CH), 2.12–2.47 (*CH₂*–CHO), 9.76 (C*H*O), 1.08 (*CH₃*–C-4ₑq), 0.91 (*CH₃*–C-4ₐx) ppm. ¹³C NMR (CDCl₃, 125.7 MHz): δ = 46.8 (C-1), 29.7(C-2), 47.5 (C-3), 34.1 (C-4), 38.7 (C-5), 29.2 (C-6), 14.1 (*CH₃*CH₂O₂C), 63.2 (CH₃*CH₂*O₂C), 119.3 (CN), 21.6 (*CH₃*–CH), 22.0 (*CH*–CH₃), 47.4 (*CH₂*–CHO), 202.0 (*CHO*), 30.1 (*CH₃*–C-4ₑq), 20.4 (*CH₃*–C-4ₐx) ppm. GC-MS (70 eV): *m/z* (%) = 236 (1), 181 (2), 162 (2), 126 (6), 107 (10), 98 (12), 69 (100). GC-TOF MS (70 eV): calcd. for [M – H]+ 278.1756, found 278.1772 (0.2).

Ethyl 4,4-Dimethyl-3-(1-methyl-3-oxopropyl)cyclohexane-1-carboxylate (3d, 3f, 3e and 3g): 40:50:4:6 relative ratio.

3d: ¹H NMR (CDCl₃, 500 MHz): δ = 2.71 (1-Hₑq), 1.97 (2-Hₑq), 1.36 (2-Hₐx), 1.25 (3-Hₐx), 1.21 (5-Hₑq), 1.34 (5-Hₐx), 1.98 (6-Hₑq), 1.60 (6-Hₐx), 1.26 (*CH₃*CH₂O₂Cₐx), 4.12–4.20 (CH₃*CH₂*O₂Cₐx), 2.36 (C*H*–CH₃), 0.97 (*CH₃*–CH), 2.14–2.47 (*CH₂*–CHO), 9.76 (dd, *J* = 0.8, 3.1 Hz, C*H*O), 1.00 (*CH₃*–C-4ₑq), 0.88 (*CH₃*–C-4ₐx) ppm. ¹³C NMR (CDCl₃, 125.7 MHz): δ = 39.7 (C-1), 23.8 (C-2), 47.7 (C-3), 33.9 (C-4), 39.2 (C-5), 23.8 (C-6), 14.2 (*CH₃*CH₂O₂Cₐx), 61.6 (CH₃*CH₂*O₂Cₐx), 175.8 (*CO*ₐx), 21.6 (*CH₃*–CH), 28.2 (*CH*–CH₃), 47.3 (*CH₂*–CHO), 202.5 (*CHO*), 30.4 (*CH₃*–C-4ₑq), 20.3 (*CH₃*–C-4ₐx) ppm. GC-MS (70 eV): *m/z* (%) = 209 (25), 183 (16), 155 (19), 136 (55), 109 (100), 100 (40). GC-TOF MS (70 eV): calcd. for [M – CH₃CHO]+ 210.1620, found 210.1606 (6).

3f: ¹H NMR (CDCl₃, 500 MHz): δ = 2.23 (1-Hₐx), 1.74 (2-Hₑq), 1.32 (2-Hₐx), 1.11 (3-Hₐx), 1.42 (5-Hₑq), 1.25 (5-Hₐx), 1.75 (6-Hₑq),

1.52 (6-H$_{ax}$), 1.26 (CH_3CH$_2$O$_2$C$_{eq}$), 4.14 (CH$_3$CH_2O$_2$C$_{eq}$), 2.45 (CH–CH$_3$), 0.96 (CH_3–CH), 2.11–2.50 (CH_2–CHO), 9.76 (dd, J = 0.8, 3.1 Hz, CHO) 0.97 (CH_3–C-4$_{eq}$), 0.88 (CH_3–C-4$_{ax}$ ppm. ^{13}C NMR (CDCl$_3$, 125.7 MHz): δ = 44.2 (C-1), 25.4 (C-2), 47.7 (C-3), 34.0 (C-4), 42.0 (C-5), 25.0 (C-6), 14.2 (CH$_3$CH$_2$O$_2$C$_{eq}$), 61.4 (CH$_3$CH$_2$O$_2$C$_{eq}$), 174.6 (CO$_{2eq}$), 21.9 (CH$_3$–CH), 25.6 (CH–CH$_3$), 47.5 (CH$_2$–CHO), 202.8 (CHO), 30.6 (CH$_3$–C-4$_{eq}$), 20.3 (CH$_3$–C-4$_{ax}$) ppm. GC-MS (70 eV): m/z (%) = 226 (1), 210 (100), 165 (32), 137 (72), 121 (38), 109 (84). GC-TOF MS (70 eV): calcd. for [M – (CH$_2$CHO)]$^+$ 211.1698, found 211.1703.

3e: GC-MS (70 eV): m/z (%) = 253 (1), 210 (90), 195 (17), 163 (26), 136 (100), 121 (39), 109 (96). GC-TOF MS (70 eV): calcd. for [M – (CH$_3$CHO)]$^+$ 210.1620, found 210.1663.

3g: GC-MS (70 eV): m/z (%) = 211 (100), 195 (17), 165 (30), 136 (69), 121 (61). GC-TOF MS (70 eV): calcd. for [M – (CH$_2$CHO)]$^+$ 211.1698, found 211.1689.

1-(Methoxymethyl)-4,4-dimethyl-3-(1-methyl-3-oxopropyl)cyclohexane (4d, 4f 4e and 4g): 48:41:7:4 relative ratio.

4d: ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 3.32 (CH_3O$_{ax}$), 3.20 (dd, J = 5.0, 3.2 Hz, CH_2OMe$_{ax}$), 0.95 (d, J = 8.0 Hz, CH_3–CH), 2.33–2.52 (CH_2–CHO), 9.72 (dd, J = 0.8, 2.6 Hz, CHO), 0.96 (CH_3–C-4$_{eq}$), 0.86 (CH_3–C-4$_{ax}$) ppm. ^{13}C NMR (CDCl$_3$, 62.8 MHz): δ = 46.2 (C-1), 23.6 and 24.2 (C-2 and C-6), 33.6 (C-3), 34.8 (C-4), 38.1 (C-5), 59.1 (CH$_3$O$_{ax}$), 79.1 (CH$_2$OMe$_{ax}$), 20.9 (CH$_3$–CH), 26.2 (CH–CH$_3$), 48.0 (CH$_2$–CHO), 203.4 (CHO), 31.1 (CH$_3$–C-4$_{eq}$), 22.3 (CH$_3$–C-4$_{ax}$) ppm. GC–MS (70 eV): m/z (%) = 225 (0.2), 194 (1), 176 (10), 163 (7), 150 (33), 123 (100), 95 (40), 81 (62), 67 (44). GC-TOF MS (70 eV): calcd. for [M]$^+$ 226.1933, found 226.1928.

4f: ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 3.31 (CH_3O$_{eq}$), 3.33 (dd, J = 5.0, 3.2 Hz, CH_2OMe$_{ax}$), 0.94 (d, J = 7.3 Hz, CH_3–CH), 2.33–2.52 (CH_2–CHO), 9.72 (dd, J = 0.8, 2.6 Hz, CHO), 0.90 (CH_3–C-4$_{eq}$), 0.82 (CH_3–C-4$_{ax}$) ppm. ^{13}C NMR (CDCl$_3$, 62.8 MHz): δ = 51.4 (C-1), 26.2 and 27.0 (C-2 and C-6), 39.4 (C-3), 34.8 (C-4), 42.9 (C-5), 59.2 (CH$_3$O$_{eq}$), 74.6 (CH$_2$OMe$_{ax}$), 21.2 (CH$_3$–CH), 26.1 (CH–CH$_3$), 48.1 (CH$_2$–CHO), 203.4 (CHO), 31.0 (CH$_3$–C-4$_{eq}$), 22.4 (CH$_3$–C-4$_{ax}$) ppm. GC-MS (70 eV): m/z (%) = 226 (0.1), 194 (1), 182 (21), 176 (7), 150 (91), 123 (100), 107 (24), 95 (57), 81 (81), 76 (52). GC-TOF MS (70 eV): calcd. for [M – H]$^+$ 225.1655, found 225.1850.

4g: GC-MS (70 eV): m/z (%) = 194 (0.1), 182 (27), 150 (100), 135 (31), 123 (69), 107 (27), 95 (43), 81 (68), 67 (47). GC-TOF MS (70 eV): calcd. for [M – (CH$_3$CHO)]$^+$ 182.1671, found 182.1667.

[4,4-Dimethyl-3-(1-methyl-3-oxopropyl)cyclohexyl]methyl Acetate (5d, 5f, 5e and 5g): Relative ratio 45:45:5:5.

5d: ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 2.05 (CH_3CO$_{ax}$), 4.07 (d, J = 7.7 Hz, CH_2OMe$_{ax}$), 0.92 (d, J = 7.5 Hz, CH_3–CH), 2.37–2.50 (CH_2–CHO), 9.73 (dd, J = 0.9, 1.8 Hz, CHO), 0.98 (CH_3–C-4$_{eq}$), 0.84 (CH_3–C-4$_{ax}$) ppm. ^{13}C NMR (CDCl$_3$, 62.8 MHz): δ = 46.0 (C-1), 23.3 and 24.2 (C-2 and C-6), 32.8 (C-3), 34.6 (C-4), 37.8 (C-5), 21.2 (CH$_3$CO$_{ax}$), 65.8 (CH$_2$O$_{ax}$), 21.2 (CH$_3$–CH), 26.1 (CH–CH$_3$), 47.9 (CH$_2$–CHO), 203.3 (CHO), 30.9 (CH$_3$–C-4$_{eq}$), 22.3 (CH$_3$–C-4$_{ax}$) ppm. GC–MS (70 eV): m/z (%) = 211 (0.5), 194 (5), 176 (8), 161 (13), 150 (57), 135 (17), 123 (100), 95 (54), 81 (65). GC-TOF MS (70 eV): calcd. for [M – (CH$_3$CO$_2$H)]$^+$ 194.1671, found 194.1676.

5f: ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 2.05 (CH_3CO$_{eq}$), 3.91 (d, J = 7.7 Hz, CH_2OMe$_{ax}$), 0.95 (d, J = 6.9 Hz, CH_3–CH), 2.37–2.50 (CH_2–CHO), 9.75 (dd, J = 0.7, 1.8 Hz, CHO), 0.99 (CH_3–C-4$_{eq}$), 0.88 (CH_3–C-4$_{ax}$) ppm. ^{13}C NMR (CDCl$_3$, 62.8 MHz): δ = 51.3 (C-1), 25.9 and 26.6 (C-2 and C-6), 38.4 (C-3), 34.8 (C-4), 42.7 (C-

5), 21.2 (CH_3CO$_{eq}$), 69.8 (CH_2O$_{eq}$), 20.8 (CH_3–CH), 26.2 (CH–CH$_3$), 48.0 (CH$_2$–CHO), 203.2 (CHO), 31.0 (CH$_3$–C-4$_{eq}$), 22.4 (CH$_3$–C-4$_{ax}$) ppm. GC- MS (70 eV): m/z (%) = 211 (0.5), 194 (6), 176 (10), 161 (10), 150 (25), 138 (9), 123 (100), 95 (48), 81 (58). GC-TOF MS (70 eV): calcd. for [M – (CH$_3$CO$_2$H)]$^+$ 194.1671, found 194.1662.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of aldehydes **1d**–**e**, **2d**–**e**, **3d**–**e**, **4d**–**e**, **5d**–**e** and GC-TOF data for **1d**–**e**, **2d**, **3d**–**g**, **4d**–**g** and **5d**–**g**.

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[27] This energy calculation was very sensitive to the force field used. Amber force field calculation on **1b** gave a population of 70% of conformer **A** leading to major aldehyde stereoisomer **1d**, while with MM2 calculation, the stability of the conformers was reversed, since only 30% of conformer **A** was present in the equilibrium at the reaction temperature.

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[29] Here again this energy calculation was very sensitive to the force field used. While with MM3 the population of the major conformer of the 1,3-dioxane derivative producing the highest *dr* was about 95% (as reported in ref.[28]), with the Amber force field calculation the amount of this isomer was lowered to 87%, and with MM2 it was only of 45%.

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[31] Furthermore, the CH$_2$ group of the ethyl ester of the nitrile derivative **2d** appeared as a clear quadruplet pattern, indicating that there is no restriction on the rotation of this fragment. This is in contrast to what was observed for compounds **1d**, **1e** and **3d** with axial carboxylate groups that show nonequivalence of their methylene ester protons.

[32] It should be noted that the ^{13}C NMR signals for C-7 and C-8 of the eight major aldehydes prepared appeared in a very narrow range – $\delta = 21.4 \pm 0.5$ and 47.4 ± 0.4 ppm, respectively – each about 5 ppm away from the corresponding C-7 and C-8 signals of the minor aldehyde stereoisomers.

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