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Studies on diastereoselective reduction of cyclic β-ketoesters with boron hydrides. Part 4: The reductive profile of functionalized cyclohexanone derivatives

Carlos A. M. Fraga,[a,b,*] Lis Helena P. Teixeira,[a,b] Carla Maria de S. Menezes,[a] Carlos Mauricio R. Sant'Anna,[a,c] Maria da Conceição K. V. Ramos,[b] Francisco R. de Aquino Neto[b] and Eliezer J. Barreiro[a,b]

[a]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, PO Box 68023, 21944971 Rio de Janeiro, RJ, Brazil*
[b]*Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[c]*Departamento de Química, ICE, Universidade Federal Rural do Rio de Janeiro, RJ 23851-970 Seropédica, Brazil*

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Abstract—Reduction of 2-allyl-2-carboalkoxycyclohexanones (**3d-f**), 2-propyl-2-carboethoxycyclohexanone (**3g**) and 2-benzyl-2-carboethoxycyclohexanone (**3h**) with boron hydrides in the presence and absence of several chelating agents were studied. Molecular modeling studies using semiempirical PM3 method were performed in order to find a suitable explanation of the diastereoselection of ketone carbonyl faces during the reductive process, which yielded *trans*-2-allyl-2-carboethoxycyclohexanol (**6e**) and *cis*-2-allyl-2-carboethoxy-cyclohexanol (**7e**) in good diastereomeric excess by using inexpensive sodium and tetrabutylammonium borohydrides.

1. Introduction

Cyclic β-ketoesters and its corresponding β-hydroxyester derivatives are important building blocks for the synthesis of natural products and many bioactive substances.[1,2] Several previous papers of our laboratory described the enantio-[3,4] and diastereoselective[5–8] preparation of cyclic β-hydroxyester derivatives, exploring the chemoselective reduction of the carbonyl group of 2-alkyl-2-carboalkoxy-cyclopentanone (**1**) and 2-acetyl-2-alkyl-butyrolactone derivatives (**2**) and their application in the synthesis of carbocyclic and heterocyclic building blocks[9–12] useful for construction of new drug candidates[13,14] (Fig. 1).

Now, we describe in this paper our studies about the reduction of 2-alkyl-2-carboalkoxycyclohexanone derivatives (**3d-m**) using boron hydrides and the investigation of its diastereoselection profile in comparison with those present by corresponding cyclopentanone derivatives (**1**). Additionally, molecular modeling studies were performed in derivatives of both series (**1**) and (**3**) in order to elucidate the structural reasons of their reductive profile (Fig. 1).

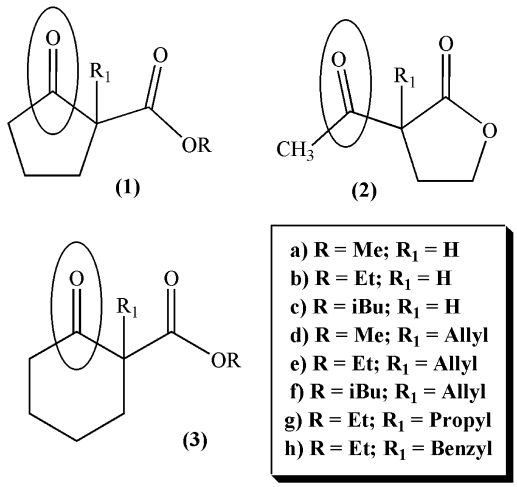

Figure 1. Cyclic β-ketoester derivatives.

2. Results and discussion

The 2-carboalkoxcyclohexanone derivatives (**3a**), (**3b**) and (**3c**) were synthesized in 90, 71 and 95% yield, respectively,

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* Corresponding author. Address: Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, PO Box 68023, 21944971 Rio de Janeiro, RJ, Brazil. Tel./fax: +55-21-25626644;
e-mail address: cmfraga@pharma.ufrj.br

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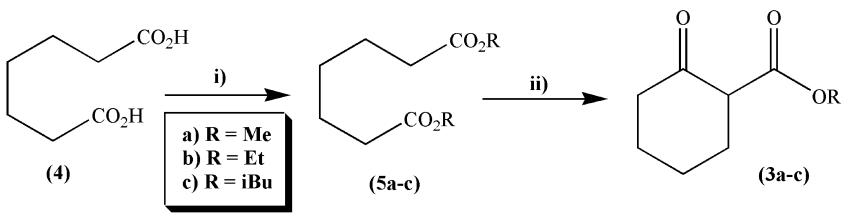


Scheme 1. (i) ROH, H_2SO_4 (cat.), reflux, 4–8 h, 98% (**5a**), 82% (**5c**); (ii) $AlCl_3$, Et_3N, rt, 2.5–4 h, 90% (**3a**), 71% (**3b**), 95% (**3c**).

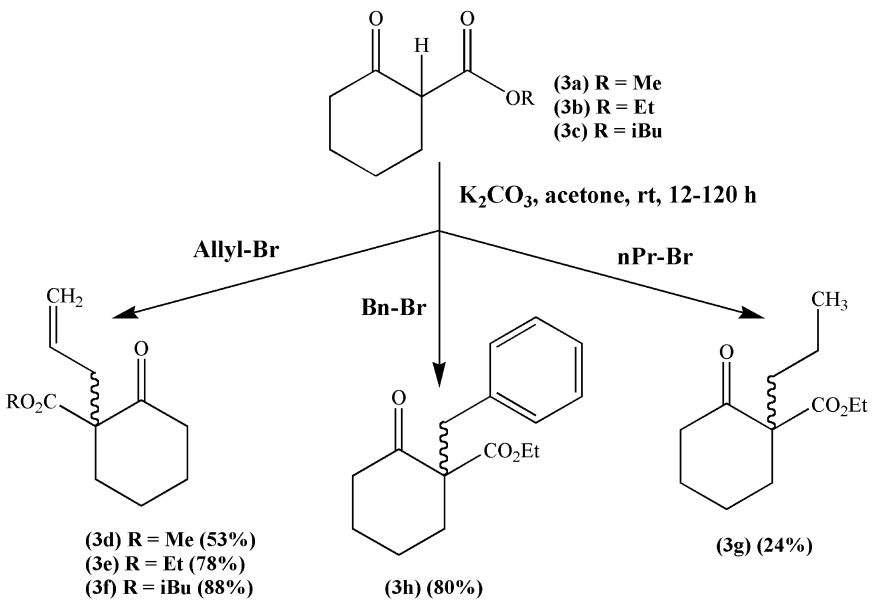
exploiting the Dieckmann condensation of the corresponding pimelic esters (**5a-c**) (Scheme 1) by treatment with $AlCl_3$ and triethylamine.[15] In spite of ethyl pimelate (**5b**) having been obtained commercially,[16] the corresponding methyl and isobutyl esters were obtained in 98 and 82% yield respectively from Fisher esterification of pimelic acid (**4**).[17]

When we employed reactive halides like allyl bromide and benzyl bromide, C-2 alkylated derivatives (**3d-f**) and (**3h**) were regioselectively obtained in yields ranging from 53 to 88%, by using a modification[18] of the classical Barco's conditions[19] which avoids the formation of the corresponding O-alkylated derivatives. Additionally, the alkylation of 2-carboethoxycyclohexanone (**3b**) with less reactive propyl bromide furnished the desired C-alkylated derivative (**3g**) in only 24% yield (Scheme 2).

Next, the 2-allyl-2-carboalkoxycyclohexanone derivatives (**3d-f**) were submitted to the chemoselective reduction with sodium borohydride in methanol, in the presence or absence of calcium chloride, in order to compare its reductive profile with that previously described for the corresponding 2-allyl-2-carboalkoxycyclopentanone derivatives[5] (**1d-f**), as showed in Table 1. The composition of the diastereomeric alcohols mixture (**6** and **7**) was elucidated by NMR spectroscopy using growing concentrations of $Eu(thd)_3$[5,7] and the relative diastereomeric ratio was determined by HRGC using a β-cyclodextrin derivative as stationary phase,[20,21] as illustrated in Figure 2. The chiral HRGC method was elected instead of normal phase GC due to the better resolution profile previously evidenced for the diastereomeric separation of functionalized β-ketoesters.[20,21]

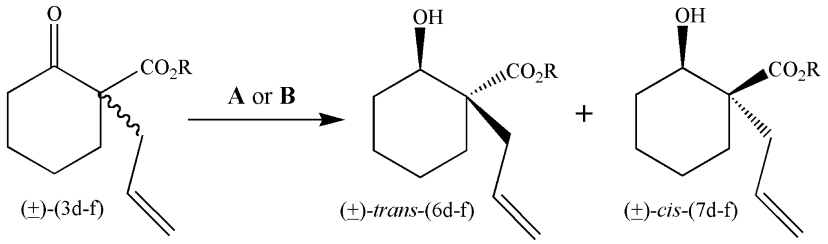
In spite of Frater[22] having described that the reduction of 2-allyl-2-carboethoxycyclohexanone (**3e**) with sodium borohydride in ethanol furnished the *cis*-cyclohexanol derivative (**7e**) in 33% de, we found that the use of methanol as solvent (entry 3, Table 1) produces a slight improvement of this diastereoselectivity profile, resulting also in the major formation of (**7e**), but in 43% de. The previous addition of 2 equiv. of $CaCl_2$ (entry 4, Table 1) resulted in the inversion of the relative configuration of the major isomer produced, that is, *cis*-cyclohexanol derivative (**6e**).

Next, we investigated the contribution of the size of ester-attached alkoxy group in the diastereoselective reductive profile of the 2-allyl-2-carboalkoxy-cyclohexanone derivatives (**3d-f**) with sodium borohydride (Table 1), following an experimental evidence related in a previous paper from our laboratory,[5] which indicated that the diastereoselectivity of the 2-allyl-2-carboalkoxycyclopentanone (**1d-f**) reduction was inversely proportional to the bulky of the alkoxy group. In fact, in that work the best diastereoselectivity index was achieved in the reduction of



Scheme 2.

Table 1. Reduction of (±)-2-allyl-2-carboalkoxycyclohexanone derivatives (**3d-f**) with sodium borohydride



Entry	Compound	R	Conditions[a]	Product **6**:**7**	Yield (%)	Diastereomeric ratio[b,c] *trans*/*cis*
1	**3d**	Me	A	**6d**:**7d**	74	1:1.6
2	**3d**	Me	B	**6d**:**7d**	85	4.3:1
3	**3e**	Et	A	**6e**:**7e**	90	1:2.5
4	**3e**	Et	B	**6e**:**7e**	96	6.5:1
5	**3f**	*i*Bu	A	**6f**:**7f**	92	1:2.4
6	**3f**	*i*Bu	B	**6f**:**7f**	96	2.2:1

[a] Conditions: (A) $NaBH_4$ (1.2 equiv.), MeOH, 0 °C, 30 min; (B) (i) $CaCl_2$ (2 equiv.), MeOH, rt, (ii) $NaBH_4$ (1.2 equiv.), 0 °C, 30 min.
[b] The relative diastereomeric ratio was determined by HRGC in a 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 capillary column (20 m×0.3 mm×0.3 μm).
[c] The qualitative determination of diastereomeric alcohols was made by analysis of ^1H NMR at 200 MHz, in presence of $Eu(thd)_3$.

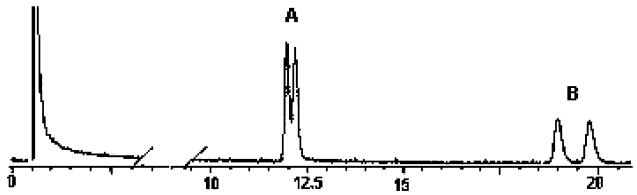


Figure 2. Chiral-HRGC of stereoisomers of the 2-allyl-2-carbomethoxycyclohexanol derivatives (**6d**) and (**7d**), at 100 °C, in a capillary glass column (20 m×0.3 mm×0.3 μm) covered with 10% of 2,3-dimetil-6-*O*-terc-butildimetilsilil-β-cyclodextrina/SE-54. A=(±)-*cis*-2-allyl-2-carbomethoxycyclohexanols (**7d**); B=(±)-*trans*-2-allyl-2-carbomethoxycyclohexanols (**6d**).

2-allyl-2-carbomethoxycyclopentanone (**1d**) with sodium borohydride in the absence or in the presence of calcium chloride[5,6] (Fig. 2). However, in the present work the diastereoselection of the ketone carbonyl faces of 2-allyl-2-carboalkoxycyclohexanone derivatives (**3d-f**) by hydride anion have no relationship with the size of the alkoxy group (Table 1) since the diastereomeric excess followed the order (**3e**)>(**3d**)>(**3f**). As showed previously, the best diastereoselective control was achieved during the reduction of the ethyl ester (**3e**) with $NaBH_4/CaCl_2$, which produced the *cis*-(±)-2-allyl-2-carboethoxycyclohexanol (**7e**) in 73% de. Intriguingly, despite applying the same experimental conditions, the diastereocourse of the reduction of the cyclohexanone derivatives with sodium borohydride in the absence or in the presence of $CaCl_2$ was opposite to that of the corresponding cyclopentanone derivatives (**1d-f**), as illustrated in Figure 3 for the reduction of methyl ester (**1d**).

In order to elucidate the possible reasons for the inversion of the diastereoselective reductive profile as consequence of the ring homologation, we made a comparison of the structural and electronic properties of the substrate molecules using the semiempirical PM3 method.[23] All optimized PM3 structures obtained in the group of 2-allyl-2-carboalkoxycyclohexanones (**3d-f**) had similar geometries, independently of the size of the ester-attached alkoxy group (OR). Similar geometries were also observed for each group of the respective complexes with the calcium ion. The optimized structures of (**3d**) and of its calcium complex (**3d**)+Ca^{2+} are presented in Figure 4. The comparison of these structures, especially the van der Waals radius representation, indicates a change in the conformation of the keto, alkoxy ester, and allyl groups in (**3d**) that allows the molecule to act as a tridentate ligand, in order to stabilize the positive charge of the calcium ion. This geometry is in accordance with the calculated geometry previously reported for the complex of (**1d**) with a Zn^{2+} ion.[6]

Electronic surfaces as MEP and frontier orbitals maps are useful theoretical tools to evaluate the 3D electronic properties of a compound, and with its associated molecular size and shape, may be of great value to interpret, elucidate and predict experimental results of stereoselective organic reactions.[24,25] The MEP illustrates the most (red) and less (blue) electron-rich regions, throughout an energetic gradient illustrated by a red–orange–yellow–green–blue scale. Also considering a similar color scale, the LUMO (Lowest Unoccupied Molecular Orbital) map shows the absolute value of the LUMO onto the total electron density surface.

The MEPs observed onto the *Re* and *Si* faces of (**3d**) (Fig. 5(A)) allow the recognition of an electron-poorer region (a more intense blue color) near the *Re* face of the ketone carbonyl group (see Fig. 5(D)) than on the corresponding region on the *Si* face (a green colored region). The LUMO maps (Fig. 5(B)) also indicate the *Re* face of the ketone carbonyl (a much more intense blue color) as the most favorable to suffer the attack of a nucleophile[26,27] (hydride anion). In addition, an electron-rich region can be seen on the *Si* face (a yellow–orange colored region in the MEP and a red–orange colored region in the LUMO map), corresponding to the oxygen atom of the alcoxy ester group, which may render unfavorable the approximation of a nucleophile due to electrostatic repulsion. Moreover, the orientation of the alkoxy ester group may also interfere with the borohydride approximation on the *Si* face by steric hindrance over the ketone carbonyl. In

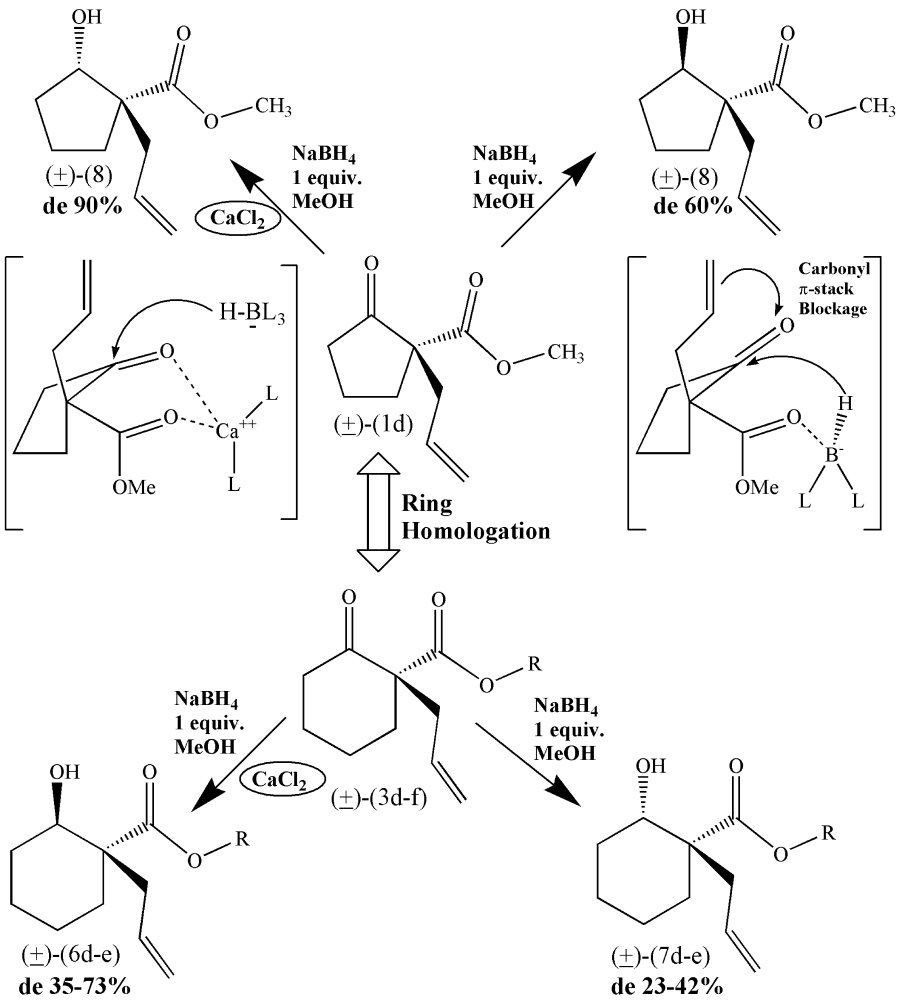


Figure 3. Inversion of the diastereoselective profile of the cyclic β-hydroxyesters (**6**-**8**) obtained from reduction of 2-allyl-2-carbomethoxycyclopentanone derivative (**1d**) or 2-allyl-2-carboalkoxycyclohexanone derivatives (**3d**-**f**) with sodium borohydride in the presence or absence of calcium chloride.

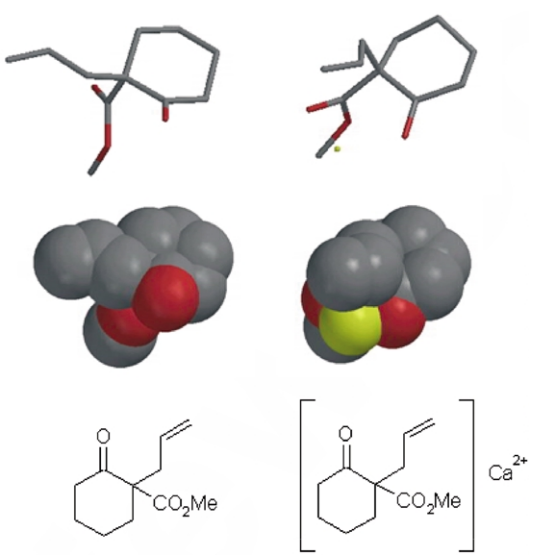


Figure 4. Tube and space-filling representations showing the conformational changes in the keto, alcoxy ester, and allyl groups of (**3d**) that allows it to interact with the calcium ion as a tridentate ligand in the (**3d**+Ca^{2+}) complex. Color code for the atoms is: carbon, gray; oxygen, red; and calcium, yellow. The hydrogen atoms were omitted for clarity.

contrast, the electronic effect of the allyl group on the *Re* face should not greatly influence the nucleophilic attack because it results in a less intense electron-rich region than the alkoxy ester group and it is oriented in the opposite direction in relation to the ketone carbonyl group.

The MEP and LUMO maps of the compounds complexed with the calcium ion, exemplified in the Figure 5 by (**3d**)+Ca^{2+}, show the region corresponding to the *Si* face on the ketone carbonyl group (Fig. 5(A.1) and (B.1)) as a relatively electron-poor region (orange–green color). On the other hand, the *Re* face of the ketone group is now almost completely hindered by the allyl group because of its conformational change towards the Ca^{2+} ion, which is better illustrated by the space-filling model representation (Fig. 5(C.1)). This steric hindrance would probably have a stronger effect on the nucleophilic attack than the electrostatic repulsion created by the oxygen atoms of the alkoxy ester group (red and red–orange regions on the MEP and LUMO maps, respectively) observed on the *Si* face. As a result, in opposition to uncomplexed (**3d**), the *Re* face of its complex with Ca^{2+} is much less susceptible to approximation and, consequently, to nucleophilic attack. Therefore, the (±)-*trans*-cyclohexanol derivatives (**6**) must be obtained

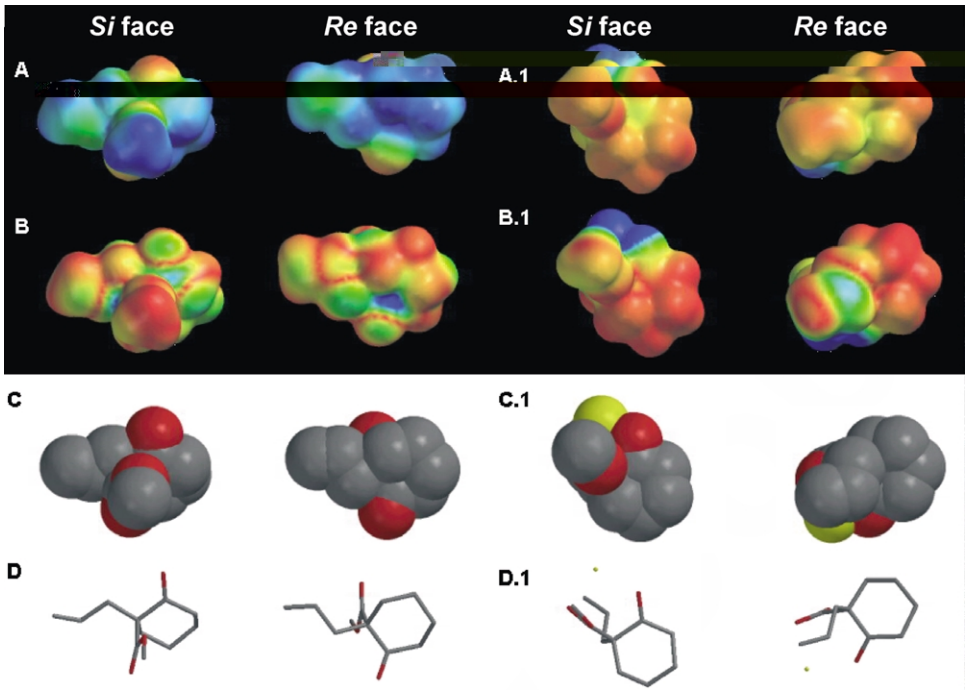


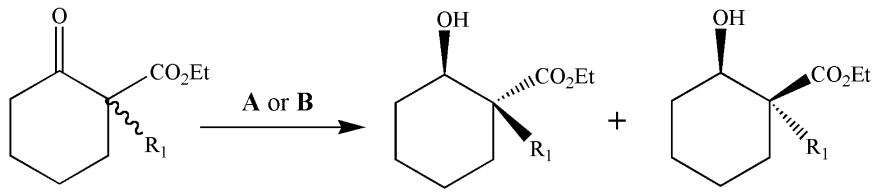
Figure 5. Representations of (**3d**) and (**3d**)+Ca^{2+}. (A) MEPs are in the range of −54 (red) to +20 (blue) kcal/mol; (B) LUMO maps in the range of 1.10^{-7} (red) to 0.030 (blue) kcal/mol; (C) space-filling model representation; (D) tube model representation; (A.1) MEPs in the range of +115 (red) to +380 (blue) kcal/mol; (B.1) LUMO maps in the range of 7.10^{-8} (red) to 0.0090 (blue) kcal/mol; (C.1) space-filling representation; (D.1) tube model representation. Color code for the atoms is: carbon, gray; oxygen, red; and calcium, yellow. The hydrogen atoms were omitted for clarity.

in greater proportion than the corresponding (±)-*cis*-cyclohexanol derivatives (**7**), which is in agreement with the experimental results (Table 1).

In order to evaluate the effect of the allyl group in the diastereoselectivity of the ethyl ester derivative (**3e**) (Table 1, entries 3 and 4) we studied the reductive profile of the corresponding saturated propyl derivative (**3g**) and the benzyl analogue (**3h**) with sodium borohydride in the presence or absence of calcium chloride. As depicted in Table 2, the reduction of saturated derivative (**3g**) resulted in the formation of a mixture of the cyclohexanol derivatives (**6g**) and (**7g**) with a decrease of the diastereomeric excess in comparison to that obtained from the reduction of the respective allyl derivatives (**6d**) and (**7d**) (Table 1), that is, 26% (entry 7, Table 2) versus 42% (entry 3, Table 1) without the use of $CaCl_2$ and 62% de (entry 8, Table 2) versus 73% (entry 4, Table 1) when $CaCl_2$ was used as a complexing agent (entry 8). These results indicated to us that the change of the allyl to propyl group in the derivative (**3g**) influenced directly of the diastereocourse of this reaction, by adopting a particular conformation that could partially block the less hindered *Re* face of the keto-carbonyl group or by the absence of formation of a ternary complex with calcium ion, as anticipated by molecular modeling studies.

The reduction of benzyl derivative (**3h**) with sodium

Table 2. Reduction of (±)-2-propyl-2-carboethoxycyclohexanone (**3g**) and (±)-2-benzyl-2-carboethoxycyclohexanone derivatives (**3h**) with sodium borohydride



(±)-(3g-h) (±)-*trans*-(6g-h) (±)-*cis*-(7g-h)

Entry	Compound	R_1	Conditions[a]	Product **6**:**7**	Yield (%)	Diastereomeric ratio[b,c] *trans*/*cis*
7	**3g**	*n*Pr	A	**6g**:**7g**	91	1:1.7
8	**3g**	*n*Pr	B	**6g**:**7g**	98	4.3:1
9	3h	Bn	A	**6h**:**7h**	98	1:2.4
10	**3h**	Bn	B	**6h**:**7h**	90	2.9:1

[a] Conditions: (A) $NaBH_4$ (1.2 equiv.), MeOH, 0 °C, 30 min; (B) (i) $CaCl_2$ (2 equiv.), MeOH, rt, (ii) $NaBH_4$ (1.2 equiv.), 0 °C, 30 min.
[b] The relative diastereomeric ratio was determined by HRGC in a 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 capillary column (20 m×0.3 mm×0.3 μm).
[c] The qualitative determination of diastereomeric alcohols was made by analysis of ^1H NMR at 200 MHz, in presence of $Eu(thd)_3$.

borohydride without $CaCl_2$ (Table 2, entry 9) did not result in any change of the diastereoselectivity in comparison with that showed by the corresponding allyl derivative (**3e**) (Table 1, entry 3). On the other hand, the use of calcium chloride as Lewis acid (Table 2, entry 10) resulted in a expressive drop of the comparative diastereoselection (see Table 1, entry 4), indicating that possibly for steric reasons benzyl group is not so able to adopt the adequate orientation which permits the formation of the ternary complex between the allyl group of compound (**3e**) and calcium ion, reducing selective blockage on the *Si* face of the ketone carbonyl group.

Considering the results described herein, we elected the 2-allyl-2-carboethoxy-cyclohexanone derivative (**3e**) for further studies varying the conditions of the reductive step as well as the nature and the size of the hydride transferring reagent, in order to optimize the diastereoselective formation of *cis*-2-allyl-2-carboethoxycyclohexanol (**7e**), obtained only in very poor de.

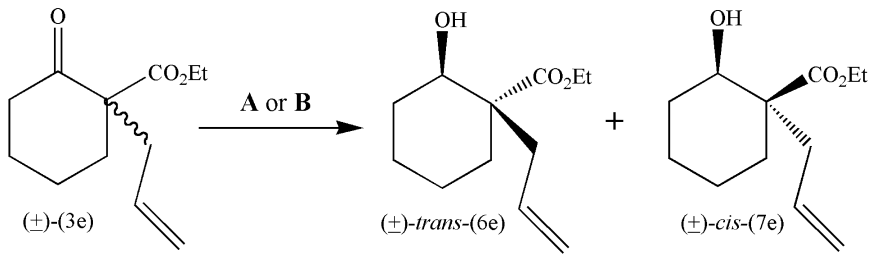
The initial modification, which consisted in the change of methanol used as solvent to isopropanol (Table 3, entries 11 and 12) or aprotic tetrahydrofuran (Table 3, entry 3), led to the loss of the diastereoselectivity evidenced before. This distinct profile may be explained by the presence of different reducing species in the media, since sodium borohydride reacts with methanol to give sterically demanding trimethoxyborohydride, whereas solutions of sodium borohydride in isopropanol or tetrahydrofuran are very stable.[28]

Once that we obtained the best diastereoselective excess by using $CaCl_2$ as complexing agent, we decide next investigate the profile of the reductive process with sodium borohydride employing four other Lewis acids presenting a variation of the atomic radius of the divalent metal from Mg^{+2} to Zn^{+2} (Table 3, entries 14–17). However, besides the reductions of the allyl derivative (**3e**) using these other metallic chlorides have not been able to improve the diastereoselectivity, the diastereofacial discrimination of the nucleophilic hydride attack to the ketone group was abolished, resulting in the equal formation of the isomers *trans*-(**6e**) and *cis*-(**7e**) (Table 3, entries 14–17). The evidenced profile indicated that, contrarily to the results previously described by Taniguchi et al.,[29] the reduction of derivative (**3e**) in the presence of Lewis acids did not show a direct correlation between the ionic radius of the metal and the diastereoselectivity of the reductive process.

Finally, the last variation in the reductant conditions consisted in the employment of other boron hydrides with different reactivity, size and solubility in the aprotic solvent THF, represented by the use of zinc borohydride,[30] lithium tri-*sec*-butylborohydride[31] (L-Selectride) and tetrabutylammonium borohydride[32] (Table 3, entries 18–20, respectively). In spite of being well-known that the use of bulky boron hydrides led to an improvement of the diastereofacial discrimination of carbonyl ketone group, the treatment of allyl functionalized derivative (**3e**) either with zinc borohydride or L-Selectride in THF resulted in an almost complete absence of the diastereoselectivity between the cyclohexanol derivatives (**6e**) and (**7e**) (Table 3, entries 18 and 19), indicating to us that bulky hydride-containing species are not able to discriminate the faces of the ketone carbonyl group.

On the other hand, the reduction of derivative (**3e**) with tetrabutylammonium borohydride in THF, furnished the *cis*-cyclohexanol derivative (**7e**) with the desired improvement of the diastereoselectivity from 42% (Table 1, entry 3) to 68% de (Table 3, entry 20). The preferential formation of the diastereomer (**7e**) by the usage of a $(n\text{Bu})_4\text{NBH}_4$ in THF (Table 3, entry 20) can be explained by the better solubility of the non-bulky hydride species in the aprotic media, which

Table 3. Reduction of 2-allyl-2-carboethoxycyclohexanone derivative (**3e**)



Entry	Redutor	Lewis acid	Solvent and temperature (°C)	Product **6**:**7**	Yield (%)	Diastereomeric ratio[a,b] *trans*/*cis*
11	$NaBH_4$	—	iPrOH, 0 °C	**6e**:**7e**	85	1:1.2
12	$NaBH_4$	$CaCl_2$	iPrOH, 0 °C	**6e**:**7e**	90	1:1.1
13	$NaBH_4$	—	THF, 0 °C	**6e**:**7e**	77	1:1
14	$NaBH_4$	$MgCl_2$	MeOH, 0 °C	**6e**:**7e**	98	1.6:1
15	$NaBH_4$	$MnCl_2$	MeOH, 0 °C	**6e**:**7e**	96	1:1.3
16	$NaBH_4$	$CeCl_3$	MeOH, 0 °C	**6e**:**7e**	91	1.2:1
17	$NaBH_4$	$ZnCl_2$	MeOH, 0 °C	**6e**:**7e**	98	1:1
18	$Zn(BH_4)_2$	—	THF, 0 °C	**6e**:**7e**	91	1.2:1
19	L-Selectride	—	THF, −78 °C	**6e**:**7e**	95	1:1.1
20	$(n\text{Bu})_4\text{NBH}_4$	—	THF, 0 °C	**6e**:**7e**	86	1:5.3
21	$(n\text{Bu})_4\text{NBH}_4$	—	MeOH, 0 °C	**6e**:**7e**	89	1:8.2

[a] The relative diastereomeric ratio was determined by HRGC in a 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 capillary column (20 m×0.3 mm×0.3 μm).

[b] The qualitative determination of diastereomeric alcohols was made by analysis of ^{1}H NMR at 200 MHz, in presence of $Eu(thd)_3$.

raised the speed of the reaction favoring the attack on the less hindered *Si* face of ketone carbonyl group (Fig. 5). Nevertheless, the change of the solvent from aprotic THF to protic methanol (Table 3, entry 21) curiously increased the diastereoselective formation of alcohol (**7e**) to 78% de. In fact, in spite of there are not many works in the literature describing the use of $(n\text{Bu})_4\text{NBH}_4$ in protic to solvents for the reduction of carbonyl compounds[29,33] is well-known that its application in the reduction of β-ketoesters[29] followed the Felkin–Ahn's model[34] with the attack of the hydride anion at the less hindered face of ketone carbonyl group (Fig. 6), in agreement with the molecular modeling and chemical results obtained in the present work.

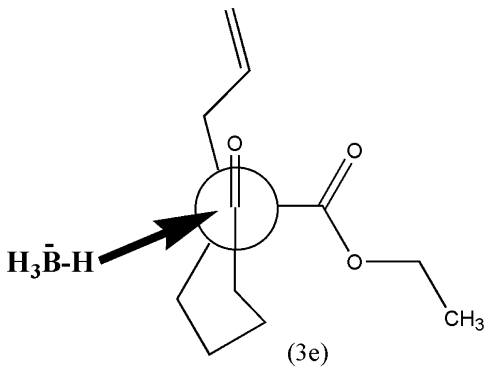


Figure 6. Felkin–Ahn's attack of hydride anion to less hindered face of cyclohexanone derivative (**3e**).

3. Conclusion

In summary, the results obtained from this research work furnished a nice approach to the diastereoselective synthesis of (±)-*trans*-cyclohexanol derivative (**6e**) and (±)-*cis*-cyclohexanol derivative (**7e**) respectively in 73 and 78% de, using available and inexpensive sodium or tetrabutylammonium borohydrides. The developed synthetic methodologies showed to be extremely dependent of the solvent and the Lewis acid employed, being the best results obtained when the reductions were carried out in methanol and, for the preparation of (**6e**), calcium chloride was used as Lewis acid.

4. Experimental

4.1. Molecular modeling

The molecular modeling analysis was performed using the SPARTAN 1.0.5 program (Wavefunction Inc., Irvine, CA, 2000) on a Pentium III 900 MHz computer. The structure of the compounds (**3d-f**) and (**1d**) and of their respective complexes with calcium ion, (**3d-f**)+Ca^{2+} and (**1d**)+Ca^{2+}, were optimized with the PM3 method.[23] This semiempirical method is parameterized for calcium, present in the Lewis acid $CaCl_2$ used in the experimental methodology, and was previously used to analyze diastereoselective experimental data.[12,35]

The optimized structures of the compounds were submitted to Hessian matrix analysis to unequivocally characterize them as true minima of the potential energy surface. A Monte Carlo conformational analysis with the PM3 method was employed. The minimal energy conformers were selected and submitted to single-point energy calculations with the ab initio 3-21G* basis set in order to better evaluate their electronic properties. In this study, the map of the electrostatic potential (MEP), and the map of the absolute value of the lowest-unoccupied molecular orbital (LUMO map), both onto an electron density surface of 0.002 e/au^3, were considered for the analysis of the stereoselectivity results obtained in the Section 4.

4.2. Chemistry

^{1}H and ^{13}C NMR spectra were determined in deuterochloroform containing ca. 1% tetramethylsilane as an internal standard with Brucker AC 200 and Varian VxR 300 spectrometers. Splitting patterns were as follows: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; dd, double doublet; ddt, double double triplet; m, multiplet. Infrared spectra (IR) spectra were obtained with a Nicolet 505 Magna spectrophotometer as neat films on sodium chloride plates. The mass spectra (MS) were obtained on a GC/VG Micromass 12 at 70 eV. Gas chromatography (HRGC) was recorded in a Hewlett Packard model 5890 series II using injection in the split mode. The HRGC analyses were performed in 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 (1% vinyl; 5% phenyl; 94% methylpolysiloxane) house made capillary column (20 m×0.3 mm×0.3 μm) at 100 °C/2 °C/min/130 °C. Microanalysis data were obtained with a Perkin–Elmer 240 analyzer, using Perkin–Elmer AD-4 balance.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm×6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were visualized with molybdatophosphoric acid in ethanol. For column chromatography Merck silica gel (70–230 mesh) was used. Solvents used in the reactions were redistilled prior use and stored over 3–4 Å molecular sieves. Reactions were generally carried out under nitrogen atmosphere and magnetic stirring. The 'usual workup' means that the organic extracts prior to concentration, under reduced pressure, were treated with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and filtered.

4.3. General procedure for the esterification of pimelic acid (4)

To a solution of pimelic acid[15] (**4**) (1 g; 6.25 mmol) in 12 mL of methyl or isobutyl alcohol was slowly added 0.73 mL of concentrated sulfuric acid. The resulting mixture was stirred at reflux until that tlc analysis indicated the total consumption of the starting material (eluent: hexanes/AcOEt 70:30). Next, the mixture was poured into crushed ice and then, extracted with dichloromethane (5×50 mL). The organic layers were washed with 5% aq. $NaHCO_3$ solution and submitted to the 'usual workup' to furnish the corresponding pimelate ester (**5a**) or (**5c**) as described above.

4.3.1. Dimethyl pimelate (5a). The spectroscopic data

of this compound, which was obtained in 99% yield, are in agreement with those previously related in literature.[36]

4.3.2. Diisobutyl pimelate (5c). This compound was obtained in 82% yield, after 8 h, as a yellow oil; IR (film): ν C–H 2875 and 2961, ν C=O 1737, ν C–O 1175 cm^{-1}; ^1H NMR (200 MHz): 0.92 (d, 12H, J=6.7 Hz, $OCH_2CH(CH_3)_2$), 1.38 (m, 2H, $O{=}CCH_2CH_2CH_2CH_2CH_2C{=}O$), 1.64 (qt, 4H, J=7.5 Hz, $O{=}CCH_2CH_2CH_2CH_2CH_2C{=}O$), 1.89 (sp, 2H, J=6.7 Hz, $OCH_2CH(CH_3)_2$), 2.31 (t, 4H, J=7.5 Hz, $O{=}CCH_2CH_2CH_2CH_2CH_2C{=}O$), 3.85 (d, 4H, J=6.7 Hz, $OCH_2CH(CH_3)_2$) ppm; ^{13}C NMR (75 MHz): 19.2 ($OCH_2CH(CH_3)_2$), 24.8 (CH_2-4), 27.8 ($OCH_2CH(CH_3)_2$), 28.8 (CH_2-3 and CH_2-5), 34.3 (CH_2-2 and CH_2-6), 70.6 ($OCH_2CH(CH_3)_2$), 173.8 ($C{=}O$) ppm. Anal. calcd for $C_{15}H_{28}O_4$: C 66.14; H 10.36. Found: C 66.21; H 10.44.

4.4. General procedure for Dieckmann cyclization[16] of the esters (5a-c)

To a suspension of anhydrous aluminum chloride (16 g, 120 mmol) in 50 mL of dichloromethane was added a solution of the corresponding pimelate ester derivative (**5a-c**) (46 mmol) in 50 mL dichloromethane. After cooling the obtained mixture at 0 °C, 16 mL of triethylamine (120 mmol) was carefully added and reaction was stirred at room temperature until that tlc analysis indicated the total consumption of the starting material. Next, a 1:1 mixture of 10% aq. HCl and crushed ice (100 mL) was added and the reaction was extracted with dichloromethane (4×40 mL). The organic layers were washed with a saturated aq. oxalic acid solution and submitted to the usual workup to furnish the corresponding 2-carboalkoxycyclohexanone derivative (**3a-c**) as described next.

4.4.1. 2-Carbomethoxycyclohexanone (3a). The spectroscopic data of this compound, which was obtained in 90% yield, are in agreement with those previously related in literature.[37]

4.4.2. 2-Carboethoxycyclohexanone (3b). The spectroscopic data of this compound, which was obtained in 71% yield, are in agreement with that previously related in literature.[38,39]

4.4.3. 2-Carboisobutoxycyclohexanone (3c). The spectroscopic data of this compound, which was obtained in 95% yield, are in agreement with that previously related in literature.[38]

4.5. General procedure for the C-alkylation of the β-ketoesters (5a-c)[17,18]

To a suspension of anhydrous potassium carbonate (2.44 g; 17.6 mmol) in anhydrous acetone (6 mL) was added a solution of 2-carboalkoxycyclohexanone derivative (**5a-c**) (5.8 mmol) in anhydrous acetone (2 mL). The reaction mixture displays a characteristic yellow color after stirring at room temperature for 30 min due to the formation of the corresponding enolate intermediate. Then, respective alkyl bromide (7.6 mmol) was added slowly and the mixture was stirred at room temperature until that tlc analyses (Hex/AcOEt, 9:1) indicated the total consumption of the starting material. The suspension was filtered, the filtrate concentrated at reduced pressure (80 mm Hg) and the residue diluted with ether (50 mL). The 'usual workup' gives the respective 2-alkyl-2-carboalkoxycyclohexanone derivative (**3d-g**).

4.5.1. 2-Allyl-2-carbomethoxycyclohexanone (3d). The spectroscopic data of this compound, which was obtained in 53% yield, are in agreement with that previously related in literature.[40]

4.5.2. 2-Allyl-2-carboethoxycyclohexanone (3e). The spectroscopic data of this compound, which was obtained in 53% yield, are in agreement with that previously related in literature.[22,40]

4.5.3. 2-Allyl-2-carboisobutoxycyclohexanone (3f). From alkylation of (**3c**) with allyl bromide (0.66 mL), this compound was obtained in 88% yield,[41] after 24 h, as a yellow oil; IR (film): ν C=C–H 3078, ν C–H 2960 and 2873, ν C=O 1737 and 1716, ν C–O 1219 and 1203 cm^{-1}; ^1H NMR (200 MHz): 0.86 (d, 6H, J=6.7 Hz, $COOCH_2CH(CH_3)_2$), 1.30–2.00 (m, 6H, $O{=}CCH_2CH_2CH_2CH_2$; $COOCH_2CH(CH_3)_2$ and $CHHCH{=}CH_2$), 2.33–2.51 (m, 5H, $O{=}CCH_2CH_2CH_2CH_2$ and $CHHCH{=}CH_2$), 3.83 (d, 2H, J=6.6 Hz, 1H, $COOCH_2CH(CH_3)_2$), 4.93–5.01 (m, 2H, $CH_2CH{=}CH_2$), 5.62–5.76 (m, 1H, $CH_2CH{=}CH_2$) ppm; ^{13}C NMR (50 MHz): 207.3 ($C{=}O$), 171.5 ($COOCH_2CH(CH_3)_2$), 133.4 ($CH_2CH{=}CH_2$), 118.1 ($CH_2CH{=}CH_2$), 71.3 ($COOCH_2CH(CH_3)_2$), 61.0 (C-2), 41.1 ($CH_2CH{=}CH_2$), 39.4 (CH_2-6), 35.7 (CH_2-3), 27.7 ($COOCH_2CH(CH_3)_2$), 27.5 (CH_2-5), 22.4 (CH_2-4), 19.1 ($COOCH_2CH(CH_3)_2$) ppm. Anal. calcd for $C_{14}H_{22}O_3$: C 70.56; H 9.30. Found: C 70.67; H 9.35.

4.5.4. 2-Benzyl-2-carboethoxy-cyclohexanone (3h). From alkylation of (**3b**) with benzyl bromide (0.83 mL), this compound was obtained in 80% yield, after 12 h, as a yellow oil; IR (film): ν –C=C–H 3085, 3062 and 3029, ν C–H 2942 and 2867, ν C=O 1740 and 1714, ν C–O 1188 cm^{-1}; ^1H NMR (200 MHz): 1.16 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 1.65–1.71 (m, 4H $O{=}CCH_2CH_2CH_2CH_2$), 1.80–2.00 (m, 3H, $O{=}CCH_2CH_2CHCHH$-*syn* to benzyl group), 2.37–2.47 (m, 3H, $O{=}CCH_2CH_2CH_2CHH$-*anti* to benzyl group), 2.86 (d, 2H, J=13.7 Hz, PhC*H*H), 3.30 (d, 2H, J=13.7 Hz, PhCH*H*), 4.08 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 7.08–7.12 (m, 2H, *meta*Ar-*H*), 7.18–7.26 (m, 3H, *ortho*Ar-*H* and *para*Ar-*H*) ppm; ^{13}C NMR (50 MHz): 207.3 ($C{=}O$), 171.1 ($COOCH_2CH_3$), 136.7 (*ipso*Ar), 130.4 (*ortho*Ar), 128.0 (*meta*Ar), 126.7 (*para*Ar), 62.2 (C-2), 61.3 ($COOCH_2CH_3$), 41.4 ($-CH_2Ph$), 40.5 (CH_2-6), 36.0 (CH_2-3), 27.7 (CH_2-5), 22.6 (CH_2-4), 14.0 ($COOCH_2CH_3$) ppm. Anal. calcd for $C_{16}H_{20}O_3$: C 73.82; H 7.74. Found: C 73.77; H 7.81.

4.5.5. 2-Propyl-2-carboethoxycyclohexanone (3g). From alkylation of (**3b**) with *n*-propyl bromide (0.65 mL), this compound was obtained in 24% yield, after 120 h, as a yellow oil; IR (film): ν C–H 2961, 2939 and 2372, ν C=O 1732 and 1715, ν C–O 1204 cm^{-1}; ^1H NMR (200 MHz): 0.90 (m, 5H, $CH_2CH_2CH_3$), 1.22–1.29 (m, 5H, $COOCH_2CH_3$

and $CH_2CH_2CH_3$), 1.39–1.68 (m, 6H, O=CCH$_2$CH_2-CH_2CH_2), 2.26–2.33 (m, 2H, O=CCH_2CH$_2$CH$_2$CH$_2$), 3.99–4.21 (m, 2H, COOCH_2CH$_3$) ppm; ^{13}C NMR (50 MHz): 205.3 (C=O), 173.7 (COOCH$_2$CH$_3$), 61.2 (C-2), 60.3 (COOCH_2CH$_3$), 41.3 (CH$_2$-6), 34.3 (CH$_2$-3), 27.8 (CH$_2$-5), 24.7 (CH_2CH$_2$CH$_3$), 22.7 (CH$_2$-4), 17.7 (CH$_2$$CH_2CH_3$), 14.4 (COOCH$_2$$CH_3$ and CH$_2$CH$_2$$CH_3$) ppm. Anal. calcd for $C_{12}H_{20}O_3$: C 67.89; H 9.50. Found: C 67.93; H 9.43.

4.6. General procedure for reduction of 2-alkyl-2-carboalkoxy-cyclohexanone derivatives (3d-g) with sodium borohydride, in the presence or in the absence of metallic halides

A solution of β-ketoester derivative (**3d**-**g**) (1 mmol) in solvent (methanol, isopropanol or THF) (6 mL), in the presence or absence of the anhydrous metallic halide (2 mmol), was stirred at room temperature for 30 min. The reaction mixture was cooled at 0 °C (or −78 °C), and 0.045 g (1.2 mmol) of sodium borohydride was slowly added. A clear solution was obtained, which was stirred at 0 °C (or −78 °C) for 30 min. The solvent was concentrated at reduced pressure (80 mm Hg). The white doughy residue was diluted with methylene chloride (30 mL). The resulting solution was washed with saturated aqueous ammonium chloride solution (30 mL). Usual workup of the organic layer afforded the mixture of diastereomeric alcohols as described in Tables 1–3.

4.7. Reduction of the 2-allyl-2-carboethoxy-cyclohexanone (3e) with zinc borohydride

To a solution of β-ketoester derivative (**3e**) (1 mmol) in anhydrous THF (6 mL), cooled at 0 °C under nitrogen atmosphere, was slowly added 2.3 mL (1.2 mmol) of 0.12 M solution[42] of zinc borohydride in anhydrous THF. The reaction mixture was stirred for 30 min at 0 °C, and afterwards the solvent was concentrated at reduced pressure (80 mm Hg). for 15 min at 0 °C, 5 mL of 1 M solution of H_2O_2 and 7 mL of 0.2 N aq. solution of NaOH were added). The white doughy residue was diluted with methylene chloride (30 mL) and the resulting solution was washed with saturated aqueous ammonium chloride solution (30 mL). Usual workup of the organic layer afforded the diastereomeric mixture of cyclohexanols (**6e**) and (**7e**) as described in Table 3.

4.8. Reduction of the 2-allyl-2-carboethoxy-cyclohexanone (3e) with lithium-tri-*sec*-butyl-borohydride (L-Selectride)

To a solution of β-ketoester derivative (**3e**) (1 mmol) in anhydrous THF (6 mL), cooled at −78 °C under nitrogen atmosphere, was slowly added 1.2 mL (1.2 mmol) of 1 M solution of lithium-tri-*sec*-butyl-borohydride in anhydrous THF. The reaction mixture was stirred for 30 min at −78 °C, then for 15 min at 0 °C, and afterwards 5 mL of 1 M solution of H_2O_2 and 7 mL of 0.2 N aq. solution of NaOH were added. After 15 min, the system was diluted with ethyl ether (10 mL) and the organic layer was separated, washed with a saturated aqueous solution of sodium bissulfite (5 mL) and submitted to the usual workup affording the mixture of diastereomeric alcohols (**6e**) and (**7e**) as described Table 3.

4.9. General procedure for reduction of 2-allyl-2-carboethoxy-cyclohexanone (3e) with tetrabutylammonium borohydride

To a solution of β-ketoester derivative (**3e**) (1 mmol) in solvent (methanol or anhydrous THF) (6 mL), cooled at 0°, was slowly added 0.325 g (1.2 mmol) of tetrabutylammonium borohydride. The mixture was stirred at 0 °C (or −78 °C) for 30 min, when the solvent was concentrated at reduced pressure (80 mm Hg). The white doughy residue was diluted with methylene chloride (30 mL). The resulting solution was washed with 1 N aq. HCl solution (30 mL). Usual workup of the organic layer afforded the mixture of diastereomeric alcohols as described in Table 3.

4.9.1. Diastereomeric mixture of *trans*- and *cis*-(±)-2-allyl-2-carbomethoxy-cyclohexanols (6d) and (7d). Prepared from reduction of (**3d**); IR (film): ν O–H 3457, ν C=C–H 3077, ν C–H 2940 and 2863, ν C=O 1727, ν C–O 1223 cm^{-1}; ^{1}H NMR (200 MHz): 1.15–1.95 (m, 8H, CH_2 in cyclohexane ring), 2.40 (dd, 1H, *J*=7.1, 14.2 Hz, C*H*HCH=CH$_2$), 2.55 (dd, 1H, *J*=7.1, 14.2 Hz, C*H*HCH=CH$_2$), 3.45 (dd, 0.7H, *J*=3.5, 9.8 Hz, C*H*(OH), *cis* diastereomer), 3.69 (s, 1H, COOCH_3), 3.71 (s, 2H, COOCH_3), 4.93 (dd, 0.3H, *J*=3.5, 8.4 Hz, C*H*(OH), *trans* diastereomer), 5.00–5.15 (m, 2H, CH$_2$CH=CH_2), 5.65–5.90 (m. 1H, CH$_2$C*H*=CH$_2$) ppm; ^{13}C NMR (50 MHz): 177.2 and 177.3 (*C*OOCH$_3$), 134.1 (CH$_2$*C*H=CH$_2$, *trans* diastereomer), 133.3 (CH$_2$*C*H=CH$_2$, *cis* diastereomer), 118.4 (CH$_2$CH=*C*H$_2$, *cis* diastereomer), 117.7 (CH$_2$-CH=*C*H$_2$, *trans* diastereomer), 74.3 (*C*HOH, *cis* diastereomer), 71.5 (*C*HOH, *trans* diastereomer), 51.7 (COO*C*H$_3$), 52.2 and 51.3 (C-2), 41.2 and 35.5 (*C*H$_2$-CH=CH$_2$), 32.3 and 31.5 (CH$_2$-6), 29.1 and 28.9 (CH$_2$-3), 23.9 and 22.6 (CH$_2$-5), 22.6 and 20.1 (CH$_2$-4) ppm. Anal. calcd for $C_{11}H_{18}O_3$: C 66.64; H 9.15. Found: C 66.51; H 9.21.

4.9.2. Diastereomeric mixture of *trans*- and *cis*-(±)-2-allyl-2-carboethoxy-cyclohexanols (6e) and (7e). Prepared from reduction of (**3e**); IR (film): ν O–H 3490, ν C=C–H 3077, ν C–H 2979, 2937 and 2863, ν C=O 1723, ν C–O 1221 and 1201 cm^{-1}; ^{1}H NMR (200 MHz): 1.27 (t, 3H, *J*=7.1 Hz, COOCH$_2$CH_3), 1.38–1.77 (m, 8H, CH_2 in cyclohexane ring), 2.35 (dd, 1H, *J*=7.5, 14.2 Hz, C*H*HCH=CH$_2$), 2.60 (dd, 1H, *J*=7.5, 14.2 Hz, C*H*HCH=CH$_2$), 3.90–4.02 (m, 1H, C*H*(OH)), 4.16 (q, 2H, *J*=7.1 Hz, COOCH_2CH$_3$), 5.02–5.10 (m, 2H, CH$_2$-CH=CH_2), 5.70–5.79 (m. 1H, CH$_2$C*H*=CH$_2$) ppm; ^{13}C NMR (50 MHz): 176.7 and 177.3 (*C*OOCH$_2$CH$_3$), 134.1 (CH$_2$*C*H=CH$_2$, *trans* diastereomer), 133.3 (CH$_2$*C*H=CH$_2$, *cis* diastereomer), 118.2 (CH$_2$CH=*C*H$_2$, *cis* diastereomer), 117.5 (CH$_2$CH=*C*H$_2$, *trans* diastereomer), 74.3 (*C*HOH, *cis* diastereomer), 71.2 (*C*HOH, *trans* diastereomer), 60.5 (COO*C*H$_2$CH$_3$), 51.7 (C-2), 41.2 (*C*H$_2$CH=CH$_2$, *cis* diastereomer), 35.7 (*C*H$_2$CH=CH$_2$, *trans* diastereomer), 32.2 (CH$_2$-6, *cis* diastereomer), 31.5 (CH$_2$-3, *cis* diastereomer), 29.6 (CH$_2$-6, *trans* diastereomer), 29.4 (CH$_2$-3, *trans* diastereomer), 23.9 (CH$_2$-5, *cis* diastereomer), 22.5 (CH$_2$-4, *cis* diastereomer), 22.3 (CH$_2$-5, *trans*

diastereomer), 21.4 (CH_2-4, *trans* diastereomer), 14.2 ($COOCH_2CH_3$) ppm. Anal. calcd for $C_{12}H_{20}O_3$: C 67.89; H 9.50. Found: C 67.74; H 9.60.

4.9.3. Diastereomeric mixture of *trans*- and *cis*-(±)-2-allyl-2-carboisobutoxy-cyclohexanols (6f) and (7f). Prepared from reduction of (**3f**); IR (film): ν O–H 3497, ν C=C–H 3077, ν C–H 2938 and 2872, ν C=O 1723, ν C–O 1222 and 1200 cm^{-1}; ^1H NMR (200 MHz): 0.95 (d, 6H, J=6.6 Hz, $COOCH_2CH(CH_3)_2$), 1.25–1.96 (m, 9H, CH_2 in cyclohexane ring and $COOCH_2CH(CH_3)_2$), 2.35 (dd, 1H, J=7.1, 14.2 Hz, $CHHCH{=}CH_2$), 2.60 (dd, 1H, J=7.1, 14.2 Hz, $CHHCH{=}CH_2$), 2.90 (s, D_2O exchangeable, 1H, CH(OH)), 3.44 (dt, 0.7H, J=9.9, 3.3 Hz, CH(OH), *cis* diastereomer), 3.57 (d, 0.3H, J=10.1 Hz, *trans* diastereomer), 3.82–3.97 (m, 2H, $COOCH_2CH(CH_3)$), 5.05 (d, 2H, J=12.8 Hz, $CH_2CH{=}CH_2$), 5.79 (qt, 1H, J=9.5 Hz, $CH_2CH{=}CH_2$) ppm; ^{13}C NMR (50 MHz): 176.9 and 176.7 ($COOCH_2CH(CH_3)_2$), 134.1 and 133.3 ($CH_2CH{=}CH_2$), 118.3 and 117.6 ($CH_2CH{=}CH_2$), 77.8 and 74.3 (CHOH), 70.9 ($COOCH_2CH(CH_3)_2$), 52.1 and 51.1 (C-2), 42.0 ($CH_2CH{=}CH_2$), 33.0 and 32.0 (CH_2-6), 29.7 (CH_2-3), 27.7 ($COOCH_2CH(CH_3)_2$), 24.4 and 23.0 (CH_2-5), 23.0 and 22.0 (CH_2-4), 19.2 and 19.1 ($COOCH_2CH(CH_3)_2$) ppm. Anal. calcd for $C_{14}H_{24}O_3$: C 69.96; H 10.07. Found: C 70.09; H 10.12.

4.9.4. Diastereomeric mixture of *trans*- and *cis*-(±)-2-propyl-2-carboethoxy-cyclohexanols (6g) and (7g). Prepared from reduction of (**3g**); IR (film): ν O–H 3477, ν C=C–H 3077, ν C–H 2955 and 2865, ν C=O 1724, ν C–O 1218 cm^{-1}; ^1H NMR (200 MHz): 0.86 (m, 3H, $CH_2CH_2CH_3$), 1.23–2.10 (m, 15H, CH_2 in cyclohexane ring, $CH_2CH_2CH_3$ and $COOCH_2CH_3$), 3.40 (m, 1H, CHOH, *trans* diastereomer), 3.90 (m, 1H, CHOH, *cis* diastereomer), 4.16 (q, 2H, J=7.0 Hz, $COOCH_2CH_3$) ppm; ^{13}C NMR (50 MHz): 175.8 ($COOCH_2CH_3$), 74.9 (CHOH, *cis* diastereomer), 72.0 (CHOH, *trans* diastereomer), 60.6 and 60.5 ($COOCH_2CH_3$), 50.6 (C-2), 32.8 ($CH_2CH_2CH_3$), 32.5 (CH_2-6, *cis* diastereomer), 31.7 (CH_2-6, *trans* diastereomer), 29.8 (CH_2-3, *cis* diastereomer), 29.5 (CH_2-3, *trans* diastereomer), 24.0 (CH_2-5, *cis* diastereomer), 22.8 (CH_2-5, *trans* diastereomer), 21.4 (CH_2-4), 17.6 and 17.5 ($CH_2CH_2CH_3$), 14.9 and 14.8 ($COOCH_2CH_3$), 14.4 ($CH_2CH_2CH_3$) ppm. Anal. calcd for $C_{12}H_{12}O_3$: C 67.26; H 10.35. Found: C 67.33; H 10.29.

4.9.5. Diastereomeric mixture of *trans*- and *cis*-(±)-2-benzyl-2-carboethoxy-cyclohexanols (6h) and (7h). Prepared from reduction of (**3h**); IR (film): ν O–H 3479, ν C=C–H 3063 and 3028, ν C–H 2979 and 2918, ν C=O 1747, ν C–O 1180 cm^{-1}; ^1H NMR (200 MHz): 1.07 (t, 0.9H, J=7.1 Hz, $COOCH_2CH_3$), 1.21 (t, 2.1H, J=7.1 Hz, $COOCH_2CH_3$), 1.27–2.20 (m, 5H $O{=}CCHHCH_2CH_2CH_2$), 2.37–2.47 (m, 3H, $O{=}CCHHCH_2CHCH_2$), 2.85 (d, 0.5H, J=14.4 Hz, PhCHH), 3.06 (s, 1.5H, PhCHH), 3.96–4.19 (m, 2H, $COOCH_2CH_3$), 7.08–7.12 (m, 2H, *meta*Ar-H), 7.10–7.30 (m, 5H, C_6H_5) ppm; ^{13}C NMR (50 MHz): 177.3 ($COOCH_2CH_3$), 130.8 (*ipso*Ar), 130.1 (*ortho*Ar), 128.1 (*meta*Ar), 126.7 and 126.5 (*para*Ar), 73.7 and 71.4 (CHOH), 60.7 and 60.6 ($COOCH_2CH_3$), 53.0 (C-2), 42.4 ($-CH_2Ph$), 32.9 and 31.8 (CH_2-6), 29.8 and 28.7 (CH_2-3), 24.5 and 22.9 (CH_2-5), 22.4 and 21.8 (CH_2-4), 14.1 and 14.0 ($COOCH_2CH_3$) ppm. Anal. calcd for $C_{16}H_{22}O_3$: C 73.25; H 8.45. Found: C 73.18; H 8.37.

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References and notes

1. Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem Rev.* **1995**, *95*, 1065–1114.
2. (a) Ghosh, A. K.; Thompson, W. J.; Munson, P. M.; Liu, W.; Huff, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 83–88. (b) Cossy, J.; Ibhi, S.; Kahn, P.; Tacchini, L. *Tetrahedron Lett.* **1995**, *36*, 7877–7880. (c) Keppens, M.; De Kimpe, M. *J. Org. Chem.* **1995**, *60*, 3916–3918.
3. Fraga, C. A. M.; Barreiro, E. J. *Chirality* **1996**, *8*, 305–310.
4. Fraga, C. A. M.; Barreiro, E. J.; da Silva, E. F.; dos Santos, A. R.; Ramos, M. C. K. V.; de Aquino Neto, F. R. *Chirality* **1997**, *9*, 321–324.
5. Fraga, C. A. M.; Barreiro, E. J. *Synth. Commun.* **1995**, *25*, 1133–1144.
6. Sant'Anna, C. M. R.; Alencastro, R. B.; Barreiro, E. J.; Fraga, C. A. *J. Mol. Struct. (Theochem)* **1995**, *340*, 193–199.
7. Teixeira, L. H. P.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Commun.* **1997**, *27*, 3241–3257.
8. Teixeira, L. H. P.; de Souza, M. C. B. V.; Ramos, M. C. K. V.; de Aquino Neto, F. R.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Commun.* **2002**, *32*, 505–526.
9. Peçanha, E. P.; Fraga, C. A. M.; Barreiro, E. J. *Heterocycles* **1998**, *48*, 2621–2630.
10. Barreiro, E. J.; Fraga, C. A. M.; Peçanha, E. P. *Trends Heterocycl. Chem.* **1999**, *6*, 37–48.
11. Santos, M. R. L.; Barreiro, E. J.; Braz-Filho, R.; Fraga, C. A. M. *Tetrahedron* **2000**, *56*, 5289–5295.
12. Peçanha, E. P.; Verli, H.; Rodrigues, C. R.; Barreiro, E. J.; Fraga, C. A. M. *Tetrahderon Lett.* **2002**, *43*, 1607–1611.
13. Fraga, C. A. M.; Miranda, A. L. P.; Barreiro, E. J. *Chem. Pharm. Bull.* **1996**, *44*, 2157–2161.
14. Peçanha, E. P.; Fraga, C. A. M.; de Sant'anna, C. M. R.; Miranda, A. L. P.; Barreiro, E. J. *Il Farmaco.* **1998**, *53*, 327–336.
15. Peçanha, E. P.; Fraga, C. A. M.; Barreiro, E. J. *Quím. Nova* **1997**, *20*, 435–437.
16. Purchased from Aldrich Co, Milwaukee, USA.
17. Micovic, V. M. *Organic synthesis*; 1943; Collect. Vol. 2. pp 264–265.
18. Araújo, A. C. V.; Almeida, F. V.; Bieber, L. W. *Quím. Nova* **1996**, *19*, 79–81.
19. Barco, A.; Benetti, S.; Pollini, G. P. *Synthesis* **1973**, 316.
20. Ramos, M. C. K. V.; Silva, E. F.; Aquino Neto, F. R.; Peçanha, E. P.; Rodrigues, C. R.; Barreiro, E. J.; Fraga, C. A. M. *Anal. Chem.* **2000**, *72*, 3056–3062.
21. Ramos, M. C. K. V.; Teixeira, L. H. P.; Aquino Neto, F. R.;

Barreiro, E. J.; Rodrigues, C. R.; Fraga, C. A. M. *J. Chromatogr. A* **2003**, *985*, 321–331.
22. Frater, G. *Helv. Chim. Acta* **1980**, *63*, 1383.
23. (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220. (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221–264. (c) Stewart, J. J. P. *J. Comput. Chem.* **1991**, *12*, 320–341.
24. Hehre, W. J.; Shusterman, A. J.; Nelson, J. E. The molecular modeling workbook for organic chemistry; Wavefunction: Irvine, 1998; p 307.
25. Höltje, H.-D.; Folkers, G. *Molecular modeling. Basic principles and applications*; Manhold, R., Kubinyi, H., Timmerman, H., Eds.; VCH: Weinheim, 1997; Vol. 5, p 194.
26. Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449–462.
27. Dalla, V.; Fonken, G. J.; Noyce, D. S. *Tetrahedron Lett.* **1999**, *40*, 5193–5196.
28. Koskinen, A. M. P.; Koskinen, T. M. *Tetrahedron Lett.* **1993**, *34*, 6765–6768.
29. (a) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1993**, *49*, 11169–11182. (b) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1995**, *51*, 679–686.
30. (a) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641–1644. (b) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *22*, 4723–4726.
31. Brown, H. C.; Krishanamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159–7161.
32. Raber, D.; Guida, W. C. *J. Org. Chem.* **1976**, *41*, 690–696.
33. Akita, H.; Chen, C. Y.; Uchida, K. *Tetrahedron: Asymmetry* **1995**, 2131–2134.
34. Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377–1386.
35. Cimarelli, C.; Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2555–2563.
36. Hamed, O.; El-Qisairi, A.; Henry, P. M. *J. Org. Chem.* **2001**, *66*, 180–185.
37. Tanabe, Y. *Bull. Chem. Soc. Jpn* **1989**, *62*, 1917–1924.
38. Pei, T.; Widenhoefer, R. A. *Chem. Commun.* **2002**, 650–651, see supplementary data.
39. Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144–4153.
40. Ando, K.; Takemasa, Y.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 1579–1588.
41. C-Alkylated derivative was obtained in the yields described here after its chromatographic separation from a mixture with the corresponding O-alkylated derivative (10%), by using a silica gel column and hexanes/AcOEt (from 99:1 to 95:5) as eluent.
42. Crabbé, P.; Garcia, G. A.; Ríus, C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 810–816.