Pergamon

Tetrahedron 57 (2001) 2155–2170

TETRAHEDRON

Copper(I) mediated highly diastereoselective conjugate addition of Grignard reagents to functionalised cycloalkenols: a general and efficient route for the stereoselective synthesis of 5- and 6-membered ring trisubstituted cycloalkanols

Valéry Dambrin,[a] Monique Villiéras,[a] Pascal Janvier,[a] Loïc Toupet,[b] Hassen Amri,[c] Jacques Lebreton[a] and Jean Villiéras[a,*]

[a]*Laboratoire de Synthèse Organique, UMR CNRS 6513, Faculté des Sciences et Techniques, 2, rue de la Houssinière, BP 92208-F44322 Nantes Cedex 03, France*

[b]*Groupe Matière Condensée et Matériaux, URA CNRS 804, Université de Rennes 1, Campus de Beaulieu, F-35042 Rennes, France*

[c]*Laboratoire de Chimie Organique, Faculté des Sciences, Campus Universitaire, 1060 Tunis, Tunisie*

Received 20 October 2000; revised 18 December 2000; accepted 9 January 2001

Abstract—The conjugate addition of magnesium cuprates to various 2-silyloxycyclopentene and 2-silyloxycyclohexene carboxylates leads diastereoselectively to related *syn–anti* cyclopentanols and cyclohexanols in fair overall yields. The β-elimination occurring with free hydroxylic derivatives is also partially or totally avoided by concomitant in situ trapping of the generated enolates. Attempts to rationalise our results are discussed.

1. Introduction

Conjugate addition of organocopper reagents and related Copper(I) mediated addition of Grignard reagents has proved to be highly effective for C–C bond formation.[1] The ability of such species to carry out the β-alkylation of α,β-unsaturated carbonyl derivatives in a stereoselective way has also been extensively used as a key-step in numerous syntheses of natural products and has been widely reviewed.[2]

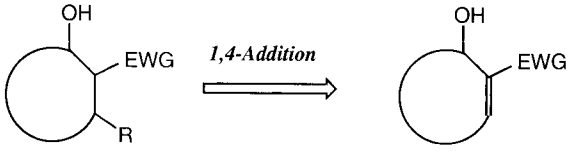
We have focused our attention on the conjugate addition reaction of magnesium organocuprates to hydroxymethylacrylates and to related cyclic analogues (Scheme 1). These building blocks seem particularly attractive in the field of bioactive and/or natural compound synthesis (e.g. prostanoids, iridoids),[3] as previously reported.[4]

Although easily performed on an acyclic substrate[5] **1** *without any protection of the hydroxylic moiety*, the conjugate addition of excess (3.5 equiv.) bromomagnesium di-*n*-butylcuprate exclusively leads to the formation of the S_N2' like by-products **5** and **6** when performed on **3** and **4**, respectively (Scheme 2), probably via an addition/β-elimination process.

A few years ago, this S_N2' process was applied to the synthesis of various cyclopentenes and cyclohexenes starting from *O*-acetyl derivatives.[4] In the present paper, we report our results concerning the method we have developed to prevent elimination. It leads to stereoselective preparations of trisubstituted 5- and 6-membered ring cycloalkanols.

2. Chemoselectivity in conjugate addition reactions to cyclopentene and cyclohexene carboxylates

First, we have studied the reaction with 5-membered ring cycloalkenols bearing an ester moiety as electron withdrawing group. Several attempts were carried out starting from *O*-protected derivatives **7** in order to prevent the



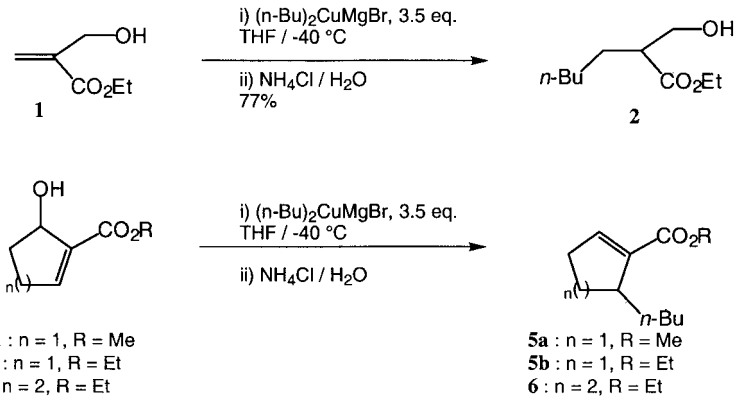
EWG = Electron Withdrawing Group
R = Alkyl group

Scheme 1.

Keywords: conjugate addition; Michaël addition; Grignard reagents; organocuprates; β-elimination; S_N2'; diastereoselectivity.

* Corresponding author. Fax: +33-2-51-12-54-02; e-mail: jean.villieras@chimie.univ-nantes.fr

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00044-8



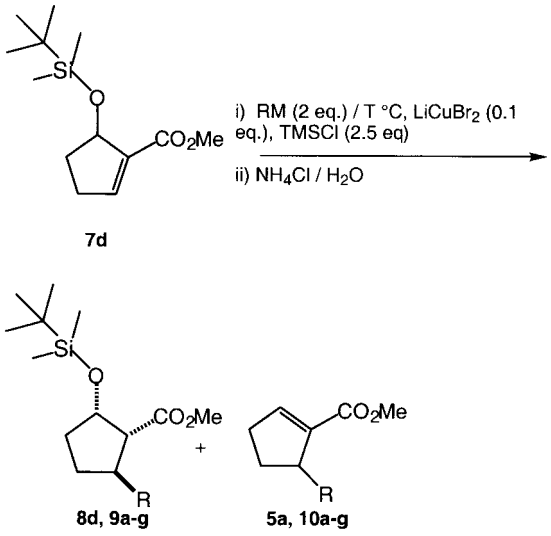
Scheme 2.

β-elimination of the intermediate OM group resulting from the initial deprotonation step (Table 1). The reactions were performed with halomagnesium di-dialkylcuprate, with or without chlorotrimethylsilane[6] (TMSCl) (Scheme 3).

The reaction was first investigated with *n*-butyl organometallic reagents. As shown in Table 1, the protection of the alcohol moiety with various groups does not, itself, avoid the β-elimination, whereas, in the presence of excess TMSCl (2.5 equiv.), the *O*-silylated 1,4-adducts **8** are obtained as major products. Indeed, increasing the bulkiness of the starting *O*-silyl derivatives **7** greatly favours the formation of **8**. Furthermore, the use of a catalytic amount of copper (I) salt seems to be quite compatible with our method since no loss of chemoselectivity (addition vs β-elimination) is observed.

The use of HMPA (as cosolvent) or more electrophilic halosilanes (TMSI, TMSBr, TMSOTf) in order to favour silylation had no influence.

The catalytic conditions were applied with various Grignard reagents on cyclopentene **7d**. The $SiMe_2t$-Bu (TBDMS) protecting group has been extensively used in our method and preferred to the more hindered and stable $SiPh_2t$-Bu (TBDPS), since epimerisation problems appeared during the last desilylation step[12] from OTBDPS derivatives.



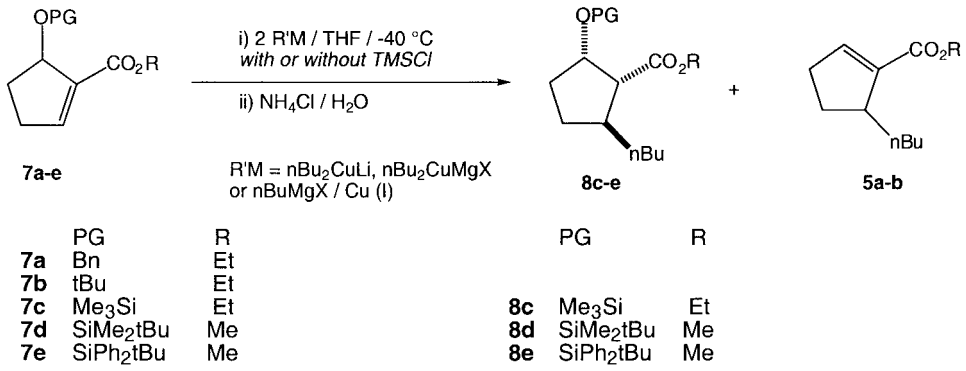
The scope and limitations of this reaction are illustrated in Table 2.

For primary alkyl chains including functionalized ones, the addition/β-elimination ratio increases up to 90:10 when the reaction was run on **7d**, as shown by ^{1}H NMR.

Table 1. Organocuprates and copper (I) mediated conjugate addition to *O*-protected cyclopentenes **7a–e**

Cyclopentenes **7**	PG	Reaction conditions		Addition/elimination[a]
7a	Bn[7]	$(n\text{-Bu})_2$CuMgBr, 2 equiv.	No TMSCl	No reaction[b]
7b	*t*-Bu[7]	$(n\text{-Bu})_2$CuMgBr, 2 equiv.	No TMSC	**7b/5a**=45:55
7c	$SiMe_3$[8]	$(n\text{-Bu})_2$CuMgBr, 2 equiv.	No TMSC	0:100
7d	$SiMe_2t$-Bu[8]	$(n\text{-Bu})_2$CuMgBr, 2 equiv.	No TMSC	0:100
7d	$SiMe_2t$-Bu[8]	$(n\text{-Bu})_2$CuLi, 2 equiv.	No TMSC	0:100
7e	$SiPh_2t$-Bu[8]	$(n\text{-Bu})_2$CuMgBr, 2 equiv.	No TMSC	0:100
7e	$SiPh_2t$-Bu[8]	$(n\text{-Bu})_2$CuLi, 2 equiv.	No TMSC	0:100
7c	$SiMe_3$[8]	$(n\text{-Bu})_2$CuMgBr, 2 equiv.	TMSCl 2.5 equiv.	**8c/5a**=75:25
7c	$SiMe_3$[8]	*n*-BuMgBr, 2 equiv. $LiCuBr_2$, 2 equiv.[c]	TMSCl 2.5 equiv.	**8c/5a**=75:25
7d	$SiMe_2t$-Bu[8]	*n*-BuMgBr, 2 equiv. $LiCuBr_2$, 2 equiv.[c]	TMSCl 2.5 equiv.	**8d/5a**=90:10
7e	$SiPh_2t$-Bu[8]	*n*-BuMgBr, 2 equiv. $LiCuBr_2$, 2 equiv.[c]	TMSCl 2.5 equiv.	**8e/5a**=95:5

[a] Estimated by ^{1}H NMR.
[b] Cyclopentene **7a** was totally recovered.
[c] Used as a previously prepared 1N solution in THF.

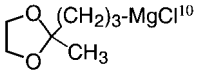
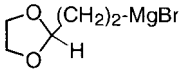


	PG	R
7a	Bn	Et
7b	tBu	Et
7c	Me_3Si	Et
7d	$SiMe_2tBu$	Me
7e	$SiPh_2tBu$	Me

	PG	R
8c	Me_3Si	Et
8d	$SiMe_2tBu$	Me
8e	$SiPh_2tBu$	Me

Scheme 3.

Table 2. Copper(I) mediated addition of Grignard reagents to cyclopentene **7d**

RM	*T* °C	Addition (%)	Elimination (%)[a]
MeMgBr	−35	**9a** (90)	**10a** (10)
EtMgBr	−35	**9b** (90)	**10b** (10)
n-BuMgBr	−35	**8d** (90)	**5a** (10)
i-PrMgCl	−10	**9c** (68)	**10c** (32)
t-BuMgCl	−10	**9d** (70)	**10d** (30)
$EtO(H_3C)CH–O–(CH_2)_5–MgCl$[9]	−35	**9e** (90)	**10e** (10)
	−35	**9f** (90)	**10f** (10)
	−35	**9g** (90)	**10g** (10)
Aryl and vinyl Grignard reagent		No reaction	
$EtO_2C–(CH_2)_3–Zn–I$[11]	rt	No reaction	

[a] Estimated by ^1H NMR.

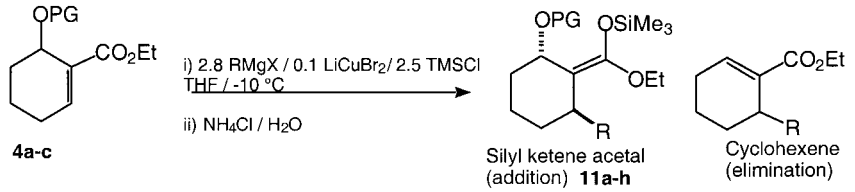
With secondary (*i*-Pr) and tertiary (*t*-Bu) alkyl chains, the reaction gives a ca. 1:1 mixture of addition/elimination compounds when performed at −40°C or at a lower temperature. Raising the temperature to −10°C leads to ca. 70:30 ratio of **9c/10e** or **9d/10d**, respectively, probably by favouring the *O*-silylation kinetics. From these results, it is clear that the chemoselectivity of such a reaction must be discussed in terms of concurrent kinetics of β-elimination and *O*-silylation processes.

This reaction has been applied with success to various protected functional (alcohol, ketone, aldehyde) primary Grignard reagents, leading to the formation of polyfunctional compounds of high synthetic potential. However, it always failed with aryl and vinyl organomagnesium reagents.

With *O*-silylcyclohexene carboxylates **4a–c**, no reaction occurred when carried out under the same catalytic conditions (*n*-BuMgBr (2 equiv.) in the presence of $LiCuBr_2$ (0.1 equiv.) and TMSCl (2.5 equiv.) at −40°C). In this case, the reaction must be performed at −10°C, using a larger excess (2.8 equiv.) of Grignard reagent. It leads to *the exclusive formation of the conjugate addition products*, except with the less bulky **4a** (20% elimination, Scheme 4), as silyl ketene acetals **11**, which are quite stable under hydrolysis conditions of the Grignard reaction (NH_4Cl/H_2O) (Table 3). Under these conditions, no cyclohexene carboxylate **4** is recovered. In the absence of TMSCl, only the elimination product is obtained.

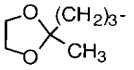
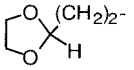
As noted for cyclopentene analogues, the protection of the hydroxyl group as a bulky silyl ether and the presence of an excess TMSCl to trap the intermediate enolate are required to improve the formation of **11**, although no β-elimination occurs with OTBDMS or OTBDPS derivatives in this case. The particular stability of compounds **11** can obviously be related to these results and it can be concluded that *exo*-cyclic silyl ketene acetals are much more stable in the cyclohexane than in the cyclopentane series.

Besides, with regard to cyclopentene **3**, the lowered reactivity

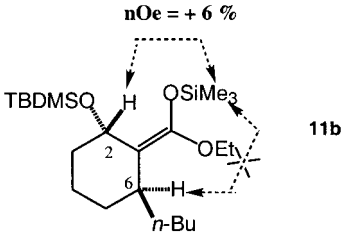


Scheme 4.

Table 3. $LiCuBr_2$ mediated conjugate addition of Grignard reagents to cyclohexenes **4a–c**

Cyclohexenes **4**	PG	R	Addition/elimination	Silyl ketene acetal
4a	$SiMe_3$	*n*-Bu	80:20[a]	**11a**
4b	$SiMe_2$*t*-Bu	*n*-Bu	0:100[b]	–
4b	$SiMe_2$*t*-Bu	*n*-Bu	100:0	**11b**
4c	$SiPh_2$*t*-Bu	*n*-Bu	100:0	**11c**
4b	$SiMe_2$*t*-Bu	Me	No reaction	–
4b	$SiMe_2$*t*-Bu	Et	100:0	**11d**
4b	$SiMe_2$*t*-Bu	*i*-Pr	100:0	**11e**
4b	$SiMe_2$*t*-Bu	*t*-Bu	No reaction	–
4b	$SiMe_2$*t*-Bu	$EtO(CH_3)CH–O–(CH_2)_5–$	100:0	**11f**
4b	$SiMe_2$*t*-Bu		100:0	**11g**
4b	$SiMe_2$*t*-Bu		100:0	**11h**

[a] Estimated by ^1H NMR.
[b] Attempt performed without TMSCl.



11b

Scheme 5.

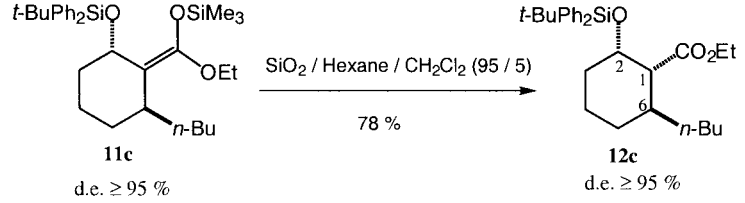
of cyclohexene **4** (harder conditions of reaction and no reaction with methyl and *t*-butyl reagents) could be considered as the result of an initial lower cycle strain and a larger steric hindrance in the initial cyclohexene ring.

2.1. Configuration determination of 11b

In a continuation of the pioneering work of C. Ainsworth et al.[13] our own results seem to be the first example of stereoselective synthesis of disubstituted cyclohexylidene silyl ketene acetal (one single diastereoisomer obtained, according to ^1H and ^{13}C NMR). Apart from the relative configuration of $H–C_2$ and $H–C_6$ that will be discussed in the following part of this paper, the conformation of **11b** has been established by performing nOe experiments in ^1H NMR at 400 MHz. Several measurements have shown a positive and mutual effect (+6%) between $H–C_2$ and the protons of $SiMe_3$, whereas no spatial interaction have been measured between the latter and $H–C_6$ (Scheme 5). These observations lead us to assign the exclusive (*Z*) configuration implying the conjugate addition reaction to occur only on the *s-trans* form of the substrate.

3. Steric course and diastereoselectivity of the reactions

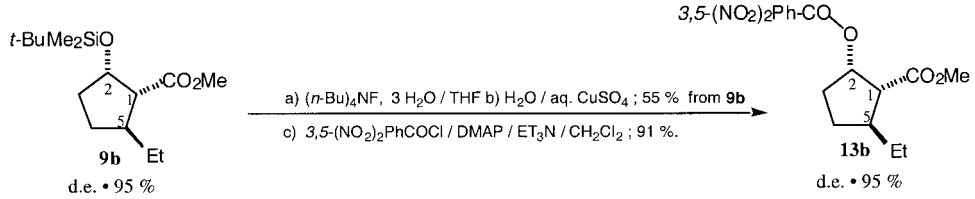
In addition to the observed chemoselectivity with *O*-silyl derivatives **7c–d** and **4b–c**, we have found that the corresponding 1,4-adducts **9** and **11** were obtained with high diastereoselectivities, since no splitting of the signals were observed, according to ^1H (400 MHz) and ^{13}C (100 MHz) NMR. Consequently, it can be deduced that conjugate addition reactions (and hydrolysis in the case of **9**) lead, in all cases, to one single diastereoisomer in the conditions described. Indeed, in ^1H NMR, β-silyloxyesters **9** have exhibited an explicit dd ($^3J \approx 5$ and 10 Hz) around 2.2 ppm for $H–C_1$ whereas, after silica gel chromatography using hexane/CH_2Cl_2 (95:5), **11c** collapsed to ester **12c** (one single diastereoisomer) in 78% yield (Scheme 6), which



11c
d.e. ≥ 95 %

12c
d.e. ≥ 95 %

Scheme 6.

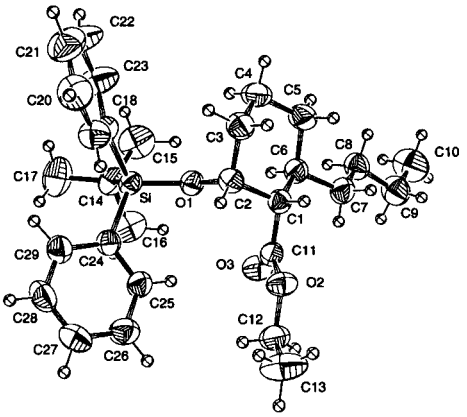


d.e. • 95 %

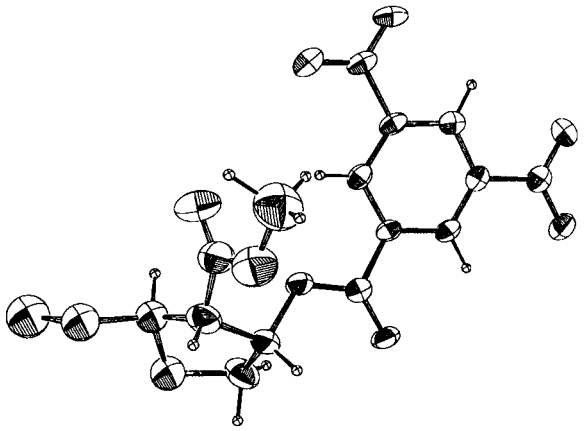
d.e. • 95 %

Scheme 7.

ORTEP of **12b**



ORTEP of **13b**



Scheme 8.

shows similar spectral data, e.g. dd ($^3J \approx 3$ and 10 Hz) around 2.15 ppm for H–C_1.

While **12c** could easily be crystallised as white needles, efforts to obtain a 5-membered crystallised analogue were unsuccessfull. Nevertheless, this problem has been bypassed by the preparation of a 3,5-dinitrobenzoyl ester **13b**, as white needles, starting from **9b** (R=Et), after desilylation[14] and DMAP-mediated esterification with 3,5-dinitrobenzoyl chloride (Scheme 7).

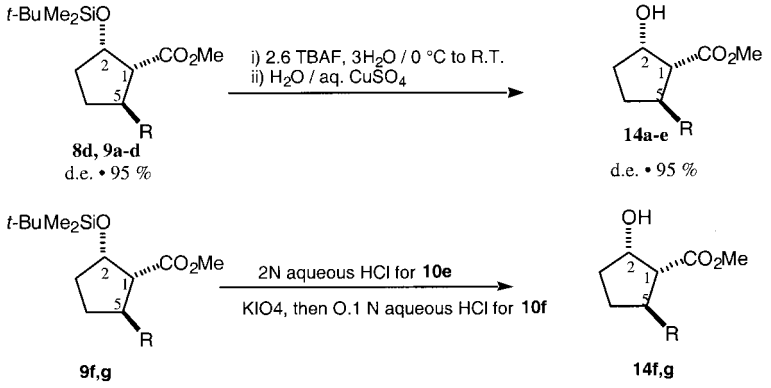
X-Ray analyses of compounds **12b** and **13b** have finally allowed the exclusive relative configuration of H–C_1–C_2–H (*syn*) and H–C_1–C_5–H (*anti*) (or H–C_1–C_6–H (*anti*)) to be established unambiguously (Scheme 8).

According to the absence of significant modification or splitting of the signals (particularly concerning H–C_1) in ^{1}H NMR along the different subsequent steps, that configuration could be related to corresponding cyclopentanes **9** and to cyclohexanes **11** (vide infra). Desilylation with

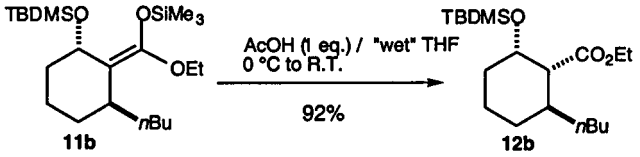
Table 4. Diastereoselective synthesis of cyclopentanols carboxylates

silylether	Alcohol **14**	R	Yield (%)[a]	d.e. (%)[b]
9a	**a**	Me^{-c}	50	≥95
9b	**b**	Et^{-c}	55	≥95
8d	**c**	*n*-Bu^{-c}	77	≥95
9c	**d**	*i*-Pr^{-c}	53	≥95
9d	**e**	*t*-Bu^{-c}	62	≥95
9e	**f**	HO–$(CH_2)_5$–$^{-d15}$	69	≥95
9f	**g**	H_3C–C(O)–$(CH_2)_3$–$^{-d16}$	75	≥95
9g	**h**	H–C(O)–$(CH_2)_2$–^{16}	[e]	≥95

[a] Overall isolated yield calculated from **7d**.
[b] Estimated by ^{1}H and ^{13}C NMR.
[c] Desilylation with TBAF.
[d] Desilylation in acidic medium.
[e] Degradation occurred during the deprotection step.



Scheme 9.



Scheme 10.

tetra-*n*-butylammonium fluoride[14] (TBAF) of **8d** and **9a–d** compounds or in acidic medium[15,16] for **9e–g** yielded *syn–anti* alcohols in moderate-to-good overall yields and with excellent diastereoselectivities (d.e.≥95%) (Table 4, Scheme 9).

Generating the cyclohexanols **15** from the corresponding silylketene acetals **11** has proved to be more tricky, as all attempts to chromatography compounds **11b,d–g** over silica gel have led to the formation of the corresponding β-elimination compounds. Neither the presence of triethylamine, nor the use of basic alumina led to a successful purification without such problems. We next decided to perform the silylketene acetal hydrolysis by other ways. Among the methods tried for this purpose (various organic and inorganic acids, TBAF, Lewis acids,…), finally, glacial acetic acid (1 equiv.) in 'wet' THF smoothly afforded *syn–anti* β-silyloxyesters **12** without the formation of β-elimination side-product (Scheme 10).

As described for 5-membered ring analogues, the last deprotection step on **12** was accomplished in acidic medium[15,16] for β-silyloxyester bearing a functionalised chain or with TBAF[14] for others. Although this latter method led to a partial epimerization of the C_1, such a drawback has been easily solved by careful chromatography, affording pure single diastereoisomers in good overall yields (Scheme 11, Table 5). The cyclohexanols carboxylates **15d–g** were obtained without isolation of the corresponding intermediate **12**.

4. Conjugate addition reactions on a β,β′-disubstituted acyclic analogue

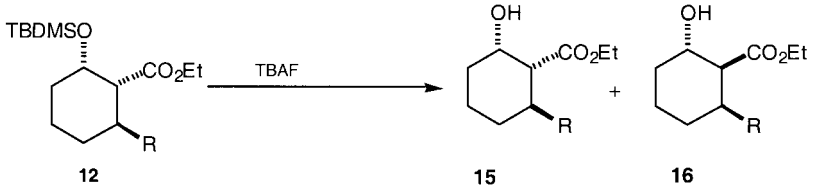
We have also explored the behaviour of a β,β′-disubstituted acyclic analogue of cyclopentenes **3** and cyclohexenes **4** in conjugate addition reactions. The compound **17b** was selectively prepared by a known procedure[17] (Scheme 12) as 3:97 *E*/*Z* mixture.

Conjugate addition of excess (3.5 equiv.) bromomagnesium di-*n*-butyl cuprate was performed on **17b**, affording exclusively (*E*) ethyl 4-methyl-oct-2-ene-3-carboxylate **18** in a 66% yield, while using our improved procedure with **19** finally yielded the desired β-hydroxy ester **20** as a ca. 5:3:2 mixture of isomers (Scheme 13).

5. Discussion

5.1. Chemoselectivity and reactivity

As described in the last example (vide supra, Scheme 13),

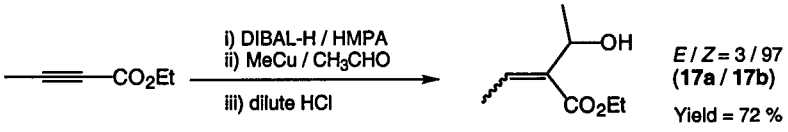


Scheme 11.

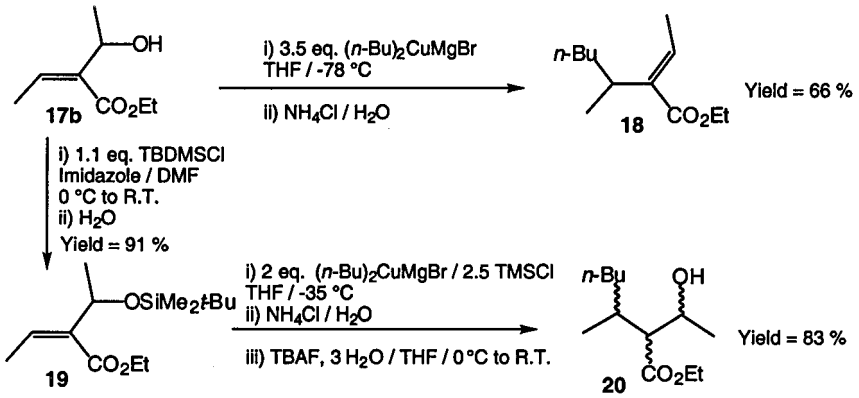
Table 5. Diastereoselective synthesis of cyclohexanols carboxylates

R	Major epimer	Minor epimer	**15/16**	Yield (%)[a]	d.e. (%)
n-Bu	**15b**	**16b**	95:5	70	90
Et	**15d**	**16d**	88:12	84	76
i-Pr	**15e**	**16e**	92:8	64	84
HO–$(CH_2)_5$–	**15f**[15]	–[b]	–	67	≥95[c]
H_3C–C(O)–$(CH_2)_3$–	**15g**[15]	–[b]	–	65	≥95[c]
H–C(O)–$(CH_2)_2$–	**15h**[16,d]	–	–	96[e]	≥95[c]

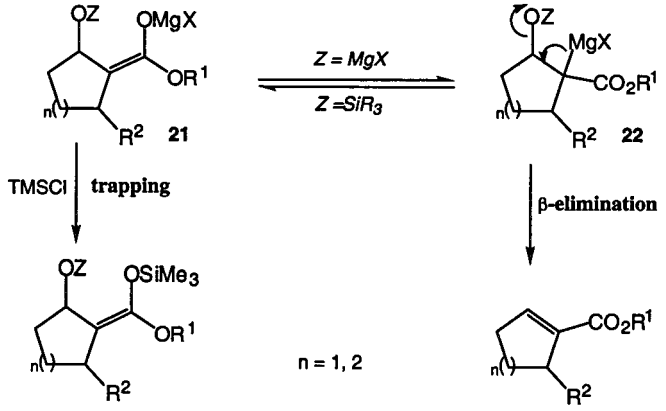
[a] Overall isolated yield calculated from **4b**.
[b] No epimerization occurs, since deprotection was performed in acidic medium.
[c] Estimated by ^1H and ^{13}C NMR.
[d] The hydrolysis of the ketene acetal and the dioxolane moieties were performed simultaneously using the (HCl/dioxan/KIO_4) procedure and gave crude β-silyloxyester **15h** which is unstable.
[e] Crude yield.



Scheme 12.



Scheme 13.



Scheme 14.

the S_N2' by-product formation seems to be a quite general case when performing conjugate addition of magnesium organocuprates on β-substituted 2-hydroxyalk-1-ene-1-carboxylates.

For the cuprate (or Grignard reagent) addition, initial deprotonation of unprotected substrates seems likely to happen, resulting in the formation of a potentially leaving group, e.g. $XMgO^-$. Further, organometallic reagent addition leads to the conjugate addition reaction itself, affording enolate **21** that stands in balance with the related carbeniate **22**, responsible of the β-elimination (Scheme 14).

In the case of **7c–e** or **4a–c**, the bulky *O*-silyl moiety tends to shift this equilibrium in the direction of the preferential formation of **21**, due to a rate-lowering effect implied by strong steric interactions. It may also be considered that bulky *O*-silyl derivatives prevent **22** from reaching a conformation, favourable to a β-elimination favourable conformation (*syn* or *anti*).

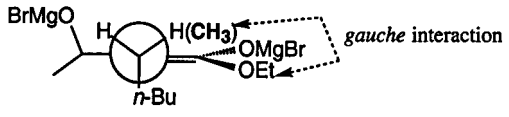
Consequently, the **21–22** tautomeric balance rate is greatly slowed down and subsequent rate limiting trapping with TMSCl can more easily occur (Scheme 14).

From this point of view, the absence of β-elimination in 6-membered ring series (compared with 5-membered ones) can be regarded as resulting from global, a lowering of steric strains leading to a more stable enolate form and enabling an easier trapping.

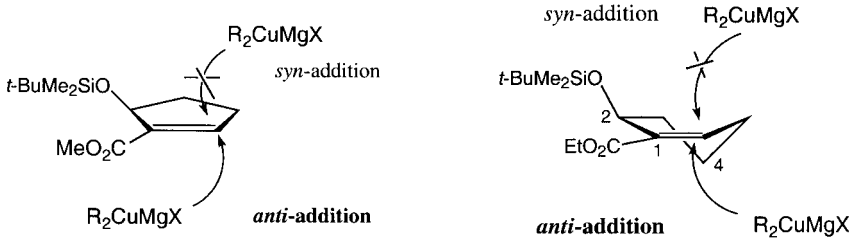
Interestingly, a comparison between **1** and **17b** leads us to the conclusion that the β-substitution of the alkene is of great influence on the global course of the conjugate addition reaction.

In fact, a methyl group (Van der Waals radius=2 Å) seems to involve strong enough gauche interaction so as to disfavour the formation of the enolate, whereas an hydrogen atom (Van der Waals radius=1.2 Å) does not induce this kind of allylic strain (Scheme 15).

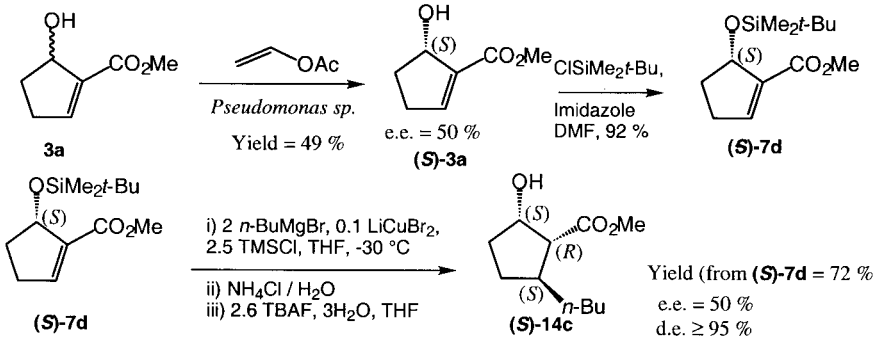
The exclusive (*Z*) configuration of the silylketene acetal **11** clearly demonstrates that *s-trans* is the exclusive reactive conformation of the substrate. In fact, calculations performed with AM-1 program on the two conformations of **4b** have shown virtually no ΔH_f difference. On the other hand, in both cases, the α,β-unsaturated carbonyl systems is found not to be planar in the initial state, allowing 66 and 140° dihedral angles, respectively, for *s-cis* **4b** and *s-trans* **4b**. In addition to those considerations, we found that the lowered LUMO energy level of **7d**, compared with the one of **4b** (0.10152 eV vs 0.19865 eV), is compatible with our experimental observations that 5-membered ring



Scheme 15.



Scheme 16.



Scheme 17.

cycloalkenols appear to be more reactive than 6-membered ring analogues.

5.2. Diastereoselectivity

From the global course of the reaction, both cuprate addition and silylketene acetal hydrolysis have proved to be highly stereoselective steps.

Quite unexpected results from the hydrolysis reaction remain unclear, while selectivity in cuprate addition can readily be explained. In the case of almost planar[18] cyclopentene carboxylates **7c**–**e**, initial attack occurs by the less hindered face of the substrates. Hence, the anti adducts (with regard to TBDMSO) are exclusively obtained (Scheme 16).

Diastereoselectivity in cuprate addition to 6-membered ring analogues seems to be less predictable, since increasing the size of the ring unarguably lead to a greater conformational freedom. In our special case, the bulky *t*-butyldimethylsilyloxy group tends to be in a pseudoaxial position in order to avoid strong allylic strain[19] with the ester moiety (Scheme 16). This conformation allows the cycle to behave like the cyclopentene analogue in conjugate addition reaction, involving 1,3-stereocontrol leading to kinetic axial *anti* alkylation. However, the below-situated C_4 methylene group can undergo steric interactions, which could explain the harder conditions required for the conjugate addition (compared to the cyclopentene analogue) and the impossibility to add the bulky *t*-butyl group (see Tables 2 and 3).

Concerning the *anti* hydrolysis (with regard to TBDMSO) of the related silylketene acetals, 1,2-stereocontrol from the *O*-silyl group may also reasonably be assumed.

6. Conclusion

In the present paper, we have described a new route to functionalised 5- and 6-membered ring cycloalkanols substituted on three contiguous atoms leading to total stereocontrol in the formation of two asymmetric centres in high overall yields. This efficient and rapid methodology also induces high chemoselectivity by enabling the minimisation or the absence of the competitive S_N2' side-reaction.

The use of a copper (I) catalyst and the ability to add new functions with Grignard reagents of choice seems to be particularly attractive in the field of multi-step synthesis.

Furthermore, preliminary experiments have shown a total compatibility while starting from enantioenriched substrate (*S*)-**3a**[20] since initial e.e. and absolute configuration[21] was recovered on (*S*)-**14c** (Scheme 17).

7. Experimental

7.1. General

All reactions involving anhydrous conditions were conducted in dry glassware under a positive argon (oxygen-free) atmosphere and monitored by TLC (Kieselgel $60F_{254}$ MERCK Art. 5735 aluminium sheets) and/or GC unless otherwise indicated. Solvents were distilled under nitrogen immediately prior to use. THF and ethyl ether were dried by distillation from sodium benzophenone ketyl, triethylamine and methylene chloride from calcium hydride, ethyl acetate from phosphorous pentoxide, and methanol from magnesium methoxide. *n*-Hexane was stirred with conc. sulphuric acid for a period of two days, treated with

potassium carbonate, washed with brine and dried over magnesium sulphate before distillation. Grignard and organolithium reagents except MeMgBr, purchased from Aldrich®, were prepared by known procedures and stored under argon atmosphere. They were titrated prior to use, e.g. with a 1 M solution of benzyl alcohol in toluene and 2,2′-biquinoline (Grignard reagents) or *o*-phenantrolin (organolithium reagents) as indicators.

NMR spectra were recorded on a BRUKER AC200 (^{1}H: 200 MHz and ^{13}C (fully decoupled): 50 MHz) or a BRUKER ARX400 (^{1}H: 400 MHz and ^{13}C (fully decoupled): 100 MHz) apparatus. The chemical shifts are given in ppm using tetramethylsilane (TMS) as internal standard. The coupling constants (*J*) are expressed in Hz, while the multiplicity of the signals are abreviated as s for singlet, d for doublet, dt for doublet of triplets, m for multiplet. IR spectra were recorded neat in KBr cells on a BRUKER IFS 45 WHR Fourier Transform Spectrometer. The wave numbers (ν) are given in cm^{-1}. GC-MS spectra were obtained on a HP 5890 chromatograph fitted with HP 1 (0.33 μm×12 m) capillary column and to a HP 5889A quadripolar spectrometer in electronic impact (70 ev) or in chemical ionization (500 ev) with NH_3 gas. The fragmentation peaks are given in relative intensity (%). MERCK Geduran SI60 Art. 10832 silica gel was used for preparative scale chromatography and MERCK Geduran SI60 Art. 11567 for flash-chromatography. Gas chromatography were performed on a CARLO ERBA 4100 chromatograph fitted with a RLS 300 ALLTECH (polymethylphenylsiloxane) capillary column (25 μm×0.25 mm). The maximum temperature allowed was 280°C, the carrier gas was N_2 and the detection was made by FID. Melting points were determined on a RCH (C. Reichert) microscope equipped with a KOFLER heating system, and are uncorrected. Optical rotation values were measured in a 100 mm cell on a Perkin–Elmer 341 polarimeter under Na lamp radiation. X-Ray analyses were performed by L. Toupet from the University of Rennes I (Groupe Matière Condensée et Matériaux, URA CNRS 804). The samples were studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatised Mo Kα radiation. Atomic scattering factors are from International Tables for X-ray Crystallography (1974). The calculations were performed on a Hewlett Packard 9000-710 for structure determination (Sheldrick, 1985) and on a Digital Micro VAX 3100 computer with the MOLEN package (Enraf-Nonius, 1990) for refinement and ORTEP calculations. Elemental analyses were performed at the 'Service Central des Analyses du CNRS', B.P. 22, 69390 VERNAISON (France). The samples were sent in sealed tubes.

7.2. Starting material syntheses

Cycloalkenols **3** and **4** as well as acrylate **1** were prepared according to the previously described procedure[22] improved in our laboratory.[5]

7.2.1. 5-Benzyloxy-cyclopent-1-enecarboxylic acid ethyl ester 7a[7]. To a solution of **3b** (1.42 g, 10 mmol, 1 equiv.) in hexane (20 mL), prepared benzyl-2,2,2-trichloroacetimidate (5.05 g, 20 mmol, 2 equiv.) and boron trifluoride diethyl etherate (200 μL, 1.6 mmol, 0.15 equiv.) were added. The mixture was stirred at rt for 20 min. before hydolysis with 20 mL of aqueous $NaHCO_3$ and extraction with diethyl ether. After removing the solvents, the 2,2,2-trichloroacetamide was precipitated with cold hexane and filtrated, the resulting solution was concentrated and the residue was purified by a Kugelrohr distillation. Colourless liquid (1.52 g, 62%), bp 50–75°C/0.1 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) d 7.35 (5H, m, aromatic ring), 6.95 (1H, td, *J*=2.6, 0.6 Hz), 5.2 (2H, s), 5.10 (1H, m), 4.2 (2H, q, *J*=7.2 Hz), 2.6 (1H, m), 2.4–2.2 (2H, m), 1.9 (1H, m), 1.3 (3H, t, *J*=7.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) d 164.2 (CO_2), 145.8, 136.1, 129.3 (Ar), 129.1 (2×Ar), 128.9 (Ar), 128.7 (Ar), 128.6 (Ar), 77.8, 61.5, 46.9, 32.0, 30.9. MS *m/z* (CI) 250 ($M-NH_4^+$), 233 ($M-H^+$). IR ν_{max} (thin film) 1734 (s, C=O), 1653 (s, C=C). Calculated for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.28; H, 7.25.

7.2.2. 5-*tert*-Butoxy-cyclopent-1-enecarboxylic acid ethyl ester 7b[7]. The title compound was prepared by the same procedure used for the synthesis of **7a** using *tert*-butyl-2,2,2-trichloroacetimidate, chromatographied with hexane/ethyl acetate (95:5). Colourless liquid (4.3 g, 92%). ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 6.9 (1H, td, *J*=2.48 Hz), 4.9 (1H, m), 4.18 (2H, qd, *J*=7.12, 5.3 Hz), 2.5 (1H, m), 2.2–1.8 (3H, m) 1.4 (9H, s), 1.15 (3H, t, *J*=7.12 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.6, 142.0, 137.8, 75.5, 60.5, 33.9, 31.9, 30.8, 28.4, 14.2. MS *m/z* (CI) 230 ($M-NH_4^+$), 213 ($M-H^+$). IR ν_{max} (thin film) 1732 (s, C=O), 1655 (s, C=C). Calculated for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.55; H, 9.32.

7.2.3. 5-(Trimethyl-silanyloxy)-cyclopent-1-enecarboxylic acid ethyl ester 7c. Typical *O*-silylation procedure: To a solution of **3b** (3.9 g, 25 mmol, 1 equiv.) and imidazole (2.12 g, 31.25 mmol, 1.25 equiv.) in dry *N*,*N*-dimethylformamide (20 mL) at 0°C chlorotrimethylsilane (TMSCl) (3.8 mL, 30 mmol, 1.2 equiv.) was slowly added. The reaction mixture was allowed to warm up to rt and stirred for an additional 24 h period. Then, supplementary TMSCl (30 mmol) was added to the mixture and stirred until completion (24 h). After hydrolysis with water (100 mL), extraction with ethyl ether, the combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvents in vacuo yielded **7c**, which was distillated under reduced pressure. Colourless liquid (4.02 g, 74%), bp 53–54°C/0.1 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 6.9 (1H, t, *J*=2.6 Hz), 5.0 (1H, m), 4.2 (2H, q, *J*=7.1 Hz), 2.8–2.6 (1H, m), 2.4–2.2 (2H, m), 1.9–1.7 (1H, m), 1.3 (3H, t, *J*=7.1 Hz), 0.14 (9H, s, Si*Me*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.3, 146.7, 138.8, 75.1, 60.3, 34.0, 30.8, 14.1, −0.1 ($SiMe_3$). MS *m/z* (rel. int., %) 213 (82), 185 (57), 75 (100). IR ν_{max} (thin film) 1719 (s, C=O), 1637 (C=C), 1065 (OSi). Calculated for $C_{11}H_{20}O_3Si$: C, 57.85; H. 8.83. Found: C, 57.82; H, 9.03.

7.2.4. 5-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enecarboxylic acid methyl ester 7d. The same procedure described for the preparation of **7c** was used with only 1.1 equiv. of dimethyl-*tert*-butylchlorosilane. Colourless liquid (10.35 g, 93%), bp 66–68°C/0.09 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 6.90 (1H, t, *J*=2.4 Hz), 5.05 (1H, m), 3.73 (3H, s), 2.8–2.5 (1H, m), 2.35 (1H, m), 2.3–2.1 (1H, m), 1.8 (1H, m), 0.88 (9H, s), 0.2 (3H, s),

0.1 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 147.2, 139.8, 76.6, 51.9, 35.2, 31.7, 26.7, 19.0, −4.0. MS *m/z* (rel. int., %) 199 (69), 171 (18), 89 (100), 75 (41), 73 (18), 65 (17), 59 (20). IR ν_{max} (thin film) 1726 (s, C=O), 1635 (s, C=C), 1069 (OSi). Calculated for $C_{13}H_{24}O_3Si$: C, 60.89; H, 9.43. Found: C, 60.71, H, 9.48.

7.2.5. 5-(*tert*-Butyl-diphenyl-silanyloxy)-cyclopent-1-enecarboxylic acid methyl ester 7e. The same procedure described for the preparation of **7d** was used with diphenyl-*tert*-butylchlorosilane affording crude *O*-silyl ether **7e** which was purified by chromatography on silica gel using Hexane/CH_2Cl_2=1:1 as eluent. Colourless visqueous oil (23.1 g, 69%). ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 7.7–7.4 (10H, m, Ar), 6.97 (1H, t, *J*=2.7 Hz), 5.13 (1H, m), 3.54 (3H, s), 2.7–2.5 (1H, m), 2.4–2.2 (1H, m), 2.0–1.8 (2H, m), 1.06 (9H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 147.0, 139.0, 135.9–127.4 (Ar), 76.4, 50.9, 34.0, 30.9, 26.9, 19.3. MS *m/z* (rel. int., %) 323 (100), 295 (36), 199 (27), 139 (89). IR ν_{max} (thin film) 3071 (Ar), 1721 (C=O), 1635 (C=C), 1258 (C–O). Calculated for $C_{23}H_{28}O_3Si$: C, 72.59; H, 7.42. Found: C, 7. 55; H, 7.23.

7.2.6. 6-(Trimethyl-silanyloxy)-cyclohex-1-enecarboxylic acid ethyl ester 4a. The same procedure described for the preparation of **7c** was used, yielding to *O*-silyl ether **4a**, which was purified by Kugelrohr distillation under reduced pressure. Colourless liquid (8.72 g, 72%), bp 80–100°C/4 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 7.0 (1, m), 4.5 (1H, m), 4.1 (2H, ABX_3 system), 2.35–1.30 (6H, m), 1.1 (3H, t, *J*=7.2 Hz), 0.15 (9H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.7, 142.1, 132.9, 62.6, 60.2, 31.5, 25.9, 17.5, 14.3, 0.4. MS *m/z* (rel. int., %) 242 (M, 1), 228 (17), 227 (100), 199 (49), 181 (41), 75 (66), 73 (35). IR ν_{max} (thin film) 1715 (s, C=O), 1646 (C=C), 1260 (C–O), 1060 (O–Si). Calculated for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.51; H, 9.37.

7.2.7. 6-(*tert*-Butyl-dimethyl-silanyloxy)-cyclohex-1-enecarboxylic acid ethyl ester 4b. The same procedure described for the preparation of **7d** was used, affording *O*-silyl ether **4b** which was distilled under reduced pressure. Colourless liquid (3.52 g, 86%), bp 63–64°C/0.09 mmHg. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 6.9 (1H,m), 4.8 (1H, t, *J*=3.1 Hz), 4.2 (2H, ABX_3 system, *J*=7.1 Hz), 2.05 (1H, m), 1.90 (3H, m), 1.45 (2H, m), 1.2 (3H, t, *J*=7.1 Hz), 1.0 (9H, s), 0.27 (3H, s), 0.25 (3H, s,). ^{13}C NMR (100 MHz, C_6D_6) δ 166.8, 142.2, 133.8, 63.2, 60.5, 32.2, 26.5, 26.4, 20.9, 16.6, 14.9, −3.9, −4.3. MS *m/z* (rel. int., %) 227 (M−57, 100), 199 (56), 181 (47), 75 (79). IR ν_{max} (thin film) 1718 (s, C=O), 1648 (C=C), 1269 (C–O), 1062 (O–Si). Calculated for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.41; H 9.97.

7.2.8. 6-(*tert*-Butyl-diphenyl-silanyloxy)-cyclohex-1-enecarboxylic acid ethyl ester 4c. The same procedure described for the preparation of **7e** was used, affording *O*-silyl ether **4c** which was purified by chromatography on silica gel (hexane/CH_2Cl_2=1:1). Colourless visquous oil (15.6 g, 77%). ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 8.1 (2H, m, Ar), 7.9 (2H, m, Ar), 7.4 (6H, m, Ar), 7.1 (1H, m, H_6), 4.9 (1H, m), 4.15 (1H, ABX_3 system), 3.85 (1H, ABX_3 system), 2.1–2.0 (2H, m), 1.9 (1H, m), 1.75 (1H, m), 1.40 (1H, m), 1.30 (9H, 2s), 1.20 (1H, m), 1.0 (3H, X_3 part of a ABX_3 system, *J*=7.1 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 166.7, 142.1, 136.6, 136.5, 135.1, 134.7, 133.5, 130.1, 129.7, 128.4, 127.8, 64.1, 60.3, 31.5, 27.4, 26.1, 19.8, 16.4, 14.4. MS *m/z* (rel. int., %) 351 (M−57, 100), 199 (68), 139 (59), 77 (51). IR ν_{max} (thin film) 3071 (Ar), 1717 (C=O), 1647 (C=C), 1259 (C–O). Calculated for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.65; H, 7.67.

7.2.9. (2*S*) 5-Hydroxy-cyclopent-1-enecarboxylic acid methyl ester (*S*)-3a.[20] A solution of (*R*,*S*) alcohol **3a** (2.5 g, 17.6 mmol, 1 equiv.) in 25 mL of vinyl acetate was stirred at rt with 250 mg of lipase *Pseudomonas* sp. The reaction was monitored by gas chromatography and stopped after ca. 50% of conversion (20 h). The lipase was removed by filtration over celite and the mixture was concentrated under reduced pressure. Purification by a flash chromatography with hexane/ether (4:1) afforded (*S*) alcohol (and (*R*) acetate). Colourless liquid (1.24 g, 49%), e.e.[21] 50%. $[\alpha]_D^{20}$=−17.4 (*c*=0.99, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 6.92 (1H, t, *J*=2.3 Hz), 5.1 (1H, m), 3.8 (3H, s), 2.7–2.55 (1H, m), 2.5–2.25 (2H, m), 2.0–1.75 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 146.38, 137.88, 74.75, 51.11, 32.08, 30.63. MS *m/z* (rel. int., %) 115 (100), 114 (45), 77 (37), 71 (32), 60 (36), 53 (24), 51 (24). IR ν_{max} (thin film) 3480 (broad, OH), 1720 (C=O), 1640 (C=C).

7.2.10. (2*S*) 5-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enecarboxylic acid methyl ester (*S*)-7d. The title silyl ether (*S*)-**7d** was prepared from (*S*)-**3a** and according to the same procedure used for the racemic material. Spectral data are identical to racemic material **7d**. Colourless liquid (1.65 g, 92%), e.e. 50%. bp 59–60°C/0.1 mmHg. $[\alpha]_D^{20}$=+6.2 (*c*=1.06, $CHCl_3$).

7.3. Conjugate addition and desilylation reactions to 5-membered ring cycloalkenols

All conjugate addition reactions were typically performed in dry glassware under argon atmosphere using a 50 mL four-necked round bottom flask fitted with a mechanical stirrer, a thermometer, a reflux condenser and an addition funnel.

7.3.1. Typical Copper(I) mediated conjugate addition of Grignard reagent procedure. To a solution of 5 mmol of cyclopentenol in 40 mL THF at a temperature between −35 and −10°C (depending on the nature of the Grignard reagent) was added 0.5 mL of a 1N solution of $LiCuBr_2$ in THF and with TMSCl (1.6 mL, 12.5 mmol, 2.5 equiv.). After 5 min, a solution of the Grignard reagent (10 mmol, 2 equiv.) was slowly added during ca. 1 h and the mixture was stirred for a remaining hour until completion. Then, the mixture was quenched at −30°C with saturated aqueous NH_4Cl. After extraction with ethyl ether, the combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvents in vacuo yielded the crude conjugate adduct which was generally used in the desilylation step with no further purification.

7.3.2. (*anti*, *syn*) 2-(*tert*-Butyl-dimethyl-silanyloxy)-5-ethyl-cyclopentanecarboxylic acid methyl ester 9b. The title cyclopentane was obtained from **7d** following typical procedure. Colourless visquous oil (1.62 g, 88%), d.e.≥95%.

^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.5 (1H, dt, J_{cis}=6.2, J=5.0 Hz, *H*C–OSi), 3.5 (3H, s), 3.2 (2H, pseudo q, J=7.0 Hz), 2.7 (1H, m, C*H*–Et), 2.3 (1H, dd, J_{cis}=6.2, J_{trans}=8.8 Hz, *H*–C–CO_2), 2.0–1.3 (4H, m), 1.1 (9H, s), 1.1 (3H, t, J=7.0 Hz, CH_3), 0.09 (3H, s), 0.08 (3H, s). ^{13}C NMR (100 MHz, C_6D_6) δ 173.2 (CO_2), 76.8 (SiO–C), 65.8, 56.9 (*C*–CO_2), 50.6, 41.6 (*C*H–Et), 35.3, 28.7, 27.1, 19.2, 15.5 (*C*H_3), −4.3. IR ν_{max} (thin film) 1728 (C=O), 1067 (Si–O).

7.3.3. (*anti*,*syn*) 2-Hydroxy-5-ethyl-cyclopentanecarboxylic acid methyl ester 14b. Typical desilylation procedure.[14] To a solution of crude *O*-silyl 5-ethylcyclopentane **9b** (ca. 5 mmol) in 10 mL THF at 0°C was added over a period of 30 min, a solution of tetra-*n*-butylammonium fluoride trihydrate (4.1 g, 13 mmol, 2.6 equiv.) in 10 mL THF. The mixture was allowed to warm up to rt and stirred for the remaining 2 h until completion. Then, the mixture was quenched with saturated dilute HCl. After extraction with ethyl acetate, the combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvents in vacuo yielded the crude alcohol **14b** as a single diastereoisomer which was purified by chromatography on silica gel (hexane/ethyl acetate=4:1). Colourless liquid (0.47 g, 55%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.33 (1H, dt, J_{cis}=5.2, 4.0 Hz, C*H*–OH), 3.40 (3H, *s*,), 2.44 (1H, dtt, J_{trans}=9.9, 8.5, 5.8 Hz, C*H*–Et), 2.2 (1H, dd, J_{trans}=9.9, J_{cis}=5.2 Hz, *C*H–CO_2), 1.97 (1H, ddt, J=14.3, 8.5, 6.6 Hz), 1.70–1.65 (2H, m), 1.50 (1H, ddq, J=14.8, 7.4, 7.3 Hz), 1.1 (1H, ddq, J=14.8, 7.4, 7.3 Hz), 1.0 (1H, m), 0.82 (3H, 2t, J=7.3 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 174.6, 74.7 (CH–OH), 55.9 (*C*H–CO_2), 51.2, 42.1 (*C*H–Et), 34.1, 29, 28.3, 12.4. MS *m*/*z* (rel. int., %) 115 (M−57, 100), 87 (32), 83 (44). IR ν_{max} (thin film) 3478 (broad, OH), 1737 (C=O), 1261 (C–O). Calculated for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.35; H, 9.73.

7.3.4. (*anti*,*syn*) 3,5 Dinitrobenzoic acid 3-ethyl-2-methoxycarbonyl-cyclopentyl ester 13b. To a solution of 3,5-dinitrobenzoyl chloride (0.428 g, 1.86 mmol, 2 equiv.) in 35 mL of methylene chloride, 4-dimethylaminopyridine (DMAP) (10 mg, 0.09 mmol, 0.01 equiv.) was added and stirred at rt for 5 min. before the addition of triethylamine (2.53 mL, 1.86 mmol, 2 equiv.) and alcohol **14b** (0.2 g, 0.93 mmol, 1equiv.). After 30 h at rt, the mixture was quenched with 10 mL of water, extracted with diethyl ether and washed with brine until pH 7. After drying over $MgSO_4$ and removing of the solvents, the crude product was chromatographed on silica gel (hexane/CH_2Cl_2=1:4) and recrystalised (ether/pentane=2:1). White crystals (0.310 g, 91%), mp 124–126°C (ether/pentane=2:1), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 8.7 (2H, d, Ar), 8.4 (1H, t, Ar), 5.52 (1H, dt, J_{cis}=5.9, 3.3 Hz, *C*H–OPh), 3.5 (3H, s), 2.5 (1H, m, C*H*–Et), 2.38 (1H, dd, J_{trans}=10.1, J_{cis}=5.9 Hz, C*H*–CO_2), 1.9–1.7 (3H, m), 1.4 (1H, dqd, J=15.3, 7.4, 7.1 Hz, CH_2(Et)), 1.1 (1H, dqd, J=15.3, 7.4, 7.1 Hz, CH_2(Et)), 0.9 (1H, m), 0.8 (3H, t, J=7.4 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 192.1 (Ph–*C*O_2), 171.9 (CO_2Me), 161.9 (Ar), 148.4 (Ar),33.5 (Ar), 128.7 (Ar), 128.3 (Ar), 122.1 (Ar), 79.5 (*C*H–OPh), 54.6 (*C*H–CO_2), 51.6, 42.4 (*C*H–Et), 31.8, 28.8, 27.9, 12.3. MS *m*/*z* (rel. int., %) 195 (M−171, 69), 171 (17), 149 (32), 115 (100), 95 (80). IR ν_{max} (thin film) 1738 (C=O), 1723 (C=O), 1633 (Ar), 1549 (Ar–NO_2). Calculated for $C_{16}H_{18}N_2O_8$: C, 52.46; H, 4,95; N, 7.65. Found: C, 52.35; H, 5.07; N, 7.55.

7.3.5. (*anti*,*syn*) 2-Hydroxy-5-methyl-cyclopentanecarboxylic acid methyl ester 14a. The title alcohol was prepared from **7d** and desilylated by the same procedure described for the preparation of **14b**. It was purified on silica gel using hexane/ethyl acetate=7:3. Colourless liquid (0.39 g, 50%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.4 (1H, dt, J_{cis}=4.9, 3.7 Hz, C*H*–OH), 3.5 (3H, s), 2.88 (1H, broad s, *OH*), 2.6 (1H, dtq, J_{trans}=10.3, 8.5, 6.7 Hz, C*H*–Me), 2.16 (1H, dd, J_{trans}=10.3, J_{cis}=4.9 Hz, C*H*–CO_2), 2.1 (1H, ddt, J=12.8, 8.5, 6.7 Hz), 1.78 (2H, m), 1.1 (4H, m). ^{13}C NMR (100 MHz, C_6D_6) δ 174.3, 74.7 (*C*H–OH), 57.9 (*C*H–CO_2), 51.0, 35.4 (*C*H–Me), 34.2, 31.8, 19.9. MS *m*/*z* (rel. int., %) 101 (M−57, 100), 87 (34), 69 (47), 41 (17). IR ν_{max} (thin film) 3467 (broad, OH), 1740 (C=O). Calculated for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.35; H, 9.23.

7.3.6. (*anti*,*syn*) 2-Hydroxy-5-*n*-butyl-cyclopentanecarboxylic acid methyl ester 14c. The title alcohol was prepared by previously described procedures from **8d**. It was purified on silica gel using hexane/ethyl acetate=3:2 as eluent. Pale yellow liquid (0.77 g, 77%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.4 (1H, dt, J_{cis}=5.1, 3.9 Hz, C*H*–OH), 3.5 (3H, s), 3.2 (1H, broad s, *OH*), 2.6 (1H, dtt, J_{trans}=9.9, 8.3, 5.1 Hz, C*H*–*n*-Bu), 2.3 (1H, dd, J_{trans}=9.9, J_{cis}=5.1 Hz, C*H*–CO_2), 2.1 (1H, ddt, J=12.7, 8.3, 6.6 Hz), 1.8 (1H, m), 1.7 (1H, m), 1.6 (1H, m), 1.4–1.1 (6H, m), 0.9 (3H, t, J=6.8 Hz, CH_3). ^{13}C NMR (100 MHz, C_6D_6) δ 174.6, 74.7 (*C*H–OH), 56.3 (*C*H–CO_2), 51.2, 40.6 (*C*H–*n*-Bu), 35.5, 34.2, 30.5, 29.4, 23.1, 13.9. MS *m*/*z* (rel. int., %) 143 (100%, M−57), 115 (57),87 (56), 83 (41), 55 (41). IR ν_{max} (thin film) 3488 (broad, OH), 1740 (C=O), 1261 (C–O). Calculated for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.29; H, 10.03.

7.3.7. (*anti*,*syn*) 2-Hydroxy-5-*iso*-propyl-cyclopentanecarboxylic acid methyl ester 14d. The title alcohol was prepared by previously described procedures. It was purified on silica gel using hexane/ethyl acetate=1:1 as eluent. Pale yellow oil solidified at −18°C (0.53 g, 57%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.3 (1H, dt, J_{cis}=5.3, 4.1 Hz, C*H*–OH), 3.5 (3H, s), 2.8 (1H, broad s, *OH*), 2.6 (1H, dm, J_{trans}=9.8 Hz, C*H*–*i*-Pr), 2.5 (1H, dd, J_{trans}=9.8, J_{cis}=5.3 Hz, C*H*–CO_2), 1.95 (1H, dddd, J=11.1, 6.3, 6.3, 5.0 Hz), 1.85 (2H, m), 1.75–1.55 (2H, m), 0.95 (3H, d, J=6.7 Hz), 0.9 (3H, d, J=6.7 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 175.4, 75.2 (*C*H–OH), 53.5 (*C*H–CO_2), 51.5, 47.8 (*C*H–*i*-Pr), 34.8, 32.0, 26.3, 21.4, 19.5. MS *m*/*z* (rel. int., %) 143 (38%), 129 (M−57, 43), 115 (67), 111 (100), 83 (57), 55 (45), (CI) 187 (M−H). IR ν_{max} (thin film) 3466 (broad, OH), 1717 (C=O). Calculated for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.48; H, 10.15.

7.3.8. (*anti*,*syn*) 2-Hydroxy-5-*tert*-butyl-cyclopentanecarboxylic acid methyl ester 14e. The title alcohol was prepared by previously described procedures. It was purified on silica gel using hexane/ethyl acetate=1:1 as eluent. Colourless liquid (0.62 g, 62%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.29 (1H, dt, J_{cis}=5.7, 4.8 Hz, C*H*–OH), 3.5 (3H, s), 2.74 (1H, broad s, *OH*), 2.70 (1H,

dd, J_{trans}=8.8, J_{cis}=5.7 Hz, C*H*–CO_2), 2.67 (1H, ddd, J_{trans}= 8.8, 16.0, 7.8 Hz, CH–*t-Bu*), 1.89 (2H, m), 1. 66 (1H, m), 1.29 (1H, m), 0.88 (9H, s). ^{13}C NMR (100 MHz, C_6D_6) δ 175.5, 75.5 (*C*H–OH), 51.6 (CH–*t*-Bu), 51.3, 51.0 (*C*H–CO_2), 35.1, 32.5, 27.3, 27.4. MS *m/z* (rel. int., %) 143 (M−57, 98), 111 (100), 83 (40), 57 (28), (CI) 218 (M−NH_4^+), 201 (M−H). IR ν_{max} (thin film) 3401 (broad, OH), 1735 (C═O). Calculated for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.52; H, 10.17.

7.3.9. (*anti*,*syn*) 2-(*tert*-Butyl-dimethyl-silanyloxy)-5-[5-(1-ethoxy-ethoxy)-pentyl]-cyclopentanecarboxylic acid methyl ester 9e. A solution of 1-chloro 7-methyl-6,8-dioxadecane (2.4 g, 12.5 mmol, 2.5 equiv.), prepared following the literature, in 10 mL of THF was stirred with magnesium (0.48 g, 20 mmol, 2 equiv.) at 45–50°C for 3 h then added to 2-silyloxycyclopentene **7d** according to typical procedure. The crude product obtained was used in the next step with no further purification. Colourless liquid (quant. yield), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.6 (1H, q, *J*=5.3 Hz), 4.4 (1H, m, C*H*–OSi), 3.6 (3H, s), 3.58–3.45 (4H, m), 2.5 (1H, m), 2.36 (1H, dd, J_{trans}=9.5, J_{cis}= 5.6 Hz, C*H*–CO_2), 2.02–1.28 (12H, m), 1.30 (3H, d, *J*= 7.1 Hz), 1.18 (3H, t, *J*=7.0 Hz), 0.82 (9H, s), 0.00 (3H, s), −0.02 (3H, s). ^{13}C NMR (100 MHz, C_6D_6) δ 172.6, 99.4, 75.5 (*C*H–OSi), 65.1, 60.5, 57.4 (CH–CO_2), 51.0, 38.8, 35.6, 34.8, 29.7, 28.9, 27.8, 26.3, 23.6, 19.7, 17.7, 15.1, −4.8, −5.4. MS *m/z* (rel. int., %) 359 (10), 327 (10), 313 (48), 269 (20), 255 (10), 199 (10), 159 (8), 115 (14), 89 (39), 75 (47), 73 (100), 45 (36), (CI) 434 (M−NH_4^+). IR ν_{max} (thin film) 1747 (s, C═O), 1065 (s, OSi).

7.3.10. (*anti*,*syn*) 2-Hydroxy-5-(5-hydroxy-pentyl)-cyclopentanecarboxylic acid methyl ester 14f.[15] 15 mL of 2N aqueous hydrochloride were added at 0°C (ice bath) to a solution of silyl ether **9e** in 10 mL of acetone. The mixture was stirred for 2 h at rt before extraction with chloroform, washing with aqueous $NaHCO_3$ and drying over $MgSO_4$. The crude product was flash-chromatographied over silica gel with ethyl ether following with $CHCl_3$. Colourless liquid (0.8 g, 69%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) d 4.57 (1H, broad s, *OH*), 4.02 (1H, m, *CH*–OH), 3.2 (1H, broad s, OH), 3.15 (2H, t, *J*=6.2 Hz), 3.1 (3H, s), 2.36 (1H, m), 1.9 (1H, dd, J_{trans}=9.8, J_{cis}=5.2, C*H*–CO_2), 1.7 (1H, m), 1.55–0.6 (11H, m). ^{13}C NMR (100 MHz, C_6D_6) δ 176.7, 74.8 (*C*H–OH), 63.1, 56.6 (*C*H–CO_2), 51.4, 40.4, 35.6, 34.1, 32.9, 29.4, 28.1, 26.1. MS *m/z* (rel. int., %) 182 (5), 180 (7), 173 (7), 155 (13), 152 (30), 141 (47), 135 (22), 123 (25), 115 (43), 111 (78), 110 (52), 97 (23), 95 (93), 87(23), 83 (100), 79 (29), 71 (31), 67 (54), 55 (72), 41 (37), (CI) 248 (M−NH_4^+), 231 (M−H). IR ν_{max} (thin film) 3400 (broad s, OH), 1725 (C═O). Calculated for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.27; H, 9.89.

7.3.11. (*anti*, *syn*) 2-(*tert*-Butyl-dimethyl-silanyloxy)-5-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-cyclopentanecarboxylic acid methyl ester 9f. A solution of 1-chloro 4-(1,3-dioxolane)-*n*-pentane (2.05 g, 12.5 mmol, 2.5 equiv.), prepared following the literature,[10] in 10 mL of THF was stirred with magnesium (0.48 g, 20 mmol, 2 equiv.) at 35–40°C for 3 h then added (at rt) to 2-silyloxycyclopentene **7d** according to typical procedure. The crude product obtained was purified over silica gel (hexane/ethyl acetate=7:3). Colourless liquid (1.8 g, 93%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.4 (1H, m, C*H*–OSi), 3.87 (4H, m), 3.6 (3H, s), 2.54 (1H, m), 2.4 (1H, dd, J_{trans}=9.5, J_{cis}= 5.8 Hz, C*H*–CO_2), 2.04 (1H, m), 1.84 (1H, m), 1.70–1.58 (4H, m), 1.45–1.1 (4H, m), 1.3 (3H, s), 0.86 (9H, s), 0.02 (3H, s), −0.01 (3H, s). ^{13}C NMR (100 MHz, C_6D_6) δ 173.0, 110.4, 75.9 (*C*H–OSi), 64.9, 57.8 (CH–CO_2), 51.5, 39.6, 39.2, 36.2, 35.3, 29.4, 25.9, 24.0, 22.9, 18.2, −4.3, −4.9. MS *m/z* (rel. int., %) 371 (5), 330 (9), 239 (38), 133 (13), 119 (16), 89 (38), 87 (100), 75 (25), 73 (14), 43 (10), (CI) 387 (M−H). IR ν_{max} (thin film) 1745 (s, C═O), 1070 (OSi).

7.3.12. (*anti*,*syn*) 2-Hydroxy-5-(4-oxo-pentyl)-cyclopentanecarboxylic acid methyl ester 14g. The dioxolane **9f** (1.8 g, 4.8 mmol, 1 equiv.) was stirred at reflux for 5 min. in a mixture of 65 mL of dioxane and 30 mL of 0.1N aqueous hydrochloride with potassium periodate (1.38 g, 6 mmol, 1.25 equiv.). After cooling to rt, the mixture was washed with water and saturated aqueous $NaHCO_3$ until pH≥7 and extracted with ethyl acetate. After removal of the solvents in vacuo, the crude product was treated at 0°C with 15 mL of 2N aqueous hydrochloride in 10 mL acetone for 1 h. Then, the mixture was extracted with chloroform, washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was flash-chromatographied over silica gel with hexane/diethyl ether=1:1 as eluent. Colourless liquid (0.81 g, 75%), d.e.≥95%. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 4.4 (1H, m, C*H*–OH), 3.85 (1H, δ, *J*=4.6 Hz, *OH*), 3.6 (3H, s), 2.42 (4H, m), 2.1 (3H, s), 2.0–1.8 (2H, m), 1.75–1.45 (4H, m), 1.30–1.1 (2H, m). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 208.8, 174.1, 75.4 (*C*H–OH), 57.7 (*C*H–CO_2), 51.9, 44.1, 40.1, 35.9, 35.1, 30.2, 29.9, 23.3. MS *m/z* (rel. int., %) 200 (2), 182 (5), 178 (10), 171 (36), 168 (10), 153 (11), 139 (27), 125 (11), 121 (10), 111 (39), 109 (19), 93 (50), 83 (38), 81 (21), 79 (14), 71 (17), 69 (10), 67 (16), 58 (12), 55 (29), 43 (100), (CI) 246 (M−NH_4^+), 229 (M−H). IR ν_{max} (thin film) 3492 (broad, OH), 1740–1734 (s, C═O). Calculated for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.87; H, 8.96.

7.3.13. (*anti*,*syn*) 2-(*tert*-Butyl-dimethyl-silanyloxy)-5-(2-[1,3]dioxolan-2-yl-ethyl)-cyclopentanecarboxylic acid methyl ester 9g. A solution of 1-bromo 3-(1,3-dioxolane)-*n*-propane (2.26 g, 12.5 mmol, 2.5 equiv.) in 10 mL of THF was stirred at 30°C with magnesium (0.48 g, 20 mmol, 2 equiv.) for 45 min, then added to 2-silyloxycyclopentene **7d** according to typical procedure. The crude product obtained was purified over silica gel (hexane/diethyl ether=9:1). Colourless liquid (1.09 g, 61%), d.e.≥95%. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 4.83 (1H, broad t), 4.44 (1H, dt, J_{cis}=5.6, 3.6 Hz, C*H*–OSi), 3.97–3.81 (4H, m), 3.65 (3H, s), 2.44 (1H, m), 2.37 (1H, dd, J_{trans}=9.3, J_{cis}=5.6 Hz, C*H*–CO_2), 2.04–1.6 (6H, m), 1.40–1.10 (2H, m), 0.84 (9H, s), 0.03 (3H, s), 0.00 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5, 104.5, 75.6 (*C*H–OSi), 64.7, 57.3 (*C*H–CO_2), 51.1, 38.6, 34.8, 32.4, 29.7, 28.9, 25.6, 17.8, −4.7, −5.3. MS *m/z* (rel. int., %) 301 (M−57, 32), 269 (32), 151 (23), 105 (15), 99 (15), 89 (60), 79 (14), 75 (34), 73 (100), 59 (15), 45 (15), (CI) 359 (M−H). IR ν_{max} (thin film) 1745 (s, C═O), 1065 (O–Si). Calculated for $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.56. Found: C, 60.67; H, 9.33.

7.3.14. (1*R*,2*S*,5*S*) 2-Hydroxy-5-butyl-cyclopentane-1-carboxylic acid methyl ester 14c. The cyclopentanol was prepared and purified according to the same procedures (Copper(I) mediated addition of *n*-butylmagnesium bromide and desilylation) used for the racemic product **7b** and gave identical spectral data described for racemic product **14c**. It was purified by silica gel chromatography (hexane/diethyl ether=4:1). Colourless liquid (0.72 g, 72%), e.e.[21] =50%. $[\alpha]D^{20}=+29.2$ (c=1.085, $CHCl_3$).

7.4. Conjugate addition reactions to 6-membered ring cycloalkenols

Conjugate addition reactions were performed according to the typical procedure described for 5-membered ring analogues and using 2.9 equiv. of Grignard reagent at −10°C.

7.4.1. (*Z*) (*anti*)1-Butyl-3-(*tert*-butyl-dimethyl-silanyloxy)-2-[ethoxy-(trimethyl-silanyloxy)-methylene]-cyclohexane 11b. Typical procedure was used from **4b**, affording the title compound without purification in order to prevent from subsequent degradation (β-elimination). Colourless liquid solidified at −18°C (2.15 g, quant. yield), d.e.≥95%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.8 (1H, m, C*H*–OSi), 3.7 (2H, ABX_3 System), 2.37 (1H, m), 1.9–1.7 (4H, m), 1.6–1.1 (8H, m), 1.2 (3H, *t*, *J*=7.1 Hz), 0.9 (9H, s), 0.9 (3H, broad t), 0.2 (9H, s), 0.05 (3H, s), 0.0 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6 (C=*C*(OSiMe3)), 106.4 (*C*=C($OSiMe_3$)), 67.5 (*C*H–OSi), 65.4, 35.2, 34.7 (CH–*n*-Bu), 33.1, 31.9, 30.7, 25.6, 22.8, 20.10, 17.8, 14.9, 13.8 (CH_3), 0.0, −4.9, −5.2. MS *m/z* (rel. int., %) 29 (M, 2), 165 (31), 147 (34), 115 (22), 107 (22), 73 (100), (CI) 415 (M−H). IR ν_{max} (thin film) 1675 (C=C), 1084 (broad, O–Si).

7.4.2. (*Z*) (*anti*) 1-Ethyl-3-(*tert*-butyl-dimethyl-silanyloxy)-2-[ethoxy-(trimethyl-silanyloxy)-methylene]-cyclohexane 11d. The same procedure described for the preparation of **11b** was used, affording the title compound without purification in order to prevent from subsequent degradation (β-elimination). Colourless liquid (2.0 g, quant. yield), d.e.≥95%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.6 (1H, m, C*H*–OSi), 3.75 (2H, ABX_3 System), 2.05–1.2 (1H, m, C*H*–Et), 1.7–1.5 (4H, m), 1.4–1.1 (4H, m), 1.05 (3H, *t*, *J*=7.1 Hz), 0.7 (9H, s), 0.7 (3H, broad t), 0.0 (9H, s), −0.15 (3H, s), −0.2 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.6 (C=C($OSiMe_3$)), 107.0 (*C*=C(OSiMe3)), 68.4 (*C*H–OSi), 66.4, 37.7 (*C*H–Et), 36.1, 32.6, 27.0, 26.6, 21.0, 18.8, 15.6, 13.9, 0.9, −3.9, −4.2.

7.4.3. (*Z*) (*anti*) 1-Isopropyl-3-(*tert*-butyl-dimethyl-silanyloxy)-2-[ethoxy-(trimethyl-silanyloxy)-methylene]-cyclohexane 11e. The same procedure described for the preparation of **11b** was used, affording the title compound without purification in order to prevent from subsequent degradation (β-elimination). Colourless liquid (1.98 g, 99%), d.e.≥95%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.6 (1H, m, C*H*–OSi), 3.6 (2H, ABX_3 System), 2.0–1.1 (8H, m), 1.0 (3H, t, *J*=7.1 Hz), 0.8 (3H, s), 0.7 (9H, s), 0.6 (3H, s), 0.0 (9H, s), −0.15 (3H, s), −0.2 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6 (C=C($OSiMe_3$)), 105.5 (*C*=C($OSiMe_3$)), 67.7 (CH–OSi), 65.4, 45.4, 35.2, 28.2, 27.9, 25.6, 22.4, 20.8, 20.1, 17.8, 14.6, 1.7, 0.0, −3.8, −4.9. MS *m/z* (rel. int., %) 386 (1), 357 (63), 223 (11), 181 (10), 151 (13), 147 (21), 115 (45), 75 (20), 73 (100), (CI) 401 (M−H). IR ν_{max} (thin film) 1682 (C=C), 1081–1044 (broad, O–Si).

7.4.4. (*anti*,*syn*) 2-(*tert*-Butyl-diphenyl-silanyloxy)-5-*n*-butyl-cyclohexanecarboxylic acid ethyl ester 12c. Typical procedure from **4c** yielded the crude silyl ketene acetal **11c** which collapsed to ester **12c** as a single diastereoisomer after chromatography on silica gel (hexane/CH_2Cl_2=95:5). Colourless visquous oil crystalized as white needles after one week at rt (1.81 g, 78%), d.e.≥95%, mp 51–53°C. ^{1}H NMR (200 MHz, C_6D_6/TMS) δ 7.66–7.36 (10H, m, Ar), 4.38 (1H, m, C*H*–OSi), 4.02–3.89 (2H, ABX_3 System), 2.3 (1H, m, C*H*–*n*-Bu), 2.15 (1H, dd, J_{trans}=10.22, J_{cis}= 3.06 Hz, C*H*–CO_2), 2.0–1.75 (12H, m), 1.6 (3H, t, *J*= 7.1 Hz), 1.55 (9H, s), 0.9 (3H, broad t). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.12, 136.04 (Ar), 136.0 (Ar), 134.8 (Ar), 134.0 (Ar), 129.5 (Ar), 127.36 (Ar), 70.12 (CH–OSi), 59.82, 54.13 (CH–CO_2), 34.32, 32.7, 32.4 (CH–*n*-Bu), 29.9, 28.9, 27.0, 22.9, 19.4, 19.3, 14.0. MS *m/z* (rel. int., %) 409 (M−57, 98), 227 (46), 199 (100), 183 (29), 135 (22), 81 (19), (CI) 467 (M−H). IR ν_{max} (thin film) 3071–3049 (Ar), 1740 (C=O). Calculated for $C_{29}H_{42}O_3Si$: C, 74.63; H, 9.07. Found: C, 74.68; H, 8.88.

7.4.5. (*anti*,*syn*) 2-(*tert*-Butyl-dimethyl-silanyloxy)-5-butyl-cyclohexanecarboxylic acid ethyl ester 12b. *Typical hydrolysis procedure*. A solution of ca. 5 mmol of crude silyl ketene acetal **11b** was stirred from 0°C to rt in 15 mL of 'wet' THF with glacial acetic acid (420 μL, 7.5 mmol, 1.5 equiv.) over a period of 3 h. The mixture was then treated with 10 mL of water and with saturated aqueous $NaHCO_3$ until pH 7. Extraction with ethyl ether, washing with brine and drying over $MgSO_4$ afforded the crude product, which was distilled under reduced pressure affording pure ester. Colourless liquid (1.57 g, 92%), d.e.≥95%, bp 96–97°C/0.04 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (1H, m, C*H*–OSi), 4.1 (2H, q, *J*=7.0 Hz), 2.06–1.25 (14H, m), 1.23 (3H, t, *J*=7.0 Hz), 0.8 (9H, s), 0.8 (3H, broad t), 0.00 (3H, s), −0.06 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 69.7 (*C*H–OSi), 60.4, 53.4 (*C*H–CO_2), 35.4, 34.3, 32.5 (CH–*n*-Bu), 31.3, 29.4, 26.3, 23.6, 19.8, 18.6, 14.9, 14.7. MS *m/z* (CI) 343 ($M-H^+$). IR ν_{max} (thin film) 1744 (C=O), 1042 (O–Si). Calculated for $C_{19}H_{38}O_3Si$: C, 66.61; H, 11.18. Found: C, 66.55; H, 11.24.

7.4.6. (*anti*,*syn*) 2-Hydroxy-5-*n*-butyl-cyclohexanecarboxylic acid ethyl ester 15b and (*syn*,*anti*) 2-Hydroxy-5-butyl-cyclohexanecarboxylic acid ethyl ester 16b. *Typical desilylation procedure*. The silyl ether **12b** (1.57 g, 4.6 mmol, 1 equiv.) was stirred in 15 mL of THF with *n*-Bu_4NF, $3H_2O$ (3.15 g, 10 mmol, 2.2 equiv.) at rt over a period of 4 h before hydrolysis with 20 mL of water and extraction with diethyl ether. Then, the combined organic layers were washed with brine and saturated aqueous $CuSO_4$, and dried over $MgSO_4$. Removal of the solvents in vacuo afforded a mixture of two diastereoisomers in a ca. 95:5 ratio according to ^{1}H NMR. Those two isomers were separated over silica gel (hexane/ether=9:1) giving the alcohols in 70% overall yield.

Major diastereoisomer (first eluted): **15b**. Colourless liquid (0.75 g), d.e.≥95%. R_f=0.38 (hexane/ether=1:1). ^{1}H NMR

(400 MHz, $CDCl_3$/TMS) δ 4.18 (2H, m), 4.07 (1H, m, C*H*–OH), 3.32 (1H, broad s, *OH*), 2.20 (1H, dd, J_{trans}=11.2, J_{cis}=1.9 Hz, C*H*–CO_2), 2.0 (1H, m, CH–*n*-Bu), 1.9–1.7 (4H, m), 1.46 (1H, m), 1.35–1.20 (6H, m), 1.25 (3H, X_3 part of a ABX_3 system, J_{A-X}=7.1 Hz), 0.9 (1H, m, H_5), 0.85 (3H, broad t, J=6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 67.4 (*C*H–OH), 61.1, 53.7 (*C*H–CO_2), 34.7, 34.0 (*C*H–*n*-Bu), 32.2, 31.2, 29.0, 23.5, 19.9, 14.8, 14.6. MS *m*/*z* (rel. int., %) 228 (M, 3), 210 (6), 200 (28), 157 (100), 143 (69), 137 (16), 129 (50), 125 (51), 115 (18), 111 (21), 81 (43), 69 (30), 57 (18), 55 (44), 41 (36), (CI) 229 ($M-H^+$). IR ν_{max} (thin film) 3522 (broad, OH), 1708 (C=O). Calculated for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.14; H, 10.77.

Minor diastereoisomer: **16b**. Colourless liquid (0.04 g), d.e.≥95%. R_f=0.35 (hexane/ether=1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 4.17 (2H, ABX_3 system), 3.96 (1H, dt, J_{trans}=9.8, 4.5 Hz, C*H*–OH), 3.03 (1H, broad s, *OH*), 2.40 (1H, dd, J_{cis}=9.8, J_{trans}=4.6 Hz, C*H*–CO_2), 2.19 (1H, m, CH–*n*-Bu), 2.00 (1H, m), 1.7 (1H, m), 1.6–1.2 (6H, m), 1.30 (3H, X_3 part of a ABX_3 system, J_{A-X}=7.2 Hz), 1.1 (2H, m), 0.8 (3H, broad t, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 67.1 (*C*H–OH), 61.0, 55.6 (*C*H–CO_2), 36.8 (CH–*n*-Bu), 33.6, 30.7, 28.3, 23.2, 19.8, 14.9, 14.6. IR and MS spectra were identical to those of the major diastereoisomer.

7.4.7. (*anti*, *syn*) 2-Hydroxy-5-ethyl-cyclohexanecarboxylic acid ethyl ester 15d and (*syn*, *anti*) 2-Hydroxy-5-ethyl-cyclohexanecarboxylic acid ethyl ester 16d. The two diastereoisomers (ca. 88:12 ratio according to ^{1}H NMR) were obtained by the same procedure described before and were separated over silica gel (hexane/ether=95:5), affording the alcohols in 84% overall yield.

Major diastereoisomer (first eluted): **15d**. Colourless liquid crystalized after 2 weeks at −18°C (0.74 g), d.e.≥95%. R_f=0.36 (hexane/ether=1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 4.10 (2H, m), 4.01 (1H, m, C*H*–OH), 3.30 (1H, broad s, *OH*), 2.14 (1H, dd, J_{trans}=11.2, J_{cis}=2.0 Hz, C*H*–CO_2), 1.90–1.60 (4H, m), 1.43 (1H, m), 1.35–1.23 (2H, m), 1.20 (3H, t, J=7.1 Hz), 1.05 (1H, m), 0.85 (1H, m), 0.80 (3H, broad t, J=7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 67.3 (*C*H–OH), 61.2, 53.3 (*C*H–CO_2), 35.4 (*C*H–Et), 32.3, 30.5, 27.6, 19.8, 14.8, 11.2. MS *m*/*z* (rel. int., %) 200 (M, 2), 172 (27), 155 (12), 143 (60), 137 (10), 129 (100), 125 (41), 115 (17), 109 (38), 101 (64), 69 (30), 97 (33), 83 (29), 79 (31), 69 (27), 55 (45), 41 (35), 29 (38). IR ν_{max} (thin film) 3511 (broad, OH), 1707 (C=O). Calculated for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.46; H, 10.23.

Minor diastereoisomer: **16d** Colourless liquid (0.1 g), d.e.≥95%. R_f=0.35 (hexane/ether=1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) d 4.12 (2H, ABX_3 system, 3.9 (1H, dt, J_{cis}=9.8, 4.5 Hz, C*H*–OH), 3.0 (1H, broad s, *OH*), 2.35 (1H, dd, J_{cis}=9.8, J_{trans}=4.5 Hz, C*H*–CO_2), 2.05 (1H, m, C*H*–Et), 1.95 (1H, m), 1.70 (1H, m), 1.55–1.0 (5H, m), 1.2 (3H, t, J=7.1 Hz), 0.80 (1H, m), 0.78 (3H, broad t, J=7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 67.4 (*C*H–OH), 61.0, 55.5 (*C*H–CO_2), 38.8 (*C*H–Et), 33.5, 27.6, 21.6, 19.6, 14.8, 13.1. IR and MS spectra were identical to those of the major diastereoisomer.

7.4.8. (*anti*, *syn*) 2-Hydroxy-5-isopropyl-cyclohexanecarboxylic acid ethyl ester 15e and (*syn*, *anti*) 2-Hydroxy-5-isopropyl-cyclohexanecarboxylic acid ethyl ester 16e. The two diastereoisomers (ca. 92:8 ratio according to ^{1}H NMR) were obtained by the same procedure described before and were separated over silica gel with hexane/ether=97:3 (major diastereoisomer) then 95:5 (minor diastereoisomer) affording the alcohols in 64% overall yield.

Major diastereoisomer (first eluted): **15e**. Colourless liquid (0.630 g), d.e.≥95%. R_f=0.42 (hexane/ether=1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 4.18 (2H, m), 4.12 (1H, m, C*H*–OH), 3.50 (1H, broad s, *OH*), 2.42 (1H, dd, J_{trans}=11.6, J_{cis}=2.03 Hz, C*H*–CO_2), 2.02 (1H, m, CH–*i*-Pr), 1.9 (1H, m), 1.83–1.63 (2H, m), 1.55 (2H, m), 1.38–1.30 (1H, m), 1.29 (3H, t, J=7.1 Hz), 1.03 (1H, m), 0.94 (3H, d, J=6.9 Hz), 0.83 (3H, d, J=6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (CO_2), 67.6 (*C*H–OH), 61.2, 51.4 (*C*H–CO_2), 39.5 (CH–*i*-Pr), 32.3, 29.9, 24.5, 21.7, 20.0, 16.5, 14.8. MS *m*/*z* (rel. int., %) 214 (M, 1), 171 (28), 143 (62), 130 (16), 125 (100), 123 (23), 114 (21), 108 (11), 97 (55), 86 (19), 83 (16), 82 (51), 79 (56), 69 (62), 67 (39), 55 (52), 43 (52), 41 (61), 29 (38). IR ν_{max} (thin film) 3479 (broad, OH), 1711 (C=O). Calculated for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.18; H, 10.20.

Minor diastereoisomer:**16e**. Colourless liquid (0.055 g), d.e.≥95%. R_f=0.39 (hexane/ether=1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) d 4.12–4.02 (3H, m), 2.63 (1H, dd, J_{cis}=5.6, J_{trans}=3.6, C*H*–CO_2), 2.39 (1H, broad s, *OH*), 1.88 (1H, m, CH–*i*-Pr), 1.7–1.4 (7H, m), 1.20 (3H, t, J=7.1 Hz), 0.83 (6H, pseudo t). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 67.9 (*C*H–OH), 60.8, 51.9 (*C*H–CO_2), 42.3 (CH–*i*-Pr), 31.4, 29.6, 27.1, 22.2, 21.8, 20.4, 14.8. IR and MS spectra were identical to those of the major diastereoisomer.

7.4.9. (*anti*,*syn*) 2-Hydroxy-5-(5-hydroxy-pentyl)-cyclohexanecarboxylic acid ethyl ester 15f. Compound **11f** was prepared from **4b** following the typical procedure described above (see also **9e** for the preparation of the organometallic reagent). The compound **15f** was prepared from the crude silylketene acetal **11f** by hydrolysis with acetic acid in THF and fully deprotected with acetone/HCl (see **14f**). Flash chromatography using hexane/diethyl ether=1:1 afforded pure diol as a single diastereoisomer. Colourless liquid (0.86 g, 67%), d.e.≥95%. ^{1}H NMR (400 MHz, C_6D_6/TMS) δ 4.07 (1H, m, C*H*–OH), 3.27–2.96 (5H, m), 2.37–2.17 (1H, m), 1.92 (1H, dd, J=10.9, 2.1 Hz, C*H*–CO_2), 1.78 (1H, m), 1.64–1.0 (13H, m), 0.9 (4H, m). ^{13}C NMR (100 MHz, C_6D_6) δ 177.0 (CO_2), 75.8, 64.2 (CH_2OH), 62.7, 57.1, 40.0, 39.5, 36.2, 33.3, 31.7, 29.9, 22.9, 21.7, 18.5. MS *m*/*z* (CI) 276 ($M-NH_4^+$), 259 (M−H). IR ν_{max} (thin film) 3550 (broad, OH), 1718 (C=O). Calculated for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.73; H, 10.42.

7.4.10. (*anti*,*syn*) 2-Hydroxy-5-(4-oxo-pentyl)-cyclohexanecarboxylic acid ethyl ester 15g. Compound **11g** was first prepared from **4b** following the typical procedure described above (see also **9f** for the preparation of the organometallic reagent). Then the crude adduct (silylketene acetal) **11g** was stirred with acetic acid in THF and removal of the protective groups was performed with acetone/HCl/KIO_4 (see **14g**)

Flash-chromatography (hexane/diethyl ether=3:7) finally afforded pure ketoalcohol as a single diastereoisomer. Colourless liquid (0.83 g, 65%), d.e.≥95%. ^{1}H NMR (400 MHz, CD_3COCD_3/TMS) δ 4.42 (1H, m, C*H*–OH), 3.85 (2H, m), 3.07 (1H, s, OH), 2.47–2.37 (4H, m), 2.08 (3H, s), 1.93–1.16 (10H, m), 0.85 (3H, t, J=7.1 Hz). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 208.7 (CO), 177.2 (CO_2), 73.9, 61.0, 52.2, 44.0, 41.2, 35.9, 35.1, 35.0, 30.5, 29.9, 23.3, 15.0. MS *m/z* (CI) 274 ($M-NH_4^+$). IR ν_{max} (thin film) 3479 (broad, OH), 1711–1694 (s, C=O). Calculated for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.47; H, 9.67.

7.4.11. (*anti*,*syn*) 2-(*tert*-Butyl-dimethyl-silanyloxy)-5-(3-oxo-propyl)-cyclohexanecarboxylic acid ethyl ester 12h. The silylketene acetal **11h** was prepared from **4b** following the typical procedure described above (see also **9f** for the preparation of the organometallic reagent). The crude silylketene acetal **11h** was directly treated according to the procedure previously described (e.g. HCl/Dioxan/KIO_4, see **14g**), to give aldehyde **12h** as a single diastereoisomer with a high level of purity without further purification in order to prevent from degradation. Colourless liquid (1.02 g, 96%), d.e.≥95%. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 9.68 (1H, broad t, J=1.6 Hz), 4.24 (1H, m, C*H*–OH), 4.11–3.96 (2H, ABX_3 system), 2.42–2.34 (2H, m), 2.10–1.16 (10H, m), 1.19 (3H, broad t, J=7.0 Hz), 0.80 (9H, s), −0.04 (3H, s), −0.1 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.7, 172.6, 68.8, 59.9, 54.3, 41.4, 33.3, 31.5, 30.3, 27.1, 25.6, 18.8, 17.8, 14.0, −4.6, −5.5. MS *m/z* (CI) 360 ($M-NH_4^+$), 343 (M−H). IR ν_{max} (thin film) 3510 (broad, OH), 1740–1710 (broad s, C=O).

7.5. Syntheses of acyclic analogues

7.5.1. 2-(1-Hydroxy-ethyl)-but-2-enoic acid ethyl ester, mixture of *E* and *Z* isomers 17a and 17b.[17] To a suspension of cuprous iodide (192 mg, 1 mmol, 0.1 equiv.) in 10 mL of dry THF, a solution of methyllithium–LiBr in diethyl ether (1.45N) (0.69 mL, 1 mmol, 0.1 equiv.) was slowly added and stirred at −30°C for 20 min. Then, a solution of HMPA (3.4 mL, 19.6 mmol, 1.9 equiv.) in 20 mL of dry THF was added prior to slow addition of a solution of di*iso*butylaluminumhydride (DIBAL-H) in toluene (1N) (15 mL, 15 mmol, 1.5 equiv.). The mixture was stirred for 2 h at −30°C, ethyl but-2-ynoate (1.12 g, 10 mmol, 1 equiv.) added and allowed to warm up to −20°C. After 5 h at this temperature, acetaldehyde (2.23 mL; 40 mmol, 4 equiv.) in 20 mL of THF was finally added and the temperature gently warmed to rt overnight. Hydrolysis with 10 mL of 1N HCl, addition of diethyl ether and washing successively with 3×10 mL of 1N HCl, 10 mL of aqueous saturated $NaHCO_3$, 2×10 mL of brine afforded an organic layer which was dried over $MgSO_4$ before concentration in vacuo. Then, chromatography over silica gel succeeded in separating the two isomers as pure products in 72% overall yield. (*E*)-isomer (first eluted with hexane/diethyl ether=9:1) **17a**. Colourless liquid (30 mg). ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 7.12 (1H, q, J=7.0 Hz), 4.16 (3H, m), 1.82 (3H, d, J=7.0 Hz), 1.25 (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.8, 136.1, 133.9, 69.3, 60.2, 21.9, 14.7, 13.8. MS *m/z* (CI) 176 ($M-NH_4^+$), 159 (M−H). IR ν_{max} (thin film) 3417 (broad, OH), 1718 (s, C=O), 1636 (C=C). (*Z*)-isomer (second eluted with hexane/diethyl ether=4/1) **17b**. Colourless liquid (1.10 g). ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 6.23 (1H, qd, ^3J=7.0, ^4J=1.0 Hz), 4.45 (1H, m), 4.23 (2H, ABX_3 system), 2.83 (1H, broad s, OH), 1.97 (3H, d, ^3J=7.0 Hz), 1.33 (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.3, 136.3, 134.5, 68.1, 59.9, 22.3, 14.8, 13.8. IR and MS spectra were identical to those of the minor diastereoisomer. Calculated for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.44; H, 9.12.

7.5.2. (*E*)-2-(1-Methyl-pentyl)-but-2-enoic acid ethyl ester 18. Alkene **18** was obtained when copper(I) mediated conjugate addition of *n*-butyl magnesium bromide was performed with **17b**. It was purified by a kugelrohr distillation. Colourless liquid. (0.35 g, 66%), bp 50–65°C/0.1 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 7.16 (1H, q, J=7.1 Hz), 4.15 (2H, broad q, J=7.2 Hz), 2.68 (1H, m), 1.76 (3H, d, J=7.1 Hz), 1.51–1.21 (6H, m), 1.16 (3H, d, J=10.4 Hz), 0.92–0.81 (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 137.7, 136.0, 59.9, 34.6, 32.3, 30.3, 22.7, 19.2, 14.2, 13.9, 13.8. MS *m/z* (rel. int., %) 198 (M, 18), 183 (13), 153 (29), 141 (29), 127 (14), 116 (100), 113 (32), 101 (47), 95 (57), 88 (22), 83 (19), 69 (44), 67 (27), 55 (33), 43 (33), 41 (39). IR ν_{max} (thin film) 1730–1713 (C=O+C=C). Calculated for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 73.03; H, 10.88.

7.5.3. (*Z*)-2-[1-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-but-2-enoic acid ethyl ester 19. The title alcohol was silylated in the same way described for the preparation of **8d**. Colourless liquid (0.355 g, 90%), bp 58–59°C/0.1 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 6.30 (1H, qd, ^3J=7.3, ^4J=1 Hz), 4.61 (1H, m), 4.28–4.14 (2H, ABX_3 system), 1.96 (3H, dd, ^3J=7.3, ^4J=1.1 Hz), 1.31 (3H, broad t, J=7.0 Hz), 1.24 (3H, d, J=6.1 Hz), 0.87 (9H, s), 0.1 (3H, s), 0.02 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.4, 137.5, 133.4, 68.0, 59.9, 25.7, 24.6, 18.0, 15.0, 14.1. MS *m/z* (rel. int., %) 257 (M−15, 3), 215 (92), 187 (41), 169 (100), 119 (14), 103 (24), 95 (28), 75 (96), 67 (29), 57 (196), 41 (21). IR ν_{max} (thin film) 1718 (s, C=O), 1654 (C=C), 1082 (O–Si). Calculated for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.55; H, 10.49.

7.5.4. 2-(1-Hydroxy-ethyl)-3-methyl-heptanoic acid ethyl ester, mixture of isomers 20. The conjugate addition reaction of *O*-silylated *Z*-butenoate **19** (0.27 g, 1 mmol, 1 equiv.) was conducted according to typical procedure (magnesium di-*n*-butylcuprate addition). Then, the crude product was desilylated as previously described affording a mixture of three diastereoisomers in a ca. 5:3:2 ratio which were unseparable over silica gel. Colourless liquid (0.180 g, 83%).

Major diastereoisomer: ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 4.30–4.05 (3H, m), 1.85 (1H, dd, ^3J=7.3, 17 Hz), 1.35–1.26 (8H, m), 0.92–0.87 (12H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.3, 65.8, 59.9, 55.7, 37.3, 35.7, 32.1, 25.6, 19.8, 15.2, 14.3, 14.0. MS *m/z* (CI) 234 ($M-NH_4^+$), 217 (M−H). IR ν_{max} (thin film) 3600 (broad, OH), 1743 (C=O).

Acknowledgements

We would like to thank Drs I. Beaudet and A. Guigant for

fruitful discussions and help, Drs J.-Y. Le Questel and B. Illien for AM-1 calculations and G. Nourisson for the recording of the mass spectra. We are grateful to Ministère de l'Enseignement Supérieur et de la Recherche for financial support.

References

1. For papers of related interest see: (a) Normant, J. F. *Synthesis* **1972**, 63–80. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1–113. (c) Lipshutz, B. H. *Synthesis* **1987**, 325–341. (d) Kozlowski, J. A. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4 (Chapter 1.4).
2. See inter alia: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806. (b) Alexakis, A. *Organocopper Reagents—A Practical Approach*; Oxford University Press: New York, 1994 (Chapter 8). (c) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186–204.
3. For a recent review concerning the synthesis of iridoïds see: Nagia, A.; Prasuna, G.; Bheema Rao, P. *Tetrahedron* **1997**, *53*, 14507–14545.
4. (a) Amri, H.; Villiéras, J. *Tetrahedron Lett.* **1987**, *28*, 5521–5524. (b) Amri, H.; Rambaud, M.; Villiéras, J. *Tetrahedron* **1990**, *46*, 3535–3546.
5. (a) Amri, H.; Rambaud, M.; Villiéras, J. *J. Organomet. Chem.* **1986**, *308*, C27–C32. (b) Dambrin, V.; Villiéras, M.; Moreau, C.; Amri, H.; Toupet, L.; Villiéras, J. *Tetrahedron Lett.* **1996**, *37*, 6323–6326.
6. Concerning the use of TMS Halide in conjugate addition reactions see for instance (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019–6022. (b) Taylor, R. J. K. *Synthesis* **1985**, 364–392. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047–1050.
7. **7a** and **b** were obtained starting from the corresponding trichloroacetimidates, following the procedure previously described: Armstrong, A.; Backenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483–2486.
8. Typical silylation involving imidazole in DMF was used, as reported by Sommer, L. H. In *Stereochemistry, Mechanism and Silicon*; McGraw-Hill, New York, 1965.
9. Villiéras, J.; Rambaud, M.; Graff, M. *Synth. Commun.* **1985**, *15*, 569–580.
10. Normant, H.; Feugeas, C. *Bull. Soc. Chim. Fr.* **1963**, 1141–1143.
11. Related cyanocuprate was prepared according to previously reported procedure: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188. (b) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390–2392.
12. When desilylation step[14] was performed from OTBDPS derivatives, a significant epimerization of C1 occured while desilylation was far from complete.
13. The synthesis of ethyl cyclohexylidene trimethylsilylketene acetal was first reported by Ainsworth, C.; Chen, F.; Yu-Neng, K. *J. Organomet. Chem.* **1972**, *46*, 59–71.
14. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549–2550.
15. The diols **14f** and **15f** were obtained after treatment with 2N aqueous HCl in acetone for 2 h at rt.
16. Removal of the dioxolane moiety was performed with potassium periodate at reflux of a mixture of dioxane and 0.1N aqueous HCl.
17. (a) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540. (b) Tsuda, T.; Yoshida, T.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 1624–1627. (c) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037–1040.
18. Cocu, F. G.; Wolczunovicz, G.; Bors, L.; Posternak, T. *Helv. Chim. Acta* **1970**, *53*, 739–742.
19. (a) Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, *87*, 5492–5495. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413. (c) Chow, Y. L.; Colon, C. J.; Tam, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821–2825.
20. (a) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114–117. (b) Yamane, T.; Takahashi, M.; Ogasawara, K. *Synthesis* **1995**, 444–448.
21. Chataignier, I.; Lebreton, J.; Durant, D.; Guingant, A.; Villiéras, J. *Tetrahedron Lett.* **1998**, *39*, 1759–1962.
22. Graff, M.; Al Dilaimi, A.; Seguineau, P.; Rambaud, M.; Villiéras, J. *Tetrahedron Lett.* **1986**, *27*, 1577–1578.