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# Highly enantioselective sequential Claisen–Ireland/metathesis: synthesis of cycloalkenes bearing two contiguous highly functionalized asymmetric centres

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**Abstract**—A sequence of two reactions, consisting of a highly stereoselective silylated ketene acetal Claisen–Ireland rearrangement followed by a ring closing metathesis, gave a stereocontrolled access to various carbocycles.


## 1. Introduction

The challenge of controlling the configuration of nearby asymmetric centres is crucial in modern organic synthesis. Despite numerous available methods, the formation of quaternary asymmetric positions still remains problematic.[1] An elegant approach to solving this problem can be found in the Claisen–Ireland rearrangement.[2] When a side chain alkene function is present, a subsequent metathesis transformation can also be applied. To the best of our knowledge, only five groups have described the Claisen–Ireland rearrangement/metathesis approach (CIM),[3] two of them using it in an asymmetric manner.[3a,e]

In 1998, Burke et al.[3a] developed the synthesis of substituted dihydropyran-2-carboxylates. Formation of silyl ketene acetal with LDA in THF at −100 °C followed by the addition of TMSCl gave good selectivities (up to 20:1 ratio) and yields (up to 84%), but were somewhat limited. For more oxygenated substrates, addition of HMPA (20%) was necessary. Metathesis using Grubbs I catalyst in various solvents needed long reaction times (4–5 days) for highly substituted compounds. Simultaneously, Piscopio et al.,[3b] described the same approach in a racemic version and extended the scope to carbocycles, sulfur heterocycles, pipecolinic acid derivatives and one seven-atom oxacycle.

In 2000, Barrett et al.[3c] reported the synthesis of bicyclic β-lactams, for which no selectivity was observed for the Claisen–Ireland rearrangement under classical conditions. In 2003, Ogilvie and Beaulieu[3d] published examples of the creation of a quaternary carbon centre, rediscovering, on this occasion, the KHMDS/toluene deprotonation conditions we showed as crucial four years before[4a] in order to promote excellent diastereoselectivities. Their work opened the way to spiroderivatives, although with poor diastereoselectivity (maximum 4.6:1 ratio). Recently, Kim et al.[3e] applied this concept to pancratistatin total synthesis. A Claisen–Ireland rearrangement was obtained by LDA deprotonation in THF/HMPA, and silylation with TBDMSCl with moderate diastereoselectivity (6:1 ratio). Ring closing metathesis afforded the desired intermediate in 91% yield.

## 2. Results and discussion

Several years ago, over the course of our studies concerning the formal total synthesis of fumagillin,[4]

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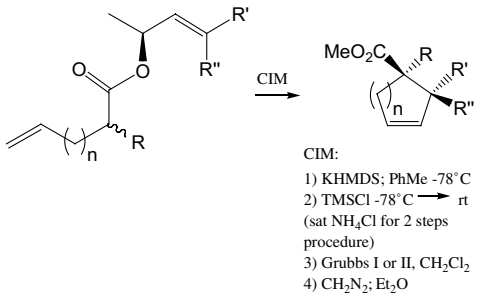
we explored an efficient two-step process. A Claisen–Ireland rearrangement (CI), which ensured highly stereoselective formation of one predictable open diastereoisomer, and the subsequent ring-closing metathesis (M), which gave a carbocyclic framework. Encouraged by this result, we decided to study the possibility of generalizing this strategy to various esters, in order to introduce various functional groups and to obtain different sized rings (Scheme 1).




**Scheme 1.** CIM transformation.

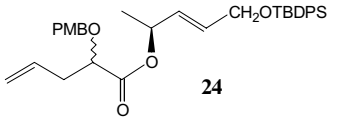
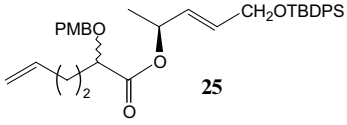
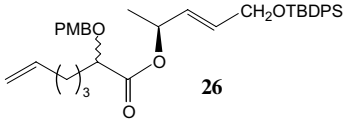
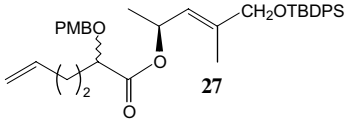
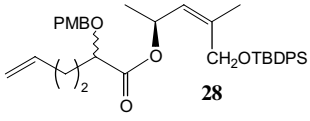
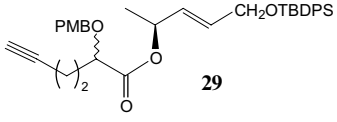
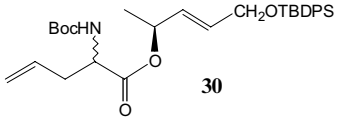
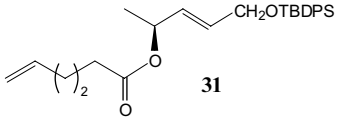
In order to prepare model esters **24**–**31** reported in Table 1, three chiral allylic alcohols **1**–**3** and six carboxylic acids **4**–**9** were used.

### 2.1. Preparation of allylic alcohols 1–3

Alcohol **1**[5] was obtained in six steps starting from (*S*)-ethyl lactate following a modified procedure described by Isobe.[5c,d] Slightly modified procedures gave the trisubstituted allylic alcohols **2** and **3** from the known aldehyde **10**. Wittig–Horner–Emmons reaction gave a 1:1 mixture of isomeric esters **11** and **12** in 81% yield. After DIBAH reduction, silica gel column chromatography gave the *E*-diastereoisomer **13** and *Z*-diastereoisomer **14** in respectively 24% and 27% yield. An intermediate fraction containing the other *E*- and *Z*-stereoisomers with respect to the THP asymmetric centre explains the limited yields. Alternatively, mixtures of **11** and **12** gave pure *E*-**15** by treatment with PPTS in ethanol (Scheme 2).

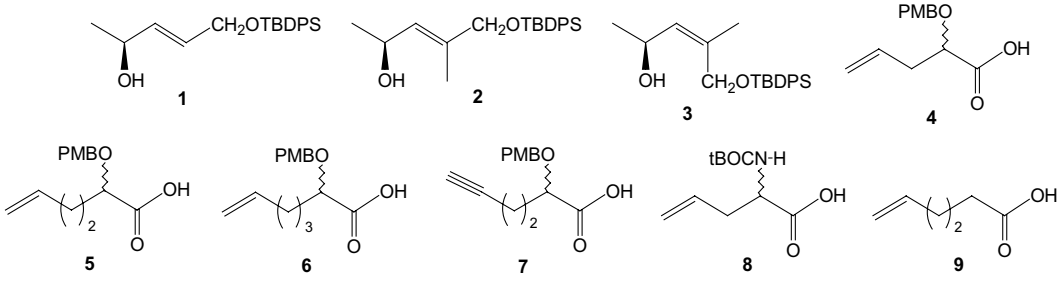
Finally, protection of **14** with a TBDPS group and careful cleavage of the THP furnished the desired **3**, along with some concomitant dehydration under reaction conditions. Similarly, selective protection of **16** with a TBDPS group gave **2** (Scheme 3).

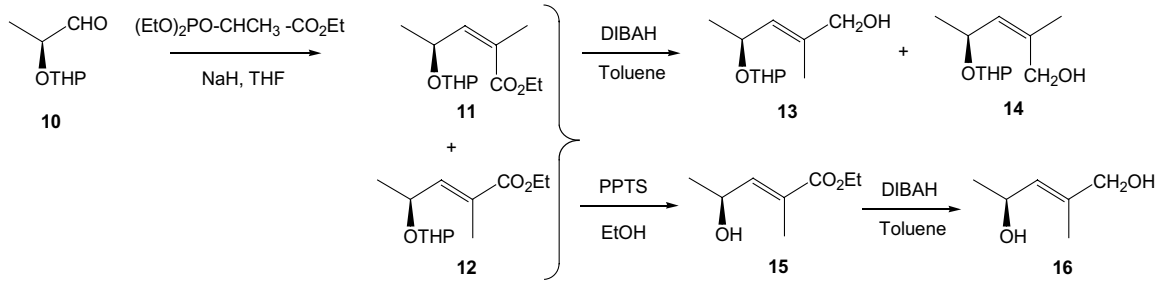
**Table 1.** Preparation of esters

| Allylic alcohol | Carboxylic acid | Ester | Yield (%) |
|---|---|---|---|
| **1** | **4** |  **24** | 44 |
| **1** | **5** |  **25** | 89 |
| **1** | **6** |  **26** | 80 |
| **2** | **5** |  **27** | 90 |
| **3** | **5** |  **28** | 69 |
| **1** | **7** |  **29** | 71 |
| **1** | **8** |  **30** | 72 |
| **1** | **9** |  **31** | 83 |

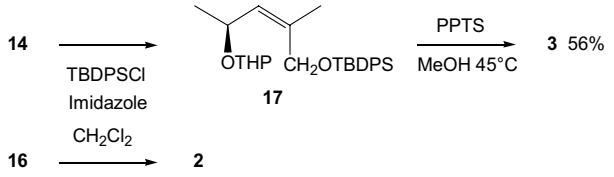
### 2.2. Preparation of carboxylic acids 4–9

The carboxylic acid **4**[6] was obtained in only two steps starting from allyl-tri-*n*-butylstannane and glyoxylic acid, in the presence of triflic acid, giving compound **18**, followed by direct protection (Scheme 4).






**Scheme 2.**



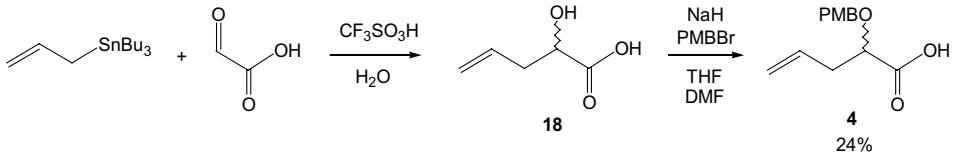

**Scheme 3.**

Carboxylic acid **5** was obtained from aldehyde **19** (previously described by Evans et al.[7]) by oxidation with $NaClO_2$ in a buffered medium (Scheme 5).

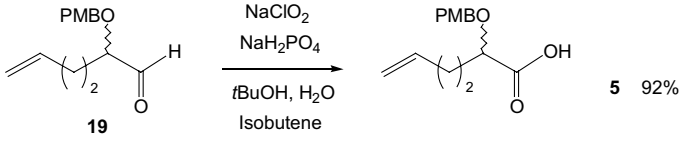
For the synthesis of **6**, some convenient modifications were brought to the Evans procedure.[7] The opening of trityl glycidol **20** with homoallyl magnesium bromide in the presence of copper (I) iodide gave alcohol **21**. After PMB protection and trityl cleavage with an acidic resin, Ley oxidation[8] followed by $NaClO_2$ treatment gave the desired carboxylic acid **6** (Scheme 6).

Alkyne carboxylic acid **7** was synthesized from **5** in 4 steps. After esterification with diazomethane and ozonolysis, aldehyde **22** was obtained by $Ph_3P$ treatment. Subsequent treatment with Bestmann–Ohira's reagent[9] gave the alkyne **23** in 69% overall yield. Finally, hydrated barium hydroxide saponification gave the desired **7** in 71% yield (Scheme 7).

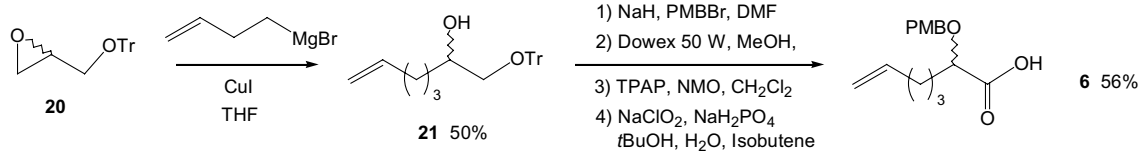
The known carboxylic acid **8**[10] was obtained in one step starting from allylglycine, by reaction with $(t\text{Boc})_2O$ in



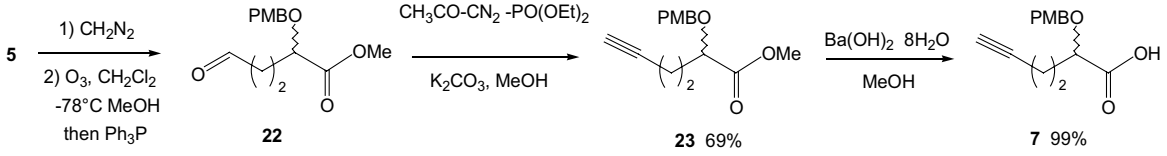

**Scheme 4.**




**Scheme 5.**




**Scheme 6.**




**Scheme 7.**

the presence of $NaHCO_3$. Carboxylic acid **9** is commercially available.

### 2.3. Preparation of esters 24–31

All esterifications were realized using the standard DCC, DMAP coupling procedure, giving precursors for CIM studies.

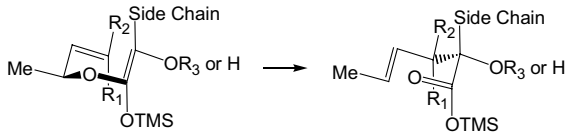
Structures and yields are reported in Table 1.

### 2.4. CIM transformation study

The CIM optimized procedure, which was applied to our fumagillin formal total synthesis,[4b,11] was extended to the esters **24**–**31** and Table 2 summarizes our results (see Procedure A in Experimental procedure). As we have already shown,[4a] the choice of KHMDS used as a base at −78 °C is crucial. The subsequent metathesis step can be easily accomplished, probably due to a Thorpe–Ingold effect generated by the quaternary carbon centre.

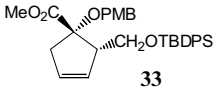
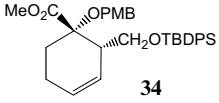
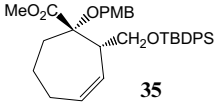
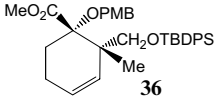
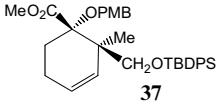
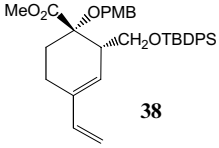
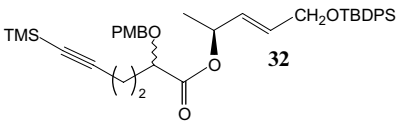
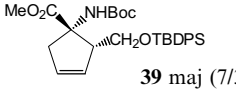
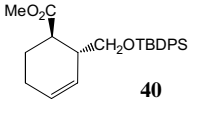
It should be noted that the final configuration can easily be predicted using a pre-chair representation of a silyl enol ester as shown below (Scheme 8).

The strategy is efficient in generating rings regardless of their size. Thus, entries A and H show that the formation of 5-carbon carbocycles **33** and **39** is a convenient process. Entries B, D, E, G and I exemplify clean




**Scheme 8.** Pre-chair transition state.

**Table 2.** CIM transformations

| Entry | Starting material | Product | Claisen–Ireland yield (%) | Metathesis yield (%) |
|---|---|---|---|---|
| A | **24** |  **33** | 60 | 70 |
| B | **25** |  **34** | 90 | 98 |
| C | **26** |  **35** | 75 | 76 |
| D | **27** |  **36** | 77 | 90 |
| E | **28** |  **37** | 78 | 88 |
| F | **29** |  **38** | F: 90 maj (7/3) G: 98 (quant. for deprotection of TMS) | 80 (under ethylene atmosphere) |
| G |  **32** | | | |
| H | **30** |  **39** maj (7/3) | 70 | Quant. |
| I | **31** |  **40** | 98 | 98 |


**Scheme 9.**

6-carbon carbocycle formation (**34**–**36**–**37**–**38** and **40**) and C is an example of a 7-carbon framework (**35**). Compounds **36** and **37** were isolated in excellent yields, without any trace of another diastereoisomer. This result strongly points to the role of the equatorial methyl group in directing the stereochemical outcome of the transposition in the transition state (Scheme 8). In a relevant application, we were pleased to see smooth formation of two nearby quaternary centres in entries D and E.

Comparison of entry I with the others could mistakenly lead to the conclusion that α-chelation with an alkoxy group doesn't play any role. In fact, the relative orientation of the enolates remains essentially the same in toluene, meaning that the side chain on the carboxylic acid fragment is always *E*-oriented (OTMS versus side chain) (Scheme 9).

Unfortunately, some cases proved to be more problematic. It is important to note that an acetylenic function needs to be protected.[12] After double deprotonation with LiHMDS at −78 °C and reaction with TMSCl in order to form a doubly silylated intermediate, careful low temperature acidic quenching afforded the protected acetylenic ester **32** (Scheme 10).

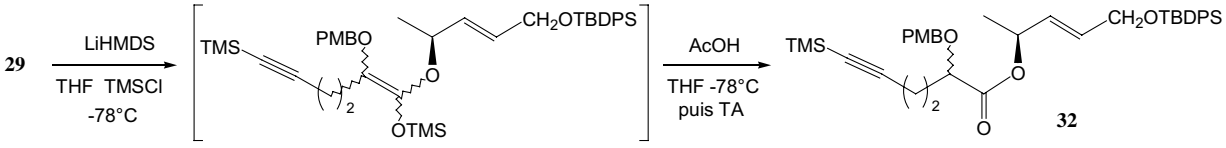
Even if the yield remains good, when the acetylenic moiety is unprotected (entry F), the diastereoselectivity in Claisen–Ireland rearrangement is low (7:3 ratio). This particular behaviour could tentatively be explained by an intramolecular deprotonation (via a chelated species) through a transition state represented as follows (Scheme 11), giving a reverse configuration for the enolate and the subsequent silylated ketene acetal.

Entry H is another case with poor diastereoselectivity (7:3), which can also be explained the same way. Even if the hypothesis of a base aggregation state seems possible, in reality it is probably not so simple, because of the thermodynamic equilibration of a dianionic species, or more complex aggregation states for metallated intermediates can take place.

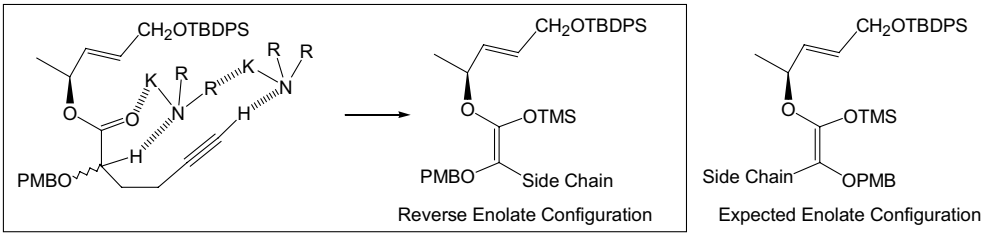
Entry G shows that ene–yne metathesis occurs efficiently,[13] extending the scope of functionalities. The remarkably efficient metathesis, even in the presence of diverse functions and by-products, allowed us to consider a 'one-pot' process. In a preliminary study (with entries B–D–I), we discovered that a 'one-pot' CIM is possible (47–74% yield) in cases where the rearrangement doesn't need any significant excess of reagents (more than 1 mmol, see Procedure B in Experimental procedure). This is especially interesting and convenient on gram-scale reactions.[11] The lower yields can be explained by the fact that an excess of reagents (TMSCl, KHMDS) is involved in Grubbs I reagent decomposition.

In order to control chirality transfer, deuterated derivatives were prepared from compounds **34**–**37** (Scheme 12). The introduction of deuterium atoms has been achieved by reducing the ester group to alcohol using lithium aluminium deuteride leading to compounds **41b**, **43**–**45**. Compound **34** (Table 2, entry B) was also reduced with lithium aluminium hydride to give **41a**, which was subsequently pivaloylated yielding ester **42a** used for an NOE study. The reduction of compound **35** (Table 2, entry C) gave **43** as a major product, with the loss of the TBDPS protecting group.

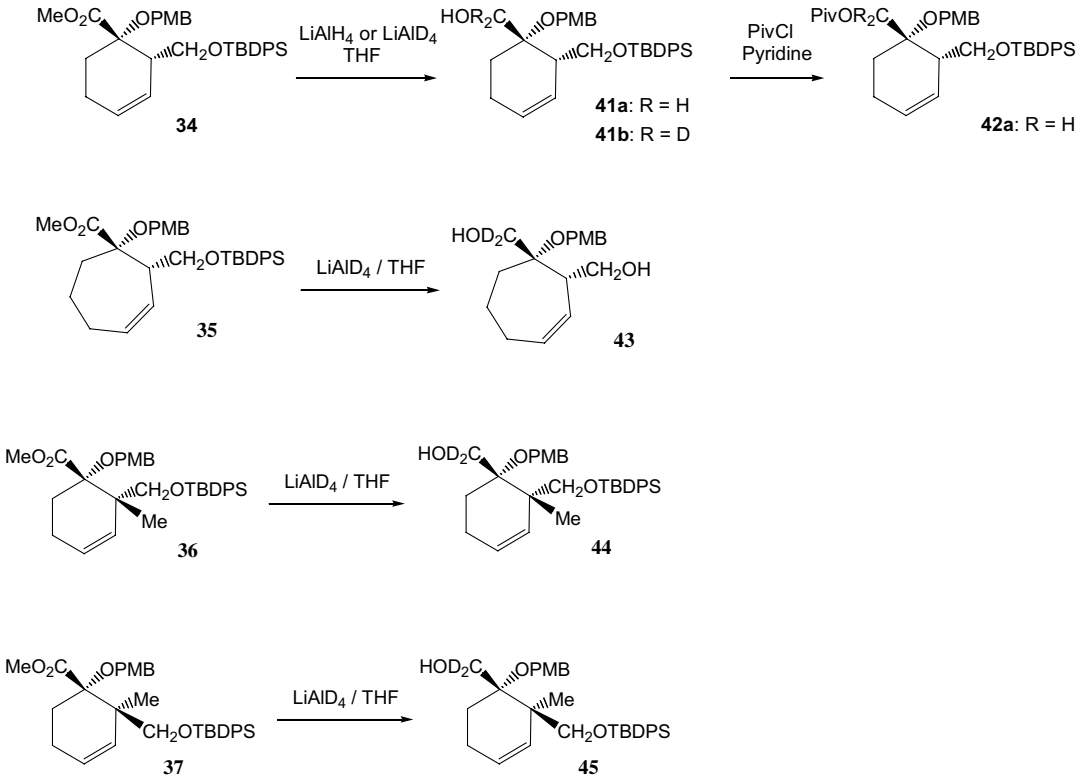
The stereoselectivity of this set of reactions as well as the enantiomeric purity of the compounds have been assessed using deuterium NMR in chiral liquid crystals. When embedded in such media, stereoisomers (enantiomers or diastereoisomers) do not assume the same orientation. This behaviour leads to a difference in their NMR spectra. The best results of this methodology were obtained using mesophases of poly-γ-benzyl-L-glutamate




**Scheme 10.**




**Scheme 11.**




**Scheme 12.**

(PBLG) in various organic solvents, through proton-decoupled deuterium ($^2H$–$\{^1H\}$) NMR.[14] For this nucleus, the NMR dominant observable is the quadrupolar interaction, which results in the splitting of a deuterium signal into a doublet. This technique is of general use in the case of enantiomeric analysis.[15] It is also extremely efficient in the observation of diastereoisomers.[16]

The $^2H$–$\{^1H\}$ NMR spectra of compounds **41b**, **43**, **44** and **45** in PBLG liquid crystals are presented in Figures 1–4, respectively. A typical spectrum exhibits two quadrupolar doublets, one for each diastereotopic deuterons. The spectra of compounds **41b**, **43** and **45** suggest the absence of any other stereoisomer. At this point, it should be noted that we did not analyze the racemic mixtures of compound **41b**, **43**, **44** and **45** to confirm that the enantiomers could be discriminated. However, these alcohols bear two diastereotopic deuterons, and to date enantiomers of such compound have always been discriminated, at least on one kind of deuterium in PBLG liquid crystals.[17] The diastereoisomeric purity of compound **34** was further supported by an NOE analysis of **42a**, which showed only one diastereoisomer (no trace of the other diastereoisomer was detected). The $^2H$–$\{^1H\}$ NMR spectrum of alcohol **44** (Fig. 3) presents additional signals, which reveal the presence of the minor enantiomer. The *ee* thus measured is 93%.

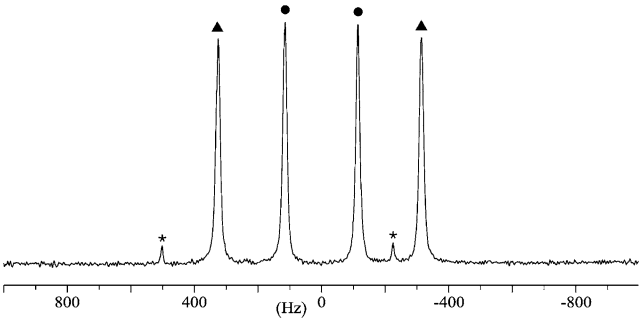



**Figure 1.** $^2H$–$\{^1H\}$ NMR spectrum of alcohol **41b** in PBLG/$CHCl_3$ liquid crystal. ● are the signals of one of the diastereotopic deuterons and ▲ are due to the second one. ★ are the $^2H$ natural abundance signals of the cosolvent ($CHCl_3$).

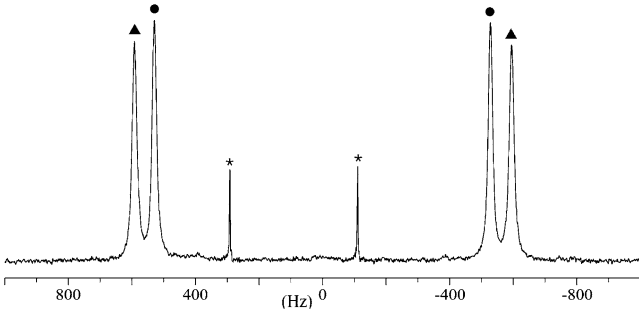



**Figure 2.** $^2H$–$\{^1H\}$ NMR spectrum of alcohol **43** in PBLG/$CH_2Cl_2$ liquid crystal. ● are the signals of one of the diastereotopic deuterium and ▲ are due to the second one. ★ are the $^2H$ natural abundance signals of the cosolvent ($CH_2Cl_2$).

When considering chirality transfer, all entries showed two crucial points:

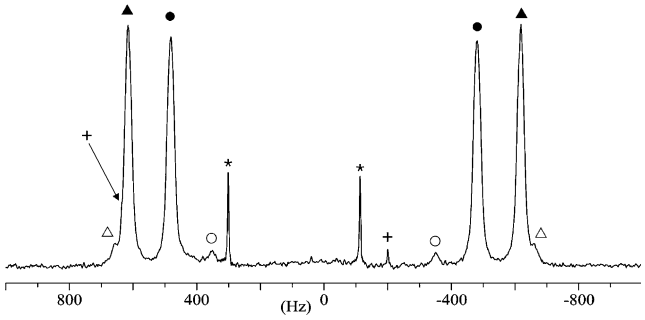



**Figure 3.** $^2H$–$\{^1H\}$ NMR spectrum of alcohol **44** in PBLG/$CH_2Cl_2$ liquid crystal. ● and ▲ are the signals of the two diastereotopic deuterons for the major enantiomer whereas △ and ○ are the signals of the minor one. ✶ are the $^2H$ natural abundance signals of the cosolvent ($CH_2Cl_2$) and + is the signal of residual $CDCl_3$.

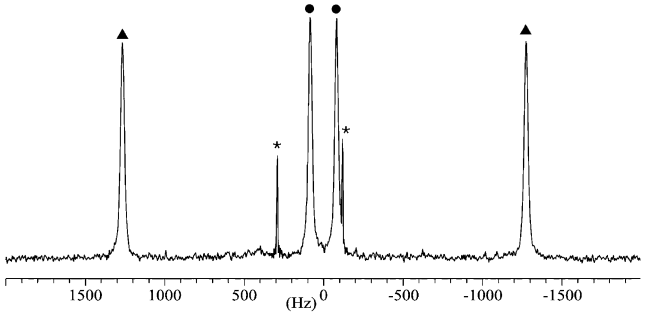



**Figure 4.** $^2H$–$\{^1H\}$ NMR spectrum of alcohol **45** in PBLG/$CH_2Cl_2$ liquid crystal. ● are the signals of one of the diastereotopic deuterium and ▲ are due to the second one. ✶ are the $^2H$ natural abundance signals of the cosolvent ($CH_2Cl_2$).

(1) The asymmetric centre of the starting material controls the chirality transfer in an enantioselective manner (verified by $^2H$ NMR in chiral liquid crystals[14]).
(2) An *E* double bond (in the allylic part) gave exclusive formation of one diastereoisomer. This was easily verified by derivatization of several cycloalkenes.

## 3. Conclusion

In conclusion, we believe that our approach to building contiguous asymmetric centres using CIM extends this concept towards the synthesis of complex biologically active natural products.

## 4. Experimental

### 4.1. Liquid-crystalline sample preparation and NMR spectra measurements

PBLG (120 mg, Mw 70,000–150,000, Sigma Chem. Co.) and dideuteroalcohol (1–5 mg) were placed in an NMR tube (5 mm) and $CH_2Cl_2$ added till about 22 wt % PBLG. After complete dissolution of the polymer, the tube was centrifuged upside and down (20 times) to homogenize the viscous solution. Dideuteroalcohol **41b** was analyzed in a PBLG/$CHCl_3$ liquid crystal (17 wt % PBLG). $^2H$ NMR spectra were recorded (61.42 MHz) on a Bruker DRX 400 spectrometer with a $^2H$-probe with broad-band proton decoupling. The temperature was kept at 298 K.

### 4.2. (2*S*,3*E*) 5-(*tert*-Butyl-diphenyl-silyloxy)-4-methyl-pent-3-en-2-ol 2

A mixture of **11** and **12** (see procedure to obtain **13** and **14**; 3.5 g, 14.52 mmol, 1 equiv) and pyridinium toluene-*p*-sulfonate (600 mg, 2.3 mmol, 0.15 equiv) were dissolved in ethanol (35 mL) and stirred at 45 °C for 1 h. The mixture was then diluted with water and concentrated to a low volume under reduced pressure. The resulting aqueous phase was extracted with diethyl ether (3 × 15 mL). The organic layer was dried, filtered and concentrated in vacuo. Purification of the resulting residue by silica gel column chromatography (55 g $SiO_2$, pentane/diethyl ether: 3:1) afforded allylic alcohol **15** (1.8 g, 11.47 mmol, 79% yield). Compound **15** (1 g, 6.37 mmol) was dissolved in toluene (10 mL) under an argon atmosphere and cooled to −78 °C. Diisobutylaluminium hydride (commercial solution in toluene 1 M, 21 mL, 21 mmol, 3.3 equiv) was added in 10 min. After 1 h, the reaction was stopped by the introduction of a small amount of methanol (until gas evolution ceased). A solution of sodium–potassium tartrate (30.4 g) in water (76 mL) was mixed with the reaction and the resulting mixture vigorously stirred overnight at room temperature. The layers were separated and the aqueous one extracted with methylene chloride (2 × 70 mL). The organic layer was dried, filtered and concentrated. The crude product was purified by silica gel column chromatography (cyclohexane/ethyl acetate: 4:1, 3:1, 2:1, 1:1). Three fractions were collected to give **16** (672 mg, 5.8 mmol, 91% yield). To a solution of diol **16** (398 mg, 3.43 mmol) and imidazole (466 mg, 11.7 mmol, 3.2 equiv) dissolved in methylene chloride (13 mL) was added *tert*-butylchlorodiphenylsilane (943 mg, 3.43 mmol, 1 equiv) dropwise. After stirring at room temperature for 12 h, the reaction mixture was poured into water. The separated aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined extracts were washed with water and brine, dried and then concentrated to give **2** (871 mg, 2.47 mmol, 72% yield).

Compound **2** $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.63–7.70 (4H, m, $\mathbf{C_{Ar}}$–**H**), 7.30–7.50 (6H, m, $\mathbf{C_{Ar}}$–**H**), 5.48 (1H, d, $\mathbf{C_3}$–**H**, $J$ = 8 Hz), 4.58 (1H, m, $\mathbf{C_2}$–**H**), 4.02 (2H, s, $\mathbf{C_5}$–**H** × 2), 1.61 (3H, s, $C_4$–**Me**), 1.22 (3H, d, $\mathbf{C_1}$–**H** × 3, $J$ = 6.25 Hz), 1.04 (9H, s, ***t*Bu**) $^{13}C$ NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 135.7 ($\mathbf{C_4}$), 135.5 ($\mathbf{C_{Ar}}$), 133.6 ($\mathbf{C_3}$), 129.5 ($\mathbf{C_{Ar}}$), 128.4 ($\mathbf{C_{qAr}}$), 128.2 ($\mathbf{C_{qAr}}$), 127.6 ($\mathbf{C_{Ar}}$), 68.2 ($\mathbf{C_2}$), 64.2 ($\mathbf{C_5}$), 26.8 (SiC**Me**$_3$), 23.4 ($C_4$–**Me**), 19.2 ($\mathbf{C_1}$), 13.6 (Si**C**Me$_3$) HRMS (electrospray) (M+Na) calculated: 377.1913; found: 377.1921. $R_f$ = 0.25 (ethyl acetate/*n*-heptane: 1:2).

### 4.3. (2*S*,3*Z*) 5-(*tert*-Butyl-diphenyl-silyloxy)-4-methyl-pent-3-en-2-ol 3

To a solution of allylic alcohol **14** (200 mg, 1 mmol) and imidazole (136 mg, 2 mmol, 2 equiv) dissolved in

THF/DMF (1:1) (6 mL) (or methylene chloride) was added *tert*-butylchlorodiphenylsilane (350 μL, 1.5 mmol, 1.5 equiv) dropwise. After stirring at room temperature for 12 h, the reaction mixture was poured into water. The separated aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined extracts were washed with water and brine, dried and then concentrated. A solution of the resulting silyl ether **17** and pyridinium toluene-*p*-sulfonate (26 mg, 0.1 mmol, 0.1 equiv) was dissolved in methanol (8 mL) and stirred at 40–45 °C for 1 h. The mixture was then diluted with water and concentrated to a low volume under reduced pressure. The resulting aqueous phase was extracted with diethyl ether (3 × 15 mL). The organic layer was dried, filtered and concentrated in vacuo. Purification of the resulting residue by silica gel column chromatography (55 g $SiO_2$, pentane/diethyl ether: 3:1) afforded allylic alcohol **3** (56% yield). Compound **3**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.63–7.70 (4H, m, **$C_{Ar}$–H**), 7.30–7.50 (6H, m, **$C_{Ar}$–H**), 5.48 (1H, d, **$C_3$–H**, $J$ = 8 Hz), 4.58 (1H, m, **$C_2$–H**), 4.02 (2H, s, **$C_5$–H** × 2), 1.61 (3H, s, $C_4$–**Me**), 1.22 (3H, d, **$C_1$–H** × 3, $J$ = 6.25 Hz), 1.04 (9H, s, ***t*Bu**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 136.1 (**$C_4$**), 135.4 (**$C_{Ar}$**), 133.3 (**$C_3$**), 131.5 (**$C_{qAr}$**), 131.2 (**$C_{qAr}$**), 129.6 (**$C_{Ar}$**), 127.6 (**$C_{Ar}$**), 63.4 (**$C_2$**), 62.7 (**$C_5$**), 26.7 (SiC**Me$_3$**), 23.3 ($C_4$–**Me**), 21.1 (**$C_1$**), 19.1 (Si**C**Me$_3$) HRMS (electrospray) (M+Na) calculated: 377.1913; found: 377.1921. $R_f$ = 0.25 (ethyl acetate/heptane: 1:2).

### 4.4. 2-(4-Methoxy-benzyloxy)-pent-4-enoic acid 4

Glyoxylic acid (92 mg, 1 mmol, 1 equiv) was dissolved in water (1 mL), then allyltributyltin (309 μL, 1 mmol, 1 equiv) was added under strong stirring. Triflic acid (88 μL, 1 mmol, 1 equiv) was introduced by syringe and the mixture stirred overnight. The reaction was quenched with brine (4 mL), and extracted with diethyl ether (2 × 10 mL) and ethylacetate (2 × 10 mL). The combined organic layers were dried, filtered and concentrated. The crude product was used in the next step without further purification.

Sodium hydride was washed twice with *n*-pentane under an argon atmosphere (84 mg, 2.5 mmol, 2.5 equiv), and a solution of *p*-methoxybenzylbromide (442 mg, 2.2 mmol, 2.2 equiv) in DMF (5 mL) added. The mixture was cooled to 0 °C, and acid **18** (1 mmol, 1 equiv) dissolved in dry THF (5 mL) added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was stopped by hydrolysis with aqueous HCl (1 M, 10 mL), and then extracted with diethyl ether (3 × 10 mL). The organic layer was dried, filtered and the diethyl ether removed under reduced pressure. Purification on silica gel column (30 g; pentane/diethyl ether 2:1 then diethyl ether), afforded 58 mg of the desired compound **4** (24.6% yield for two steps). Compound **4**: $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 7.15–7.30 (2H, m, **$C_{PMBar}$–H**), 6.75–6.90 (2H, m, **$C_{PMBar}$–H**), 5.65–5.90 (1H, m, **$C_4$–H**), 5.00–5.20 (2H, m, **$C_5$–H** × 2), 4.60 (2H, s, Ar–**$CH_2$**), 4.03 (1H, t, **$C_2$–H**), 3.75 (3H, s, **OMe**), 2.45–2.60 (2H, m, **$C_3$–H** × 2) HRMS (electrospray) ($RCOO^-$) calculated: 235.0970; found: 235.0960. $R_f$ (ether) = 0.2.

### 4.5. 2-(4-Methoxy-benzyloxy)-hex-5-enoic acid 5

Aldehyde **19** (1.11 mmol, 1 equiv) was dissolved in *tert*-butanol (25 mL) and 2-methylbut-2-ene (13 mL). A solution of $NaClO_2$ (6.44 mmol, 6 equiv) and $NaH_2PO_4$ (3.99 mmol, 3.6 equiv) in water (5.5 mL) was added dropwise during 15 min. The reaction mixture was stirred for 1 h. The reaction was stopped by addition of a saturated aqueous solution of $NH_4Cl$ (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried, filtered and concentrated. Crude material was purified by silica gel column chromatography (60 g $SiO_2$, pentane/diethyl ether 2:1). 157 mg of product was obtained for acid **5** (59% yield for two steps). Compound **5**: $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 7.27 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 6.86 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 5.60–5.90 (1H, m, **$C_5$–H**), 4.90–5.10 (2H, m, **$C_6$–H** × 2), 4.20–4.75 (2H, syst AB, Ar–**$CH_2$**), 3.90–4.15 (1H, m, **$C_2$–H**), 3.79 (3H, s, **OMe**), 2.10–2.30 (2H, m, **$C_4$–H** × 2), 1.75–1.95 (2H, m, **$C_3$–H** × 2) $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ (ppm): 177.9 (**$C_1$**), 159.5 (**$C_{qAr}$**–OMe), 137.1 (**$C_5$**), 129.8 (**$C_{Ar}$**), 129.0 (**$C_{qAr}$**), 115.6 (**$C_6$**), 113.9 (**$C_{Ar}$**), 76.3 (**$C_2$**), 72.3 ($C_{PMBar}$–**$CH_2$**O), 55.2 (O**$CH_3$**), 31.7 (**$C_4$**), 29.1 (**$C_3$**) HRMS (electrospray) ($RCOO^-$) calculated: 249.1126; found: 249.1125.

### 4.6. 2-(4-Methoxy-benzyloxy)-hept-6-enoic acid 6

Sodium hydride was washed twice with *n*-pentane under an argon atmosphere (150 mg, 6.25 mmol, 1.5 equiv), and a solution of *p*-methoxybenzylbromide (1.01 g, 5 mmol, 1.2 equiv) in DMF (10 mL) added. The mixture was cooled to 0 °C, and alcohol **21** (1.5 g, 4.7 mmol) dissolved in dry THF (10 mL) added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was stopped by hydrolysis with aqueous HCl (1 N, 10 mL), and then extracted with diethyl ether (3 × 15 mL). The organic layer was dried, filtered and the diethyl ether removed under reduced pressure. The crude product was dissolved in methanol (10 mL) and Dowex 50W (1 g) added in one portion. The reaction was stirred overnight, then the acidic resin was removed by filtration. The filtrate was concentrated under reduced pressure and the residue purified by chromatography on silica gel (80 g $SiO_2$, pentane/diethyl ether: 1:1). The primary alcohol (monoprotected with a PMB group) was obtained as a colourless oil (787 mg, 67% yield). $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 7.20–7.40 (2H, m, **$C_{PMBar}$–H**), 6.80–6.95 (2H, m, **$C_{PMBar}$–H**), 5.60–5.90 (1H, m, **$C_6$–H**), 4.90–5.10 (2H, m, **$C_7$–H** × 2), 4.40–4.60 (2H, syst AB, Ar–**$CH_2$**), 3.82 (3H, s, **OMe**), 3.60–3.80 (1H, m, **$C_2$–H**), 3.40–3.60 (2H, m, **$C_1$–H** × 2), 2.00–2.20 (2H, m, **$C_5$–H** × 2), 1.85–2.00 (1H, m, **OH**), 1.30–1.75 (4H, m, **$C_4$–H** × 2, **$C_3$–H** × 2) MS (electrospray) (M+Na) found: 273.1. $R_f$ (pentane/diethyl ether: 1:1) = 0.25.

The alcohol (345 mg, 1.38 mmol) and NMO (254 mg, 2.17 mmol, 1.6 equiv) were dissolved in dry methylene chloride (7 mL) and the mixture cooled to 0 °C. TPAP (38 mg, 0.14 mmol, 0.1 equiv) was added dropwise in methylene chloride (2 mL) and the resulting black

mixture stirred for 3 h at 0 °C. The reaction was filtered on Celite, washed three times with methylene chloride (25 mL), and the filtrate concentrated under reduced pressure. The aldehyde was pure enough for the second oxidation step (88% yield). $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 9.61 (1H, br s or d, C**HO**), 7.10–7.30 (2H, m, $\mathbf{C_{PMBar}}$–**H**), 6.75–6.90 (2H, m, $\mathbf{C_{PMBar}}$–**H**), 5.65–5.85 (1H, m, $\mathbf{C_6}$–**H**), 4.85–5.05 (2H, m, $\mathbf{C_7}$–**H** × 2), 4.40–4.65 (2H, syst AB, Ar–$\mathbf{CH_2}$), 3.89 (3H, s, **OMe**), 3.60–3.90 (1H, m, $\mathbf{C_2}$–**H**), 1.90–2.20 (2H, m, $\mathbf{C_5}$–**H** × 2), 1.30–1.80 (4H, m, $\mathbf{C_4}$–**H** × 2, $\mathbf{C_3}$–**H** × 2) MS (electrospray) (M+Na) found: 271.1. $R_f$ (pentane/diethyl ether: 2:1) = 0.22.

The obtained aldehyde (1.11 mmol, 1 equiv) was dissolved in *tert*-butanol (25 mL) and 2-methylbut-2-ene (13 mL). A solution of $NaClO_2$ (6.44 mmol, 6 equiv) and $NaH_2PO_4$ (3.99 mmol, 3.6 equiv) in water (5.5 mL) was added dropwise during 15 min. The reaction mixture was then stirred for 1 h. The reaction was stopped by the addition of a saturated aqueous solution of $NH_4Cl$ (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried, filtered and concentrated. The crude material was purified by silica gel column chromatography (60 g $SiO_2$, pentane/diethyl ether 2:1), to give 157 mg of acid **6** (52% yield for two steps). Compound **6**: $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 9.50–9.90 (1H, br s, COO**H**), 7.25–7.35 (2H, m, $\mathbf{C_{PMBar}}$–**H**), 6.85–7.00 (2H, m, $\mathbf{C_{PMBar}}$–**H** $\mathbf{C_{PMBar}}$–**H**), 5.70–5.90 (1H, m, $\mathbf{C_6}$–**H**), 4.90–5.10 (2H, m, $\mathbf{C_7}$–**H** × 2), 4.30–4.75 (2H, syst AB, Ar–$\mathbf{CH_2}$), 3.80–4.05 (1H, m, $\mathbf{C_2}$–**H**), 3.80 (3H, s, **OMe**), 2.00–2.20 (2H, m, $\mathbf{C_5}$–**H** × 2), 1.70–1.90 (2H, m, $\mathbf{C_3}$–**H** × 2), 1.40–1.65 (2H, m, $\mathbf{C_4}$–**H** × 2) HRMS (electrospray) ($RCOO^-$) calculated: 263.1283; found: 263.1280.

### 4.7. 2-(4-Methoxy-benzyloxy)-hex-5-ynoic acid 7

Ester **23** (181 mg, 0.69 mmol, 1 equiv) was dissolved in methanol (5 mL). Barium oxide octahydrate (2.2 g, 6.9 mmol, 10 equiv) was introduced in one portion. The reaction stirred at room temperature for 4 h. Methanol was removed by evaporation under reduced pressure and the residue dissolved in diethyl ether (10 mL) and washed with 0.5 N HCl solution (10 mL). The acidic layer was then extracted with diethyl ether (2 × 10 mL). The organic layer was dried, filtered and concentrated to give 171 mg of acid **7** (99% yield). Compound **7**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.31 (2H, d, $\mathbf{C_{PMBar}}$–**H**, $J$ = 8 Hz), 6.80 (2H, d, $\mathbf{C_{PMBar}}$–**H**, $J$ = 8 Hz), 4.30–4.75 (2H, syst AB, Ar–$\mathbf{CH_2}$), 4.05–4.15 (1H, m, $\mathbf{C_2}$–**H**), 3.80 (3H, s, **OMe**), 3.76 (3H, s, $CO_2\mathbf{CH_3}$), 2.25–2.45 (2H, m, $\mathbf{C_3}$–**H** × 2), 1.85–2.05 (3H, m, $\mathbf{C_4}$–**H** × 2, $\mathbf{C_6}$–**H**) HRMS (electrospray) ($RCOO^-$) calculated: 247.0970; found: 247.0968. $R_f$ = 0.3–0.5 (diethyl ether/pentane: 2:1).

### 4.8. (4*S*)-2-Methyl-4-(tetrahydro-pyran-2′-yloxy)-pent-2-en-1-ol 13 and 14

Sodium hydride (320 mg, 13.3 mmol, 1.05 equiv) was washed twice with *n*-pentane under an argon atmosphere. After the introduction of dry THF (25 mL), the NaH suspension was cooled to 0 °C and the phosphonate introduced (3.50 mL, 16.5 mmol, 1.3 equiv) in dry THF (50 mL). After 10 min, aldehyde **10** (2 g, 12.7 mmol, 1 equiv) dissolved in THF (10 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with 50 mL of a 10% $NH_4Cl$ aqueous solution and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 40 mL), and the combined organic layers dried and filtered and the solvent removed under reduced pressure. Crude material was purified by silica gel column chromatography (300 g $SiO_2$, heptane/ethyl acetate: 7:3) giving 2.53 g of a mixture of the four diastereoisomers of ester **11** and **12** (82% yield). This mixture of **11** and **12** (2 g, 8.3 mmol, 1 equiv) was dissolved in dry methylene chloride (50 mL) under an argon atmosphere and cooled to −78 °C. Diisobutylaluminium hydride (commercial solution in $CH_2Cl_2$ 1 M, 20 mL, 20 mmol, 2.31 equiv) was added in 10 min. After 1 h, the reaction was stopped by the introduction of a small amount of methanol (until gas evolution ceased). A solution of sodium-potassium tartrate (30.4 g) in water (76 mL) was mixed with the reaction and the resulting mixture vigorously stirred overnight at room temperature. The layers were separated and the aqueous one was extracted with methylene chloride (2 × 70 mL). The organic layer was dried, filtered and concentrated. The crude product was purified by silica gel column chromatography (cyclohexane/ethyl acetate: 4:1, 3:1, 2:1, 1:1). Three fractions were collected (1.87 g, 90% yield: 24% of *Z* alkene, 49% *Z* + *E* and 27% *E* alkene). Compound **13**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 5.49 (1H, d, $\mathbf{C_3}$–**H**, $J$ = 7.5 Hz), 4.68 (1H, m, $\mathbf{C_{1'}}$–**H**), 4.56 (1H, m, $\mathbf{C_4}$–**H**), 3.96 (2H, m, $\mathbf{C_{6'}}$–**H** × 2), 3.65 (2H, syst AB, $\mathbf{C_1}$–**H** × 2), 2.64 (1H, br s, **OH**), 1.3–1.95 (6H, m, $\mathbf{C_{3'}}$–**H** × 2, $\mathbf{C_{4'}}$–**H** × 2, $\mathbf{C_{5'}}$–**H** × 2), 1.50 (3H, s, $C_2$–**Me**), 1.18 (3H, d, $\mathbf{C_5}$–**H** × 3, $J$ = 6 Hz) MS (electrospray) (M+Na); found: 223.1. $R_f$ = 0.26 (ethyl acetate/cyclohexane: 1:1).

Compound **14**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ (ppm): 5.08 (1H, d, $\mathbf{C_3}$–**H**, $J$ = 10.4 Hz), 4.75 (1H, m, $\mathbf{C_{1'}}$–**H**), 4.60 (1H, m, $\mathbf{C_4}$–**H**), 4.32 (1H, dd, $\mathbf{C_1}$–**Ha**, $J$ = 2.9 Hz $J$ = 12 Hz), 3.80 (2H, m, $\mathbf{C_{6'}}$–**H** × 2), 3.60 (1H, d, $\mathbf{C_1}$**Hb**, $J$ = 11 Hz), 2.87 (1H, br s, **OH**), 1.5–1.95 (9H, m, $\mathbf{C_{3'}}$–**H** × 2, $\mathbf{C_{4'}}$–**H** × 2, $\mathbf{C_{5'}}$–**H** × 2, $C_2$–**Me**), 1.26 (3H, d, $\mathbf{C_5}$–**H** × 3, $J$ = 6.1 Hz) MS (electrospray) (M+Na) calculated: 223.1; found: 223.1. $R_f$ = 0.37 (ethyl acetate/cyclohexane: 1:1).

### 4.9. 1-Trityloxy-hept-6-en-2-ol 21

Magnesium turnings (972 mg, 40 mmol) were introduced in a round-bottom flask under argon with a magnetic stirrer. After mechanical activation (overnight), dry diethyl ether (10 mL) was added. Homoallylbromide (4.78 g, 30 mmol, 3 equiv) dissolved in dry THF (37 mL) was slowly introduced. The mixture was heated to reflux for 2 h. The supernatant was transferred by cannula in a solution of tritylglycidol **20** (3 g, 10 mmol, 1 equiv) and

copper iodide (286 mg, 1.5 mmol, 0.13 equiv) in dry THF (13 mL) at −10 °C. The resulting black solution was allowed to warm to room temperature and stirred for two hours. The reaction mixture was quenched with aqueous saturated $NH_4Cl$ solution (30 mL), the layers separated and the aqueous one was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried, filtered and concentrated to afford 1.6 g of a pale yellow oil (50% yield). The crude product was used in the next step without further purification. Compound **21**: $^1$H NMR: 200 MHz, $CDCl_3$, $\delta$ (ppm): 7.15–7.50 (15H, m, **$C_{Ar}$–H**), 5.60–5.85 (1H, m, **$C_6$–H**), 4.85–5.05 (2H, m, **$C_7$–H** × 2), 3.65–3.90 (1H, m, **$C_2$–H**), 3.20 (1H, dd, **$C_1$–H**, $J$ = 5 Hz, $J$ = 17 Hz), 3.01 (1H, dd, **$C_1$–H**, $J$ = 8Hz, $J$ = 17 Hz), 2.25–2.45 (1H, br s, **OH**), 1.90–2.10 ppm (2H, m, **$C_5$–H** × 2), 1.20–1.60 (4H, m, **$C_4$–H** × 2, **$C_3$–H** × 2) MS (electrospray) (M+Na) calculated: 395.2; found: 395.2. $R_f$ (methylene chloride) = 0.55.

### 4.10. 2-(4-Methoxy-benzyloxy)-hex-5-ynoic acid methyl ester 23

Acid **6** (250 mg, 1 mmol, 1 equiv) was esterified by treatment with diazomethane. After evaporation of the solvent, the methyl ester was dissolved in a methylene chloride/methanol mixture (9:1) and cooled to −78 °C. This solution was submitted to ozone bubbling until a blue colour appeared. Excess triphenylphosphine was then added, and the reaction allowed to warm to room temperature and stirred overnight. The reaction mixture was then concentrated under reduced pressure and the residue triturated in diethyl ether (10 mL) in order to remove triphenylphosphine oxide by filtration. The filtrate was concentrated to afford crude aldehyde **22**, which was used in the next step without further purification. Compound **22** was dissolved in methanol (10 mL) with $K_2CO_3$ (2.2 mmol, 2.2 equiv, 304 mg). The freshly prepared Bestmann–Ohira reagent (211 mg, 2.2 mmol, 2.2 equiv) was then added over 2 min with stirring. After 1 h, methanol was removed by evaporation under reduced pressure. The crude product was dissolved in diethyl ether (10 mL) and washed with water (10 mL), and the layers separated. The aqueous layer extracted with diethyl ether (3 × 10 mL), the combined organic layers dried and filtered and the solvent removed under reduced pressure. Purification by silica gel column chromatography (20 g $SiO_2$, pentane/diethyl ether: 5:1) gave 181 mg of alkyne **23** (69% yield for three steps).

Compound **23**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ (ppm): 7.28 (2H, d, **$C_{PMBar}$–H**, $J$ = 9 Hz), 6.87 (2H, d, **$C_{PMBar}$–H**, $J$ = 9 Hz), 4.30–4.75 (2H, syst AB, Ar–**$CH_2$**), 4.10 (1H, dd, **$C_2$–H**, $J$ = 5 Hz $J$ = 5.75 Hz), 3.80 (3H, s, **OMe**), 3.76 (3H, s, $CO_2$**$CH_3$**), 2.25–2.45 (2H, m, **$C_3$–H** × 2), 2.01 (1H, d, **$C_6$–H**, $J$ = 2.5 Hz), 1.85–1.99 (2H, m, **$C_4$–H** × 2) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 172.8 (**$C_1$**), 159.2 (**$C_{qAr}$**–OMe), 129.6 (**$C_{Ar}$**), 129.3 (**$C_{qAr}$**), 113.6 (**$C_{Ar}$**), 82.8 (**$C_5$**), 75.8 (**$C_6$**), 72.2 ($C_{PMBar}$–$CH_2$O), 69.0 (**$C_2$**), 55.1 (ArO**Me**), 51.8 ($CO_2$**Me**), 31.5 (**$C_4$**), 14.4 (**$C_3$**) HRMS (electrospray) (M+Na) calculated: 285.1103; found: 285.1099. $R_f$ = 0.6 (diethyl ether/pentane: 1:5).

### 4.11. General procedure for DCC esterification

The chiral allylic alcohols **1**–**3** (1 mmol) and carboxylic acid **4**–**9** (1 mmol or 1.1 mmol when possible) were dissolved in dry methylene chloride (10 mL) with a catalytic amount of DMAP (0.1 mmol). The flask was cooled to 0 °C with an ice bath and stirred for 10 min. A solution of DCC (1.2 mmol) in methylene chloride (4 mL) was added dropwise in 10 min. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was then filtered on Celite, washed with methylene chloride (5 mL) and the filtrate concentrated under reduced pressure. The residue was triturated in diethyl ether in order to remove traces of DCU by filtration. The crude material was purified by silica gel column chromatography (75 g $SiO_2$, pentane/diethyl ether: 4:1) to afford the desired compound as a colourless oil.

### 4.12. (2*RS*,1′*S*,2′*E*) 2-(4-Methoxy-benzyloxy)-pent-4-enoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′-methyl-but-2′-enyl ester 24

44% yield **24**: $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 7.55–7.75 (4H, m, **$C_{Ar}$–H**), 7.28–7.45 (6H, m, **$C_{Ar}$–H**), 7.25 (2H, d, **$C_{PMBAr}$–H**, $J$ = 8.6 Hz), 6.85 (2H, d, **$C_{PMBAr}$–H**, $J$ = 8.6 Hz), 5.70–5.85 (2H, m, **$C_{2'}$–H**, **$C_{3'}$–H**), 5.40–5.55 (1H, m., **$C_4$–H**), 5.00–5.20 (2H, m, **$C_5$–H** × 2), 4.60–4.70 (1H, m, **$C_{1'}$–H**), 4.35 (2H, syst AB, **$C_{4'}$–H** × 2), 4.15–4.25 (2H, m, Ar–**$CH_2$**), 3.95 (1H, t, **$C_2$–H**, $J$ = 6.4 Hz), 3.75 (3H, s, **OMe**), 2.40–2.60 (2H, m, **$C_3$–H** × 2), 1.20–1.40 (3H, m, $C_{1'}$–**Me**), 1.10 (9H, s, Si–***t*Bu**) $^{13}$C NMR: 62.5 MHz, $CDCl_3$, $\delta$ (ppm): 172.8 (**$C_1$**), 159.5 (**$C_{PMBAr}$**–OMe), 135.7 (**$C_4$**), 135.5 (**$C_{Ar}$**), 133.5 (**$C_{qAr}$**), 131.3 and 130.9 (**$C_{2'}$** and **$C_{PMBAr}$**–$CH_2$O), 130.1 and 129.2 (**$C_{Ar}$** et **$C_{PMBAr}$**), 128.8 (**$C_{3'}$**), 127.9 (**$C_{Ar}$**), 115.6 (**$C_5$**), 113.7 (**$C_{PMBAr}$**), 77.0 (**$C_2$**), 71.8 ($C_{PMBar}$–**$CH_2$O**), 71.0 (**$C_{1'}$**), 63.4 (**$C_{4'}$**), 55.2 (ArO**Me**), 28.7 (**$C_3$**), 26.4 (SiC**$Me_3$**), 20.1 ($C_{1'}$–**Me**), 19.1 (Si**C**$Me_3$) HRMS (electrospray) (M+Na) calculated: 581.2699; found: 581.2695. $R_f$ (pentane/diethyl ether: 6:1) = 0.55.

### 4.13. (2*RS*,1′*S*,2′*E*) 2-(4-Methoxy-benzyloxy)-hex-5-enoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′-methyl-but-2′-enyl ester 25

89% yield **25**: $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 7.50–7.75 (4H, m, **$C_{Ar}$–H**), 7.30–7.43 (6H, m, **$C_{Ar}$–H**), 7.26 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 6.85 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 5.77–5.83 (2H, m, **$C_{2'}$–H**, **$C_{3'}$–H**), 5.55–5.85 (1H, m, **$C_5$–H**), 5.38–5.57 (1H, m, **$C_{1'}$–H**), 4.90–5.05 (2H, m, **$C_6$–H** × 2), 4.63 (1H, d, Ph**C**H–**$H_a$**, $J$ = 11.1 Hz (dia 1 and 2)), 4.30 (1H, d, Ph**C**H–**$H_b$**, $J$ = 11.1 Hz (dia 1)), 4.28 (1H, d, Ph**C**H–**$H_b$**, $J$ = 11.1 Hz (dia 2)), 4.15–4.25 (2H, m, **$C_{4'}$H** × 2), 3.89 (1H, t, **$C_2$–H**, $J$ = 6.4 Hz), 3.78 (3H, s, **OMe**), 2.10–2.25 (2H, m, **$C_4$–H** × 2), 1.72–1.91 (2H, m, **$C_3$–H** × 2), 1.33 (3H, d, $C_{1'}$–**Me**, $J$ = 6.5 Hz (dia1)), 1.32 (3H, d, $C_{1'}$–**Me**, $J$ = 6.5 Hz (dia 2)), 1.04 (9H, s, Si–***t*Bu**) $^{13}$C NMR: 62.5 MHz, $CDCl_3$, $\delta$ (ppm): 172.1 (**$C_1$**), 159.5 (**$C_{PMBAr}$**–OMe), 135.7 (**$C_5$**), 135.5 (**$C_{Ar}$**), 133.5 (**$C_{qAr}$**), 131.4 and 131.2 (**$C_{2'}$** and **$C_{PMBar}$**–$CH_2$O),

129.7 and 129.6 ($C_{Ar}$ and $C_{PMBar}$), 128.8 ($C_{3'}$), 127.9 ($C_{Ar}$), 115.6 ($C_6$), 113.7 ($C_{PMBar}$), 77.0 ($C_2$), 71.8 ($C_{PMBar}$–$CH_2O$), 71.0 ($C_{1'}$), 63.4 ($C_{4'}$), 55.2 (ArO**Me**), 29.4 and 32.1 ($C_3$ and $C_4$), 26.7 (SiC$Me_3$), 20.3 ($C_1$–**Me**), 19.2 (Si**C**$Me_3$) HRMS (electrospray) (M+Na) calculated: 595.2855; found: 595.2856. $R_f$ (pentane/diethyl ether: 8:3) = 0.75.

### 4.14. (2*RS*,1′*S*,2′*E*) 2-(4-Methoxy-benzyloxy)-hept-6-enoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′-methyl-but-2′-enyl ester 26

80% yield **26**: $^1$H NMR: 250 MHz, $CDCl_3$, $\delta$ (ppm): 7.65–7.75 (4H, m, $C_{Ar}$–**H**), 7.30–7.50 (6H, m, $C_{Ar}$–**H**), 7.27 (2H, d, $C_{PMBar}$–**H**, $J$ = 8.6 Hz), 6.86 (2H, d, $C_{PMBar}$–**H**, $J$ = 8.6 Hz), 5.78–5.86 (2H, m, $C_{2'}$–**H**, $C_{3'}$–**H**), 5.65–5.90 (1H, m, $C_6$–**H**), 5.40–5.55 (1H, m, $C_{1'}$–**H**), 4.88–5.05 (2H, m, $C_7$–**H** × 2), 4.62 (1H, d, Ph**C**H–$H_a$, $J$ = 11.1 Hz), 4.31 (1H, d, Ph**C**H–$H_b$, $J$ = 11.1 Hz), 4.18–4.25 (2H, m, $C_{4'}$–**H** × 2), 3.88 (1H, t, $C_2$–**H**, $J$ = 6.5 Hz), 3.79 (3H, s, **OMe**), 1.95–2.11 (2H, m, $C_5$–**H** × 2), 1.65–1.82 (2H, m, $C_3$–**H** × 2), 1.39–1.65 (2H, m, $C_4$–**H** × 2), 1.34 (3H, dd, $C_{1'}$–**Me**, $J$ = 3.1 Hz $J$ = 5.1 Hz (dia 1 and 2)), 1.06 (9H, s, Si–*t***Bu**).

$^{13}$C NMR: 62.5 MHz, $CDCl_3$, $\delta$ (ppm): 172.1 ($C_1$), 159.5 ($C_{PMBAr}$–OMe), 135.7 ($C_6$), 135.5 ($C_{Ar}$), 133.5 ($C_{qAr}$), 131.0 et 130.9 ($C_{2'}$ and $C_{PMBar}$–$CH_2O$), 129.7 and 129.3 ($C_{Ar}$ and $C_{PMBar}$), 128.5 ($C_{3'}$), 128.0 ($C_{Ar}$), 116.6 ($C_7$), 113.9 ($C_{PMBAr}$), 77.3 ($C_2$), 71.7 ($C_{PMBar}$–$CH_2O$), 69.7 ($C_{1'}$), 63.5 ($C_{4'}$), 55.2 (ArO**Me**), 28.4 and 31.1 ($C_5$ and $C_4$), 27.2 ($C_3$), 26.6 (SiC$Me_3$), 19.9 ($C_1$–**Me**), 19.1 (Si**C**$Me_3$) HRMS (electrospray) (M+Na) calculated: 609.3012; found: 609.3010. $R_f$ (pentane/diethyl ether: 5:1) = 0.65.

### 4.15. (2*RS*,1′*S*,2′*E*) 2-(4-Methoxy-benzyloxy)-hex-5-enoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′,3′-dimethyl-but-2′-enyl ester 27

90% yield **27**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.59–7.74 (4H, m, $C_{Ar}$–**H**), 7.25–7.50 (6H, m, $C_{Ar}$–**H**), 7.29 (2H, d, $J$ = 8.6 Hz, $C_{PMBar}$–**H**), 6.87 (2H, d, $J$ = 8.6 Hz, $C_{PMBar}$–**H**), 5.60–5.77 (2H, m, $C_{2'}$–**H**, $C_5$–**H**), 5.50–5.60 (1H, m, $C_{1'}$–**H**), 4.85–5.05 (2H, m, $C_6$–**H** × 2), 4.63 (1H, d, $J$ = 11.1 Hz, Ph**C**H–$H_a$), 4.28 (1H, d, $J$ = 11.1 Hz, Ph**C**H–$H_b$), 4.00–4.10 (2H, m, $C_{4'}$**H** × 2), 3.88 (1H, t, $J$ = 6.4 Hz, $C_2$–**H**), 3.78 (3H, s, **OMe**), 2.06–2.28 (2H, m, $C_4$–**H** × 2), 1.71–1.90 (2H, m, $C_3$–**H** × 2), 1.63 (3H, s, $C_{3'}$–**Me**), 1.32 (3H, dd, $J$ = 3.1 Hz, $J$=5.2 Hz, $C_{1'}$–**Me** (dia 1 and 2)), 1.05 (9H, s, Si–*t***Bu**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 172.3 ($C_1$), 159.3 ($C_{PMBAr}$–OMe), 138.2 ($C_{2'}$), 138.1 ($C_{3'}$), 137.5 ($C_{qAr}$), 135.4 ($C_{Ar}$), 133.4 ($C_{PMBar}$–$CH_2O$), 129.7 ($C_{Ar}$ and $C_{PMBar}$), 127.6 ($C_{Ar}$), 123.2 ($C_5$),115.3 ($C_6$), 113.7 ($C_{PMBar}$), 77.0 ($C_2$), 71.8 ($C_{PMBar}$–$CH_2O$), 68.2 ($C_{1'}$), 67.7 ($C_{4'}$), 55.2 (ArO**Me**), 32.2 ($C_4$), 29.4 ($C_3$), 26.8 (SiC$Me_3$), 20.8 ($C_1$–**Me**), 19.4 (Si**C**$Me_3$), 13.8 ($C_{3'}$) HRMS (electrospray) (M+Na) calculated: 609.3012; found: 609.3009. $R_f$ = 0.65 (diethyl ether/pentane: 1:5).

### 4.16. (2*RS*,1′*S*,2′*Z*) 2-(4-Methoxy-benzyloxy)-hex-5-enoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′,3′-dimethyl-but-2′-enyl ester 28

69% yield **28**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.65–7.76 (4H, m, $C_{Ar}$–**H**), 7.32–7.50 (6H, m, $C_{Ar}$–**H**), 7.25 (2H, d, $J$ = 8.6 Hz, $C_{PMBar}$–**H**), 6.86 (2H, d, $J$ = 8.6 Hz, $C_{PMBar}$–**H**), 5.65–5.82 (2H, m, $C_{2'}$–**H**, $C_5$–**H**), 5.50–5.65 (1H, m, $C_{1'}$–**H**), 5.19–5.31 (1H, m, $C_{1'}$–**H**), 4.92–5.05 (2H, m, $C_6$–**H** × 2), 4.57 (1H, dd, $J$ = 11.5 Hz $J$ = 3 Hz, Ph**C**H–$H_a$), 4.28 (1H, dd, $J$ = 12.3 Hz $J$ = 9.3, Ph**C**H–$H_b$), 4.18–4.32 (2H, m, $C_{4'}$**H** × 2), 3.77–3.89 (1H, m, $C_2$–**H**), 3.79 (3H, s, **OMe**), 2.08–2.22 (2H, m, $C_4$–**H** × 2), 1.68–1.89 (2H, m, $C_3$–**H** × 2), 1.86 (3H, s, $C_{3'}$–**Me**), 1.22 (3H, d, $J$ = 6.8 Hz, $C_{1'}$–**Me** (dia 1 and 2)), 1.08 (9H, s, Si–*t***Bu**) HRMS (electrospray) (M+Na) calculated: 609.3012; found: 609.3011. $R_f$ = 0.65 (diethyl ether/pentane: 1:5).

### 4.17. (2*RS*,1′S,2′*E*) 2-(4-Methoxy-benzyloxy)-hex-5-ynoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′-methyl-but-2′-enyl ester 29

71% yield **29**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ (ppm): 7.67 (4H, m, $C_{Ar}$–**H**), 7.39 (6H, m, $C_{Ar}$–**H**), 7.27 (2H, d, $C_{PMBar}$–**H**, $J$ = 8.6 Hz), 6.86 (2H, d, $C_{PMBar}$–**H**, $J$ = 8.6 Hz), 5.81 (2H, m, $C_{2'}$–**H**, $C_{3'}$–**H**), 5.47 (1H, m, $C_{1'}$–**H**), 4.65 (1H, d, Ph**C**H–$H_a$, $J$ = 11 Hz), 4.34 (1H, dd, Ph**C**H–$H_b$, $J$ = 11 Hz $J$ = 2.3 Hz), 4.20 (2H, m, $C_{4'}$**H** × 2), 4.03–4.09 (1H, m, $C_2$–**H** (dia 1 and 2)), 3.79 (3H, s, **OMe**), 2.34 (2H, m, $C_4$–**H** × 2), 1.89–2.01 (3H, m, $C_3$–**H** × 2, $C_6$–**H**), 1.34 (3H, dd, $C_{1'}$–**Me** (dia 1 and 2)), 1.06 (9H, s, Si–*t***Bu**) HRMS (electrospray) (M+Na) calculated: 593.2699; found: 593.2697. $R_f$ = 0.55 (diethyl ether/pentane: 1:5).

### 4.18. (2*RS*,1′*S*,2′*E*) 2-*tert*-Butoxycarbonylamino-pent-4-enoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′-methyl-but-2′-enyl ester 30

72% yield **30**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.62–7.74 (4H, m, $C_{Ar}$–**H**), 7.32–7.50 (6H, m, $C_{Ar}$–**H**), 5.76–5.83 (2H, m, $C_{2'}$–**H**, $C_{3'}$–**H**), 5.59–5.78 (1H, m, $C_4$–**H**), 5.38–5.50 (1H, m, $C_{1'}$–**H**), 5.02–5.20 (2H, m, $C_5$–**H** × 2), 4.32–4.42 (1H, m, $C_2$–**H**), 4.18–4.28 (2H, m, $C_{4'}$**H** × 2), 2.43–2.62 (2H, m, $C_3$–**H** × 2), 1.86 (3H, s, $C_{3'}$–**Me**), 1.44 (9H, s, O–*t***Bu**), 1.32 (3H, dd, $C_{1'}$–**Me** (dia 1 and 2), $J$ = 6.8 Hz $J$ = 6.5 Hz), 1.06 (9H, s, Si–*t***Bu**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 171.1 ($C_1$), 155.1 (**C**(O)Boc), 135.4 ($C_{Ar}$), 133.4 ($C_{qAr}$), 132.2 ($C_{2'}$), 131.4 ($C_{3'}$), 129.6 ($C_{Ar}$), 128.5 ($C_4$), 127.6 ($C_{Ar}$), 119.0 ($C_5$), 79.6 (O**C**$Me_3$), 71.6 ($C_{1'}$), 63.3 ($C_{4'}$), 52.8 ($C_2$), 36.8 ($C_3$), 28.2 (OC$Me_3$), 26.7 (SiC$Me_3$), 20.1 ($C_{1'}$–**Me**), 19.1 (Si**C**$Me_3$) HRMS (electrospray) (M+Na) calculated: 560.2808; found: 560.2805. $R_f$ = 0.65 (diethyl ether/pentane: 1:2).

### 4.19. (1′*S*,2′*E*) Hex-5-enoic acid 4′-(*tert*-butyl-diphenyl-silyloxy)-1′-methyl-but-2′-enyl ester (31)

83% yield **31**: $^1$H NMR (360 MHz, $CDCl_3$): (ppm): 7.63–7.72 (4H, m, $C_{Ar}$–**H**), 7.32–7.48 (6H, m, $C_{Ar}$–**H**), 5.69–5.88 (1H, m, $C_5$–**H**), 5.73–5.82 (2H, m, $C_{2'}$–**H**,

**$C_{3'}$–H**), 5.32–5.43 (1H, m, **$C_{1'}$–H**), 4.92–5.08 (2H, m, **$C_6$–H** × 2), 4.19 (2H, s, **$C_{4'}$H** × 2), 2.31 (2H, t, **$C_2$–H** × 2, $J$ = 7.8 Hz), 2.19 (2H, q, **$C_4$–H** × 2, $J$ = 7.8 Hz), 1.73 (2H, quint, **$C_3$–H** × 2, $J$ = 7.4 Hz), 1.29 (3H, d, **$C_{1'}$–Me**, $J$ = 6.5 Hz), 1.06 (9H, s, Si–***t*Bu**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 172.8 (**$C_1$**), 137.7 (**$C_4$**), 135.5 (**$C_{Ar}$**), 133.4 (**$C_{qAr}$**), 130.7 (**$C_{2'}$**), 129.6 (**$C_{Ar}$**), 129.2 (**$C_{3'}$**), 128.8 (**$C_5$**), 127.9 (**$C_{Ar}$**), 115.3 (**$C_6$**), 70.2 (**$C_{1'}$**), 63.5 (**$C_{4'}$**), 33.8 (**$C_2$**), 24.9 (**$C_3$**), 26.8 (SiC**$Me_3$**), 20.3 ($C_{1'}$–**Me**), 19.2 (Si**C**$Me_3$) HRMS (electrospray) (M+Na) calculated: 459.2331; found: 459.2333. $R_f$ = 0.65 (diethyl ether/pentane: 1:4).

## 5. CIM sequence

### 5.1. Two-step general procedure A

The ester (1 mmol) was dissolved in dry toluene (10 mL) under argon and then cooled to −78 °C. A solution of KHMDS in toluene (0.5 M) was added dropwise (3 mL, 1.5 mmol) over 15 min. After 45 min, freshly distilled TMSCl (2.5 mmol) was added and the resulting mixture stirred for 5 min. The mixture was warmed to room temperature and stirred for an additional 3 h. The mixture was hydrolyzed with a 10% $NH_4Cl$ aqueous solution and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic layers dried, filtered and the solvent removed under reduced pressure. The crude product was esterified with diazomethane, so the resulting methyl ester could be purified by silica gel column chromatography.

The resulting compound (1 mmol) was dissolved in methylene chloride (5 mL) and then added to a flask containing Grubbs catalyst (first or second generation) (0.1 mmol) in $CH_2Cl_2$ or toluene (5 mL). This solution was heated to 40 °C for 1 h. After cooling, the mixture was concentrated, and the crude product purified on silica gel column to afford pure cyclized methyl ester.

### 5.2. One-pot general procedure B

The ester (1 mmol) was dissolved under argon in dry toluene (10 mL) and then cooled to −78 °C. A solution of KHMDS in toluene (0.5 M) was added dropwise (3 mL, 1.5 mmol) over 15 min. After 45 min, freshly distilled TMSCl (2.5 mmol) was added and the resulting mixture was stirred for 5 min. The mixture was warmed to room temperature and stirred for an additional 3 h. The solution was then transferred by cannula to a flask containing Grubbs catalyst (first or second generation) (0.1 mmol) in $CH_2Cl_2$ or toluene (10 mL). This solution was heated to 40 °C for 2 h. After cooling, the reaction was quenched with 10% $NH_4Cl$ solution and the layers separated. The aqueous layer was extracted with methylene chloride or diethyl ether (3 × 10 mL), the combined organic layers dried, filtered and the solvent removed under reduced pressure. The crude product was esterified with diazomethane, and the resulting methyl ester purified by silica gel column chromatography to give the cyclized methyl ester.

### 5.3. (1*S*,2*S*) Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}-methyl)-1-[(4-methoxybenzyl)oxy]-3-cyclopentene-1-carboxylate 33

*Procedure A*: 42% yield.

Compound **33**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.60–7.75 (4H, m, **$C_{Ar}$–H**), 7.25–7.45 (6H, m, **$C_{Ar}$–H**), 7.18 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 6.80 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 5.70–5.85 (2H, m, **$C_3$–H**, **$C_4$–H**), 4.25–4.55 (2H, AB syst, Ar–**$CH_2$**, $J$ = 11 Hz), 3.75–4.15 (2H, AB syst, $C_2$–**$CH_2$**–OSi), 3.78 (3H, s, **OMe**), 3.71 (3H, s, **COOMe**), 3.25–3.35 (1H, m, **$C_2$–H**), 3.01 (1H, d, **$C_5$–Ha**, $J$ = 16Hz), 2.80 (1H, d, **$C_5$–Hb**, $J$ = 16Hz), 1.03 (9H, s, *t*-Bu) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 174.8 (**C**OOMe), 158.8 (**$C_{qAr}$**–OMe), 135.7 (**$C_{Ar}$**), 135.5 (**$C_{qAr}$**), 130.8 (**$C_{qAr}$**), 130.5 (**$C_4$**), 129.4 (**$C_{Ar}$**), 128.5 (**$C_3$**), 128.0 (**$C_{Ar}$**), 127.5 (**$C_{Ar}$**), 113.5 (**$C_{Ar}$**), 87.5 (**$C_1$**), 67.5 ($C_{PMBar}$–**$CH_2$**O), 62.4 ($C_2$–**$CH_2$**–OSi), 56.6 (ArO**Me**), 55.2 (COO**Me**), 52.2 (**$C_2$**), 39.8 (**$C_5$**), 26.7 (SiC**$Me_3$**), 19.2 (Si**C**$Me_3$) IR (film): $\nu$ (cm$^{-1}$): 3658, 2931, 2856, 1736, 1614, 1514, 1463, 1250 $[\alpha]_D^{20}$ = −28.6 ($c$ 0.2, $CHCl_3$) HRMS (electrospray) (M+Na) calculated: 553.2386; found: 553.2378. $R_f$ = 0.4 (diethyl ether/pentane: 1:5).

### 5.4. (1*S*,2*S*) Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}-methyl)-1-[(4-methoxybenzyl)oxy]-cyclohex-3-ene-1-carboxylate 34

*Procedure A*: 88% yield.

*Procedure B*: 74% yield.

Compound **34**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.55–7.75 (4H, m, **$C_{Ar}$–H**), 7.25–7.42 (6H, m, **$C_{Ar}$–H**), 7.16 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 6.78 (2H, d, **$C_{PMBar}$–H**, $J$ = 8.6 Hz), 5.65–5.83 (2H, m, **$C_3$–H**, **$C_4$–H**), 4.25–4.60 (2H, AB syst, Ar–**$CH_2$**, $J$ = 11 Hz), 3.70–3.95 (2H, AB syst, $C_2$–**$CH_2$**–OSi), 3.78 (3H, s, **OMe**), 3.53 (3H, s, **COOMe**), 3.15–3.25 (1H, m, **$C_2$–H**), 1.95–2.30 (4H, m, **$C_5$–H** × 2, **$C_7$–H** × 2), 1.20–1.40 (2H, m, **$C_6$–H** × 2), 1.02 (9H, s, *t* Bu) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 173.8 (**C**OOMe), 158.8 (**$C_{qAr}$**–OMe), 135.6 (**$C_{Ar}$**), 133.2 (**$C_{qAr}$**), 131.4 (**$C_{Ar}$**), 131.2 (**$C_{qAr}$**), 130.2 (**$C_{Ar}$**), 129.5 (**$C_{Ar}$**), 128.6 (**$C_3$**), 127.6 (**$C_4$**), 113.5 (**$C_{Ar}$**), 81.6 (**$C_1$**), 65.4 ($C_{PMBar}$–**$CH_2$**O), 64.2 ($C_2$–**$CH_2$**–OSi), 55.2 (ArO**Me**), 51.6 (COO**Me**), 46.9 (**$C_2$**), 35.8 (**$C_5$**), 28.5 (**$C_7$**), 26.8 (SiC**$Me_3$**), 21.9 (**$C_6$**), 19.2 (Si**C**$Me_3$) IR (film): $\nu$ (cm$^{-1}$): 3020, 3000, 2920, 2840, 1733, 1505.

$[\alpha]_D^{20}$ = −35.3 ($c$ 1.60, $CHCl_3$) HRMS (electrospray) (M+Na) calculated: 567.2542; found: 567.2542. $R_f$ = 0.52 (diethyl ether/pentane: 1:5).

### 5.5. (1*S*,2*S*) Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}-methyl)-1-[(4-methoxybenzyl)oxy]-3-cycloheptene-1-carboxylate 35

*Procedure A*: 57% yield.

Compound **35**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.55–7.75 (4H, m, **$C_{Ar}$–H**), 7.25–7.50 (6H, m, **$C_{Ar}$–H**),

7.19 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.6 Hz), 6.82 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.6 Hz), 5.65–5.92 (2H, m, **C$_3$–H**, **C$_4$–H**), 4.25–4.60 (2H, AB syst, Ar–**CH$_2$**, $J$ = 11 Hz), 3.70–3.95 (2H, AB syst, C$_2$–**CH$_2$**–OSi), 3.78 (3H, s, **OMe**), 3.53 (3H, s, **COOMe**), 3.15–3.25 (1H, m, **C$_2$–H**), 1.95–2.30 (4H, m, **C$_5$–H** × 2, **C$_7$–H** × 2), 1.20–1.40 (2H, m, **C$_6$–H** × 2), 1.02 (9H, s, ***t*Bu**).

$^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 173.8 (**C**OOMe), 158.8 (**C$_{qAr}$**–OMe), 135.6 (**C$_{Ar}$**), 133.2 (**C$_{qAr}$**), 131.4 (**C$_4$**), 131.2 (**C$_{qAr}$**), 130.2 (**C$_3$**), 129.5 (**C$_{Ar}$**), 128.6 (**C$_{Ar}$**), 127.6 (**C$_{Ar}$**), 113.5 (**C$_{Ar}$**), 81.6 (**C$_1$**), 65.4 (C$_{PMBar}$–**C**H$_2$O), 64.2 (C$_2$–**C**H$_2$–OSi), 55.2 (ArO**Me**), 51.6 (COO**Me**), 46.9 (**C$_2$**), 35.8 (**C$_5$**), 28.5 (**C$_7$**), 26.8 (SiC**Me$_3$**), 21.9 (**C$_6$**), 19.2 (Si**C**Me$_3$) IR (film): $\nu$ (cm$^{-1}$): 3648, 2998, 2933, 2858, 1735, 1613, 1588, 1514, 1464, 1249 $[\alpha]_D^{20} = -40.9$ ($c$ 1.1, $CHCl_3$) HRMS (electrospray) ($MH^+$) calculated: 559.2880; found: 559.2897. $R_f$ = 0.55 (diethyl ether/pentane: 1:5).

### 5.6. (1*S*,2*S*) Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}-methyl)-1-[(4-methoxybenzyl)oxy]-2-methyl-3-cyclohexene-1-carboxylate 36

*Procedure A*: 69% yield.

*Procedure B*: 47% yield.

Compound **36**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ (ppm): 7.60–7.70 (4H, m, **C$_{Ar}$–H**), 7.30–7.50 (6H, m, **C$_{Ar}$–H**), 7.10 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.4 Hz), 6.77 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.4 Hz), 5.87 (1H, d, **C$_3$–H**, $J$ = 10.2 Hz), 5.60–5.70 (1H, m, **C$_4$–H**), 4.10–4.40 (2H, AB syst, Ar–**CH$_2$**, $J$ = 10.7 Hz), 3.99 (2H, AB syst, C$_2$–**CH$_2$**–OSi), 3.77 (3H, s, **OMe**), 3.56 (3H, s, **COOMe**), 2.00–2.30 (4H, m, **C$_5$–H** × 2, **C$_6$–H** × 2), 1.06 (9H, s, ***t*Bu**), 1.04 (3H, s, C$_2$–**Me**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 173.3 (**C**OOMe), 158.6 (**C$_{qAr}$**–OMe), 135.7 (**C$_{Ar}$**), 133.9 (**C$_{qAr}$**), 131.0 (**C$_{Ar}$**), 130.6 (**C$_{qAr}$**), 129.3 (**C$_{Ar}$**), 128.0 (**C$_{Ar}$**), 127.8 (**C$_{Ar}$**), 127.4 (**C$_{Ar}$**), 123.9 (**C$_3$**), 113.4 (**C$_4$**), 83.5 (**C$_1$**), 66.8 (C$_{PMBar}$–**C**H$_2$O), 66.3 (C$_2$–**C**H$_2$–OSi), 55.1 (ArO**Me**), 51.3 (COO**Me**), 43.7 (**C$_2$**), 26.9 (SiC**Me$_3$**), 23.6 (**C$_5$**), 22.3 (C$_2$–**Me**), 21.6 (**C$_6$**), 19.4 (Si**C**Me$_3$) IR (film): $\nu$ (cm$^{-1}$): 3657, 2996, 2952, 2858, 1729, 1613, 1588, 1464, 1302 $[\alpha]_D^{20} = +64.6$ ($c$ 1.45, $CHCl_3$) HRMS (electrospray) (M+Na) calculated: 581.2699; found: 581.2699. $R_f$ = 0.55 (diethyl ether/pentane: 1:5).

### 5.7. (1*S*,2*R*) Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}-methyl)-1-[(4-methoxybenzyl)oxy]-2-methyl-3-cyclohexene-1-carboxylate 37

*Procedure A*: 68% yield.

Compound **37**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ (ppm): 7.65–7.75 (4H, m, **C$_{Ar}$–H**), 7.30–7.50 (6H, m, **C$_{Ar}$–H**), 7.30 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.4 Hz), 6.85 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.4 Hz), 5.70–5.80 (1H, d, **C$_3$–H**, $J$ = 10.2 Hz), 5.20–5.30 (1H, d, **C$_4$–H**, $J$ = 10.2 Hz), 4.15–4.45 (2H, AB syst, Ar–**CH$_2$**, $J$ = 10.6 Hz), 3.77 (3H, s, **OMe**), 3.60 (3H, s, **COOMe**), 3.40 (2H, AB syst, C$_2$–**CH$_2$**–OSi), 2.40–2.50 (1H, m, **C$_5$–H**), 2.23 (1H, m, **C$_6$–H**), 2.00–2.15 (2H, m, **C$_5$–H**, **C$_6$–H**), 1.20 (3H, s, C$_2$–**Me**), 1.06 (9H, s, ***t*Bu**).

$^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 173.3 (**C**OOMe), 158.8 (**C$_{qAr}$**–OMe), 135.7 (**C$_{Ar}$**), 133.3 (**C$_{qAr}$**), 131.9 (**C$_{Ar}$**), 130.8 (**C$_{qAr}$**), 129.5 (**C$_{Ar}$**), 128.5 (**C$_{Ar}$**), 127.8 (**C$_{Ar}$**), 127.5 (**C$_{Ar}$**), 125.9 (**C$_3$**), 113.5 (**C$_4$**), 82.0 (**C$_1$**), 69.2 (C$_{PMBar}$–**C**H$_2$O), 65.6 (C$_2$–**C**H$_2$–OSi), 55.2 (ArO**Me**), 51.5 (COO**Me**), 45.0 (**C$_2$**), 26.8 (SiC**Me$_3$**), 24.0 (**C$_5$**), 21.5 (**C$_6$**), 19.3 (C$_2$–**Me**), 18.5 (Si**C**Me$_3$) IR (film): $\nu$ (cm$^{-1}$): 3663, 2998, 2933, 2858, 1728, 1613, 1588, 1513, 1464, 1302 $[\alpha]_D^{20} = +133.3$ ($c$ 1.3, $CHCl_3$) HRMS (electrospray) (M+Na) calculated: 581.2699; found: 581.2710. $R_f$ = 0.55 (diethyl ether/pentane: 1:5).

### 5.8. (1*S*,2*S*) Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}-methyl)-1-[(4-methoxybenzyl)oxy]-4-vinyl-3-cyclohexene-1-carboxylate 38

Ester **29** (350 mg, 0.61 mmol) was dissolved in dry THF (5 mL) under argon and cooled to −78 °C. LiHMDS (1 M solution in hexane, 1.6 mL, 1.6 mmol, 2.6 equiv) was added dropwise over 15 min. The reaction was stirred for 2 h to form the dianionic species. Freshly distilled TMSCl (0.6 mL, 2.4 mmol, 4 equiv) was introduced over 2 min and the mixture stirred for an additional 30 min at −78 °C. A solution of acetic acid (0.5 mL) in dry THF (2 mL) was quickly added and the mixture allowed to warm to room temperature. After 3 h, the reaction was hydrolyzed by a 10% $NH_4Cl$ aqueous solution and extracted with diethyl ether (3 × 5mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (30 mL). The organic layer was then dried, filtered and concentrated to afford 420 mg of pure TMS protected acetylenic ester (98% yield).

Compound **32**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.66 (4H, m, **C$_{Ar}$–H**), 7.39 (6H, m, **C$_{Ar}$–H**), 7.28 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.5 Hz), 6.85 (2H, d, **C$_{PMBar}$–H**, $J$ = 8.5 Hz), 5.80 (2H, m, **C$_{2'}$–H**, **C$_{3'}$–H**), 5.47 (1H, m, **C$_{1'}$–H**), 4.65 (1H, d, PhC**H**–**H$_a$**, $J$ = 11 Hz), 4.34 (1H, dd, PhC**H**–**H$_b$**, $J$ = 11 Hz $J$=2.3 Hz), 4.20 (2H, m, **C$_{4'}$H** × 2), 4.00–4.05 (1H, m, **C$_2$–H**), 3.78 (3H, s, **OMe**), 2.36 (2H, m, **C$_4$–H** × 2), 1.85–1.95 (2H, m, **C$_3$–H** × 2), 1.34 (3H, dd, C$_{1'}$–**Me** (dia 1 and 2)), 1.06 (9H, s, Si–***t*Bu**), 0.13 (9H, s, Si**Me$_3$**).

$^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 171.7 (**C$_1$**), 159.3 (**C$_{qAr}$**–OMe), 135.4 (**C$_{Ar}$**), 133.4 (**C$_{qAr}$**), 131.4 and 131.2 (**C$_{2'}$** and **C$_{PMBar}$**–CH$_2$O), 129.6 (**C$_{Ar}$**), 128.7 (**C$_{3'}$**), 127.6 (**C$_{Ar}$** and **C$_{PMBar}$**), 113.7 (**C$_{PMBar}$**), 105.8 (**C$_6$**), 85.2 (**C$_5$**), 76.2 (**C$_2$**), 72.2 (C$_{PMBar}$–**C**H$_2$–O), 71.1 (**C$_{1'}$**), 63.3 (**C$_{4'}$**), 55.1 (ArO**Me**), 31.7 (**C$_4$**), 26.7 (SiC**Me$_3$**), 20.2 (C$_{1'}$–**Me**), 19.1 (Si**C**Me$_3$), 16.0 (**C$_3$**), 0.1 (Si**Me$_3$**) HRMS (electrospray) (M+Na) calculated: 665.3094; found: 665.3090. $R_f$ = 0.7 (diethyl ether/pentane: 1:5).

The TMS protected acetylenic ester **32** (330 mg, 0.51 mmol) was dissolved under argon in dry toluene (5 mL) and then cooled to −78 °C. A solution of KHMDS in toluene (0.3 M) was added dropwise

(2.2 mL, 0.66 mmol, 1.3 equiv) over 15 min. After 45 min, freshly distilled TMSCl (300 μL) was added and the resulting mixture was stirred for 5 min. The mixture was warmed to room temperature and stirred for an additional 3 h. The mixture was hydrolyzed with a 10% $NH_4Cl$ solution and the layers separated. The aqueous layer was extracted with diethyl ether ($3 \times 10$ mL), the combined organic layers dried, filtered and the solvent was removed under reduced pressure. The crude product was esterified with diazomethane, and after evaporation, dissolved in methanol (5 mL). Solid $K_2CO_3$ (300 mg, 2.1 mmol, 4 equiv) was added in one portion and this suspension stirred for 4 h at room temperature. After evaporation under reduced pressure, the product was dissolved in diethyl ether (10 mL) and washed with water (5 mL). The layers were separated and the aqueous one extracted with diethyl ether ($2 \times 10$ mL). The combined organic layers were dried, filtered and concentrated.

The compound was dissolved in toluene (5 mL) and then added to a flask under an ethylene atmosphere containing a second generation Grubbs catalyst (0.05 mmol) solution in toluene (3 mL). This solution was heated to 50 °C for 1 h. After cooling, the mixture was concentrated, and the crude product was purified on silica gel column chromatography (30 g $SiO_2$, pentane/diethyl ether: 4:1) to afford pure cyclized methyl ester **35**. (226 mg, 78% yield).

Compound **38**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.60–7.70 (4H, m, **$C_{Ar}$–H**), 7.30–7.50 (6H, m, **$C_{Ar}$–H**), 7.17 (2H, d, **$C_{PMBar}$–H**, $J = 8.4$ Hz), 6.79 (2H, d, **$C_{PMBar}$–H**, $J = 8.4$ Hz), 6.32–6.43 (1H, dd, $J = 10.7$ Hz, $J = 17.5$ Hz, $C_4$–**C**HCH$_2$), 5.74 (1H, d, **$C_3$–H**, $J = 2.5$ Hz), 4.95–5.11 (2H, m, $C_4$–CH**C**H $\times$ 2), 4.30–4.60 (2H, AB syst, Ar–**$CH_2$**, $J = 12.5$ Hz), 3.40–3.99 (2H, AB syst, $C_2$–C**$H_2$**–OSi), 3.78 (3H, s, **OMe**), 3.60 (3H, s, **COOMe**), 3.08 (1H, m, **$C_2$–H**), 2.10–2.40 (4H, m, **$C_5$–H** $\times$ 2, **$C_6$–H** $\times$ 2), 1.03 (9H, s, ***t*Bu**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 174.0 (**C**OOMe), 158.7 (**$C_{qAr}$**–OMe), 139.1 ($C_4$–**C**HCH$_2$), 135.5 (**$C_{Ar}$**), 135.1 (**$C_4$**), 133.6 (**$C_{qAr}$**), 133.5 (**$C_{qAr}$**), 130.8 (**$C_{qAr}$**), 129.4 (**$C_{Ar}$**), 128.4 (**$C_3$**), 128.3 (**$C_{Ar}$**), 127.5 (**$C_{Ar}$**), 113.5 (**$C_{Ar}$**), 111.1 ($C_4$–CH**C**H$_2$), 79.1 (**$C_1$**), 65.4 ($C_{PMBar}$–**C**H$_2$O), 63.5 ($C_2$–**C**H$_2$–OSi), 55.2 (ArO**Me**), 51.8 (COO**Me**), 45.5 (**$C_2$**), 27.1 (**$C_5$**), 26.7 (SiC**$Me_3$**), 20.8 (**$C_6$**), 19.1 (Si**C**$Me_3$) IR (film): $\nu$ (cm$^{-1}$): 3657, 2952, 2932, 2857, 1742, 1613, 1587, 1514, 1463, 1248.

$[\alpha]_D^{20} = -87.5$ ($c$ 1.32, $CHCl_3$) HRMS (electrospray) (M+Na) calculated: 593.2699; found: 593.2698. $R_f = 0.45$ (diethyl ether/pentane: 1:5).

### 5.9. (1*S*,2*S*) Methyl 1-[(*tert*-butoxycarbonyl)amino]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-cyclopentene-1-carboxylate 39

*Procedure A*: 46% yield.

Compound **39**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.60–7.80 (4H, m, **$C_{Ar}$–H**), 7.30–7.55 (6H, m, **$C_{Ar}$–H**), 5.70–5.80 (1H, m, **$C_3$–H**), 5.25–5.40 (1H, m, **$C_4$–H**), 3.65–3.95 (2H, m, $C_2$–**$CH_2$**–OSi), 3.73 (3H, s, **COOMe**), 3.30–3.45 (1H, m, **$C_5$–Ha**), 2.95–3.05 (1H, m, **$C_2$–H**), 2.65–2.80 (1H, m, **$C_5$–Hb**), 1.43 (9H, s, O–***t*Bu**), 1.09 (9H, s, Si–***t*Bu**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 174.8 (**C**OOMe), 156.0 (**C**OO*t*Bu), 135.6 (**$C_{Ar}$**), 132.6 (**$C_{qAr}$**) 131.4 (**$C_4$**), 129.9 (**$C_{Ar}$**), 127.8 (**$C_{Ar}$**), 127.3 (**$C_3$**), 79.2 (O**C**Me$_3$), 67.0 (**$C_1$**), 62.8 ($C_2$–**C**H$_2$–OSi), 54.7 (COO**Me**), 52.4 (**$C_2$**), 43.6 (**$C_5$**), 28.3 (OC**$Me_3$**), 26.7 (SiC**$Me_3$**), 19.1 (Si**C**Me$_3$).

IR (film): $\nu$ (cm$^{-1}$): 3377, 2932, 2859, 1740, 1708, 1590, 1500, 1367, 1290 $[\alpha]_D^{20} = -13.2$ ($c$ 0.88, $CHCl_3$) HRMS (electrospray) ($MH^+$) calculated: 510.2676; found 510.2666. $R_f = 0.4$ (diethyl ether/pentane: 1:2).

### 5.10. (1*R*,2*R*) Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}-methyl)-cyclohex-3-ene carboxylate 40

*Procedure A*: 96% yield.

*Procedure B*: 48% yield.

Compound **40**: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 7.55–7.75 (4H, m, **$C_{Ar}$–H**), 7.25–7.45 (6H, m, **$C_{Ar}$–H**), 5.55–5.85 (2H, m, **$C_3$–H**, **$C_4$–H**), 3.45–3.70 (2H, AB syst, $C_2$–**$CH_2$**–OSi), 3.61 (3H, s, **COOMe**), 2.70–2.85 (1H, m, **$C_2$–H**), 2.50–2.65 (1H, m, **$C_1$–H**), 1.65–2.15 (4H, m, **$C_5$–H** $\times$ 2, **$C_6$–H** $\times$ 2), 1.04 (9H, s, ***t*Bu**) $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm): 176.2 (**C**OOMe), 135.6 (**$C_{Ar}$**), 133.6 (**$C_{qAr}$**), 129.5 (**$C_4$**), 127.6 (**$C_{Ar}$**), 127.2 (**$C_3$**), 66.3 ($C_2$–**C**H$_2$–OSi), 51.5 (COO**Me**), 41.9 (**$C_1$**), 40.1 (**$C_2$**), 26.8 (SiC**$Me_3$**), 25.0 (**$C_5$**), 24.2 (**$C_6$**), 19.2 (Si**C**Me$_3$) IR (film): $\nu$ (cm$^{-1}$): 3053, 2932, 2859, 1731, 1472, 1428, 1265 $[\alpha]_D^{20} = -68.3$ ($c$ 1.05, $CHCl_3$) HRMS (electrospray) ($MH^+$) calculated: 409.2199; found: 409.2187. $R_f = 0.6$ (diethyl ether/pentane: 1:4).

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