Title	Stereocontrolled synthesis of carbocyclic compounds with a quaternary carbon atom based on SN2 ' alkylation of , - epoxy- , -unsaturated ketones
Author(s)	Yoshimura, Fumihiko; Kowata, Ayano; Tanino, Keiji
Citation	Organic & Biomolecular Chemistry, 10(28), 5431-5442 https://doi.org/10.1039/c2ob25719j
Issue Date	2012-07-28
Doc URL	http://hdl.handle.net/2115/52793
Rights	Org. Biomol. Chem., 2012,10, 5431-5442 - Reproduced by permission of The Royal Society of Chemistry (RSC)
Type	article (author version)
File Information	OBC10-28_5431-5442.pdf

[Instructions for use](#)

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Stereocontrolled synthesis of carbocyclic compounds with a quaternary carbon atom based on S_N2' alkylation of γ,δ -epoxy- α,β -unsaturated ketones

Fumihiko Yoshimura,* Ayano Kowata and Keiji Tanino*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

We developed a new method for stereoselective construction of an all-carbon quaternary stereogenic center on a carbocyclic ring based on regio- and stereoselective S_N2' alkylation reactions of γ,δ -epoxy- α,β -unsaturated cyclic ketones. Treatment of the ketones, which were readily prepared in enantiomerically pure form by means of aldol condensations between 3-ethoxy-2-cycloalkenones and α,β -epoxy aldehydes, with a R₂Zn–CuCN reagent afforded *anti*-S_N2' products stereoselectively. Conversely, the corresponding *syn*-S_N2' products were stereoselectively obtained through two-step transformations of the same γ,δ -epoxy- α,β -unsaturated cyclic ketones: (1) conversion of the epoxide moiety to a chlorohydrin by treatment with MgCl₂ and (2) subsequent S_N2' substitution of the chlorohydrin with a R₂Zn–CuCN reagent. These substitution products with their chiral *trans*-allylic alcohol moieties are promising precursors for complex molecules. For example, Eschenmoser–Claisen rearrangement of one of the substitution products resulted in stereoselective formation of a keto amide having contiguous quaternary and tertiary stereogenic centers.

Introduction

Enantioselective construction of an all-carbon quaternary stereogenic center on a carbocyclic ring represents a significant challenge in organic synthesis because such centers, which are present in important bioactive natural products and medicines, require the stereoselective formation of a C–C bond between sterically congested carbon atoms. A number of methods for the synthesis of such centers have been reported, and these methods can be divided into two approaches: the enantioselective approach and the diastereoselective approach.¹ The enantioselective approach involves enantioselective C–C bond formation from a prochiral substrate. Typical examples include catalytic asymmetric conjugate additions,² alkylation reactions,³ and Diels–Alder reactions.⁴ Although this approach is the ultimate goal and significant progress has been made in the last two decades, the approach suffers from limitations associated with the availability of substrates and reactants.⁵ The diastereoselective approach involves stereospecific transformation of an optically active substrate into a product with the desired all-carbon quaternary stereogenic center. When the substrate can be easily prepared, this approach is attractive and generally applicable. Typical examples include Claisen-type rearrangements, which allow stereospecific 1,3-transposition of readily available enantiomerically pure allylic alcohols to afford the desired products with an excellent level of 1,3-chiral transfer.⁶ Chiral auxiliary mediated asymmetric reactions, such as alkylations of SAMP-/RAMP-hydrazones⁷ and conjugate

additions of chiral enamines,⁸ are additional examples in this approach. However, because the quaternary stereocenter newly formed by means of this approach is defined by the transition state leading to the product, stereodivergent synthesis of both stereoisomers is difficult in principle.

Scheme 1 Stereoselective construction of an acyclic quaternary carbon center through S_N2' alkylation reactions.

Our laboratory has been engaged in a research program aimed at developing a new method for constructing an all-carbon quaternary stereogenic center by means of the diastereoselective approach. We previously reported two methods for regio- and stereoselective α -methylation reactions of γ,δ -epoxy- α,β -unsaturated esters (Scheme 1):⁹ (1) an *anti*-S_N2' alkylation reaction with Et₂Zn–CuCN (1 to 2-*anti*)^{9a} and (2) a two-step *syn*-

Scheme 2 Strategy for stereodivergent S_N2' alkylation reactions for construction of an all-carbon quaternary stereogenic center on a carbocyclic ring.

S_N2' alkylation reaction sequence involving regioselective γ -substitution with a chloride ion with trimethylsilyl chloride/charcoal and subsequent S_N2' alkylation of the resulting γ -chloro- δ -hydroxy derivative with Et_3Al -CuCN (**1**□**3**□**2-syn**).^{9b} Because the optically active γ,δ -epoxy- α,β -unsaturated esters are readily available by the Katsuki–Sharpless asymmetric epoxidation of allylic alcohols¹⁰ and the Shi asymmetric epoxidation of dienoates,¹¹ these two methods are applicable for enantioselective construction of all-carbon quaternary stereogenic centers in acyclic substrates.¹² In an extension of this approach, we report herein a new method for stereoselective construction of an all-carbon quaternary stereogenic center on a carbocyclic ring based on regio- and stereoselective S_N2' alkylation reactions of γ,δ -epoxy- α,β -unsaturated cyclic ketones with complementary diastereoselection with respect to the newly formed stereogenic center depending on the choice of the reaction conditions.

Results and discussion

Our strategy for stereoselective construction of an all-carbon quaternary stereogenic center on a carbocyclic ring was as follows (Scheme 2). Optically active epoxy aldehydes **5** would be prepared by Katsuki–Sharpless asymmetric epoxidation of the corresponding allylic alcohols **6**.¹⁰ Aldol condensation between **5** and cyclic ketones **4** followed by dehydration would provide key γ,δ -epoxy- α,β -unsaturated cyclic ketones **7**. On the basis of our previous results (Scheme 1),⁹ we expected that upon treatment of **7** with a R_2Zn –CuCN reagent, *anti*- S_N2' alkylation would proceed to afford *anti*- S_N2' products **8-anti**. Conversely, the corresponding *syn*- S_N2' alkylation reaction sequence would be achieved through an S_N2 substitution reaction of **7** with a chloride ion at the γ -position and subsequent S_N2' alkylation of the resulting chlorohydrins **9** with a R_3Al –CuCN reagent to provide *syn*- S_N2' products **8-syn**. Thus, by using epoxy aldehydes **5** as the chiral source, we could stereodivergently construct an all-carbon quaternary stereocenter on a carbocycle, that is, on the α -position of γ,δ -epoxy- α,β -unsaturated cyclic ketones **7**, by choosing the appropriate reaction conditions. Because epoxy ketones **7** possessed several reactive sites, our challenge was to develop reaction sequences that would allow construction of the stereogenic center both regioselectively (S_N2' vs S_N2) and stereoselectively (*anti* vs *syn*).

As a model substrate for our initial studies, we chose racemic γ,δ -epoxy- α,β -unsaturated cyclic ketone **12**, which was synthesized as follows (Scheme 3). The zinc enolate generated

from cyclohexanone was allowed to react with known racemic *trans*-epoxy aldehyde **10**¹³ to provide aldol adduct **11** as a mixture of four diastereomers. Because **11** underwent a retro-aldol process on silica gel, the crude aldol mixture was used for the next reaction. The mixture was stereoselectively converted to (*E*)-**12** by mesylation and treatment of the resulting mesylate with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in one-pot (49% yield for two steps).

Scheme 3 Synthesis of **12**.

Our initial task was to identify a suitable reagent for alkylation (particularly methylation) of **12** (Scheme 4). Reaction of **12** with Me_2Zn (2.1 equiv) and CuCN (2.1 equiv) in dimethylformamide (DMF) at 0 °C, which gives the best results in the acyclic γ,δ -epoxy- α,β -unsaturated ester system,⁹ produced the desired product **13-anti** in 42% yield, but a significant amount of S_N2 product **14** was also obtained (33% yield). Other cuprates, such as Me_2CuLi , $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$, Me_3Al –CuCN, and MeMgBr –CuCN, were all ineffective, affording predominantly **14** (11–35% yield) along with only trace amounts of **13-anti** (2–8% yield). In contrast, a two-step *syn*-methylation reaction gave satisfactory results; substitution reaction of **12** with MgCl_2 ¹⁴ followed by treatment of the resulting chlorohydrin **15** with Me_3Al (3 equiv) and CuCN (1.5 equiv) stereospecifically furnished *syn*-product **13-syn**, which has an all-carbon quaternary stereogenic center on the cyclohexane ring, in 77% overall yield from **12**. Note that the use of trimethylsilyl chloride and charcoal as a source of chloride ion^{9b} resulted in the formation of **15** with lower diastereoselectivity (76% yield, diastereomeric ratio = 63:37).

At this stage, we recognized that the competition between the direct *anti*- S_N2' methylation reaction and the alternative S_N2 substitution pathway was a serious drawback to our strategy, even though the analogous *anti*- S_N2' alkylation reaction in the acyclic γ,δ -epoxy- α,δ -unsaturated ester system (**1**) proceeds regio- and

stereoselectively (Scheme 1).⁹ We assumed that the electron density on the carbonyl oxygen atom of the substrate affected the regioselectivity in the R_2Zn – $CuCN$ mediated *anti*- S_N2' alkylation reaction; that is, the carbonyl oxygen of the ester in **1**, which undergoes highly regioselective *anti*- S_N2' alkylation, possesses higher electron density than the carbonyl oxygen of the ketone in **12** because of electron donation from the ethoxy oxygen (Figure 1). Therefore, we designed new substrate **16a**, which contains a vinylogous ester moiety in the cyclic ketone. We reasoned that electron donation from the ethoxy oxygen of **16a** would increase the electron density on the carbonyl oxygen and would thus favor the *anti*- S_N2' alkylation reaction.

Scheme 4 Initial attempts at S_N2' methylation reactions of **12**.

Fig. 1 Design of new substrate **16a**.

The *anti*- S_N2' methylation reaction of **16a** did in fact proceed regio- and stereoselectively as expected (Table 1). Substrate **16a** was synthesized in 62% overall yield from commercially available 3-ethoxy-2-cyclohexenone and epoxy aldehyde **10** by means of an aldol condensation followed by dehydration, in a sequence similar to that used for the synthesis of **12**.¹⁵ Upon treatment of **16a** with Me_2Zn (2.1 equiv) and $CuCN$ (2.1 equiv) in DMF at $-50\text{ }^\circ\text{C}$, the *anti*- S_N2' methylation reaction proceeded smoothly to give *anti*-adduct **17a-anti**¹⁶ in 84% yield in a highly diastereoselective manner (entry 1). Formation of the undesired S_N2 methylation product **18a** was significantly suppressed (7% yield). The two-step *syn*-methylation reaction of **16a**, that is, chlorination with $MgCl_2$ (91% yield) and subsequent S_N2' methylation of the resulting chlorohydrin **19a-anti** with Me_2Zn (2.1 equiv) and $CuCN$ (2.1 equiv) in DMF, also proceeded diastereoselectively to give *syn*-adduct **17a-syn**¹⁶ in 86% yield (entry 2). Interestingly, Me_2Zn – $CuCN$ gave better results than Me_3Al – $CuCN$ in the S_N2' methylation reaction of **19a-anti**:

treatment of **19a-anti** with the latter reagent resulted in the formation of **17a-syn** in 70% yield along with substantial amounts of unidentified products (ca. 20% yield). Additionally, the use of R_2Zn reagents has an advantage over the use of R_3Al reagents because several R_2Zn reagents can be easily prepared from the corresponding Grignard reagents and $ZnCl_2$,¹⁷ whereas R_3Al reagents have limited availability and are difficult to prepare. Note that the two *anti*- and *syn*-methylation reactions described above proceeded without any loss of optical purity when optically active (+)-**16a** was used as the substrate.¹⁸

The excellent results of the preliminary experiments encouraged us to investigate the scope of the new synthetic methodology with various substrates and zinc reagents. We initially focused on the substrates (Table 1). *anti*- S_N2' methylation of racemic *cis*-epoxide congener **16b**, which was readily prepared from the corresponding *cis*-epoxy aldehyde and 3-ethoxy-2-cyclohexenone, also proceeded smoothly upon treatment with Me_2Zn – $CuCN$ in DMF at $-50\text{ }^\circ\text{C}$ to afford *syn*-product **17a-syn** in 70% yield (entry 3). That the S_N2' methylation reaction of the corresponding *trans*-epoxide **16a** provided *anti*-product **17a-anti** (entry 1) confirmed that the methylation reaction proceeded stereospecifically. *anti*-Product **17a-anti** was obtained in 78% overall yield from *cis*-epoxide **16b** by means of the two-step reaction sequence: chlorination of **16b** with $MgCl_2$ (88% yield) and subsequent S_N2' methylation reaction of the resulting chlorohydrin **19b-syn** with Me_2Zn – $CuCN$ (entry 4). Our methodology tolerated a range of substituents on the side chain of the epoxide. For example, S_N2' methylation of *trans*-epoxide **16c**, which has no ether oxygen atom on the side chain, and *trans*-epoxide **16d**, which has a *tert*-butyldimethylsilyl ether on the side chain, proceeded smoothly to furnish methylation products **17c-anti** and **17d-anti**, respectively, upon treatment with Me_2Zn – $CuCN$ (entries 5 and 7); whereas **17c-syn** and **17d-syn** were obtained by way of chlorohydrins **19c-anti** and **19d-anti** from **16c** and **16d**, respectively (entries 6 and 8). All the *anti*-methylation reactions and the two-step *syn*-methylation reaction sequences proceeded with high regio- and diastereoselectivities in good to excellent yields (entries 5 to 8).

Our methodology was also applicable to a five-membered-ring carbocycle with similar efficiency (Table 1, entries 9 and 10). *anti*- S_N2' methylation of *trans*-epoxide **16e**, which was prepared from 3-ethoxy-2-cyclopentenone¹⁹ and epoxy aldehyde **10**, afforded *anti*-product **17e-anti** in 77% yield (entry 9). In contrast, the substitution reaction of **16e** with $MgCl_2$ (92% yield) followed by treatment of the resulting chlorohydrin **19e-anti** with Me_2Zn – $CuCN$ produced only *syn*-product **17e-syn** (80% yield, entry 10).

Next, we explored various R_2Zn – $CuCN$ reagents in the *anti*- S_N2' reactions of *trans*-epoxide **16a** (Table 2). In addition to the methyl group, ethyl, *n*-butyl, and *i*-propyl groups could be installed on the carbocycle when the corresponding R_2Zn reagents, Et_2Zn ,²⁰ $n\text{-Bu}_2Zn$,²¹ and $i\text{-Pr}_2Zn$,²⁰ respectively, were used in the reaction with **16a** to give *anti*- S_N2' products **20-anti** (entries 1–3). The results shown in Table 2 indicate that increasing the steric bulk of the R_2Zn reagents tended to decrease the ratio of S_N2' products **20-anti** to undesired products **21** resulting from the competing S_N2 methylation reaction. Unfortunately, installation of a vinyl group on **16a** was unsuccessful, presumably because of the low nucleophilicity of

Table 1 *anti*- and *syn*-S_N2' methylation reactions of γ,δ -epoxy- α,β -unsaturated cyclic enones **16**^a

Entry	Epoxide	Method	Product	Yield of 17 (%) ^{b,c}	17:18 ^d	17-anti:17-syn ^d
1	16a	A	17a-anti	84	91:9	>95:5
2	16a	B	17a-syn	78	>95:5	<5:95
3	16b	A ^e	17a-syn	70 ^h	93:7	<5:95
4	16b	B ^f	17a-anti	78	93:7	>95:5
5	16c	A ^g	17c-anti	91	94:6	>95:5
6	16c	B ^f	17c-syn	70	>95:5	<5:95
7	16d	A ^g	17d-anti	81	87:13	>95:5
8	16d	B ^f	17d-syn	85 ^h	94:6	<5:95
9	16e	A ^g	17e-anti	77	>95:5	>95:5
10	16e	B ^g	17e-syn	74	>95:5	<5:95

^a Method A: Me₂Zn, CuCN, DMF, −50 °C. Method B: 1) MgCl₂, MeCN, rt; 2) Me₂Zn, CuCN, DMF, −50 °C. ^b Isolated yield after purification. ^c Two step yield in the case of Method B. ^d Determined by ¹H-NMR of the crude product. ^e The S_N2' methylation reaction was performed at −20 °C. ^f The chlorination reaction was performed at 60 °C. ^g The S_N2' methylation reaction was performed at −50 to 0 °C. ^h Inseparable mixture with **18**.

⁵ *sp*²-hybridized organocopper species; all the starting material was recovered unchanged (entry 4).

The S_N2' reactions of chlorohydrin **19a-anti** with various R₂Zn–CuCN reagents showed promising results (Table 3). S_N2' ethylation and butylation reactions of **19a-anti** smoothly furnished *syn*-alkylation products **20a-syn** (61% yield, entry 1) and **20b-syn** (80% yield, entry 2), respectively, with high diastereoselectivities. The reaction of **19a-anti** with *i*-Pr₂Zn–CuCN provided *syn*-product **20c-syn**, albeit in lower yield (46% yield), along with S_N2 product **21c** (11% yield; entry 3). Interestingly, installation of a vinyl group on **19a-anti** was accomplished by treatment with divinylzinc^{22,23}–CuCN to afford vinylation product **20d-syn** as a single diastereomer (30% yield, entry 4).

The synthetic utility of **17a-syn**, which possesses a chiral secondary *trans*-allylic alcohol, was briefly investigated because it is a promising precursor of complex molecules (Scheme 5). Upon treatment of **17a-syn** with *N,N*-dimethylacetamide dimethyl acetal at 100 °C, Eschenmoser–Claisen rearrangement²⁴ smoothly and stereospecifically afforded keto amide **22** (94% yield), which has contiguous quaternary and tertiary stereogenic centers. Alternatively, a two-step *syn*-S_N2' methylation reaction sequence of **17a-syn** involving esterification with trifluoroacetic anhydride in the presence of Et₃N and 4-dimethylaminopyridine and subsequent *anti*-S_N2' methylation reaction of the resulting trifluoroacetate **23** with Me₂Zn–CuCN stereospecifically furnished methylation product **24** (65% yield for 2 steps), which bears contiguous quaternary and tertiary stereogenic centers. Furthermore, the 1,2-addition of methyl lithium to **17a-syn**

occurred selectively to afford γ,γ -disubstituted cyclohexenone **25** (98% yield) after aqueous acidic work-up in one pot.²⁵ These representative transformations clearly illustrate the potential versatility and importance of this alkylation product as a chiral building block in organic synthesis.

Table 2 S_N2' reactions of **16a** with various R₂Zn–CuCN reagents

Entry	R	Temp.	Yields (%) ^a		
			20-anti	21	20-anti:20-syn ^b
1	Et	−50 °C	20a-anti : 66	21a : 20	>95:5
2	<i>n</i> -Bu	−50 to 0 °C	20b-anti : 43	21b : 45	>95:5
3	<i>i</i> -Pr	−50 °C	20c-anti : 53	21c : 29	>95:5
4	CH=CH ₂	−50 to 0 °C	20d-anti : 0	21d : 0	–

^a Isolated yield after purification. ^b Determined by ¹H-NMR of the crude product.

Table 3 S_N2' reactions of chlorohydrin **19a-anti** with various R₂Zn–CuCN reagents

Entry	R	Temp.	Yields (%) ^a		
			20-syn	21	20-anti:20-syn ^b
1	Et	–50 to 0 °C	20a-syn: 61	21a: 11	<5:95
2	<i>n</i> -Bu	–50 to –20 °C	20b-syn: 80	21b: 12	<5:95
3	<i>i</i> -Pr	–50 °C	20c-syn: 46	21c: 11	<5:95
4	CH=CH ₂	0 °C to rt	20d-syn: 30	21d: 0	<5:95

^a Isolated yield after purification. ^b Determined by ¹H-NMR of the crude product.

5

Scheme 5 Transformations of methylation product **17a-syn**.

Conclusions

In conclusion, we developed a new method for stereoselective construction of an all-carbon quaternary stereogenic center on a carbocyclic ring by means of regio- and stereoselective S_N2' alkylation reactions of γ,δ-epoxy-α,β-unsaturated cyclic ketones bearing a vinylogous ester moiety. Treatment of the ketones, which were easily prepared by means of aldol condensations between 3-ethoxy-2-cycloalkenone and α,β-epoxy aldehydes, with a R₂Zn–CuCN reagent stereoselectively afforded *anti*-S_N2' products. Conversely, the corresponding *syn*-S_N2' products were stereoselectively obtained from the same substrates by means of a two-step transformation involving chlorination with MgCl₂ and S_N2' alkylation of the resulting chlorohydrin with a R₂Zn–CuCN reagent. Our new methodology was applicable to various

substrates and R₂Zn reagents. Note that starting from a single substrate, we could readily obtain both diastereomers of the substitution products exhibiting complementary stereochemical outcomes with respect to the newly formed all-carbon quaternary stereogenic center. Furthermore, we demonstrated the potential versatility and importance of one of the alkylation products as a chiral building block by carrying out further transformations, including an Eschenmoser–Claisen rearrangement and a two-step S_N2' methylation reaction sequence, to afford products having contiguous quaternary and tertiary stereogenic centers. Because optically active γ,δ-epoxy-α,β-unsaturated cyclic ketones are readily available by the Katsuki–Sharpless asymmetric epoxidation of allylic alcohols, the new methodology should be useful for organic synthesis. Application of this methodology to natural product synthesis is in progress in our laboratory.

Experimental

General

The reactions were performed using flame-dried glassware under a positive pressure of argon. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous MeCN, CH₂Cl₂, and DMF were purchased from Kanto Chemical Co. Triethylamine and diisopropylamine were distilled from CaH₂ under argon and stored in the presence of NaOH (pellets). All other reagents and solvents were used as received from commercial sources without further purification. All reactions were monitored by thin-layer chromatography on 0.25 mm Merck Kieselgel 60 F₂₅₄ plates. Components were visualized by illumination with UV light (254 nm) and by staining with one of the following reagents: 6% ethanolic *p*-anisaldehyde (with 6% concd sulfuric acid and 1% acetic acid), 8% ethanolic phosphomolybdic acid, or ceric ammonium molybdate in 10% sulfuric acid. Kanto Chemical Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for flash column chromatography. ¹H NMR spectra were measured using a JEOL ECA-500 (500 MHz) spectrometer in CDCl₃ (δ_H 7.26) with tetramethylsilane as an internal standard. ¹³C NMR spectra were measured using a JEOL ECA-500 (125.8 MHz) spectrometer in CDCl₃ (δ_C 77.0) with tetramethylsilane as an internal standard. IR spectra were recorded on a Jasco FT/IR-4100 spectrophotometer. High-resolution mass spectra were recorded on a JEOL JMS-T100GCV or JEOL JMS-SX102A spectrometer at the GC-MS & NMR Laboratory, Graduate School of Agriculture, Hokkaido University.

65

General procedure for the preparation of γ,δ-epoxy-α,β-unsaturated cyclic ketones.

To a freshly prepared THF solution of lithium diisopropylamide, which was prepared from *i*-Pr₂NH (180 μL, 1.30 mmol) and *n*-BuLi (2.76 M in hexane, 440 μL, 1.20 mmol) in THF (5.0 mL) at 0 °C, was slowly added 3-ethoxy-2-cyclohexenone (140 μL, 1.05 mmol) at –78 °C. After the solution was stirred at this temperature for 2 h, a solution of aldehyde **10**¹³ (192 mg, 1.0 mmol) in THF (1.5 mL) was added, and the mixture was stirred at –50 °C for 1 h, –20 °C for 1 h, and then 0 °C for 0.5 h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution. After the layers were separated, the aqueous layer was

extracted with ethyl acetate (EtOAc). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The crude aldol product was used for the next step.

To a solution of the crude aldol product in CH_2Cl_2 (5.0 mL) were added Et_3N (340 μL , 2.40 mmol) and methanesulfonyl chloride (95 μL , 1.20 mmol) at 0 $^\circ\text{C}$. After the solution was stirred at room temperature for 0.5 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (400 μL , 2.40 mmol) was added, and the mixture was stirred at room temperature for 0.5 h. The reaction was quenched with saturated aqueous NaHCO_3 solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane/EtOAc = 4:1) to give *trans*-epoxide **16a** (193.2 mg, 0.615 mmol, 62% for 2 steps).

(E)-6-(((2S*,3S*)-3-((Benzyloxy)methyl)oxiran-2-yl)methylene)-3-ethoxycyclohex-2-enone (16a)

Yellow oil; IR (neat) ν 3064, 3031, 2982, 2939, 2901, 2860, 1669, 1603, 1383, 1312, 1198, 1106, 1028 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.27–7.36 (m, 5H), 6.20 (d, J = 9.2 Hz, 1H), 5.47 (s, 1H), 4.57 (dd, J = 14.4, 12.1 Hz, 2H), 3.93 (t, J = 6.9 Hz, 2H), 3.78 (dd, J = 11.5, 2.9 Hz, 1H), 3.59 (dd, J = 10.9, 5.2 Hz, 1H), 3.57 (dd, J = 9.2, 2.3 Hz, 1H), 3.23 (dt, J = 5.2, 4.6 Hz, 1H), 2.90 (dtd, J = 14.9, 5.7, 1.7 Hz, 1H), 2.75 (dddd, J = 14.9, 8.0, 6.3, 1.7 Hz, 1H), 2.54 (ddd, J = 17.2, 8.0, 5.7 Hz, 1H), 2.48 (dt, J = 17.2, 6.3 Hz, 1H), 1.37 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 187.6, 177.0, 138.5, 131.0, 128.4, 127.8, 127.8, 102.8, 73.4, 69.2, 64.5, 58.8, 51.6, 28.7, 24.1, 14.1; MS (FD) m/z 315 (M^+ , 100%); HRMS (FD) calcd for $\text{C}_{19}\text{H}_{23}\text{O}_4$ ($[\text{M}+\text{H}]^+$): 315.1596, found: 315.1596.

(E)-6-(((2S,3S)-3-((Benzyloxy)methyl)oxiran-2-yl)methylene)-3-ethoxycyclohex-2-enone [(+)-16a]

This compound was prepared in 57% yield (713.0 mg, 2 steps) from 3-ethoxy-2-cyclohexenone and ((2S,3S)-3-((benzyloxy)methyl)oxiran-2-yl)methanol²⁶ [(+)-**26**, 92% ee]. ^1H -NMR spectrum was consistent with that of **16a**: $[\alpha]_{\text{D}}^{26}$ 1.42 (c 1.07, CHCl_3).

((2S,3S)-3-((Benzyloxy)methyl)oxiran-2-yl)methanol [(+)-26]

This compound was prepared according to the literature procedure²⁶: $[\alpha]_{\text{D}}^{25}$ 19.9 (c 1.02, CHCl_3); Chiral HPLC resolution conditions: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 85:15; flow rate = 1.0 mL/min, T = 20 $^\circ\text{C}$; 254 nm; t = 12.6 min (major), t = 14.3 min (minor); 92% ee.

(E)-6-(((2S*,3R*)-3-((Benzyloxy)methyl)oxiran-2-yl)methylene)-3-ethoxycyclohex-2-enone (16b)

This compound was prepared in 52% yield (160.0 mg, 2 steps) from 3-ethoxy-2-cyclohexenone and (2S*,3S*)-4-(benzyloxy)-2,3-epoxybutanal²⁷: Yellow oil; IR (neat) ν 3063, 3030, 2982, 2940, 2902, 2867, 1667, 1604, 1382, 1317, 1248, 1199, 1175,

1095, 1028, 848, 741, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.29–7.36 (m, 5H), 6.37 (dt, J = 8.0, 1.7 Hz, 1H), 5.41 (s, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 3.95 (q, J = 7.0 Hz, 2H), 3.72 (dd, J = 7.5, 4.0 Hz, 1H), 3.71 (t, J = 4.0 Hz, 1H), 3.59 (dd, J = 10.9, 6.3 Hz, 1H), 3.45 (dt, J = 6.3, 4.0 Hz, 1H), 2.87 (dtd, J = 14.9, 6.3, 1.7 Hz, 1H), 2.78 (dtd, J = 14.9, 14.3, 1.7 Hz, 1H), 2.52 (dt, J = 17.8, 6.6 Hz, 1H), 2.47 (dt, J = 17.2, 6.6 Hz, 1H), 1.38 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 187.2, 177.0, 139.1, 137.6, 128.4, 128.2, 127.9, 127.7, 102.7, 73.3, 68.4, 64.4, 57.3, 52.0, 28.5, 24.1, 14.0; MS (FD) m/z 314 (M^+ , 100%); HRMS (FD) calcd for $\text{C}_{19}\text{H}_{22}\text{O}_4$ (M^+): 314.1518, found: 314.1522.

(E)-3-Ethoxy-6-(((2S*,3S*)-3-propyloxiran-2-yl)methylene)cyclohex-2-enone (16c)

This compound was prepared in 44% yield (700.9 mg, 2 steps) from 3-ethoxy-2-cyclohexenone and (2S*,3R*)-2,3-epoxyhexanal²⁸: Yellow oil; IR (neat) ν 2960, 2935, 2873, 1716, 1670, 1604, 1541, 1383, 1315, 1238, 1198, 1029, 915, 851, 817 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.21 (d, J = 8.6 Hz, 1H), 5.48 (s, 1H), 3.94 (q, J = 6.9 Hz, 2H), 3.34 (dd, J = 8.6, 2.3 Hz, 1H), 2.98 (td, J = 5.7, 2.3 Hz, 1H), 2.72 (ddd, J = 14.9, 5.7, 1.1 Hz, 1H), 2.76 (dddd, J = 14.9, 8.6, 6.3, 2.3 Hz, 1H), 2.56 (ddd, J = 16.6, 8.6, 5.8 Hz, 1H), 2.48 (dt, J = 16.6, 6.3 Hz, 1H), 1.42–1.65 (m, 4H), 1.38 (t, J = 6.9 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 187.7, 176.9, 137.6, 132.0, 102.8, 64.4, 60.3, 54.2, 33.9, 28.7, 24.0, 19.1, 14.0, 13.8; MS (EI) m/z 236 (M^+ , 8%); HRMS (FD) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ (M^+): 236.1412, found: 236.1411.

(E)-6-(((2S*,3S*)-3-((tert-Butyldimethylsilyloxy)methyl)oxiran-2-yl)methylene)-3-ethoxycyclohex-2-enone (16d)

This compound was prepared in 59% yield (962.7 mg, 2 steps) from 3-ethoxy-2-cyclohexenone and (2S*,3R*)-2,3-epoxy-4-(tert-butyldimethylsiloxy)-butanal²⁹: Yellow solid; IR (neat) ν 2953, 2929, 2896, 2857, 1716, 1670, 1653, 1605, 1472, 1383, 1312, 1254, 1198, 1108, 1030, 838, 778 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.21 (d, J = 9.2 Hz, 1H), 5.46 (s, 1H), 3.92 (dd, J = 14.4, 6.9 Hz, 2H), 3.85 (dd, J = 12.1, 3.5 Hz, 1H), 3.77 (dd, J = 12.1, 4.0 Hz, 1H), 3.55 (dd, J = 8.6, 1.7 Hz, 1H), 3.12 (dd, J = 5.8, 4.0 Hz, 1H), 2.90 (dtd, J = 14.9, 5.7, 1.2 Hz, 1H), 2.74 (dddd, J = 14.9, 8.0, 6.3, 1.7 Hz, 1H), 2.54 (ddd, J = 17.2, 8.0, 6.3 Hz, 1H), 2.46 (dt, J = 17.2, 6.3 Hz, 1H), 1.36 (t, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 187.6, 176.9, 138.1, 131.3, 102.8, 64.5, 62.4, 60.2, 51.5, 28.7, 25.8, 24.1, 18.3, 14.1, –5.36, –5.38; MS (EI) m/z 339 ($[\text{M}+\text{H}]^+$, 26%); HRMS (FD) calcd for $\text{C}_{18}\text{H}_{31}\text{O}_4\text{Si}$ ($[\text{M}+\text{H}]^+$): 339.1992, found: 339.1966.

(E)-5-(((2S*,3S*)-3-((Benzyloxy)methyl)oxiran-2-yl)methylene)-3-ethoxycyclopent-2-enone (16e)

This compound was prepared in 25% yield (65.8 mg, 2 steps) from 3-ethoxy-2-cyclopentenone¹⁹ and **10**¹³: Yellow oil; IR (neat) ν 3088, 3064, 3030, 2984, 2928, 2903, 2859, 1699, 1662, 1581, 1342, 1225, 1202, 1103, 1026, 867, 698, 668 cm^{-1} ; ^1H NMR (500

MHz, CDCl₃) δ 7.26–7.37 (m, 5H), 6.18 (dt, J = 8.0, 1.8 Hz, 1H), 5.47 (s, 1H), 4.58 (dd, J = 14.3, 12.0 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.78 (dd, J = 11.5, 3.4 Hz, 1H), 3.59 (dd, J = 11.5, 3.4 Hz, 1H), 3.42 (dd, J = 8.3, 2.0 Hz, 1H), 3.33 (d, J = 20.0 Hz, 1H), 3.27 (d, J = 20.0 Hz, 1H), 3.21–3.23 (m, 1H), 1.43 (t, J = 6.9 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 192.8, 185.6, 137.7, 137.6, 128.4, 127.7, 126.8, 105.7, 73.4, 69.2, 67.7, 58.7, 52.5, 32.2, 14.1; MS (FD) m/z 301 ([M+H]⁺, 100%); HRMS (FD) calcd for C₁₈H₂₁O₄ ([M+H]⁺): 301.1440, found: 301.1433.

10

General procedure for the S_N2' alkylation reaction of γ,δ -epoxy- α,β -unsaturated cyclic ketones with a R₂Zn–CuCN reagent.

To a mixture of *trans*-epoxide **16a** (80.2 mg, 0.255 mmol) and CuCN (49.0 mg, 0.536 mmol) in DMF (640 μ L) was added Me₂Zn (2.0 M in toluene, 270 μ L, 0.536 mmol) at –50 °C; upon addition, the mixture turned from pale green to yellow. After the reaction mixture was stirred at this temperature for 3 h, it was quenched by the addition of a mixture of saturated aqueous NH₄Cl and 35% aqueous NH₄OH (9:1) and extracted with diethyl ether (Et₂O). The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. Purification of the residue by preparative thin-layer chromatography (SiO₂, hexane/EtOAc = 1:2) afforded alkylation product **17a-anti** (70.6 mg, 0.213 mmol, 84%).

(R*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-methylcyclohex-2-enone (17a-anti)

Colorless oil; IR (neat) ν 3200–3500 (br), 3063, 3030, 2981, 2931, 2898, 2860, 1649, 1605, 1453, 1380, 1361, 1246, 1193, 1110, 1041, 1025, 971, 893, 850, 819, 740, 699 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.27–7.37 (m, 5H), 5.90 (dd, J = 16.1, 1.3 Hz, 1H), 5.46 (dd, J = 16.1, 5.8 Hz, 1H), 5.29 (s, 1H), 4.56 (s, 2H), 4.30–4.36 (m, 1H), 3.90 (dq, J = 9.8, 6.9 Hz, 1H), 3.87 (dd, J = 9.8, 6.9 Hz, 1H), 3.50 (dd, J = 9.6, 3.5 Hz, 1H), 3.33 (dd, J = 9.6, 8.9 Hz, 1H), 2.46–2.53 (m, 2H), 2.32 (dt, J = 17.8, 5.2 Hz, 1H), 1.95 (dt, J = 13.3, 5.2 Hz, 1H), 1.87 (ddd, J = 13.3, 9.7, 5.2 Hz, 1H), 1.35 (t, J = 6.9 Hz, 3H), 1.20 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.3, 176.4, 137.8, 135.2, 128.5, 128.3, 127.8, 127.8, 101.6, 74.2, 73.3, 71.1, 64.2, 46.1, 33.6, 26.4, 23.5, 14.1; MS (FD) m/z 331 (M⁺, 100%); HRMS (FD) calcd for C₂₀H₂₇O₄ ([M+H]⁺): 331.1909, found: 331.1914.

(R)-6-((3R,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-methylcyclohex-2-enone [(–)-17a-anti]

This compound was obtained in 82% yield (47.3 mg) by treatment of (+)-**16a** (92% ee) with Me₂Zn–CuCN. ¹H-NMR spectrum was consistent with that of **17a-anti**: Colorless oil; [α]_D²⁷ –28.0 (c 0.54, CHCl₃); Chiral HPLC resolution conditions: Daicel Chiralcel AD-H, hexane/*i*-PrOH = 90:10; flow rate = 1.0 mL/min, T = 20 °C; 254 nm; t = 17.0 min (major), t = 18.9 min (minor); 92% ee.

(S*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-methylcyclohex-2-enone (17a-syn)

This compound was obtained in 70% yield (40.2 mg) by treatment of **16b** with Me₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3500 (br), 3063, 3031, 2979, 2925, 2855, 1647, 1636, 1604, 1193, 1109, 1041, 972, 849, 738 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.37 (m, 5H), 5.87 (dd, J = 16.0, 1.7 Hz, 1H), 5.44 (dd, J = 15.8, 6.0 Hz, 1H), 5.29 (s, 1H), 4.54 (s, 2H), 4.31–4.36 (m, 1H), 3.88 (dq, J = 9.8, 6.7 Hz, 1H), 3.68 (dq, J = 9.8, 6.7 Hz, 1H), 3.49 (dd, J = 9.6, 3.5 Hz, 1H), 3.33 (dd, J = 9.6, 8.3 Hz, 1H), 2.49 (ddd, J = 17.8, 9.2, 4.6 Hz, 1H), 2.32 (dt, J = 17.8, 5.2 Hz, 1H), 1.93 (dt, J = 13.5, 5.2 Hz, 1H), 1.88 (ddd, J = 13.5, 9.8, 5.2 Hz, 1H), 1.35 (t, J = 6.7 Hz, 3H), 1.20 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.3, 176.4, 137.8, 135.6, 128.4, 127.8, 127.8, 127.7, 101.7, 74.1, 73.3, 71.2, 64.2, 46.1, 33.6, 26.4, 23.8, 14.1; MS (FD) m/z 330 (M⁺, 100%); HRMS (FD) calcd for C₂₀H₂₆O₄ (M⁺): 330.1831, found: 330.1844.

(R*)-3-Ethoxy-6-((3S*,1E)-3-hydroxyhex-1-en-1-yl)-6-methylcyclohex-2-enone (17c-anti)

This compound was obtained in 91% yield (47.4 mg) by treatment of **16c** with Me₂Zn–CuCN: Colorless oil; IR (neat) ν 3200–3600 (br), 2958, 2931, 2871, 1716, 1698, 1684, 1647, 1636, 1541, 1457, 1317, 1246, 1193, 1041, 1022, 970, 898, 850 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 5.72 (dd, J = 16.1, 1.2 Hz, 1H), 5.45 (dd, J = 16.1, 6.9 Hz, 1H), 5.29 (s, 1H), 4.06 (dd, J = 13.2, 6.3 Hz, 1H), 3.87 (dq, J = 14.4, 4.0 Hz, 2H), 2.46 (ddd, J = 17.2, 9.8, 5.2 Hz, 1H), 2.31 (dt, J = 17.8, 5.2 Hz, 1H), 1.93 (dt, J = 13.8, 5.2 Hz, 1H), 1.85 (ddd, J = 14.9, 9.7, 5.2 Hz, 1H), 1.71 (br, 1H), 1.40–1.51 (m, 2H), 1.34 (t, J = 6.9 Hz, 3H), 1.24–1.35 (m, 2H), 1.19 (s, 3H), 0.89 (t, J = 7.5 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.6, 176.3, 133.6, 132.6, 101.6, 72.6, 64.2, 45.9, 39.4, 33.5, 26.4, 23.6, 18.6, 14.1, 13.9; MS (EI) m/z 252 (M⁺, 6%); HRMS (FD) calcd for C₁₅H₂₄O₃ (M⁺): 252.1725, found: 252.1740.

(R*)-6-((3R*,1E)-4-((tert-Butyldimethylsilyl)oxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-methylcyclohex-2-enone (17d-anti)

This compound was obtained in 81% yield (58.0 mg) by treatment of **16d** with Me₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3600 (br), 2954, 2928, 2857, 1652, 1608, 1380, 1251, 1193, 1112, 1042, 837, 777 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 5.83 (dd, J = 16.0, 1.2 Hz, 1H), 5.42 (dd, J = 16.0, 5.8 Hz, 1H), 5.28 (s, 1H), 4.12 (br, 1H), 3.86 (qnd, J = 6.9, 2.9 Hz, 2H), 3.60 (dd, J = 10.0, 3.8 Hz, 1H), 3.39 (dd, J = 10.0, 7.8 Hz, 1H), 2.56 (d, J = 2.9 Hz, 1H), 2.48 (ddd, J = 17.8, 9.7, 5.2 Hz, 1H), 2.30 (dt, J = 17.8, 5.2 Hz, 1H), 1.94 (dt, J = 13.8, 5.2 Hz, 1H), 1.86 (ddd, J = 13.2, 9.7, 5.2 Hz, 1H), 1.33 (t, J = 6.9 Hz, 3H), 1.18 (s, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.3, 176.3, 135.0, 128.0, 101.6, 72.5, 67.1, 64.2, 46.1, 33.7, 26.4, 25.8, 23.5, 18.2, 14.1, –5.39, –5.43; MS (EI) m/z 354 (M⁺, 2%); HRMS (FD) calcd for C₁₉H₃₄O₄Si (M⁺): 354.2226, found: 354.2247.

(R*)-5-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-5-methylcyclopent-2-enone (17e-anti)

This compound was obtained in 77% yield (21.7 mg) by treatment of **16e** with Me₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3500 (br), 3088, 3062, 3030, 2980, 2958, 2925, 2863, 1695,

1592, 1375, 1338, 1107, 1026, 739, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.26–7.37 (m, 5H), 5.82 (dd, *J* = 15.5, 1.1 Hz, 1H), 5.56 (dd, *J* = 15.5, 6.3 Hz, 1H), 5.19 (s, 1H), 4.56 (dd, *J* = 13.5, 12.3 Hz, 2H), 4.34 (m, 1H), 4.05 (q, *J* = 7.3 Hz, 2H), 3.52 (dd, *J* = 9.5, 3.2 Hz, 1H), 3.36 (t, *J* = 8.9 Hz, 1H), 2.74 (d, *J* = 17.8 Hz, 1H), 2.47–2.51 (m, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.27 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 207.4, 187.4, 137.8, 135.7, 128.4, 127.8, 127.8, 127.4, 101.9, 74.1, 73.3, 71.1, 67.7, 49.4, 43.1, 31.6, 23.4, 14.1; MS (FD) *m/z* 317 ([M+H]⁺, 100%); HRMS (FD) calcd for C₁₉H₂₅O₄ ([M+H]⁺): 317.1753, found: 317.1717.

General procedure for the chlorination reaction of γ,δ-epoxy-α,β-unsaturated cyclic ketones with MgCl₂.

A mixture of *trans*-epoxide **16a** (156.3 mg, 0.497 mmol) and MgCl₂ (238 mg, 2.49 mmol) in MeCN (2.5 mL) was stirred at room temperature for 2.5 h. Water was added, and then the mixture was extracted thoroughly with EtOAc. The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was quickly purified by flash column chromatography (SiO₂, hexane/EtOAc = 1:1) to give chlorohydrin **19a-anti** (157.8 mg, 0.450 mmol, 91%).

(*E*)-6-((2*R**,3*S**)-4-(Benzyloxy)-2-chloro-3-hydroxybutylidene)-3-ethoxycyclohex-2-enone (**19a-anti**)

Orange oil; IR (neat) ν 3300–3500 (br), 3087, 3063, 3031, 2981, 2939, 2905, 2865, 1667, 1600, 1383, 1254, 1199, 1110, 1065, 1027, 740 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.38 (m, 5H), 6.69 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.51 (s, 1H), 4.81 (dd, *J* = 10.3, 6.3 Hz, 1H), 4.56 (s, 1H), 4.01 (td, *J* = 10.3, 5.2 Hz, 1H), 3.95 (q, *J* = 6.9 Hz, 2H), 3.72 (dd, *J* = 9.8, 5.2 Hz, 1H), 2.57–2.59 (m, 1H), 2.52 (dt, *J* = 17.2, 6.9 Hz, 1H), 2.46 (dt, *J* = 17.2, 6.9 Hz, 1H), 1.38 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 187.9, 177.2, 137.6, 137.2, 130.2, 128.4, 127.8, 127.7, 103.1, 73.6, 73.3, 70.4, 64.6, 56.2, 28.6, 24.2, 14.1; MS (FD) *m/z* 350 (M⁺, 100%); HRMS (FD) calcd for C₁₉H₂₃³⁵ClO₄ (M⁺): 350.1285, found: 350.1273.

(*E*)-6-((2*S**,3*S**)-4-(Benzyloxy)-2-chloro-3-hydroxybutylidene)-3-ethoxycyclohex-2-enone (**19b-syn**)

This compound was obtained in 88% yield (30.6 mg) by treatment of **16b** with MgCl₂ at 60 °C: Orange oil; IR (neat) ν 3200–3700 (br), 3087, 3063, 3030, 2981, 2939, 2904, 2867, 1663, 1599, 1384, 1254, 1200, 1111, 1028, 898, 848, 818, 743, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.36 (m, 5H), 6.68 (dt, *J* = 10.9, 1.7 Hz, 1H), 5.53 (s, 1H), 4.90 (dd, *J* = 10.3, 5.8 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.94 (q, *J* = 6.9 Hz, 2H), 3.93 (d, *J* = 15.5 Hz, 1H), 3.64 (dd, *J* = 9.8, 4.6 Hz, 1H), 3.54 (dd, *J* = 9.7, 4.6 Hz, 1H), 2.77 (dtd, *J* = 14.9, 5.7, 1.8 Hz, 1H), 2.66 (dtd, *J* = 14.9, 8.0, 2.3 Hz, 1H), 2.50 (dt, *J* = 17.8, 6.9 Hz, 1H), 2.42 (dt, *J* = 17.2, 6.3 Hz, 1H), 1.37 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 187.8, 177.3, 137.6, 137.5, 136.7, 129.6, 128.4, 127.8, 127.7, 103.1, 73.6, 73.3, 70.3, 64.6, 58.8, 28.5, 24.2, 14.1; MS (FD) *m/z* 350 (M⁺, 100%); HRMS (FD) calcd for C₁₉H₂₃³⁵ClO₄ (M⁺): 350.1285, found: 350.1308.

(*E*)-6-((2*R**,3*S**)-2-Chloro-3-hydroxyhexylidene)-3-ethoxycyclohex-2-enone (**19c-anti**)

This compound was obtained in 77% yield (22.0 mg) by treatment of **16c** with MgCl₂ at 60 °C: Orange oil; IR (neat) ν 3100–3600 (br), 2958, 2937, 2871, 1666, 1601, 1383, 1325, 1254, 1199, 1028, 926, 848, 817 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.69 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.51 (s, 1H), 4.66 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.94 (q, *J* = 6.9 Hz, 2H), 3.82 (br, 1H), 2.80 (dtd, *J* = 14.9, 6.3, 1.2 Hz, 1H), 2.69 (tdd, *J* = 14.9, 6.3, 1.7 Hz, 1H), 2.44–2.58 (m, 2H), 1.47–1.59 (m, 4H), 1.38 (t, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 187.9, 177.2, 137.1, 129.9, 103.1, 74.1, 64.6, 60.7, 35.0, 28.7, 24.3, 18.9, 14.1, 13.9; MS (FD) *m/z* 272 (M⁺, 100%); HRMS (FD) calcd for C₁₄H₂₁³⁵ClO₃ (M⁺): 272.1179, found: 272.1174.

(*E*)-6-((2*R**,3*S**)-4-((*tert*-Butyldimethylsilyloxy)-2-chloro-3-hydroxybutylidene)-3-ethoxycyclohex-2-enone (**19d-anti**)

This compound was obtained in 97% yield (59.1 mg) by treatment of **16d** with MgCl₂ at 60 °C: Orange oil; IR (neat) ν 3100–3600 (br), 2952, 2929, 2895, 2856, 1717, 1667, 1472, 1384, 1254, 1173, 1112, 838, 778 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.68 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.45 (s, 1H), 4.75 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.92 (dd, *J* = 14.3, 6.9 Hz, 2H), 3.81–3.86 (m, 2H), 3.69–3.73 (m, 1H), 2.83 (d, *J* = 5.2 Hz, 1H), 2.67–2.78 (m, 2H), 2.51 (dd, *J* = 17.2, 6.3 Hz, 1H), 2.45 (dd, *J* = 17.2, 6.9 Hz, 1H), 1.36 (t, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 187.9, 177.0, 137.0, 130.4, 103.1, 64.5, 63.2, 55.8, 28.6, 25.8, 24.2, 18.2, 14.1, –5.44, –5.48; MS (FD) *m/z* 375 ([M+H]⁺, 86%); HRMS (FD) calcd for C₁₈H₃₂³⁵ClO₄Si ([M+H]⁺): 375.1758, found: 375.1761.

(*E*)-5-((2*R**,3*S**)-4-(Benzyloxy)-2-chloro-3-hydroxybutylidene)-3-ethoxycyclopent-2-enone (**19e-anti**)

This compound was obtained in 92% yield (37.3 mg) by treatment of **16e** with MgCl₂: Yellow oil; IR (neat) ν 3200–3500 (br), 3031, 2982, 2922, 2858, 1698, 1653, 1576, 1559, 1340, 1226, 1108, 1072, 1023, 738, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.37 (m, 5H), 6.57 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.48 (s, 1H), 4.60 (dd, *J* = 10.0, 6.0 Hz, 1H), 4.55 (s, 1H), 4.09 (q, *J* = 6.9 Hz, 2H), 4.03 (qn, *J* = 4.6 Hz, 1H), 3.70 (q, *J* = 4.6 Hz, 1H), 3.62 (q, *J* = 4.6 Hz, 1H), 3.26 (dt, *J* = 20.6, 2.2 Hz, 1H), 3.17 (dd, *J* = 20.6, 2.2 Hz, 1H), 2.85 (d, *J* = 5.2 Hz, 1H), 1.43 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 193.0, 185.5, 137.5, 137.2, 128.5, 127.9, 127.8, 126.2, 106.2, 73.6, 73.1, 70.3, 67.7, 58.0, 32.1, 14.0; MS (FD) *m/z* 336 ([M+H]⁺, 100%); HRMS (FD) calcd for C₁₈H₂₁³⁵ClO₄ (M⁺): 336.1128, found: 336.1131.

General procedure for the S_N2' alkylation reaction of γ-chloro-δ-hydroxy-α,β-unsaturated cyclic ketones with a R₂Zn–CuCN reagent.

To a mixture of chlorohydrin **19a-anti** (430 mg, 1.23 mmol) and CuCN (231 mg, 2.58 mmol) in DMF (3.1 mL) was added Me₂Zn (2.0 M in toluene, 1.4 mL, 2.71 mmol) at –50 °C; upon addition, the mixture turned from pale green to yellow. After the reaction mixture was stirred at this temperature for 40 min, it was quenched by the addition of a mixture of saturated aqueous

NH₄Cl and 35% aqueous NH₄OH (9:1) and extracted with Et₂O. The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane/EtOAc = 1:1) to give alkylation product **17a-syn** (351 mg, 1.06 mmol, 86%).

(S)-6-((3R,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-methylcyclohex-2-enone [(+)-17a-syn]

This compound was obtained in 76% yield by treatment of the optically active chlorohydrin **19a-anti** (92% ee) with Me₂Zn–CuCN. ¹H-NMR spectrum was consistent with that of **17a-syn**: Yellow oil; [α]_D²⁸ 35.2 (c 0.61, CHCl₃); Chiral HPLC resolution conditions: Daicel Chiralcel AD-H, hexane/*i*-PrOH = 90:10; flow rate = 1.0 mL/min, *T* = 20 °C; 254 nm; *t* = 15.2 min (major), *t* = 16.7 min (minor); 88% ee.

(R*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-methylcyclohex-2-enone (17a-anti)

This compound was obtained in 89% yield by treatment of **19b-syn** with Me₂Zn–CuCN. All the spectral data of this compound were identical with those synthesized by the reaction of *trans*-epoxide **16a** with Me₂Zn–CuCN.

(S*)-3-Ethoxy-6-((3S*,1E)-3-hydroxyhex-1-en-1-yl)-6-methylcyclohex-2-enone (17c-syn)

This compound was obtained in 91% yield (40.2 mg) by treatment of **19c-anti** with Me₂Zn–CuCN: Colorless oil; IR (neat) ν 3200–3600 (br), 2958, 2931, 2871, 1716, 1647, 1636, 1605, 1541, 1507, 1457, 1379, 1361, 1194, 1041, 1022 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.70 (dd, *J* = 16.1, 1.2 Hz, 1H), 5.45 (dd, *J* = 16.1, 6.6 Hz, 1H), 5.28 (s, 1H), 4.06 (dd, *J* = 12.6, 6.3 Hz, 1H), 3.86 (dq, *J* = 17.2, 6.9 Hz, 2H), 2.45 (ddd, *J* = 17.8, 8.6, 5.2 Hz, 1H), 2.33 (dt, *J* = 17.8, 5.2 Hz, 1H), 1.92 (dt, *J* = 13.2, 5.2 Hz, 1H), 1.84 (ddd, *J* = 13.2, 9.2, 4.0 Hz, 1H), 1.39–1.50 (m, 2H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.24–1.32 (m, 2H), 1.19 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.7, 176.4, 133.6, 132.7, 101.5, 72.5, 64.2, 45.9, 39.3, 33.7, 26.3, 23.4, 18.5, 14.1, 13.9; MS (EI) *m/z* 252 (M⁺, 11%); HRMS (FD) calcd for C₁₅H₂₄O₃ (M⁺): 252.1725, found: 252.1705.

(S*)-6-((3R*,1E)-4-((tert-Butyldimethylsilyl)oxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-methylcyclohex-2-enone (17d-syn)

This compound was obtained in 88% yield (598 mg) by treatment of **19d-anti** with Me₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3600 (br), 2953, 2929, 2857, 1716, 1652, 1607, 1472, 1380, 1361, 1251, 1193, 1112, 837, 777 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.82 (dd, *J* = 16.0, 1.2 Hz, 1H), 5.39 (dd, *J* = 16.0, 6.3 Hz, 1H), 5.29 (s, 1H), 4.13 (br, 1H), 3.86 (dq, *J* = 13.8, 6.9 Hz, 2H), 3.58 (dd, *J* = 10.3, 3.5 Hz, 1H), 3.38 (dd, *J* = 10.3, 7.5 Hz, 1H), 2.55 (d, *J* = 3.5 Hz, 1H), 2.48 (ddd, *J* = 16.9, 9.8, 5.2 Hz, 1H), 2.31 (dt, *J* = 17.8, 5.2 Hz, 1H), 1.92 (dt, *J* = 13.8, 5.2 Hz, 1H), 1.86 (ddd, *J* = 13.2, 9.8, 5.2 Hz, 1H), 1.35 (t, *J* = 6.9 Hz, 3H), 1.20 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ¹³C NMR (125.8 MHz,

CDCl₃) δ 201.3, 176.4, 135.4, 128.0, 101.7, 72.6, 67.0, 64.2, 46.1, 33.6, 26.4, 25.8, 23.9, 18.2, 14.1, –5.41, –5.45; MS (EI) *m/z* 297 ([M–*t*-Bu]⁺, 100%); HRMS (FD) calcd for C₁₉H₃₄O₄Si (M⁺): 354.2226, found: 354.2215.

(S*)-5-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-5-methylcyclopent-2-enone (17e-syn)

This compound was obtained in 80% yield (29.2 mg) by treatment of **19e-anti** with Me₂Zn–CuCN: Yellow oil; IR (neat) ν 3300–3500 (br), 3088, 3063, 3030, 2980, 2959, 2924, 2864, 1696, 1592, 1374, 1340, 1229, 1194, 1107, 1027, 738, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.37 (m, 5H), 5.84 (dd, *J* = 15.8, 1.4 Hz, 1H), 5.55 (dd, *J* = 15.8, 6.0 Hz, 1H), 5.18 (s, 1H), 4.5d (dd, *J* = 14.3, 12.0 Hz, 2H), 4.34 (m, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.50 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.34 (dd, *J* = 9.5, 8.3 Hz, 1H), 2.74 (dd, *J* = 17.8, 1.1 Hz, 1H), 2.57 (br, 1H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.28 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 207.5, 187.2, 137.8, 135.5, 128.4, 127.7, 127.3, 101.8, 74.0, 73.3, 71.0, 67.6, 49.3, 42.9, 23.9, 14.1; MS (FD) *m/z* 317 ([M+H]⁺, 100%); HRMS (FD) calcd for C₁₉H₂₅O₄ ([M+H]⁺): 317.1753, found: 317.1752.

(R*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-ethylcyclohex-2-enone (20a-anti)

This compound was obtained in 66% yield (16.1 mg) by treatment of **16a** with Et₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3600 (br), 3062, 3029, 2964, 2934, 2859, 1645, 1607, 1380, 1192, 1111, 1028, 979, 739, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.36 (m, 5H), 5.86 (dd, *J* = 16.1, 1.2 Hz, 1H), 5.44 (dd, *J* = 16.1, 5.8 Hz, 1H), 5.28 (s, 1H), 4.55 (s, 2H), 4.34 (m, 1H), 3.89 (dq, *J* = 9.8, 6.9 Hz, 1H), 3.85 (dq, *J* = 9.8, 6.9 Hz, 1H), 3.50 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.34 (dd, *J* = 9.2, 8.6 Hz, 1H), 2.47 (ddd, *J* = 17.2, 9.2, 4.6 Hz, 1H), 2.42 (d, *J* = 2.9 Hz, 1H), 2.33 (dt, *J* = 17.8, 5.2 Hz, 1H), 1.97 (ddd, *J* = 13.8, 9.2, 5.2 Hz, 1H), 1.89 (dt, *J* = 13.8, 5.7 Hz, 1H), 1.71 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.58 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.35 (t, *J* = 6.9 Hz, 1H), 0.79 (t, *J* = 7.5 Hz, 1H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.1, 176.2, 137.8, 134.2, 128.4, 128.4, 127.8, 127.7, 102.1, 74.3, 73.3, 71.3, 64.2, 49.4, 29.2, 28.7, 26.1, 14.1, 8.36; MS (EI) *m/z* 345 (M⁺, 100%); HRMS (FD) calcd for C₂₁H₂₉O₄ ([M+H]⁺): 345.2066, found: 345.2079.

(R*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-6-butyl-3-ethoxycyclohex-2-enone (20b-anti)

This compound was obtained in 43% yield (13.9 mg) by treatment of **16a** with *n*-Bu₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3500 (br), 3063, 3031, 2952, 2930, 2858, 1733, 1716, 1646, 1636, 1607, 1456, 1380, 1190, 1110, 1028, 978, 737, 698, 670 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.28–7.38 (m, 5H), 5.88 (d, *J* = 16.1 Hz, 1H), 5.42 (dd, *J* = 16.1, 6.3 Hz, 1H), 5.28 (s, 1H), 4.56 (s, 2H), 4.34 (br, 1H), 3.87 (dq, *J* = 13.8, 6.9 Hz, 2H), 3.50 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.35 (dd, *J* = 9.2, 8.6 Hz, 1H), 2.42–2.49 (m, 2H), 2.32 (dt, *J* = 17.8, 5.2 Hz, 1H), 1.97 (ddd, *J* = 14.4, 9.8, 4.6 Hz, 1H), 1.91 (dt, *J* = 13.8, 5.2 Hz, 1H), 1.65–1.69 (m, 1H), 1.53 (td, *J* = 11.5, 5.2 Hz, 1H), 1.35 (t, *J* = 6.9 Hz, 3H), 1.24–1.28 (m, 2H), 1.13–1.20 (m, 1H), 0.86 (t, *J* = 7.5 Hz, 3H);

¹³C NMR (125.8 MHz, CDCl₃) δ 201.1, 176.2, 137.8, 134.5, 128.4, 128.1, 127.8, 127.7, 102.0, 74.2, 73.3, 71.3, 64.2, 49.3, 36.5, 29.4, 26.1, 23.2, 14.1, 14.0; MS (EI) *m/z* 372 (M⁺, 2.4%); HRMS (FD) calcd for C₂₃H₃₂O₄ (M⁺): 372.2301, found: 372.2281.

(S*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-isopropylcyclohex-2-enone (20c-anti)

This compound was obtained in 53% (24.3 mg) yield by treatment of **16a** with *i*-Pr₂Zn–CuCN: Yellow oil; IR (neat) ν 3300–3500 (br), 3087, 3063, 3030, 2958, 2872, 1608, 1381, 1192, 1111, 739, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.36 (m, 5H), 5.86 (dd, *J* = 16.0, 1.2 Hz, 1H), 5.46 (dd, *J* = 16.0, 5.7 Hz, 1H), 5.28 (s, 1H), 4.55 (s, 2H), 4.35 (m, 1H), 3.88 (dq, *J* = 9.8, 6.9 Hz, 1H), 3.84 (dq, *J* = 9.8, 6.9 Hz, 1H), 3.50 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.36 (dd, *J* = 9.8, 8.0 Hz, 1H), 2.43–2.51 (m, 2H), 2.30 (dt, *J* = 17.8, 5.2 Hz, 1H), 2.27 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.99 (ddd, *J* = 13.8, 10.3, 4.6 Hz, 1H), 1.85 (dt, *J* = 13.8, 5.2 Hz, 1H), 1.34 (t, *J* = 6.9 Hz, 1H), 0.82 (d, *J* = 6.9 Hz, 1H), 0.80 (d, *J* = 6.9 Hz, 1H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.0, 176.1, 137.8, 133.4, 129.0, 128.4, 127.8, 127.7, 102.5, 74.3, 73.3, 71.4, 64.1, 52.4, 32.4, 25.8, 24.3, 18.1, 16.7, 14.1; MS (FD) *m/z* 358 (M⁺, 100%); HRMS (FD) calcd for C₂₂H₃₀O₄ (M⁺): 358.2144, found: 358.2141.

(S*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-ethylcyclohex-2-enone (20a-syn)

This compound was obtained in 61% yield (23.4 mg) by treatment of **19a-anti** with Et₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3600 (br), 3063, 3030, 2967, 2937, 2862, 1728, 1643, 1607, 1453, 1380, 1312, 1247, 1192, 1111, 1027, 979, 740, 699 cm⁻¹; ¹H NMR (500 MHz) δ 7.29–7.36 (m, 5H), 5.86 (d, *J* = 16.1 Hz, 1H), 5.41 (dd, *J* = 16.1, 6.3 Hz, 1H), 5.28 (s, 1H), 4.55 (s, 2H), 4.35 (m, 1H), 3.48 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.84 (dd, *J* = 9.2, 8.1 Hz, 1H), 2.42–2.48 (m, 2H), 2.33 (dt, *J* = 17.8, 5.2 Hz, 1H), 1.97 (ddd, *J* = 14.3, 9.7, 5.2 Hz, 1H), 1.86 (dt, *J* = 13.7, 5.2 Hz, 1H), 1.72 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.58 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.34 (t, *J* = 6.9 Hz, 1H), 0.82 (t, *J* = 7.5 Hz, 1H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.1, 176.3, 137.8, 134.6, 128.4, 128.3, 127.7, 127.7, 102.1, 74.2, 73.3, 71.4, 64.2, 49.5, 29.4, 28.8, 26.1, 14.1, 8.38; MS (FD) *m/z* 344 (M⁺, 100%); HRMS (FD) calcd for C₂₁H₂₈O₄ (M⁺): 344.1988, found: 344.1992.

(S*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-6-butyl-3-ethoxycyclohex-2-enone (20b-syn)

This compound was obtained in 80% yield (27.4 mg) by treatment of **19a-anti** with *n*-Bu₂Zn²¹–CuCN: Yellow oil; IR (neat) ν 3100–3600 (br), 3063, 3032, 2932, 2859, 2357, 1643, 1606, 1380, 1190, 1114, 1026, 738, 696 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.27–7.37 (m, 5H), 5.87 (d, *J* = 16.1 Hz, 1H), 5.40 (dd, *J* = 16.1, 6.3 Hz, 1H), 5.28 (s, 1H), 4.55 (s, 2H), 4.34 (br, 1H), 3.86 (dq, *J* = 13.8, 6.9 Hz, 2H), 3.49 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.33 (dd, *J* = 9.7, 8.1 Hz, 1H), 2.46 (dd, *J* = 10.1, 2.3 Hz, 1H), 2.43 (dd, *J* = 9.2, 5.2 Hz, 1H), 2.32 (dt, *J* = 17.8, 5.2 Hz, 1H), 1.98 (ddd, *J* = 17.8, 8.6, 4.6 Hz, 1H), 1.88 (dt, *J* = 13.8, 5.2 Hz, 1H), 1.65 (ddd, *J* = 13.8, 11.5, 5.2 Hz, 1H), 1.53 (td, *J* = 12.3, 5.2 Hz, 1H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.14–1.29 (m, 3H), 0.87 (t, *J* =

7.2 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.1, 176.2, 137.8, 134.9, 128.4, 128.1, 127.8, 127.7, 102.0, 74.2, 73.3, 71.4, 64.2, 49.3, 36.6, 29.4, 26.1, 23.2, 14.1, 14.0; MS (EI) *m/z* 372 (M⁺, 1.2%); HRMS (FD) calcd for C₂₃H₃₂O₄ (M⁺): 372.2301, found: 372.2265.

(R*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-isopropylcyclohex-2-enone (20c-syn)

This compound was obtained in 46% yield (23.0 mg) by treatment of **19a-anti** with *i*-Pr₂Zn–CuCN: Yellow oil; IR (neat) ν 3200–3600 (br), 3063, 3030, 2958, 2871, 1725, 1661, 1643, 1605, 1382, 1321, 1251, 1195, 1111, 1027, 897, 849, 819, 739, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.36 (m, 5H), 5.86 (dd, *J* = 16.0, 1.1 Hz, 1H), 5.46 (dd, *J* = 16.3, 6.0 Hz, 1H), 5.28 (s, 1H), 4.56 (s, 2H), 4.35 (m, 1H), 3.87 (dq, *J* = 9.8, 7.5 Hz, 1H), 3.84 (dq, *J* = 9.8, 7.5 Hz, 1H), 3.51 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.36 (dd, *J* = 9.7, 6.0 Hz, 1H), 2.47 (ddd, *J* = 14.9, 10.3, 4.6 Hz, 1H), 2.38 (d, *J* = 3.4 Hz, 1H), 2.30 (dt, *J* = 17.8, 4.6 Hz, 1H), 2.27 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.99 (ddd, *J* = 13.8, 10.3, 5.2 Hz, 1H), 1.85 (dt, *J* = 9.3, 4.6 Hz, 1H), 1.34 (t, *J* = 7.5 Hz, 1H), 0.82 (d, *J* = 6.9 Hz, 1H), 0.80 (d, *J* = 7.4 Hz, 1H); ¹³C NMR (125.8 MHz, CDCl₃) δ 201.0, 176.1, 137.8, 133.7, 128.9, 128.4, 127.8, 127.7, 127.7, 102.5, 74.2, 73.3, 71.5, 64.1, 52.4, 32.5, 25.9, 24.6, 18.1, 16.7, 14.1; MS (FD) *m/z* 359 ([M+H]⁺, 100%); HRMS (FD) calcd for C₂₂H₃₁O₄ ([M+H]⁺): 359.2222, found: 359.2221.

(R*)-6-((3R*,1E)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3-ethoxy-6-vinylcyclohex-2-enone (20d-syn)

This compound was obtained in 30% yield (11.9 mg) by treatment of **19a-anti** with divinylzinc²²–CuCN: Yellow oil; IR (neat) ν 3200–3600 (br), 3063, 3030, 2981, 2936, 2859, 1726, 1646, 1605, 1381, 1248, 1192, 1110, 1027, 918, 740, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.36 (m, 5H), 5.92 (dd, *J* = 17.5, 10.6 Hz, 2H), 5.48 (dd, *J* = 16.0, 6.3 Hz, 1H), 5.34 (s, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 5.06 (d, *J* = 17.2 Hz, 1H), 4.55 (s, 2H), 4.37 (m, 1H), 3.88 (q, *J* = 7.1 Hz, 2H), 3.51 (dd, *J* = 9.2, 2.9 Hz, 1H), 3.36 (dd, *J* = 9.7, 8.1 Hz, 1H), 2.49 (m, 1H), 2.42 (t, *J* = 6.3 Hz, 1H), 2.01–2.08 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 199.0, 176.7, 139.2, 133.7, 129.3, 128.4, 128.3, 127.8, 127.7, 115.5, 101.9, 74.1, 73.3, 71.2, 64.3, 52.9, 31.0, 26.3, 14.1; MS (FD) *m/z* 343 ([M+H]⁺, 100%); HRMS (FD) calcd for C₂₁H₂₆O₄ (M⁺): 342.1831, found: 342.1835.

(3S*,4E)-6-(Benzyloxy)-3-((1S*)-4-ethoxy-1-methyl-2-oxocyclohex-3-en-1-yl)-N,N-dimethylhex-4-enamide (22)

A mixture of methylation product **17a-syn** (152.7 mg, 0.460 mmol) and *N,N*-dimethylacetamide dimethyl acetal (375 μL, 2.56 mmol) in toluene (1.5 mL) was heated at 100 °C for 4.5 h. After the reaction mixture was cooled to room temperature, brine was added and the product was thoroughly extracted with EtOAc. The organic extracts were dried over MgSO₄ and the volatile materials were removed under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane/EtOAc = 1:1~0:1) to give keto amide **22** (172.7 mg, 0.430 mmol, 94%) as a yellow oil. IR (neat) ν 3086, 3063, 3029, 2979, 2934, 2855, 1647, 1607, 1453, 1377, 1315, 1245, 1192, 1110, 978, 739, 699

cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.36 (m, 5H), 5.75 (dt, *J* = 15.5, 5.7 Hz, 1H), 5.63 (dd, *J* = 15.5, 9.2 Hz, 1H), 5.21 (s, 1H), 4.48 (s, 2H), 3.97–4.04 (m, 2H), 3.87 (q, *J* = 6.9 Hz, 2H), 3.07 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.95 (s, 3H), 2.86 (s, 3H), 2.60 (ddd, *J* = 18.3, 10.3, 5.2 Hz, 1H), 2.36 (d, *J* = 6.9 Hz, 1H), 2.25 (dt, *J* = 18.3, 4.0 Hz, 1H), 2.00 (dt, *J* = 9.8, 4.0 Hz, 1H), 1.69–1.75 (m, 1H), 1.35 (t, *J* = 6.9 Hz, 3H), 1.05 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 203.4, 176.1, 171.6, 138.3, 132.3, 129.8, 128.3, 127.7, 127.5, 101.1, 71.6, 70.3, 64.2, 45.4, 41.6, 37.2, 35.5, 33.2, 32.0, 25.5, 18.2, 14.1; MS (FD) *m/z* 399 (M⁺, 100%); HRMS (FD) calcd for C₂₄H₃₃NO₄ (M⁺): 399.2410, found: 399.2402.

(*S)-6-((2*R**,3*E*)-5-(Benzyloxy)pent-3-en-2-yl)-3-ethoxy-6-methylcyclohex-2-enone (24)**

To a solution of methylation product **17a-syn** (19.6 mg, 0.0590 mmol), Et₃N (25 μL, 0.18 mmol), and 4-dimethylaminopyridine (3.0 mg, 0.0180 mmol) in CH₂Cl₂ (0.6 mL) was added trifluoroacetic anhydride (17 μL, 0.120 mmol) at –40 °C. After the reaction mixture was stirred at this temperature for 1 h, it was quenched by the addition of water and the product was thoroughly extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude trifluoroacetate **23** was used for the next step without further purification.

To a mixture of the crude trifluoroacetate **23** and CuCN (14.0 mg, 0.125 mmol) in DMF (0.3 mL) was added a solution of Me₂Zn (2.0 M solution in toluene, 63 μL, 0.125 mmol) at 0 °C. After the reaction mixture was stirred at this temperature for 0.5 h, it was quenched by the addition of a mixture of saturated aqueous solution of NH₄Cl and 35% aqueous solution of NH₄OH (9:1) and extracted with Et₂O. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Purification of the residue by preparative thin-layer chromatography (SiO₂, hexane/EtOAc = 1:1) afforded methylation product **24** as a yellow oil (12.6 mg, 0.0384 mmol, 65% for 2 steps). IR (neat) ν 3063, 3030, 2964, 2935, 2870, 1726, 1649, 1609, 1455, 1387, 1361, 1317, 1241, 1190, 1109, 1039, 975, 899, 822, 783, 738, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.28–7.35 (m, 5H), 5.62 (d, *J* = 15.5 Hz, 1H), 5.59 (d, *J* = 15.5 Hz, 1H), 5.27 (s, 1H), 4.50 (s, 2H), 3.99 (dd, *J* = 18.0, 14.0 Hz, 1H), 3.88 (q, *J* = 7.1 Hz, 1H), 2.77 (m, 1H), 2.44 (ddd, *J* = 14.3, 9.2, 5.2 Hz, 1H), 2.36 (dt, *J* = 17.8, 5.2 Hz, 1H), 2.03 (ddd, *J* = 14.9, 9.2, 5.2 Hz, 1H), 1.59–1.63 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 1H); ¹³C NMR (125.8 MHz, CDCl₃) δ 203.6, 175.7, 138.4, 135.3, 128.3, 127.8, 127.6, 127.5, 102.0, 71.8, 70.8, 64.1, 46.3, 40.8, 27.8, 25.7, 21.0, 15.5, 14.2; MS (FD) *m/z* 328 (M⁺, 100%); HRMS (FD) calcd for C₂₁H₂₈O₃ (M⁺): 328.2038, found: 328.2058.

(*S)-4-((3*R**,1*E*)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-3,4-dimethylcyclohex-2-enone (25)**

A solution of methylolithium in THF (1.12 M solution in Et₂O, 200 μL, 0.230 mmol) was added to a solution of methylation product **17a-syn** (15.0 mg, 0.0450 mmol) in THF (230 μL) at 0 °C. After stirred at this temperature for 1 h, HCl (0.5 M aqueous solution, 450 μL) was added and the mixture was stirred

at room temperature for 0.5 h. Saturated aqueous sodium bicarbonate was added to the mixture and the product was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, hexane/EtOAc = 1:2) afforded γ,γ-disubstituted cyclohexenone **25** (13.3 mg, 0.0440 mmol, 98%) as a colorless oil. IR (neat) ν 3200–3700 (br), 3087, 3062, 3029, 2921, 2858, 1666, 1618, 1454, 1377, 1337, 1110, 1028, 1008, 976, 862, 740, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.26–7.38 (m, 5H), 5.90 (d, *J* = 1.1 Hz, 1H), 5.71 (dd, *J* = 15.8, 1.4 Hz, 1H), 5.40 (dd, *J* = 16.0, 5.2 Hz, 1H), 4.56 (s, 2H), 4.36–4.38 (m, 1H), 3.52 (dd, *J* = 9.5, 3.2 Hz, 1H), 3.33 (dd, *J* = 9.5, 7.7 Hz, 1H), 2.54 (d, *J* = 3.4 Hz, 1H), 2.41 (ddd, *J* = 17.2, 10.3, 6.3 Hz, 1H), 2.32 (dt, *J* = 17.2, 5.2 Hz, 1H), 1.87–1.91 (m, 2H), 1.85 (d, *J* = 1.1 Hz, 3H), 1.25 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 199.3, 165.3, 137.7, 135.5, 128.5, 128.2, 128.0, 127.9, 127.8, 74.1, 73.4, 70.8, 41.3, 36.2, 34.1, 24.8, 20.7; MS (FD) *m/z* 301 ([M+H]⁺, 100%); HRMS (FD) calcd for C₁₉H₂₅O₃ ([M+H]⁺): 301.1804, found: 301.1804.

Acknowledgements

We acknowledge Dr. Eri Fukushi, Mr. Kenji Watanabe, and Mr. Yusuke Takata (GC-MS & NMR Laboratory, Graduate School of Agriculture, Hokkaido University) for mass spectral measurements. This work was supported by a Grant-in-Aid for Young Scientists (B) (No. 22710206) and the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

- Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan. Fax: +81 11 706 4920; Tel: +81 11 706 2716 (F.Y.); +81 11 706 2705 (K.T.); E-mail: fumi@sci.hokudai.ac.jp (F.Y.); ktanino@sci.hokudai.ac.jp (K.T.)
- † Electronic Supplementary Information (ESI) available: Experimental procedure and compound characterization for **12–15**, Nuclear Overhauser effect (NOE) data for structural assignments of **16a**, **17a-anti**, and **17a-syn**, copies of the ¹H and ¹³C NMR spectra, and chiral HPLC chromatograms for (+)-**26**, (–)-**17a-anti**, and (+)-**17a-syn**. See DOI: 10.1039/b000000x/
- For reviews, see: (a) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (b) I. Denissova and L. Barriault, *Tetrahedron*, 2003, **59**, 10105; (c) K. Fujii, *Chem. Rev.*, 1993, **93**, 2037.
 - For recent examples, see: (a) T. L. May, M. J. Dabrowski and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 736; (b) Y. Kawato, N. Takahashi, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2010, **12**, 1484.
 - For significant recent advances, see: (a) T. A. Moss, D. R. Fenwick and D. J. Dixon, *J. Am. Chem. Soc.*, 2008, **130**, 10076; (b) B. M. Trost and J. Xu, *J. Am. Chem. Soc.*, 2005, **127**, 2846; (c) A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2005, **127**, 62; (d) D. C. Behenna and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 15044; (e) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2003, **42**, 3796; (f) Y. Yamashita, K. Odashima and K. Koga, *Tetrahedron Lett.*, 1999, **40**, 2803; (g) B. M. Trost, R. Radinov and E. M. Grenzer, *J. Am. Chem. Soc.*, 1997, **119**, 7879.
 - For a recent example, see: Y. Huang, T. Iwama and V. H. Rawal, *Org. Lett.*, 2002, **4**, 1166.
 - (a) M. Bella and T. Gasperi, *Synthesis*, 2009, 1583; (b) J. T. Mohr and B. M. Stoltz, *Chem. Asian J.*, 2007, **2**, 1476; (c) B. M. Trost and

- C. Jiang, *Synthesis*, 2006, 369; (d) E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388.
- 6 (a) A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939; (b) Y. Chai, S. Hong, H. A. Lindsay, C. McFarland and M. C. McIntosh, *Tetrahedron*, 2002, **58**, 2905.
- 7 A. Job, C. F. Janeck, W. Bettray, R. Peters and D. Enders, *Tetrahedron*, 2002, **58**, 2253.
- 8 J. d'Angelo, D. Desmaële, F. Dumas and A. Guingant, *Tetrahedron: Asymmetry*, 1992, **3**, 459.
- 10 9 (a) A. Hirai, A. Matsui, K. Komatsu, K. Tanino and M. Miyashita, *Chem. Commun.*, 2002, 1970; (b) F. Yoshimura, A. Matsui, A. Hirai, K. Tanino and M. Miyashita, *Tetrahedron Lett.*, 2009, **50**, 5126.
- 10 For a review, see: T. Katsuki and V. S. Martin, *Org. React.*, 1996, **48**, 1.
- 15 11 For a review, see: O. A. Wong and Y. Shi, *Chem. Rev.*, 2008, **108**, 3958.
- 12 In this connection, Breit and co-workers reported an elegant stereospecific and stereodivergent allylic substitution reaction of a chiral cyclohexenol derivative by using a switchable directing/nondirecting leaving group; see: B. Breit, P. Demel, D. Grauer and C. Studte, *Chem. Asian J.*, 2006, **1**, 586.
- 20 13 K. C. Nicolaou and J. Uenishi, *J. Chem. Soc., Chem. Commun.*, 1982, 1292.
- 14 J. D. Ha, S. Y. Kim, S. J. Lee, S. K. Kang, J. H. Ahn, S. S. Kim and J. Choi, *Tetrahedron Lett.*, 2004, **45**, 5969.
- 25 15 The olefin geometry of **16a** was unambiguously determined to be the *E*-configuration by ¹H NMR NOE study. Details are shown in Supporting Information.
- 16 The stereochemistries of methylation products **17a-anti** and **17a-syn** were unambiguously determined by the NOE studies after their conversion into bicyclic compounds. Details are shown in Supporting Information.
- 30 17 E. Nakamura, in *Organometallics in Synthesis: A Manual*, ed. M. Schlosser, John Wiley & Sons Ltd., New York, 2nd edn., 2002, pp. 579–664.
- 35 18 Optically active epoxide (+)-**16a** was prepared from the corresponding optically active epoxy alcohol (+)-**26** (92% ee), which was easily accessible through the Katsuki–Sharpless asymmetric epoxidation. Enantiomeric excesses of (–)-**17a-anti** and (+)-**17a-syn** were determined by HPLC analysis with a chiral column (see Supporting Information).
- 40
- temperature for 2 h and was used directly without removal of magnesium salts.¹⁷
- 50 22 Divinylzinc was prepared from ZnCl₂ and vinylmagnesium bromide and was used directly without removal of magnesium salts; see: R. L. Soucy, D. Kozhinov and V. Behar, *J. Org. Chem.*, 2002, **67**, 1947.
- 23 The use of salt-free divinylzinc did not affect either the yield of the alkylation products or the diastereomeric ratio of **20d-syn** to **21d**.
- 55 For preparation of salt-free R₂Zn reagents, see: J. L. Von dem Bussche-Hünnefeld and D. Seebach, *Tetrahedron*, 1992, **48**, 5719.
- 24 A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425.
- 25 G. Stork and R. L. Danheiser, *J. Org. Chem.*, 1973, **38**, 1775.
- 60 26 K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis and T. K. Chakraborty, *J. Am. Chem. Soc.*, 1988, **110**, 4672.
- 27 H. Pettersson-Fasth, S. W. Riesinger and J. Bäckvall, *J. Org. Chem.*, 1995, **60**, 6091.
- 28 G. Righi, A. Chionne and C. Bonini, *Eur. J. Org. Chem.*, 2000, 3127.
- 65 29 Y. Hayashi, M. Shoji, T. Mukaiyama, H. Gotoh, S. Yamaguchi, M. Nakata, H. Kakeya and H. Osada, *J. Org. Chem.*, 2005, **70**, 5643.

19 B. B. Kikani, J. R. McKee and M. Zanger, *Synthesis*, 1991, 176.

20 Commercially available Et₂Zn (1.0 M hexane solution) and *i*-Pr₂Zn (1.0 M toluene solution) were used as received.

21 *n*-Bu₂Zn was prepared by treatment of 1 equiv of anhydrous ZnCl₂ with 2 equiv of *n*-BuMgCl (2.9 M THF solution) in THF at room