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PAPER

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

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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 R_2Zn–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 $MgCl_2$ and (2) subsequent S_N2' substitution of the chlorohydrin with a R_2Zn–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-hydrazones[7] 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.

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 Et_2Zn–CuCN (**1** → **2-*anti***)[9a] and (2) a two-step *syn*-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 alcohols[10] and the Shi asymmetric epoxidation of dienoates,[11] these two methods are applicable for

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†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 ^{13}C NMR spectra, and chiral HPLC chromatograms for (+)-**26**, (−)-**17a-*anti***, and (+)-**17a-*syn***. See DOI: 10.1039/c2ob25719j

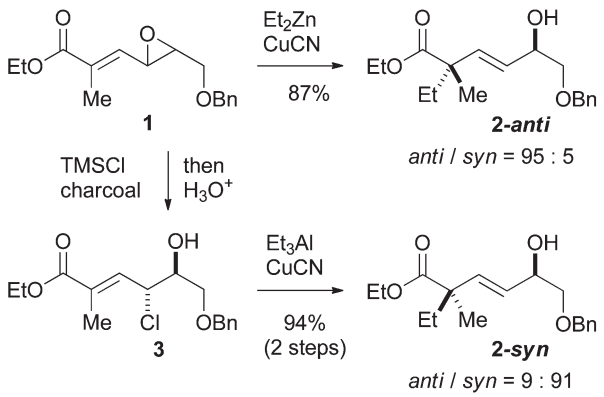
enantioselective construction of all-carbon quaternary stereogenic centers in acyclic substrates.[12] In an extension of this approach, we report herein a new method for stereoselective construction of an all-carbon quaternary stereogenic center on a carbocyclic ring based on regio- and stereoselective 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

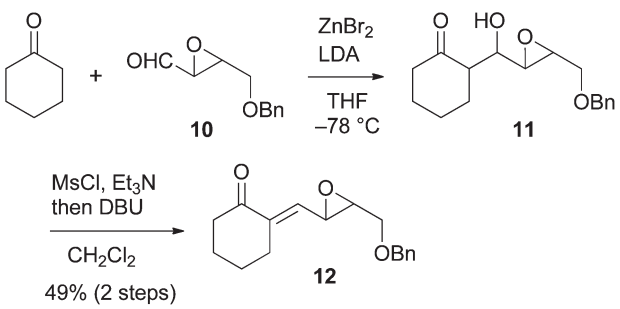
Our strategy for stereoselective construction of an all-carbon quaternary stereogenic center on a carbocyclic ring was as follows (Scheme 2). Optically active epoxy aldehydes **5** would be prepared by Katsuki–Sharpless asymmetric epoxidation of the corresponding allylic alcohols **6**.[10] Aldol condensation 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).

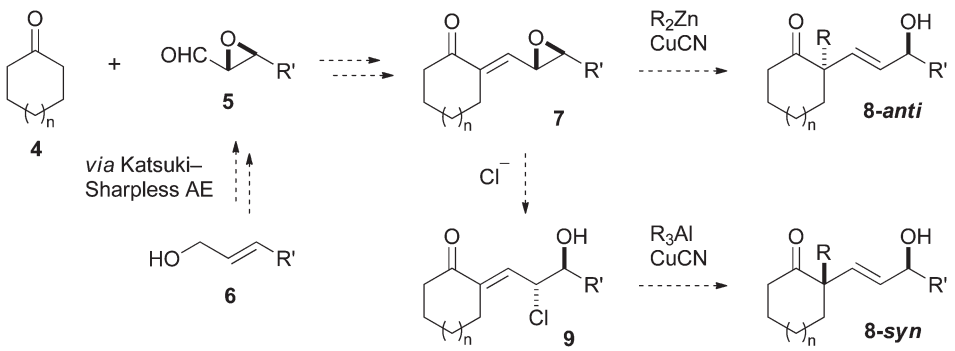
Our initial task was to identify a suitable reagent for alkylation (particularly methylation) of **12** (Scheme 4). Reaction of **12** with Me_2Zn (2.1 equiv.) and CuCN (2.1 equiv.) in dimethylformamide (DMF) at 0 °C, which gives the best results in the acyclic γ,δ-epoxy-α,β-unsaturated ester system,[9] 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, $Me_2Cu(CN)Li_2$, 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; a 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



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



Scheme 3 Synthesis of **12**.

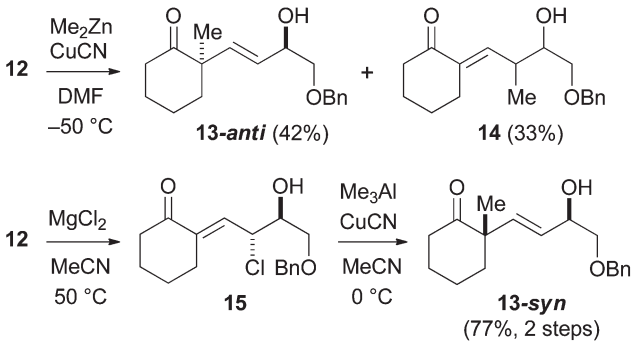


Scheme 2 Strategy for stereodivergent S_N2' alkylation reactions for construction of an all-carbon quaternary stereogenic center on a carbocyclic ring.

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 the 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 (Fig. 1). Therefore, we designed a 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.

The *anti*-S_N2' methylation reaction of **16a** did in fact proceed regio- and stereoselectively as expected (Table 1). Substrate **16a**



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

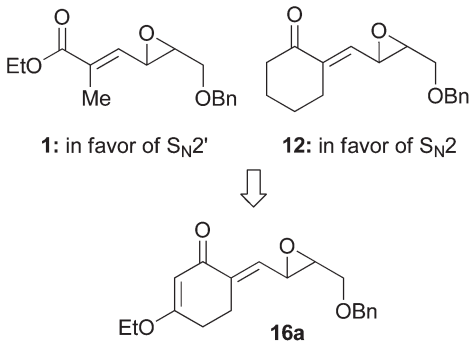
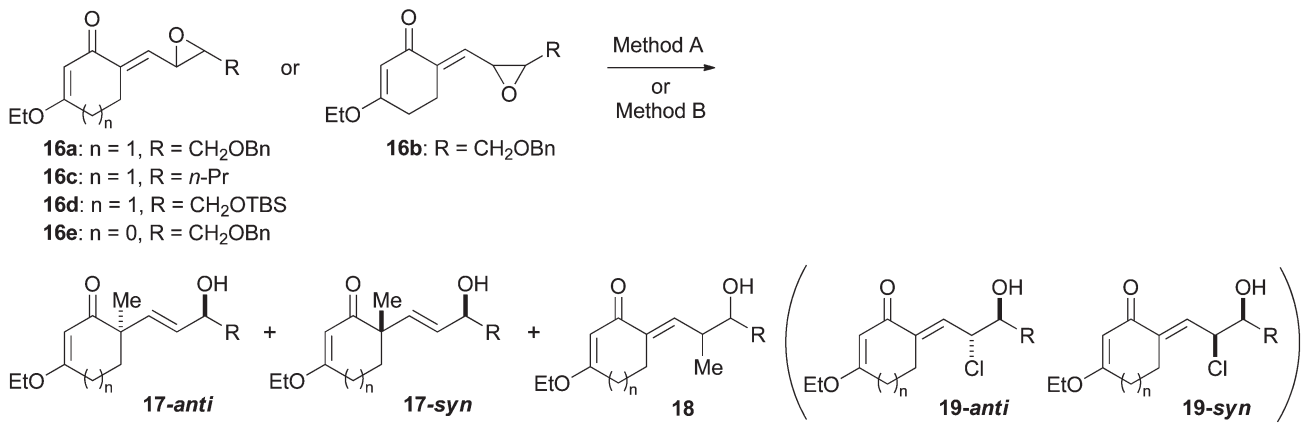


Fig. 1 Design of new substrate **16a**.

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

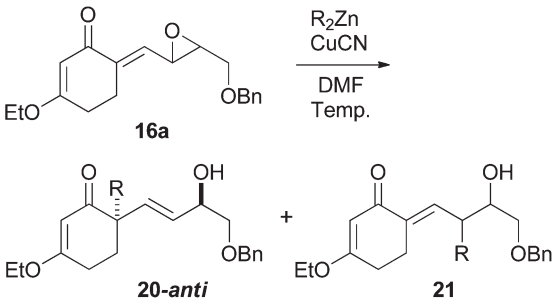
[a] Method A: Me_2Zn, CuCN, DMF, −50 °C. Method B: (1) $MgCl_2$, MeCN, rt; (2) Me_2Zn, CuCN, DMF, −50 °C. [b] Isolated yield after purification. [c] Two step yield in the case of Method B. [d] Determined by ^{1}H-NMR of the crude product. [e] The S_N2' methylation reaction was performed at −20 °C. [f] 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**.

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 °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 −20 °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-cyclopentenone[19] 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).

Table 2 S_N2' reactions of **16a** with various R_2Zn–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	*n*-Bu	−50 to 0 °C	**20b-*anti***: 43	**21b**: 45	>95 : 5
3	i-Pr	−50 °C	**20c-*anti***: 53	**21c**: 29	>95 : 5
4	CH═CH_2	−50 to 0 °C	**20d-*anti***: 0	**21d**: 0	—

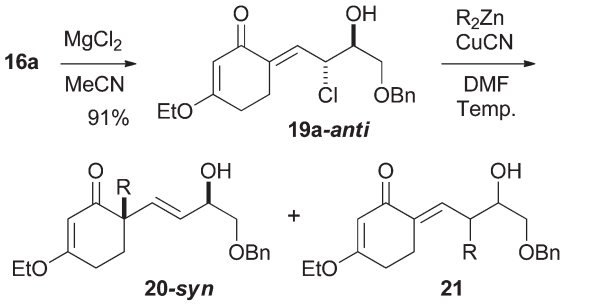
[a] Isolated yield after purification. [b] Determined by ^{1}H-NMR of the crude product.

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*-Bu_2Zn,[21] and i-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 sp^2-hybridized organocopper species; all the starting material was recovered unchanged (entry 4).

The S_N2' reactions of chlorohydrin **19a-*anti*** with various R_2Zn–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-Pr_2Zn–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).

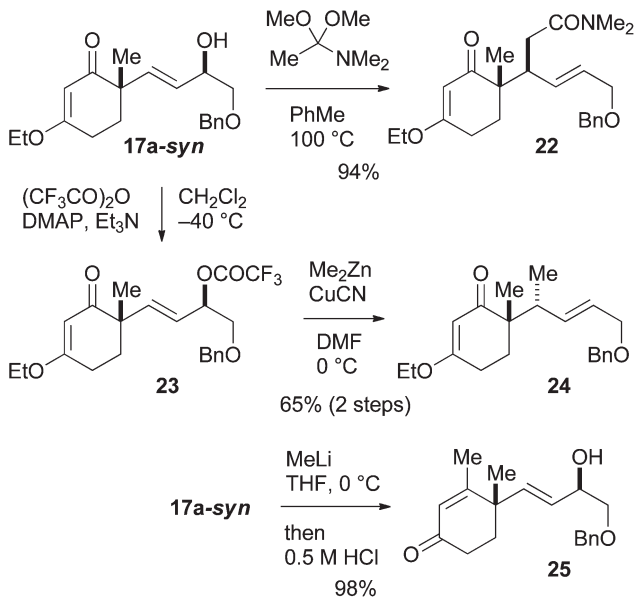
The synthetic utility of **17a-*syn***, which possesses a chiral secondary *trans*-allylic alcohol, was briefly investigated because it is a promising precursor of complex molecules (Scheme 5). Upon treatment of **17a-*syn*** with *N*,*N*-dimethylacetamide dimethyl acetal at 100 °C, Eschenmoser–Claisen rearrangement[24] smoothly and stereospecifically afforded keto amide **22** (94% yield), which has contiguous quaternary and tertiary

Table 3 S_N2' reactions of chlorohydrin **19a-*anti*** with various R_2Zn–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	*n*-Bu	−50 to −20 °C	**20b-*syn***: 80	**21b**: 12	<5 : 95
3	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 ^{1}H-NMR of the crude product.



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

stereogenic centers. Alternatively, a two-step *syn*-S_N2' methylation reaction sequence of **17a-*syn*** involving esterification with trifluoroacetic anhydride in the presence of Et_3N and 4-dimethylaminopyridine and subsequent *anti*-S_N2' methylation reaction of the resulting trifluoroacetate **23** with Me_2Zn–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 methyllithium 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.

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 R_2Zn–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 $MgCl_2$ and S_N2' alkylation of the resulting chlorohydrin with a R_2Zn–CuCN reagent. Our new methodology was applicable to various substrates and R_2Zn 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, CH_2Cl_2, and DMF were purchased from Kanto Chemical Co. Triethylamine and diisopropylamine were distilled from CaH_2 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 nm Merck Kieselgel 60 F_{254} 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. ^{1}H NMR spectra were measured using a JEOL ECA-500 (500 MHz) spectrometer in $CDCl_3$ (δ_H 7.26) with tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured using a JEOL ECA-500 (125.8 MHz) spectrometer in $CDCl_3$ (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.

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-Pr_2NH (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 NH_4Cl 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 °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-(((2*S**,3*S**)-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), 4.60 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 3.93 (q, 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 $C_{19}H_{23}O_4$ ([M + H]$^+$): 315.1596, found: 315.1596.

(*E*)-6-(((2*S*,3*S*)-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 ((2*S*,3*S*)-3-((benzyloxy)-methyl)oxiran-2-yl)methanol[26] [(+)-**26**, 92% ee]. The ^1H-NMR spectrum was consistent with that of **16a**: $[\alpha]_D^{26}$ 1.42 (c 1.07, $CHCl_3$).

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

This compound was prepared according to the literature procedure:[26] $[\alpha]_D^{25}$ 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^{-1}, T = 20 °C; 254 nm; t = 12.6 min (major), t = 14.3 min (minor); 92% ee.

(*E*)-6-(((2*S**,3*R**)-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 (2*S**,3*S**)-4-(benzyloxy)-2,3-epoxybutanal:[27] 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 $C_{19}H_{22}O_4$ (M^+): 314.1518, found: 314.1522.

(*E*)-3-Ethoxy-6-(((2*S**,3*S**)-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 (2*S**,3*R**)-2,3-epoxy-hexanal:[28] 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 $C_{14}H_{20}O_3$ (M^+): 236.1412, found: 236.1411.

(*E*)-6-(((2*S**,3*S**)-3-(((*tert*-Butyldimethylsilyl)oxy)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 (2*S**,3*R**)-2,3-epoxy-4-(*tert*-butyldimethylsiloxy)-butanal:[29] 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 ([M + H]$^+$, 26%); HRMS (FD) calcd for $C_{18}H_{31}O_4Si$ ([M + H]$^+$): 339.1992, found: 339.1966.

(*E*)-5-(((2*S,3*S**)-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-cyclopentenone[19] 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}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 6.18 (dt, J = 8.0, 1.8 Hz, 1H), 5.47 (s, 1H), 4.60 (d, J = 12.1 Hz, 1H), 4.57 (d, J = 12.1 Hz, 1H), 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{18}H_{21}O_4$ ([M + H]$^+$): 301.1440, found: 301.1433.

General procedure for the S_N2' alkylation reaction of γ,δ-epoxy-α,β-unsaturated cyclic ketones with a R_2Zn–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 μL) was added Me_2Zn (2.0 M in toluene, 270 μL, 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 NH_4Cl and 35% aqueous NH_4OH (9 : 1) and extracted with diethyl ether (Et_2O). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by preparative thin-layer chromatography (SiO_2, hexane–EtOAc = 1 : 2) afforded alkylation product **17a-*anti*** (70.6 mg, 0.213 mmol, 84%).

(*R)-6-((3*R**,1*E*)-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}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{20}H_{27}O_4$ ([M + H]$^+$): 331.1909, found: 331.1914.

(*R*)-6-((3*R*,1*E*)-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 Me_2Zn–CuCN. The ^{1}H-NMR spectrum was consistent with that of **17a-*anti***: colorless oil; $[\alpha]_D^{27}$ −28.0 (c 0.54, $CHCl_3$); chiral HPLC resolution conditions: Daicel Chiralcel AD-H, hexane–i-PrOH = 90 : 10; flow rate = 1.0 mL min^{-1}, T = 20 °C; 254 nm; t = 17.0 min (major), t = 18.9 min (minor); 92% ee.

(*S)-6-((3*R**,1*E*)-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 Me_2Zn–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}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{20}H_{26}O_4$ (M$^+$): 330.1831, found: 330.1844.

(*R)-3-Ethoxy-6-((3*S**,1*E*)-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 Me_2Zn–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}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{15}H_{24}O_3$ (M$^+$): 252.1725, found: 252.1740.

(*R)-6-((3*R**,1*E*)-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 Me_2Zn–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{19}H_{34}O_4Si$ (M^+): 354.2226, found: 354.2247.

(*R)-5-((3*R**,1*E*)-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 Me_2Zn–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, $CDCl_3$) 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), 4.58 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.6 Hz, 1H), 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{19}H_{25}O_4$ ($[M + H]^+$): 317.1753, found: 317.1717.

General procedure for the chlorination reaction of γ,δ-epoxy-α,β-unsaturated cyclic ketones with $MgCl_2$

A mixture of *trans*-epoxide **16a** (156.3 mg, 0.497 mmol) and $MgCl_2$ (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 $MgSO_4$, and concentrated under reduced pressure. The residue was quickly purified by flash column chromatography (SiO_2, 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, $CDCl_3$) 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, 2H), 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{19}H_{23}{}^{35}ClO_4$ (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 $MgCl_2$ 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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{19}H_{23}{}^{35}ClO_4$ (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 $MgCl_2$ 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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{14}H_{21}{}^{35}ClO_3$ (M^+): 272.1179, found: 272.1174.

(*E*)-6-((2*R,3*S**)-4-((*tert*-Butyldimethylsilyl)oxy)-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 $MgCl_2$ 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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{18}H_{32}{}^{35}ClO_4Si$ ($[M + H]^+$): 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 $MgCl_2$: 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, $CDCl_3$) 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, 2H), 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{18}H_{21}{}^{35}ClO_4$ (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 R_2Zn–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 Me_2Zn (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 NH_4Cl and 35% aqueous NH_4OH (9 : 1) and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–EtOAc = 1 : 1) to give alkylation product **17a-*syn*** (351 mg, 1.06 mmol, 86%).

(*S*)-6-((3*R*,1*E*)-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 Me_2Zn–CuCN. The ^1H-NMR spectrum was consistent with that of **17a-*syn***: yellow oil; $[\alpha]_D^{28}$ 35.2 (c 0.61, $CHCl_3$); chiral HPLC resolution conditions: Daicel Chiralcel AD-H, hexane–i-PrOH = 90 : 10; flow rate = 1.0 mL min^{-1}, T = 20 °C; 254 nm; t = 15.2 min (major), t = 16.7 min (minor); 88% ee.

(*R)-6-((3*R**,1*E*)-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 Me_2Zn–CuCN. All the spectral data of this compound were identical with those synthesized by the reaction of *trans*-epoxide **16a** with Me_2Zn–CuCN.

(*S)-3-Ethoxy-6-((3*S**,1*E*)-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 Me_2Zn–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{15}H_{24}O_3$ (M^+): 252.1725, found: 252.1705.

(*S)-6-((3*R**,1*E*)-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 Me_2Zn–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 ($[M - t\text{-Bu}]^+$, 100%); HRMS (FD) calcd for $C_{19}H_{34}O_4Si$ (M^+): 354.2226, found: 354.2215.

(*S)-5-((3*R**,1*E*)-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 Me_2Zn–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, $CDCl_3$) 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), 4.57 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 207.5, 187.2, 137.8, 135.5, 128.4, 127.7, 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 $C_{19}H_{25}O_4$ ($[M + H]^+$): 317.1753, found: 317.1752.

(*R)-6-((3*R**,1*E*)-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 Et_2Zn–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{21}H_{29}O_4$ ($[M + H]^+$): 345.2066, found: 345.2079.

(*R)-6-((3*R**,1*E*)-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*-Bu_2Zn[21]–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{23}H_{32}O_4$ (M^+): 372.2301, found: 372.2281.

(*S)-6-((3*R**,1*E*)-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-Pr_2Zn–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{22}H_{30}O_4$ (M^+): 358.2144, found: 358.2141.

(*S)-6-((3*R**,1*E*)-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 Et_2Zn–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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{21}H_{28}O_4$ (M^+): 344.1988, found: 344.1992.

(*S)-6-((3*R**,1*E*)-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*-Bu_2Zn[21]–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{23}H_{32}O_4$ (M^+): 372.2301, found: 372.2265.

(*R)-6-((3*R**,1*E*)-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-Pr_2Zn–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, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{22}H_{31}O_4$ ([M + H]$^+$): 359.2222, found: 359.2221.

(*R)-6-((3*R**,1*E*)-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 divinylzinc[22]–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}; ^{1}H NMR (500 MHz, $CDCl_3$) *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); ^{13}C NMR (125.8 MHz, $CDCl_3$) *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 $C_{21}H_{26}O_4$ (M$^+$): 342.1831, found: 342.1835.

(3*S,4*E*)-6-(Benzyloxy)-3-((1*S**)-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 $MgSO_4$ and the volatile materials were removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 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}; ^{1}H NMR (500 MHz, $CDCl_3$) *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); ^{13}C NMR (125.8 MHz, $CDCl_3$) *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 $C_{24}H_{33}NO_4$ (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), Et_3N (25 μL, 0.18 mmol), and 4-dimethylaminopyridine (3.0 mg, 0.0180 mmol) in CH_2Cl_2 (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 $MgSO_4$ 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 Me_2Zn (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 a saturated aqueous solution of NH_4Cl and a 35% aqueous solution of NH_4OH (9 : 1) and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative thin-layer chromatography (SiO_2, 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}; ^{1}H NMR (500 MHz, $CDCl_3$) *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); ^{13}C NMR (125.8 MHz, $CDCl_3$) *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 $C_{21}H_{28}O_3$ (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 methyllithium in THF (1.12 M solution in Et_2O, 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 stirring 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 $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 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}; ^{1}H NMR (500 MHz, $CDCl_3$) *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); ^{13}C NMR (125.8 MHz, $CDCl_3$) *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 $C_{19}H_{25}O_3$ ([M + H]$^+$): 301.1804, found: 301.1804.

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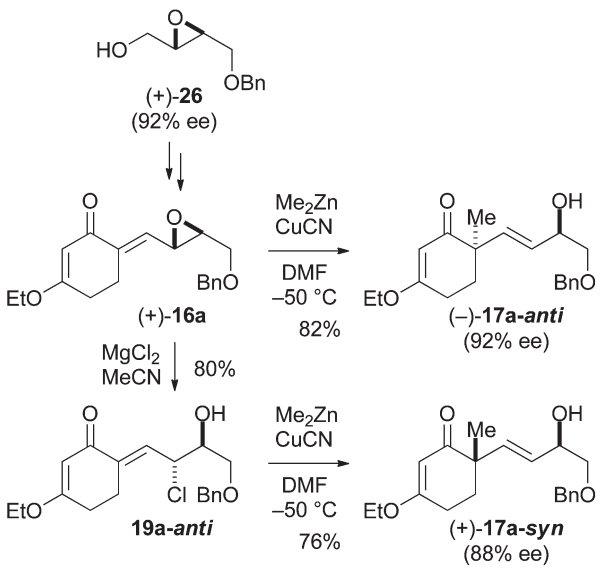

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