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Synthetic studies on polymaxenolides: model studies for constructing dihydropyran portion and synthesis of lower portion

Yutaka Matsuda, Masaya Kato, Tomonori Kawaguchi, Takayuki Koyama, Yoko Saikawa, Masaya Nakata *

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

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ABSTRACT

With a goal of the total synthesis of polymaxenolide, the first hybrid marine natural product, the model studies for constructing the dihydropyran portion based on the originally proposed biosynthesis (C–C bond formation followed by dehydrative cyclization) and the synthesis of the lower portion (the C1–C3, C7–C17 portion) based on an iodide-induced Morita–Baylis–Hillman type reaction (a three-component assembly) followed by Suzuki–Miyaura cross-coupling are described.

1. Introduction

Hybridization is an important natural phenomenon as a new source of molecular and structural diversity. In 2004, polymaxenolide (**1**) was isolated by Slattery and co-workers as the first different-biosynthetic-origin (hybrid) marine natural product from the hybrid soft coral *Sinularia maxima*×*Sinularia polydactyla* collected at Piti Bomb Holes, Guam (Fig. 1).[1] The relative configuration of **1** was determined by NMR experiments and X-ray crystallography.[1] In 2009, Kamel, Slattery, and co-workers isolated five new polymaxenolides (**2**–**6**) from the same hybrid soft coral (Fig. 1).[2] Their structures, including the absolute configurations, were determined by detailed NMR analysis, experimental and theoretically calculated electronic circular dichroism, and X-ray crystallographic analysis.[2] The absolute configuration of **1** has not been reported. Polymaxenolide (**1**) would be expected to have the absolute configuration as depicted in Fig. 1 because of the structural similarity to the six isolated polymaxenolides.[1,2]

Originally, these terpenoids are considered to be synthesized biogenetically from the africane-type sesquiterpenoid unit **7** possessing bicyclo[5.3.0]decane and oxirane structures and the cembrane-type diterpenoid unit **8** (common partial structure shown) via C–C bond formation followed by dehydrative cyclization of the coupling product **9** (Scheme 1).[1] In contrast, Li and Pattenden recently suggested a different biosynthesis of polymaxenolides[3] involving a hetero Diels–Alder reaction between $\Delta^{9(15)}$-africanene (**10**)[4,5] and the diterpenoid unit **11** or **12** (Scheme 1).

The proposed biosynthesis and the structural complexity and uniqueness of the polymaxenolides have attracted interest. Recently, we reported the first racemic synthesis of the sesquiterpenoid units **7** and **10** (together with four other africane-type sesquiterpenoids) using a three-component assembly followed by ring-closing metathesis as the key steps and without the use of protecting groups.[6] These results revealed that the africane-type sesquiterpenoid unit **7**, claimed to have been isolated from the soft coral *Sinularia dissecta* in 1999 by the Venkateswarlu group,[7] was not the natural product.[6] On the other hand, $\Delta^{9(15)}$-africanene (**10**) is the natural product.[4–6]

With a goal of the total synthesis of polymaxenolide (**1**), model studies for constructing the dihydropyran portion were performed based on the originally proposed biosynthesis (C–C bond formation followed by dehydrative cyclization as shown in Scheme 1). Synthesis of the lower portion (the C1–C3, C7–C17 portion)[8] based on an iodide-induced Morita–Baylis–Hillman type reaction (a three-component assembly) followed by Suzuki–Miyaura cross-coupling also was done.

The proposed synthetic strategy of polymaxenolide (**1**) is shown in Scheme 2. Polymaxenolide (**1**) would be obtained from its precursor **13** by oxidative rearrangement (from the C8-position to the C6-position) of the tertiary allylic alcohol together with oxidation

* Corresponding author. Tel.: +81 45 566 1577; fax: +81 45 566 1551; e-mail address: msynktxa@applc.keio.ac.jp (M. Nakata).

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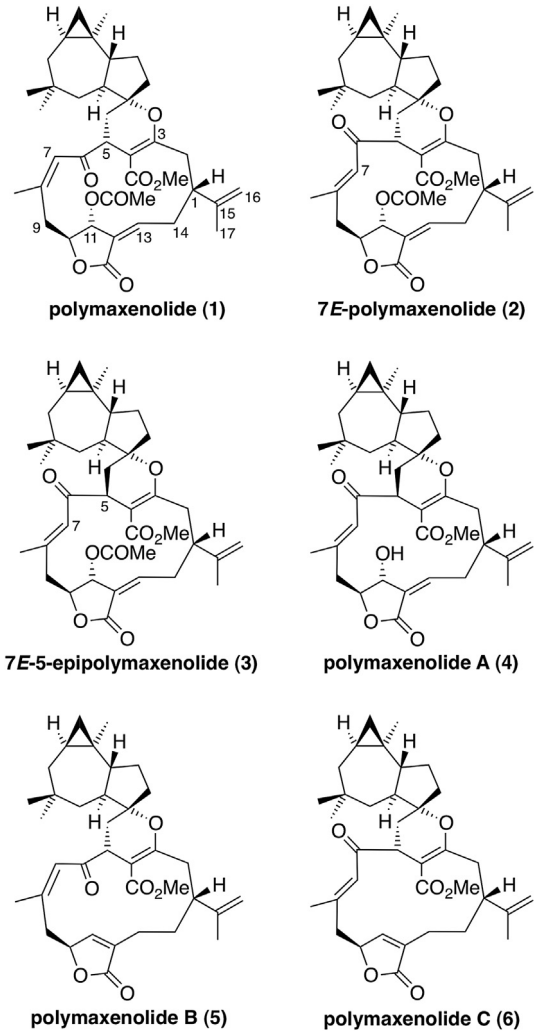


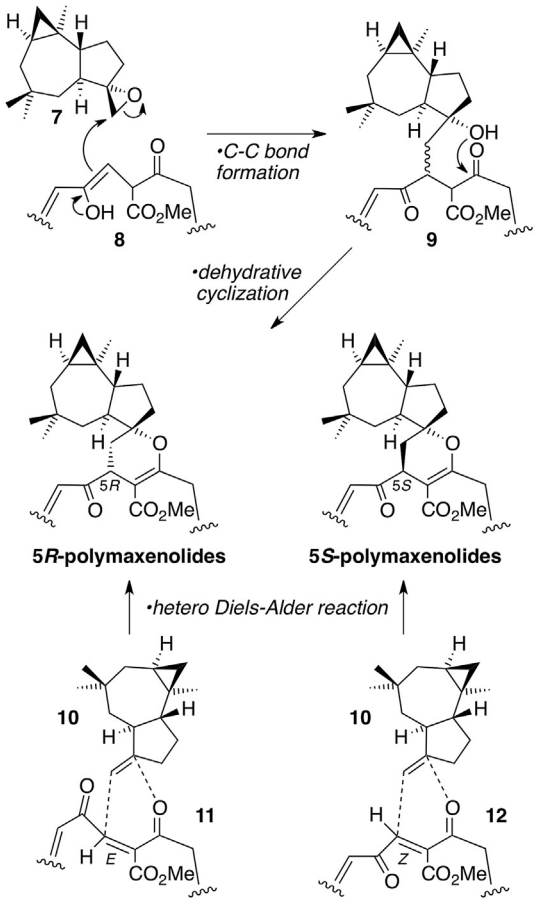
Fig. 1. Natural polymaxenolides.

at the C3-hydroxy group followed by dehydrative cyclization. We anticipated that the lower diterpenoid portion in **13** would be constructed by a ring-closing metathesis of **14**, which would be prepared from the upper portion **15** and the lower portion **16** (the C1–C3, C7–C17 portion) by an aldol coupling. The upper portion **15** would be obtained by C–C bond formation (epoxide-opening reaction) of africene oxide (**7**)[6,9] with an appropriate segment. On the other hand, the lower portion **16** was planned to be secured by Suzuki–Miyaura cross-coupling[10] between (*Z*)-vinyl iodide **17** and alkylborate **18** derived from the corresponding alkyl iodide. A key reaction to produce (*Z*)-vinyl iodide **17** was the iodide-induced Morita–Baylis–Hillman type reaction (vide infra).

2. Results and discussion

2.1. Model studies for constructing dihydropyran portion

A crucial point in the Slattery polymaxenolide biosynthesis is the C–C bond formation between africene oxide (**7**) and the cembrane-type diterpenoid unit **8** (Scheme 1). To investigate the reactivity of such epoxide, the ring-opening reactions of the model epoxide **19**[11] were conducted using several nucleophiles (Table 1). These data provided important information for selecting the best nucleophile for the C–C bond formation partner with africene oxide (**7**). First, we selected the enolate derived from acetophenone

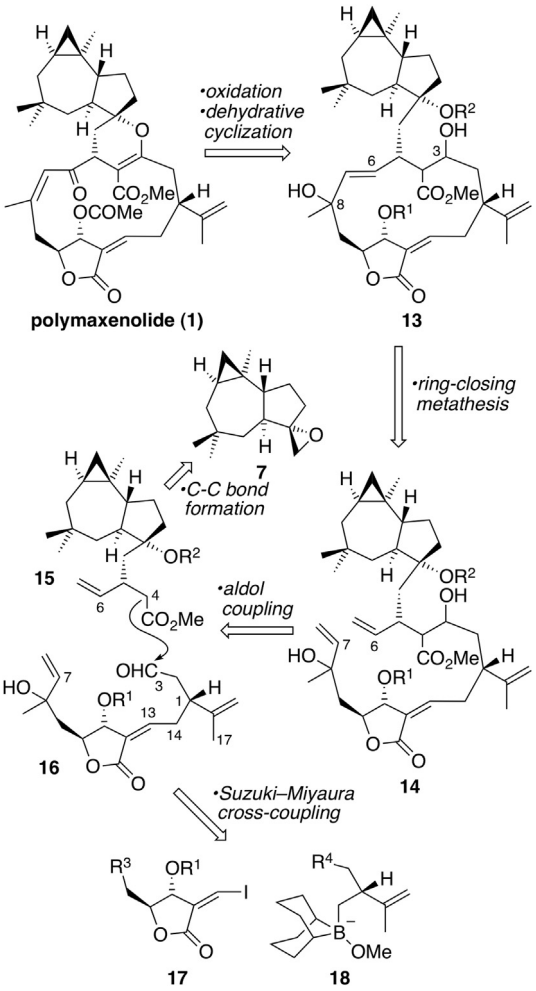


Scheme 1. Proposed biosynthesis of polymaxenolides.

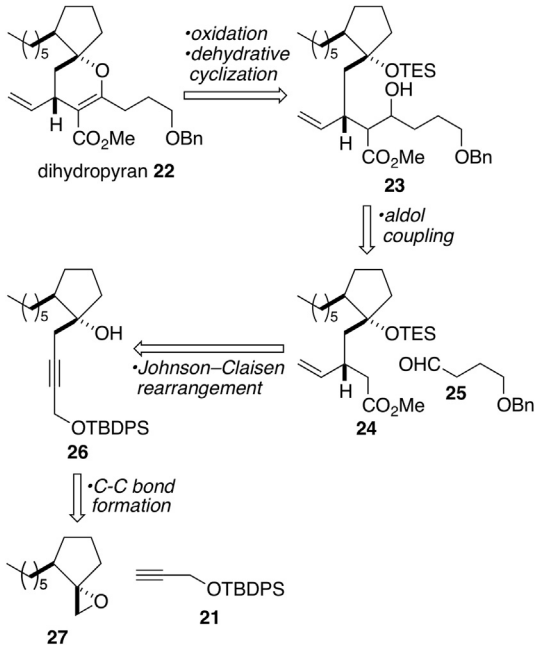
and LDA as a model nucleophile for **8** (Scheme 1), resulting in no reaction even in the presence of $BF_3{\cdot}OEt_2$ (entry 1). Next, we selected some nucleophiles, which have a foothold for the construction of the dihydropyran skeleton. Allyl Grignard reagent attacked epoxide **19** to afford the coupling product **20a** in moderate to good yields together with the brominated product **20b** (entries 2 and 3). 2-Lithio-1,3-dithiane did not react with epoxide **19**, even in the presence of Bu_2Mg[12] (entry 4). The acetylenic anion derived from ethyl propiolate and ^{n}BuLi reacted with epoxide **19** in the presence of $BF_3{\cdot}OEt_2$[13] to give **20c** in 40% yield (entry 5). Finally, we found that the acetylenic anion derived from propargyl silyl ether **21**[14] and ^{n}BuLi reacted with epoxide **19** in the presence of $BF_3{\cdot}OEt_2$[13] to afford the coupling product **20d** in 88% yield (entry 6).

Encouraged by the C–C bond formation studies shown in Table 1, we started the model studies for constructing the dihydropyran portion using another model epoxide (Scheme 3). Dihydropyran **22** was considered as a model dihydropyran portion of polymaxenolide (**1**). We anticipated that dihydropyran **22** would be obtained from hydroxy ester **23** by oxidation of the hydroxy group followed by desilylation and dehydrative cyclization. Hydroxy ester **23** then would be prepared by an aldol coupling between ester **24** and aldehyde **25**. Ester **24** would be secured via Johnson–Claisen rearrangement from **26**, which would be obtained from the new model epoxide **27** by C–C bond formation with propargyl silyl ether **21**.

The synthesis of epoxide **27** is shown in Scheme 4. Olefin **29**,[15] derived from 2-hexylcyclopentanone (**28**) by Wittig methylenation, was subjected to dihydroxylation under OsO_4–NMO conditions to afford an inseparable mixture of diols, whose primary hydroxy group was selectively acetylated with AcCl and Et_3N to



Scheme 2. Synthetic strategy of polymaxenolide (**1**).

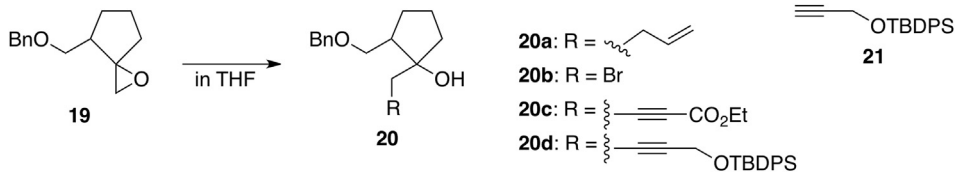


Scheme 3. Synthetic strategy of dihydropyran **22**.

afford the coupling product **26** in 79% yield (Scheme 5). Silylation of **26** with TESOTf and 2,6-lutidine gave bis-silyl ether, which was subjected to selective desilylation using TBAF–AcOH[17] to afford propargylic alcohol. Reduction of this propargyl alcohol with $LiAlH_4$ afforded (*E*)-allylic alcohol **32** in 46% yield from **26**. Johnson–Claisen rearrangement of **32** using trimethyl orthoacetate and phenol in *tert*-butylbenzene at 140 °C gave a 1.1:1 inseparable mixture of esters **24** in 51% yield.

We next conducted the aldol coupling of ester **24** with the model aldehyde **25**[18] (Scheme 6). A 1.1:1 mixture of ester **24** was treated with LDA and the resulting enolate was reacted with

Table 1
Ring-opening reactions of model epoxide **19** with several nucleophiles

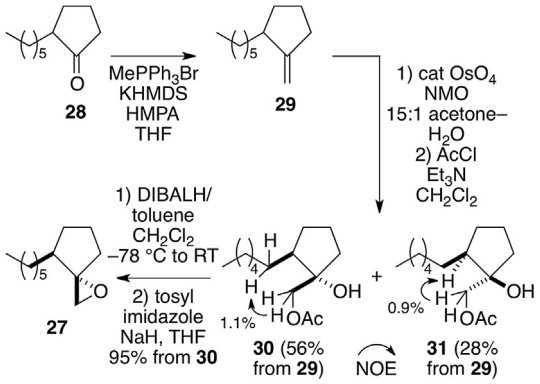


Entry	Conditions[a]	Temperature (°C)	Time (h)	Yield (%)
1	Acetophenone (1.0), LDA (1.0), $BF_3{\cdot}OEt_2$ (1.0)	0	8	nr[b]
2	$CH_2{=}CHCH_2MgBr$ (4.0)	0	2	39 (**20a**), 20 (**20b**)
3	$CH_2{=}CHCH_2MgBr$ (4.0)	0 to 60	6	78 (**20a**), 8 (**20b**)
4	1,3-Dithiane (1.0), ^{n}BuLi (1.0), Bu_2Mg (0.3)	rt[c]	12	nr[b]
5	Ethyl propiolate (5.0), ^{n}BuLi (4.0), $BF_3{\cdot}OEt_2$ (1.0)	−78 to rt[c]	1	40 (**20c**)
6	**21** (5.0), ^{n}BuLi (4.0), $BF_3{\cdot}OEt_2$ (1.0)	−78 to rt[c]	1.5	88 (**20d**)

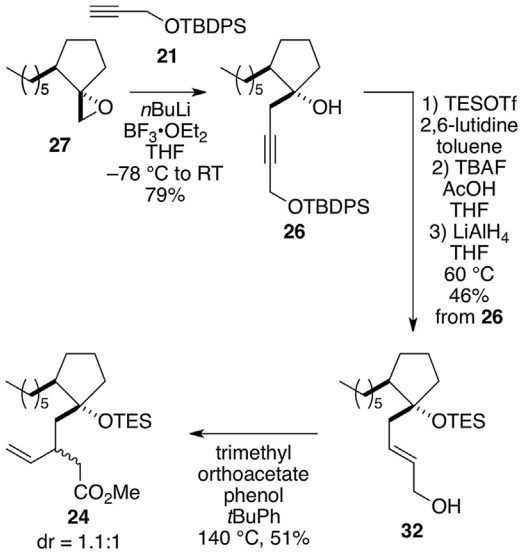
[a] Number in parenthesis shows the equivalent of the reagent based on **19**.
[b] nr=no reaction.
[c] rt=room temperature.

afford acetate **30** and its epimer **31** in 56% and 28% yields, respectively, from **29**. The stereochemistry of these compounds was determined by NOE measurement in ^{1}H NMR experiments shown in Scheme 4. Deacetylation of the major acetate **30** with DIBALH followed by epoxidation using tosyl imidazole[16] provided epoxide **27** in 95% yield.

Epoxide **27** was treated with the acetylenic anion derived from propargyl silyl ether **21**[14] and ^{n}BuLi in the presence of $BF_3{\cdot}OEt_2$[13] to aldehyde **25** to afford the separable products **23** and **33** in 48% and 36% yields, respectively. Each coupling product was found to be a stereoisomer at the C5 position and a mixture at the newly-formed two stereocenters (vide infra). Desilylation of **23** with TBAF in THF or with CSA in MeOH resulted in the formation of lactone **34**. Therefore, we tried oxidation of the hydroxy group before desilylation. After several experiments, PCC oxidation[19] was found to be the best method, which gave, concomitant with



Scheme 4. Synthesis of model epoxide **27**.



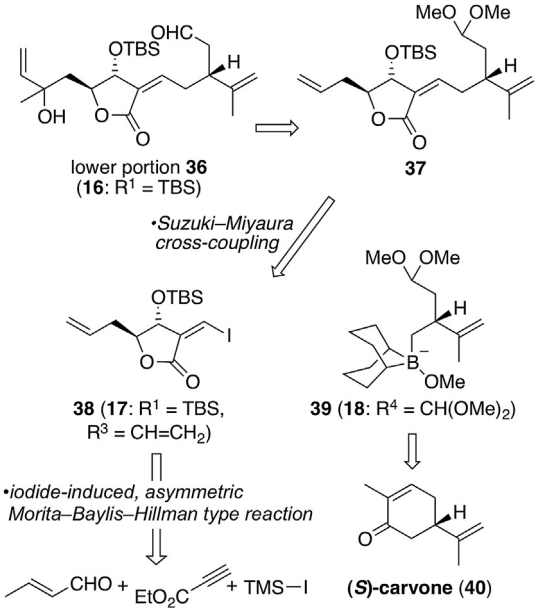
Scheme 5. Synthesis of model upper segment **24**.

spontaneous desilylation and dehydrative cyclization, the model dihydropyran **22** in 42% yield. The C5 isomer **33** also was transformed into dihydropyran **35** in 40% yield under the same reaction conditions. The stereochemistry of **22** and **35** was determined by NOE measurement in ^{1}H NMR experiments shown in Scheme 6, which implies that the coupling products **23** and **33** are stereoisomers at the C5 position.

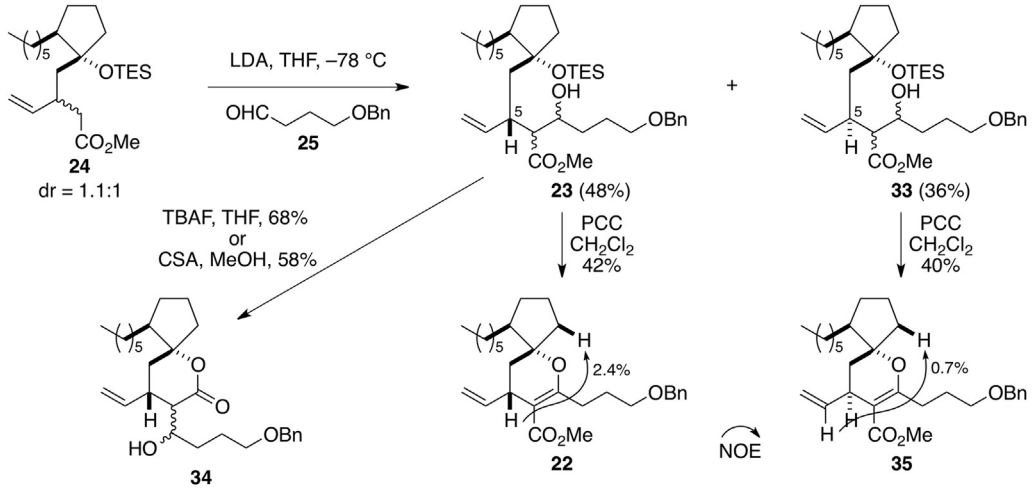
Although the stereochemistry at the C5 position could not be controlled in the model studies, we anticipate that the control will be possible in the case of the real upper portion having the bulky bicyclo[5.3.0]decane structure. The success of the model studies provided strong support for a synthetic strategy to construct the dihydropyran portion of polymaxenolide (**1**) as shown in Scheme 2.

2.2. First-generation synthetic studies toward lower portion

First-generation synthetic strategy of the lower portion **36** (**16** in Scheme 2, R^1=TBS) is depicted in Scheme 7. The tertiary allylic alcohol part in **36** would be obtained from **37** by Wacker oxidation



Scheme 7. First-generation synthetic strategy of lower portion **36**.

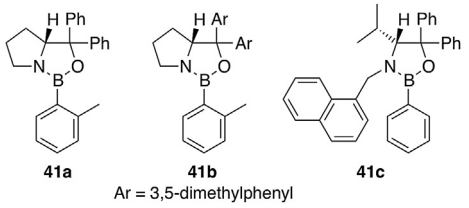


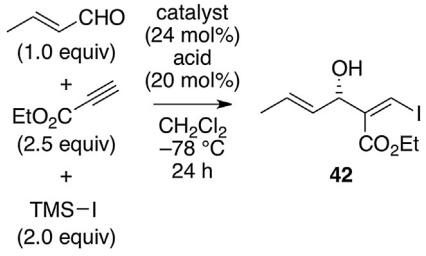
Scheme 6. Model dihydropyran formation.

followed by vinylation. We anticipated, as shown in Scheme 2, **37** would be secured by Suzuki–Miyaura cross-coupling between (*Z*)-vinyl iodide **38** (**17** in Scheme 2, R^1=TBS, R^3=CH=CH_2) and alkylborate **39** (**18** in Scheme 2, R^4=$CH(OMe)_2$). We applied an iodide-induced, asymmetric Morita–Baylis–Hillman type reaction[20] to prepare the precursor for **38**. Alkylborate **39** could be prepared from (*S*)-carvone (**40**).

Taniguchi and Kishi reported the synthesis of β-iodo Morita–Baylis–Hillman carbonyl compounds based on a three-component assembly including an α,β-acetylenic carbonyl compound, an iodide source, and an aldehyde.[21] Its asymmetric version was developed by the Li,[22] Paré,[23] and Ryu[24] groups. We used the Ryu's catalytic asymmetric version of the three-component coupling[24] and the relevant results are shown in Table 2. To a solution of the Corey's oxazaborolidine catalyst **41a**[25] (24 mol %) and TfOH (20 mol %) in CH_2Cl_2 were added successively at −78 °C crotonaldehyde (1.0 equiv), ethyl propiolate (2.5 equiv), and TMSI (2.5 equiv). After 24 h at −78 °C, the reaction mixture was analyzed; but, only trace amounts of the desired coupling product **42** was obtained (entry 1). A dramatic improvement was secured when the acid was changed from TfOH to $AlBr_3$ (entry 2).[26] Under these reaction conditions, an 80% yield of **42**[22b] with 56% ee was obtained.[27] The combination of another Corey's oxazaborolidine catalyst **41b**[25] with $AlBr_3$ did not improve either the yield or % ee (entry 3). Using the Yamamoto's oxazaborolidine catalyst **41c**[28] and $AlBr_3$ gave only the racemic **42** (entry 4). The combination of oxazaborolidine catalyst **41c** with $SnCl_4$[28] resulted in decomposition (entry 5).

Table 2
Iodide-induced Morita–Baylis–Hillman type reaction—**1**





Entry	Catalyst	Acid	Yield (%)	% ee
1	**41a**	TfOH	Trace	—
2	**41a**	$AlBr_3$	80	56
3	**41b**	$AlBr_3$	76	50
4	**41c**	$AlBr_3$	75	0
5	**41c**	$SnCl_4$	0	—

Enantioselectivity of this reaction can be explained similarly by the Corey's pre-transition-state model for the enantioselective oxazaborolidinium-catalyzed Diels–Alder reaction (Fig. 2).[29] Crotonaldehyde is coordinated to the boron center of the catalyst through the lone pair of the carbonyl group. The formyl CH···O hydrogen bond[30] strengthens this complex (pre-transition-state model A). The *si*-face (back) of the formyl carbon is effectively shielded by the aryl group; thus, attack of the β-iodo allenolate

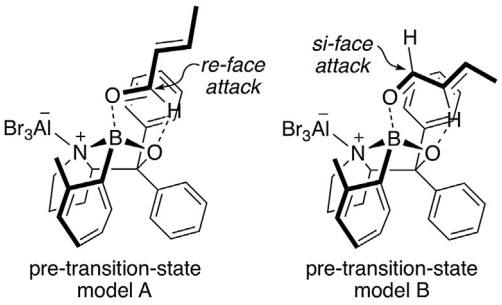
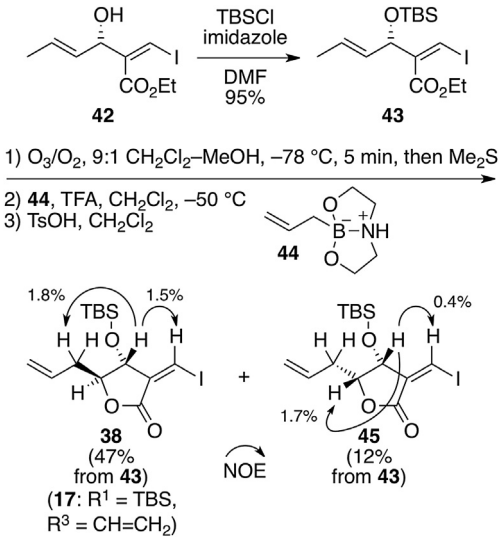


Fig. 2. Proposed two pre-transition-state models.

derived from ethyl propiolate and TMSI from the *re*-face (front) of the formyl carbon will occur. The high *Z* selectivity of the vinyl iodide portion has been well documented.[21,22a,b,23,24a] In the present case, however, crotonaldehyde has an α-hydrogen atom that also can coordinate to the oxygen atom in the catalyst (pre-transition-state model B).[29] In this case, the *si*-face attack is preferred; as a result, the ee of the coupling product **42** did not exceed 56%.[31]

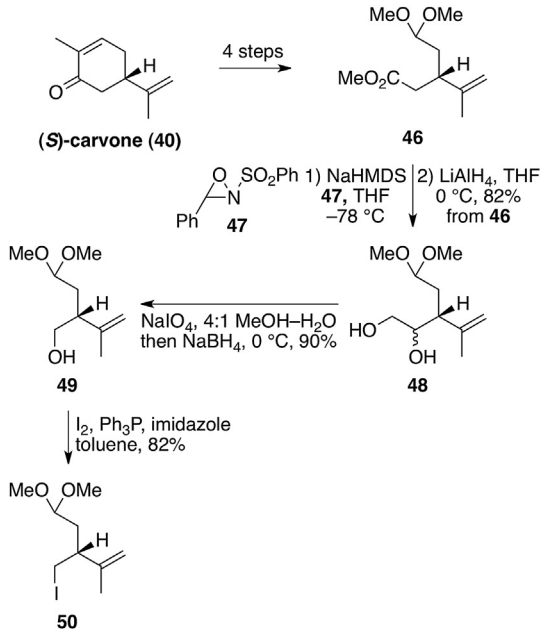
The obtained three-component coupling product **42** (56% ee) was silylated with TBSCl and imidazole, giving **43** in 95% yield (Scheme 8). Selective cleavage of the disubstituted double bond in **43** with OsO_4–$NaIO_4$ resulted in decomposition. In contrast, ozonolysis of **43** followed by Me_2S work-up successfully afforded the unstable aldehyde; but, treatment of this aldehyde with allylmagnesium bromide at −78 °C resulted in decomposition. Next, Rychnovsky's allylation reaction[32] was attempted with this unstable aldehyde using allyldioxazabororidine **44** and TFA in CH_2Cl_2 at −50 °C, affording a 4:1 inseparable mixture of the allylated products. The diastereoselectivity in this allylation would be explained by the general Felkin–Anh model[33] (the OTBS group is the largest substituent). Treatment of this mixture with TsOH in CH_2Cl_2 gave (*Z*)-α-iodomethylene-γ-lactones **38** (**17** in Scheme 2, R^1=TBS, R^3=CH=CH_2) and **45** in 47% and 12% yields, respectively. The stereochemistry of these lactones was determined by NOE measurement in ^{1}H NMR experiments as shown in Scheme 8.



Scheme 8. First-generation synthesis of lower-left segment.

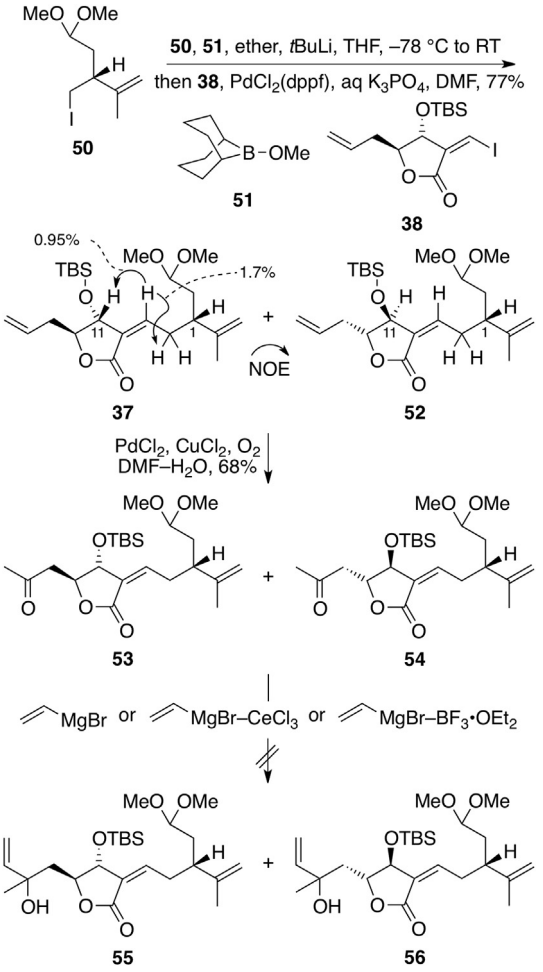
Synthesis of alkyl iodide **50** (Scheme 9, the precursor of alkylborate **39**) as the lower-right segment started with ester **46**,[34] which was derived from (*S*)-carvone (**40**) in four steps in good overall yield. Ester **46** was treated with sodium bis(trimethylsilyl)

amide (NaHMDS) in THF at −78 °C; to the resulting ester enolate was added Davis oxaziridine **47** to afford α-hydroxy ester. This was reduced with $LiAlH_4$ to give diol **48** in 82% yield from **46**. Diol scission of **48** with $NaIO_4$ followed by one-pot $NaBH_4$ reduction afforded alcohol **49** in 90% overall yield. Finally, iodination of alcohol **49** with iodine, triphenylphosphine, and imidazole provided alkyl iodide **50** in 82% yield.



Scheme 9. Synthesis of lower-right segment.

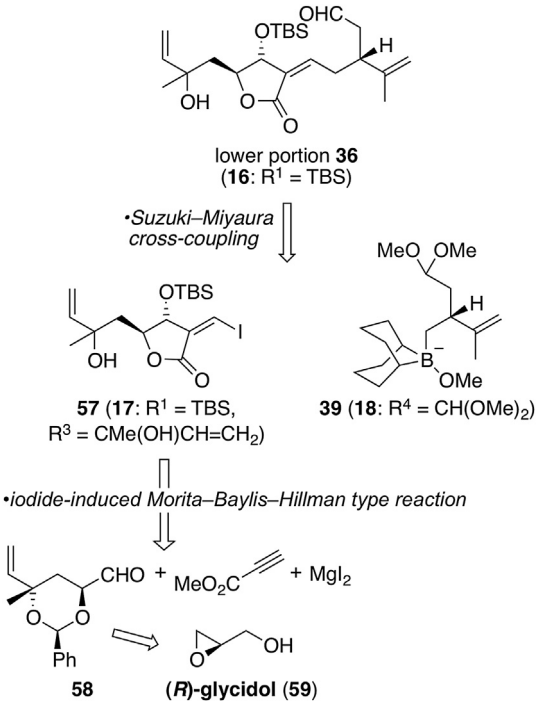
With both (*Z*)-vinyl iodide **38** and alkyl iodide **50** in hand, attention was focused on the crucial Suzuki–Miyaura cross-coupling[10] (Scheme 10). We tried conversion of alkyl iodide **50** to alkylborate **39** by lithiation with ^{t}BuLi and subsequent addition of *B*-methoxy-9-BBN **51**.[35a] However, only decomposition of alkyllithium derived from **50** was observed. Therefore, lithiation of **50** (2.5 equiv) with ^{t}BuLi (5.0 equiv) was conducted in the presence of *B*-methoxy-9-BBN **51** (6.0 equiv),[35b] and the resulting alkylborate **39** was in situ reacted with vinyl iodide **38** (1.0 equiv) in the presence of aqueous K_3PO_4 (5.0 equiv) and $PdCl_2$(dppf) (10 mol %) in DMF to give an inseparable mixture of the coupling product **37** and its diastereomer **52** in 77% combined yield.[36] The diastereomer **52** arose from the inherent enantiomer of vinyl iodide **38**. Preservation of the *Z*-configuration in **37** was confirmed by NOE measurement in ^{1}H NMR experiments as shown in Scheme 10. Wacker oxidation[37] of the mixture of **37** and **52** using $PdCl_2$, $CuCl_2$, and oxygen in aqueous DMF afforded an inseparable mixture of methyl ketone **53** and its diastereomer **54** in 68% combined yield.[36] The final step to obtain the desired lower portion (**55**+**56**) was selective vinylation of the ketone functionality in preference to the lactone functionality. However, all attempts to realize this task were unsuccessful and only decomposition of the starting material (**53**+**54**) occurred.



Scheme 10. First-generation synthetic studies toward lower portion.

2.3. Second-generation synthesis of lower portion

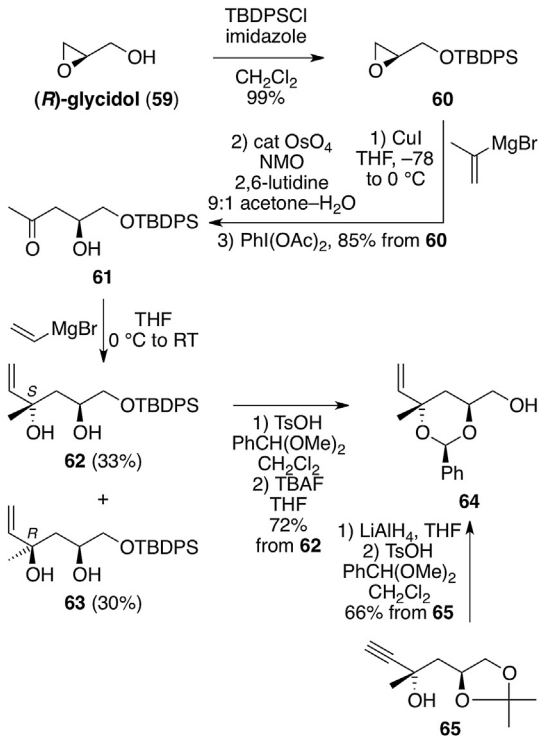
We next chose vinyl iodide **57** (Scheme 11, **17** in Scheme 2, R^1=TBS, R^3=CMe(OH)CH=CH_2), which already contained the allylic tertiary hydroxy group, as an alternative candidate for the lower-left segment. Furthermore, since we could not realize the high % ee in the catalytic asymmetric Morita–Baylis–Hillman



Scheme 11. Second-generation synthetic strategy of lower portion **36**.

type reaction (Table 2), we next adopted a diastereoselective Morita–Baylis–Hillman type reaction using a chiral aldehyde partner **58**. To this end, (*R*)-glycidol (**59**) was selected as a starting material.

Isopropenylmagnesium bromide was added to the known TBDPS ether **60**,[38] prepared from (*R*)-glycidol (**59**) by silylation, in the presence of CuI to afford the addition product, the double bond of which was cleaved by OsO_4–NMO dihydroxylation followed by $PhI(OAc)_2$ treatment,[39] giving methyl ketone **61** in 85% overall yield from **60** (Scheme 12). Subsequent vinylmagnesium bromide addition afforded the adduct **62** (33%) and its diastereomer **63** (30%). Although both adducts can be used for the subsequent transformations, only (*S*)-alcohol **62** was used for further transformation at this stage. Benzylidene acetal formation of **62** using benzaldehyde dimethylacetal and TsOH followed by desilylation by TBAF furnished alcohol **64** in 72% overall yield. The stereochemistry of **64** (and hence **62**) was confirmed as follows. The stereochemically confirmed propargylic alcohol **65**,[40] prepared from L-malic acid, was transformed into **64** by $LiAlH_4$ reduction of the triple bond and the subsequent benzylidenation in 66% yield (two steps). The ^1H and ^{13}C NMR spectra of **64** from both syntheses were identical.

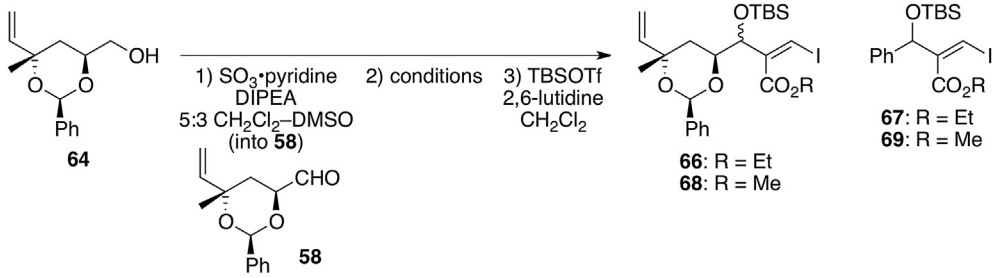


Scheme 12. Second-generation synthesis of lower-left segment—**1**.

First, we tried an iodide-induced Morita–Baylis–Hillman type reaction between aldehyde **58**, derived from alcohol **64** by Parikh–Doering oxidation,[41] ethyl propiolate, and TMSI in the presence of the Corey's oxazaborolidine catalyst **41a**[25] using $AlBr_3$ or TfOH as an acidic activator (Table 3, entries 1 and 2). After work up, the reaction mixture was silylated with TBSOTf and 2,6-lutidine in order to easily isolate the products; however, the three-component coupling product **67** derived from benzaldehyde was the only compound isolated in low yield. Benzaldehyde might be released from the starting aldehyde by the action of the acid catalyst or the iodinating reagent. Next, the Paré's MgI_2-promoted Morita–Baylis–Hillman type reaction[42] was conducted (entry 3). Aldehyde **58** (1.0 equiv), derived from alcohol **64** by Parikh–Doering oxidation,[41] was treated with MgI_2 (3.0 equiv) in CH_2Cl_2 at 0 °C for 5 min, and ethyl propiolate (3.0 equiv) was added and the mixture was stirred at room temperature for 18 h, giving a 1.3:1 inseparable mixture of **66** (18%) together with **67** (35%) after silylation. The use of less Lewis acidic $MgI_2 \cdot OEt_2$ instead of MgI_2 reduced the production of **67**, but the yield of **66** also decreased (entry 4). The use of methyl propiolate instead of ethyl propiolate tended toward increasing the isolated yield (entries 5 and 6). Finally, we found that lowering the mixing temperature of aldehyde and $MgI_2 \cdot OEt_2$ to −20 °C resulted in an 85% yield of **68** as a 1.2:1 inseparable mixture along with a trace amount of **69** (entry 7).

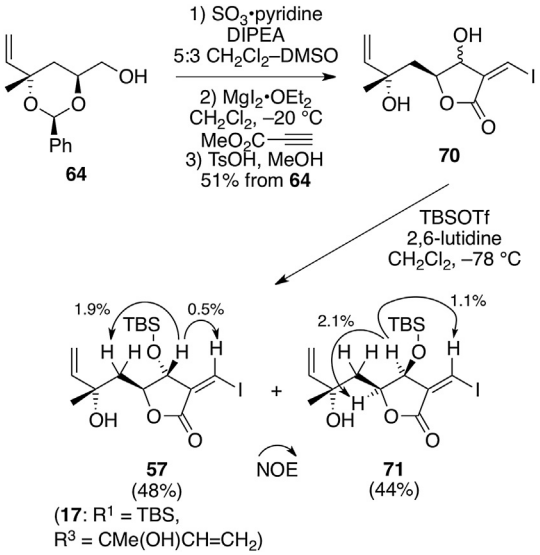
Based on these experiments, the three-component coupling product without silylation was subjected to lactonization using TsOH in MeOH to provide a 1.1:1 inseparable mixture of **70** in 51% yield from **64** (Scheme 13). This lactone **70** was then silylated with TBSOTf and 2,6-lutidine to afford the desired lower-left segment **57** and its epimer **71** in 48% and 44% yields, respectively. The stereochemistry of these compounds was determined by NOE measurement in ^1H NMR experiments as shown in Scheme 13.

Table 3
Iodide-induced Morita–Baylis–Hillman type reaction—**2**



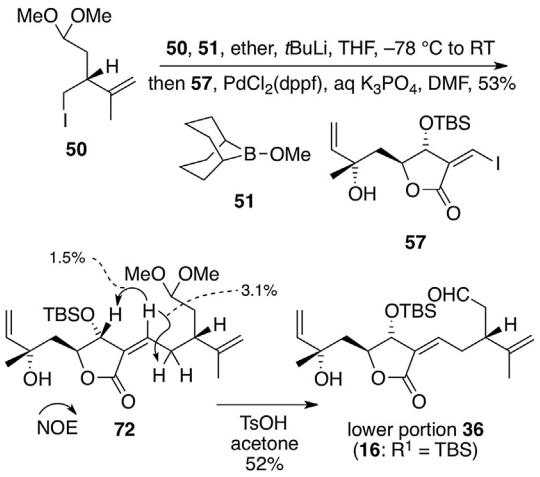
Entry	Conditions[a]	Products (yield (%))
1	**41a** (0.24), $AlBr_3$ (0.2), ethyl propiolate (3.0), TMSI (1.8), CH_2Cl_2, −78 °C, 24 h	**67** (22)
2	**41a** (0.24), TfOH (0.2), ethyl propiolate (3.0), TMSI (1.8), CH_2Cl_2, −78 °C, 24 h	**67** (15)
3	MgI_2 (3.0), CH_2Cl_2, 0 °C, 5 min, then ethyl propiolate (3.0), rt, 18 h	**66** (18),[b] **67** (35)
4	$MgI_2 \cdot OEt_2$ (3.0), CH_2Cl_2, 0 °C, 5 min, then ethyl propiolate (3.0), rt, 18 h	**66** (2),[b] **67** (15)
5	MgI_2 (3.0), CH_2Cl_2, 0 °C, 5 min, then methyl propiolate (3.0), rt, 18 h	**68** (27),[b] **69** (38)
6	$MgI_2 \cdot OEt_2$ (3.0), CH_2Cl_2, 0 °C, 5 min, then methyl propiolate (3.0), rt, 18 h	**68** (43),[b] **69** (7)
7	$MgI_2 \cdot OEt_2$ (3.0), CH_2Cl_2, −20 °C, 5 min, then methyl propiolate (3.0), rt, 18 h	**68** (85),[b] **69** (trace)

[a] Number in parenthesis shows the equivalent of the reagent based on **64**.
[b] The diastereomer ratio: 1.3:1 (entries 3 and 4), 1.2:1 (entries 5–7).



Scheme 13. Second-generation synthesis of lower-left segment—**2**.

Lithiation of **50** (2.5 equiv) with ^{t}BuLi (5.0 equiv) was conducted in the presence of *B*-methoxy-9-BBN **51** (6.0 equiv),[35b] and the resulting alkylborate **39** was in situ reacted with vinyl iodide **57** (1.0 equiv) in the presence of aqueous K_3PO_4 (5.0 equiv) and $PdCl_2$(dppf) (10 mol %) in DMF to give the coupling product **72** in 53% yield (Scheme 14). The stereochemistry of **72** was determined by NOE measurement in ^{1}H NMR experiments as shown in Scheme 14. Finally, acidic treatment of **72** afforded the desired lower portion **36** (**16** in Scheme 2, R^1=TBS) in 52% yield.



Scheme 14. Second-generation synthesis of lower portion **36**.

3. Conclusions

We succeeded in the model studies for constructing the spirocyclic dihydropyran portion of polymaxenolide (**1**), featuring C–C bond formation between the epoxide and the acetylenic anion, an aldol reaction between the ester and the aldehyde, and oxidation concomitant with spontaneous desilylation and dehydrative cyclization. The sequence of this synthesis was based on Slattery's proposed biosynthesis. The synthesis of the lower portion (the C1–C3, C7–C17 portion) of polymaxenolide (**1**) featuring the iodide-induced Morita–Baylis–Hillman type reaction followed by Suzuki–Miyaura cross-coupling also was accomplished. Progress toward the total synthesis of polymaxenolide (**1**) along with the strategy described here is now underway.

4. Experimental section

4.1. General information

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 polarimeter. IR spectra were obtained on a KBr cell and recorded on a Bruker ALPHA FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL Lambda 300, a Varian MERCURY plus 300, or a JEOL ECA-500. Chemical shifts of ^{1}H NMR spectra in $CDCl_3$ are expressed in parts per million relative to tetramethylsilane 0.00 unless otherwise noted. Chemical shifts of ^{13}C NMR spectra were expressed in ppm relative to solvent signal=77.00 in $CDCl_3$, 128.06 in benzene-d_6. The assignments of ^{1}H and ^{13}C NMR spectra of the major and minor isomers in an inseparable mixture of the products (**24**, **48**, **66**, **68**, and **70**) were done by judging an integral value (^{1}H) and intensity (^{13}C) of the signals. In the case of the signal overlap, such signals were assigned to both the major and minor isomers. High- and low-resolution mass spectra were recorded on a JEOL GC mate (EI and FAB). Analytical thin layer chromatography (TLC) was performed using pre-coated Merck TLC 60F-254 plates (0.25 mm), and visualization was accomplished with ethanolic phosphomolybdic acid. Column chromatography was performed on Fuji silysia PSQ 100B spherical silica gel (particle size 100 μm). Experiments requiring anhydrous conditions were carried out in well-dried glassware under an argon atmosphere. Organic solvents were distilled by appropriate procedures and stored under argon atmosphere.

4.2. Experimental procedure and characterization data for compounds

*4.2.1. (±)-Methyl 6-(benzyloxy)-2-((S)-1-((1R,2S)-2-hexyl-1-(triethylsilyloxy)cyclopentyl)but-3-en-2-yl)-3-hydroxyhexanoate (**23**) and (±)-methyl 6-(benzyloxy)-2-((R)-1-((1R,2S)-2-hexyl-1-(triethylsilyloxy)cyclopentyl)but-3-en-2-yl)-3-hydroxyhexanoate (**33**).* To a stirred solution of diisopropylamine (0.137 mL, 0.951 mmol) in dry THF (1.50 mL) was added 1.65 M hexane solution of ^{n}BuLi (0.558 mL, 0.920 mmol) at 0 °C. After 45 min at 0 °C, **24** (126 mg, 0.307 mmol) in dry THF (0.307 mL) was added at −78 °C. After 1 h at −78 °C, **25** (274 mg, 1.54 mmol) in dry THF (0.307 mL) was added at −78 °C. After 1 h, saturated aqueous NH_4Cl solution was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10.0 g, hexane/EtOAc=20:1) to afford **23** (86.4 mg, 48%, a diastereomer ratio was not determined) as a colorless syrup and **33** (64.8 mg, 36%, a diastereomer ratio was not determined) as a colorless syrup. Compound **23**: R_f=0.58 (hexane/EtOAc=5:1); IR (neat, cm^{-1}) 3448, 2954, 2928, 2875, 2856, 1733, 1456, 1435, 1415, 1361, 1238, 1198, 1160, 1102, 1007, 915, 736, 698; ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 0.51–0.71 (m, 6H), 0.85–0.90 (m, 3H), 0.91–1.00 (m, 9H), 1.12 (m, 1H), 1.23–1.32 (m, 10H), 1.41–1.57 (m, 6H), 1.60–2.01 (m, 6H), 2.40–2.57 (m, 1H), 2.78–2.87 (m, 1H), 3.46–3.52 (m, 2H), 3.60 (s, 1.95H), 3.67 (s, 1.05H), 3.67 (br s, 0.23H), 3.72 (br s, 0.77H), 3.90 (m, 1H), 4.50 (s, 2H), 4.95–5.11 (m, 2H), 5.69–5.93 (m, 1H), 7.31–7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 6.4, 6.5, 7.07, 7.14, 14.1, 19.1, 19.5, 22.6, 26.0, 26.3, 27.9, 28.78, 28.83, 28.9, 29.0, 29.7, 29.8, 31.1, 31.6, 31.9, 32.3, 35.4, 36.0, 36.1, 37.3, 40.1, 50.1, 50.7, 51.0, 51.1, 58.0, 58.3, 69.5, 70.3, 72.2, 72.7, 72.8, 86.4, 86.5, 114.9, 115.0, 127.37, 127.43, 127.5, 127.6,

128.3, 138.5, 138.6, 142.4, 142.6, 173.7, 173.8; LRMS (EI) m/z $(M)^+$ 588.4; HRMS (EI-quadrupole) m/z $(M)^+$ calcd for $C_{35}H_{60}O_5Si$ 588.4210, found 588.4192. Compound **33**: R_f=0.50 (hexane/EtOAc=5:1); IR (neat, cm^{-1}) 3443, 2954, 2929, 2875, 2857, 1733, 1456, 1436, 1415, 1362, 1237, 1201, 1157, 1103, 1011, 913, 737, 698; ^1H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 0.56 (q, J=8.0 Hz, 6H), 0.88 (t, J=7.2 Hz, 3H), 0.93 (t, J=8.0 Hz, 9H), 0.95 (m, 1H), 1.10–1.17 (m, 2H), 1.22–1.34 (m, 8H), 1.41–1.54 (m, 4H), 1.64–1.99 (m, 6H), 2.49 (dd, J=8.9, 4.6 Hz, 1H), 2.55 (ddd, J=7.1, 7.1, 1.7 Hz, 1H), 2.62 (br d, J=5.1 Hz, 1H), 2.79 (br d, J=9.7 Hz, 1H), 2.83 (m, 1H), 2.94 (dddd, J=8.9, 8.7, 4.6, 4.6 Hz, 1H), 3.45 (m, 1H), 3.48–3.52 (m, 2H), 3.66 (s, 2.27H), 3.70 (s, 0.53H), 3.84 (m, 1H), 4.44–4.51 (m, 2H), 5.00 (dd, J=10.1, 2.0 Hz, 0.82H), 5.07 (dd, J=17.4, 2.0 Hz, 0.82H), 5.08 (d, J=1.4 Hz, 0.18H), 5.12 (d, J=1.7 Hz, 0.18H), 5.60 (ddd, J=17.2, 10.0, 10.0 Hz, 0.18H), 5.90 (ddd, J=17.4, 10.1, 8.7 Hz, 0.82H), 7.27–7.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 6.7, 7.3, 14.1, 19.7, 19.9, 22.7, 26.1, 28.2, 28.6, 29.4, 29.8, 31.9, 32.6, 37.6, 37.7, 38.6, 50.4, 51.2, 57.4, 70.2, 70.4, 73.0, 85.2, 115.2, 127.5, 127.6, 127.7, 128.4, 130.2, 140.9, 173.6; LRMS (EI) m/z $(M)^+$ 588.4; HRMS (EI-quadrupole) m/z $(M)^+$ calcd for $C_{35}H_{60}O_5Si$ 588.4210, found 588.4210.

*4.2.2. (±)-(1S,5R,9S)-8-(4-(Benzyloxy)-1-hydroxybutyl)-1-hexyl-9-vinyl-6-oxaspiro[4.5]decan-7-one (**34**).* To a stirred solution of **23** (25.6 mg, 0.0435 mmol) in THF (0.435 mL) was added 1.0 M TBAF in THF (0.0870 mL, 0.0870 mmol) at room temperature. After 1 h, saturated aqueous NH_4Cl solution was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.0 g, hexane/EtOAc=5:1) to afford **34** (13.1 mg, 68%) as a colorless syrup: R_f=0.51 (hexane/EtOAc=5:1); IR (neat, cm^{-1}) 3440, 2954, 2928, 2856, 1699, 1454, 1364, 1266, 1204, 1102, 1028, 994, 968, 919, 735, 698; ^1H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 0.88 (t, J=6.9 Hz, 3H), 1.02 (m, 1H), 1.18–1.39 (m, 9H), 1.45–1.52 (m, 2H), 1.62–1.82 (m, 7H), 1.87–1.96 (m, 2H), 1.99–2.08 (m, 2H), 2.52 (m, 1H), 2.57 (dd, J=11.2, 3.1 Hz, 1H), 3.46–3.56 (m, 2H), 3.75 (br s, 1H), 3.77 (br s, 1H), 3.84 (m, 1H), 4.47–4.52 (m, 2H), 5.11 (br d, J=10.3 Hz, 1H), 5.12 (br d, J=16.9 Hz, 1H), 5.65 (ddd, J=16.9, 10.3, 7.7 Hz, 1H), 7.27–7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 14.1, 21.2, 22.6, 26.5, 28.1, 28.9, 29.4, 29.5, 29.6, 31.8, 34.6, 36.2, 37.9, 49.6, 51.3, 69.8, 70.5, 72.8, 93.2, 116.8, 127.5, 127.6, 127.7, 128.3 (2C), 138.5, 139.6, 173.9; LRMS (EI) m/z $(M)^+$ 442.4; HRMS (EI-quadrupole) m/z $(M)^+$ calcd for $C_{28}H_{42}O_4$ 442.3083, found 442.3088.

*4.2.3. (±)-(1S,5R,9S)-Methyl 7-(3-benzyloxypropyl)-1-hexyl-9-vinyl-6-oxaspiro[4.5]dec-7-ene-8-carboxylate (**22**).* To a stirred solution of **23** (59.0 mg, 0.100 mmol) in CH_2Cl_2 (1.00 mL) was added PCC (43.2 mg, 0.200 mmol) at room temperature. After 8 h, the mixture was directly purified by column chromatography on silica gel (1.0 g, hexane/EtOAc=10:1) to afford **22** (19.1 mg, 42%) as a colorless syrup: R_f=0.72 (hexane/EtOAc=5:1); IR (neat, cm^{-1}) 2953, 2928, 2856, 1710, 1641, 1615, 1454, 1434, 1268, 1188, 1096, 912, 735, 698; ^1H NMR (500 MHz, benzene-d_6, solvent residual peak=7.16) δ 0.81 (m, 1H), 0.91 (t, J=7.1 Hz, 3H), 1.06–1.14 (m, 2H), 1.20–1.30 (m, 7H), 1.32–1.45 (m, 3H), 1.35 (m, 1H), 1.52–1.61 (m, 2H), 1.56 (m, 1H), 1.70 (m, 1H), 1.91 (m, 1H), 1.96–2.11 (m, 2H), 2.80 (ddd, J=14.6, 9.2, 5.8 Hz, 1H), 3.13 (ddd, J=14.6, 8.6, 6.6 Hz, 1H), 3.34 (dt, J=9.2, 7.7 Hz, 1H), 3.44 (t, J=6.6 Hz, 2H), 3.50 (s, 3H), 4.34 (s, 2H), 5.02 (dd, J=10.0, 1.1 Hz, 1H), 5.18 (br d, J=17.7 Hz, 1H), 5.76 (ddd, J=17.7, 10.0, 7.7 Hz, 1H), 7.08 (m, 1H), 7.15–7.18 (m, 2H), 7.30 (d, J=6.9 Hz, 2H); ^{13}C NMR (125 MHz, benzene-d_6, benzene-d_6=128.06) δ 14.4, 21.5, 23.1, 28.6, 28.6, 29.7, 30.0, 30.1, 30.2, 32.3, 34.4, 35.5, 36.2, 48.6, 50.5, 70.2, 72.9, 87.8, 105.0, 114.4, 127.5 (2C), 127.8 (2C), 128.5, 139.6, 142.2, 164.5, 168.5; LRMS (EI) m/z $(M)^+$ 454.3; HRMS (EI-quadrupole) m/z $(M)^+$ calcd for $C_{29}H_{42}O_4$ 454.3083 found 454.3082.

*4.2.4. (±)-(1S,5R,9R)-Methyl 7-(3-benzyloxypropyl)-1-hexyl-9-vinyl-6-oxaspiro[4.5]dec-7-ene-8-carboxylate (**35**).* To a stirred solution of **33** (64.8 mg, 0.110 mmol) in CH_2Cl_2 (1.10 mL) was added PCC (47.4 mg, 0.220 mmol) at room temperature. After 8 h, the mixture was directly purified by column chromatography on silica gel (1.50 g, hexane/EtOAc=10:1) to afford **35** (20.0 mg, 40%) as a colorless syrup: R_f=0.72 (hexane/EtOAc=5:1); IR (neat, cm^{-1}) 2954, 2928, 2856, 1707, 1612, 1454, 1437, 1271, 1089, 913, 737, 698; ^1H NMR (500 MHz, benzene-d_6, solvent residual peak=7.16) δ 0.75 (m, 1H), 0.92 (t, J=7.2 Hz, 3H), 1.10 (m, 1H), 1.22–1.34 (m, 9H), 1.41 (m, 1H), 1.49 (m, 1H), 1.56 (dd, J=13.7, 4.6 Hz, 1H), 1.66 (m, 1H), 1.75 (m, 1H), 1.75 (dd, J=13.7, 7.1 Hz, 1H), 1.91 (m, 1H), 1.94 (m, 1H), 2.04 (m, 1H), 2.14 (m, 1H), 2.90 (m, 1H), 3.06 (ddd, J=13.2, 9.2, 5.8 Hz, 1H), 3.48 (t, J=6.6 Hz, 2H), 3.49 (s, 3H), 3.54 (m, 1H), 4.36 (s, 2H), 5.00 (ddd, J=10.2, 1.4, 1.4 Hz, 1H), 5.14 (ddd, J=16.9, 1.7, 1.4 Hz, 1H), 5.81 (ddd, J=16.9, 10.2, 6.3 Hz, 1H), 7.08 (m, 1H), 7.14–7.18 (m, 2H), 7.30–7.32 (m, 2H); ^{13}C NMR (125 MHz, benzene-d_6, benzene-d_6=128.06) δ 14.4, 21.9, 23.1, 28.4, 28.7, 28.8, 29.9, 30.1, 30.6, 32.3, 32.8, 35.4, 36.6, 48.5, 50.7, 70.3, 72.9, 88.7, 103.6, 114.2, 127.5 (2C), 128.4 (2C), 128.5, 139.6, 142.8, 165.5, 168.6; LRMS (EI) m/z $(M)^+$ 454.4; HRMS (EI-quadrupole) m/z $(M)^+$ calcd for $C_{29}H_{42}O_4$ 454.3083, found 454.3075.

*4.2.5. Ethyl (3S,2Z,4E)-3-hydroxy-2-(iodomethylene)hex-4-enoate (**42**).* To a stirred solution of oxazaborolidinium catalyst **41a** (120 mg, 0.339 mmol) in CH_2Cl_2 (1.41 mL) was added at −40 °C $AlBr_3$ (58.5 mg, 0.282 mmol). After 20 min at −40 °C, a pale yellow homogeneous catalyst solution was obtained. The catalyst solution was cooled to −78 °C and crotonaldehyde (0.120 mL, 1.41 mmol) was then added dropwise to the mixture. After 20 min stirring at −78 °C, ethyl propiolate (0.358 mL, 3.53 mmol) and TMSI (0.442 mL, 2.82 mmol) were added sequentially and quickly to the mixture. After 24 h at −78 °C, water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20.0 g, hexane/EtOAc=4:1) to afford **42**[22b] (334 mg, 80%, 56% ee) as a yellow syrup: R_f=0.51 (hexane/EtOAc=3:1); $[\alpha]_D^{20.1}$ +2.35 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz, TMS=0.00) δ 1.36 (t, J=7.0 Hz, 3H), 1.70 (d, J=6.6 Hz, 3H), 2.77 (d, J=6.0 Hz, 1H), 4.31 (q, J=7.0 Hz, 2H), 4.88 (m, 1H), 5.50 (ddq, J=15.4, 6.6, 1.2 Hz, 1H), 5.78 (ddq, J=15.4, 6.6, 1.0 Hz, 1H), 7.18 (d, J=1.2 Hz, 1H).

*4.2.6. Ethyl (S,2Z,4E)-3-(tert-butyldimethylsilyloxy)-2-(iodomethylene)hex-4-enoate (**43**).* To a stirred solution of **42** (70.0 mg, 0.236 mmol, 56% ee) in DMF (0.788 mL) were added imidazole (32.2 mg, 0.473 mmol) and TBSCl (53.4 mg, 0.355 mmol) at room temperature. After 1 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was extracted with hexane. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2.9 g, hexane/EtOAc=5:1) to afford **43** (92.2 mg, 95%) as a yellow syrup: R_f=0.75 (hexane/EtOAc=3:1); $[\alpha]_D^{24.2}$ +2.3 (c 0.50, $CHCl_3$); IR (neat, cm^{-1}) 2957, 2931, 2887, 2858, 1728, 1472, 1464, 1367, 1304, 1275, 1257, 1183, 1097, 1039, 965, 871, 837, 778; ^1H NMR ($CDCl_3$, 500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.047 (s, 3H), 0.053 (s, 3H), 0.88 (s, 9H), 1.33 (t, J=7.1 Hz, 3H), 1.67 (dd, J=6.6, 0.7 Hz, 3H), 4.21–4.32 (m, 2H), 4.91 (br d, J=7.1 Hz, 1H), 5.36 (ddq, J=15.5, 7.2, 0.7 Hz, 1H), 5.65 (ddq, J=15.5, 6.6, 1.0 Hz, 1H), 6.99 (d, J=1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −5.1, −4.5, 14.1, 17.6, 18.2, 25.8 (3C), 61.1, 75.2, 81.9, 127.9, 131.0, 147.2, 166.2;

LRMS (EI) *m/z* (M−^{t}Bu)$^+$ 353.0; HRMS (EI-quadrupole) *m/z* (M−^{t}Bu)$^+$ calcd for $C_{11}H_{18}O_3SiI$ 353.0070, found 353.0068.

*4.2.7. (4R,5S,3Z)-5-(Prop-2-enyl)-4-tert-(butyldimethylsilyloxy)-3-(iodomethylene) dihydrofuran-2(3H)-one (**38**) and (4R,5R,3Z)-5-(prop-2-enyl)-4-(tert-butyldimethylsilyloxy)-3-(iodomethylene)dihydrofuran-2(3H)-one (**45**).* A stirred solution of **43** (60.0 mg, 0.146 mmol) in CH_2Cl_2 (1.33 mL) and MeOH (0.132 mL) was cooled to −78 °C and O_3/O_2 was bubbled through the solution. After 5 min at −78 °C, oxygen was bubbled through the solution. After 5 min at −78 °C, dimethyl sulfide (0.0763 mL, 1.46 mmol) was added and the mixture was warmed to room temperature. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude aldehyde as a yellow oil, which was used for the next reaction without purification. To a stirred solution of this crude aldehyde and allyldioxazaborolidine **44** (27.2 mg, 0.175 mmol) in CH_2Cl_2 (0.243 mL) was added trifluoroacetic acid (0.0130 mL, 0.175 mmol) at −50 °C. After 15 h at −50 °C, water was added at room temperature and the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude alcohol as a yellow oil, which was used for the next reaction without purification. To a stirred solution of this crude alcohol in CH_2Cl_2 (1.46 mL) was added *p*-toluenesulfonic acid (2.8 mg, 0.015 mmol) at room temperature. After 2 h at room temperature, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (24 g, hexane/EtOAc=5:1) to afford **38** (27.1 mg, 47% for three steps) as a colorless syrup and **45** (6.9 mg, 12% for three steps) as a colorless syrup. Compound **38**: R_f=0.71 (hexane/EtOAc=3:1); $[\alpha]_D^{22.5}$ +27.7 (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}) 2955, 2930, 2897, 2858, 1767, 1626, 1471, 1385, 1353, 1259, 1152, 1118, 1090, 839, 778; ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.12 (s, 6H), 0.90 (s, 9H), 2.39 (m, 1H), 2.49 (m, 1H), 4.18 (m, 1H), 4.52 (dd, *J*=4.3, 2.1 Hz, 1H), 5.19 (m, 1H), 5.20 (m, 1H), 5.78 (m, 1H), 7.48 (d, *J*=2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −4.3, −4.2, 17.9, 25.6 (3C), 36.5, 75.6, 82.6, 91.3, 119.6, 131.4, 139.2, 166.5; LRMS (EI) *m/z* (M−^{t}Bu)$^+$ 337.0; HRMS (EI-quadrupole) *m/z* (M−^{t}Bu)$^+$ calcd for $C_{10}H_{14}O_3SiI$ 336.9757, found 336.9754. Compound **45**: R_f=0.64 (hexane/EtOAc=3:1); $[\alpha]_D^{22.6}$ +5.9 (*c* 0.50, $CHCl_3$); IR (neat, cm^{-1}) 2956, 2859, 1763, 1630, 1471, 1363, 1340, 1259, 1165, 1124, 1079, 1004, 919, 839, 779; ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.11 (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H) 2.38−2.50 (m, 2H), 4.37 (m, 1H), 4.83 (dd, *J*=5.7, 1.7 Hz, 1H), 5.14 (m, 1H), 5.17 (m, 1H), 5.80 (m, 1H), 7.41 (d, *J*=1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −4.7, −4.5, 18.1, 25.6 (3C), 33.6, 73.9, 79.9, 89.7, 118.8, 132.3, 139.1, 166.6; LRMS (EI) *m/z* (M−^{t}Bu)$^+$ 337.0; HRMS (EI-quadrupole) *m/z* (M−^{t}Bu)$^+$ calcd for $C_{10}H_{14}O_3SiI$ 336.9757, found 336.9763.

*4.2.8. (3R)-3-(2,2-Dimethoxyethyl)-4-methylpent-4-ene-1,2-diol (**48**).* To a stirred solution of **46** (2.00 g, 9.25 mmol) in THF (46.2 mL) was added 1.0 M NaHMDS in THF (18.5 mL, 18.5 mmol) at −78 °C. After 20 min at −78 °C, Davis' oxaziridine **47** (3.62 g, 13.9 mmol) was added. After 3 h at −78 °C, saturated aqueous NH_4Cl solution was added at 0 °C and the reaction mixture was extracted with hexane. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude hydroxy ester as a colorless oil, which was used for the next reaction without purification. To a stirred solution of this crude hydroxy ester in dry THF (40 mL) was added $LiAlH_4$ (363 mg, 9.55 mmol) at 0 °C. After 1 h at 0 °C, potassium sodium (+)-tartrate tetrahydrate and water were added at 0 °C and the reaction mixture was warmed up to room temperature. After 2 h at room temperature, water was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100 g, hexane/EtOAc=1:1) to afford a 3:1 inseparable mixture (judged by ^{1}H NMR spectrum) of **48** (1.55 g, 82% for two steps) as a colorless syrup. *Major isomer of* **48**: R_f=0.32 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.66 (m, 1H), 1.68 (s, 3H), 2.11 (ddd, *J*=14.3, 8.0, 4.6 Hz, 1H), 2.26 (ddd, *J*=14.3, 13.5, 4.3 Hz, 1H), 2.29 (br s, 1H), 2.79 (br s, 1H), 3.32 (s, 3H), 3.33 (s, 3H), 3.42 (m, 1H), 3.55−3.64 (m, 2H), 4.37 (dd, *J*=8.0, 3.7 Hz, 1H), 4.81 (s, 1H), 4.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 19.9, 32.8, 46.2, 52.8, 53.2, 65.3, 73.3, 103.3, 113.6, 144.7. *Minor isomer of* **48**: R_f=0.32 (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS=0.00) δ 1.66 (m, 1H), 1.75 (s, 3H), 1.77 (m, 1H), 2.29 (br s, 1H), 2.37 (ddd, *J*=12.3, 7.8, 4.6 Hz, 1H), 2.60 (br s, 1H), 3.31 (s, 3H), 3.33 (s, 3H), 3.42 (m, 1H), 3.55−3.64 (m, 1H), 3.70 (m, 1H), 4.31 (dd, *J*=8.0, 3.4 Hz, 1H), 4.88 (s, 1H), 4.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 19.5, 32.1, 45.9, 52.9, 53.3, 64.5, 72.5, 103.2, 115.2, 144.4. *Mixture of two isomers of* **48**: IR (neat, cm^{-1}) 3418, 2938, 2832, 1645, 1443, 1380, 1192, 1129, 1057, 897, 756; LRMS (EI) *m/z* (M)$^+$ 204.1; HRMS (EI-quadrupole) *m/z* (M)$^+$ calcd for $C_{10}H_{20}O_4$ 204.1362, found 204.1355.

*4.2.9. (R)-2-(2,2-Dimethoxyethyl)-3-methylbut-3-en-1-ol (**49**).* To a stirred solution of a 3:1 mixture of **48** (1.21 g, 5.92 mmol) in MeOH (19.0 mL) and H_2O (4.75 mL) was added $NaIO_4$ (1.67 g, 6.75 mmol) at 0 °C and the reaction mixture was warmed up to room temperature. After 2 h at room temperature, $NaBH_4$ (1.38 g, 36.5 mmol) was added at 0 °C. After 30 min at 0 °C, water was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (40.0 g, hexane/EtOAc=3:1) to afford **49** (903 mg, 90%) as a colorless syrup: R_f=0.52 (hexane/EtOAc=1:2); $[\alpha]_D^{21.6}$ −8.2 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3425, 2941, 2831, 1646, 1443, 1383, 1192, 1129, 1051, 960, 893; ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.67 (ddd, *J*=14.0, 8.0, 4.4 Hz, 1H), 1.70 (s, 3H), 1.74 (ddd, *J*=14.0, 7.2, 6.2 Hz, 1H), 1.83 (br s, 1H), 2.41 (m, 1H), 3.32 (s, 3H), 3.34 (s, 3H), 3.53−3.55 (m, 2H), 4.39 (dd, *J*=7.2, 4.3 Hz, 1H), 4.84 (br s, 1H), 4.93 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 19.6, 32.9, 45.5, 52.6, 53.2, 64.2, 103.1, 113.4, 145.0; LRMS (FAB) *m/z* (M+H)$^+$ 175.1; HRMS (FAB-quadrupole) *m/z* (M+H)$^+$ calcd for $C_9H_{19}O_3$ 175.1334, found 175.1307.

*4.2.10. (R)-3-(Iodomethyl)-5,5-dimethoxy-2-methylpent-1-ene (**50**).* To a stirred solution of **49** (575 mg, 3.30 mmol) and Ph_3P (1.56 g, 5.94 mmol) in toluene (11.0 mL) were added imidazole (806 mg, 13.2 mmol) and iodine (1.59 g, 6.27 mmol) at 0 °C. After 1.5 h at room temperature, saturated aqueous sodium thiosulfate solution and saturated aqueous $NaHCO_3$ solution were added and the mixture was extracted with hexane. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10.0 g, hexane/$CHCl_3$=5:2) to afford **50** (773 mg, 82%) as a colorless syrup: R_f=0.75 (hexane/EtOAc=4:1); $[\alpha]_D^{19.5}$ +9.6 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 2952, 2830, 1646, 1437, 1378, 1190, 1125, 1059, 899; ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.66 (ddd, *J*=14.1, 9.8, 4.0 Hz, 1H), 1.69 (s, 3H), 1.91 (ddd, *J*=14.1, 7.7, 4.8 Hz, 1H), 2.48 (m, 1H), 3.18 (dd, *J*=9.8, 7.7 Hz, 1H), 3.24 (dd, *J*=9.8, 6.3 Hz, 1H), 3.31 (s, 3H), 3.32 (s, 3H), 4.34 (dd, *J*=7.7, 4.0 Hz, 1H), 4.82 (s, 1H), 4.93 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 11.0, 18.7, 35.8, 45.2, 52.7, 52.8, 102.7, 113.7,

144.7; LRMS (EI) m/z $(M)^+$ 284.1; HRMS (EI-quadrupole) m/z $(M)^+$ calcd for $C_9H_{17}IO_2$ 284.0274, found 284.0246.

*4.2.11. (4R,5S,3Z)-5-Prop-2-enyl-4-(tert-butyldimethylsilyloxy)-3-[(R)-3-(2,2-dimethoxyethyl)-4-methyl-pent-4-en-1-ylidene] dihydrofuran-2(3H)-one (**37**) and (4S,5R,3Z)-5-prop-2-enyl-4-(tert-butyldimethylsilyloxy)-3-[(R)-3-(2,2-dimethoxyethyl)-4-methyl-pent-4-en-1-ylidene]dihydrofuran-2(3H)-one (**52**).* To a stirred solution of **50** (8.0 mg, 0.032 mmol) and 1.00 M hexane solution of **51** (0.0762 mL, 0.0762 mmol) in dry Et_2O (0.0975 mL) were rapidly added at −78 °C 1.58 M pentane solution of ^{t}BuLi (0.0401 mL, 0.0635 mmol) and dry THF (0.0975 mL). After 10 min at −78 °C, the resulting suspension was warmed to room temperature. After 30 min at room temperature, 3.0 M aqueous K_3PO_4 (0.0210 mL, 0.0635 mmol) was added and then a solution of **38** (5.0 mg, 0.0127 mmol) and $PdCl_2$(dppf) (1.0 mg, 0.00126 mmol) in DMF (0.127 mL) was added. After 3 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane/EtOAc=5:1) to afford an inseparable mixture of **37** and **52** (5.4 mg, 77% combined yield) as a colorless syrup. Judging from ^{1}H and ^{13}C NMR spectra, it seems to be only one diastereomer. Therefore, the diastereomer ratio could not be determined. Compound **37**: R_f=0.74 (hexane/EtOAc=4:1); IR (neat, cm^{-1}) 2953, 2931, 2858, 1761, 1677, 1645, 1472, 1464, 1442, 1374, 1254, 1167, 1127, 1092, 893, 839, 778; ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.64 (br s, 3H), 1.68–1.72 (m, 2H), 2.32–2.46 (m, 3H), 2.76–2.87 (m, 2H), 3.29 (s, 3H), 3.31 (s, 3H), 4.19 (m, 1H), 4.35 (dd, J=6.9, 4.8 Hz, 1H), 4.41 (m, 1H), 4.76 (s, 1H), 4.81 (br s, 1H), 5.16 (m, 1H), 5.17 (m, 1H), 5.78 (m, 1H), 6.24 (dt, J=7.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −4.3, −4.2, 17.9, 18.2, 25.7 (3C), 30.9, 35.8, 37.0, 43.0, 52.5, 53.1, 73.6, 83.9, 102.7, 112.9, 119.1, 129.6, 131.9, 145.3, 145.9, 168.2; LRMS (EI) m/z $(M-{}^t\mathrm{Bu})^+$ 367.2; HRMS (EI-quadrupole) m/z $(M-{}^t\mathrm{Bu})^+$ calcd for $C_{19}H_{31}O_5Si$ 367.1941, found 367.1966.

*4.2.12. (4R,5S,3Z)-4-(tert-Butyldimethylsilyloxy)-3-((R)-3-(2,2-dimethoxyethyl)-4-methylpent-4-en-1-ylidene)-5-(2-oxopropyl)dihydrofuran-2(3H)-one (**53**) and (4S,5R,3Z)-4-(tert-butyldimethylsilyloxy)-3-((R)-3-(2,2-dimethoxyethyl)-4-methylpent-4-en-1-ylidene)-5-(2-oxopropyl)dihydrofuran-2(3H)-one (**54**).* To a stirred solution of an inseparable mixture of **37** and **52** (12.0 mg, 0.0282 mmol) in dry DMF (0.141 mL) and water (0.0282 mL) bubbled with oxygen was added $PdCl_2$ (2.0 mg, 0.11 mmol) and $CuCl_2$ (0.8 mg, 0.06 mmol) at room temperature. This solution was again bubbled with oxygen and the resulting mixture was stirred for additional 48 h. 1.0 M Aqueous solution of HCl was then added at room temperature and the mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane/EtOAc=5:1) to afford an inseparable mixture (the diastereomer ratio could not be determined) of **53** and **54** (8.5 mg, 68% combined yield) as a colorless syrup: R_f=0.50 (hexane/EtOAc=2:1); IR (neat, cm^{-1}) 2953, 2931, 2857, 1759, 1721, 1677, 1448, 1374, 1257, 1162, 1128, 1092, 839, 779; ^{1}H NMR ($CDCl_3$, 500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.65 (br s, 3H), 1.69–1.72 (m, 2H), 2.21 (s, 3H), 2.39 (m, 1H), 2.67 (dd, J=16.9, 5.1 Hz, 1H), 2.76 (dd, J=16.9, 7.1 Hz, 1H), 2.81 (br dd, J=7.4, 7.4 Hz, 2H), 3.30 (s, 3H), 3.31 (s, 3H), 4.35 (dd, J=6.9, 4.8 Hz, 1H), 4.46 (m, 1H), 4.52 (m, 1H), 4.76 (s, 1H), 4.81 (br s, 1H), 6.26 (dt, J=7.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −4.4, −4.3, 17.8, 18.1, 25.6 (3C), 30.8, 30.9, 35.9, 42.9, 45.9, 52.6, 53.3, 74.1, 80.6, 102.9, 113.1, 129.0, 145.6, 145.8, 167.8, 204.5; LRMS (FAB) m/z $(M+H)^+$ 441.1; HRMS (FAB-quadrupole) m/z $(M+H)^+$ calcd for $C_{23}H_{41}O_6Si$ 441.2672, found 441.2698.

*4.2.13. (S)-5-(tert-Butyldiphenylsilyloxy)-4-hydroxypentan-2-one (**61**).* To a stirred solution of CuI (9.50 g, 49.9 mmol) in THF (400 mL) was added 0.5 M THF solution of isopropenylmagnesium bromide (800 mL, 400 mmol) at 0 °C. After 5 min at 0 °C, this black solution was cooled to −78 °C and **60** (56.8 g, 200 mmol) in THF (250 mL) was added with stirring and the reaction mixture was warmed to 0 °C. After 1.5 h at 0 °C, saturated aqueous NH_4Cl solution was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude alcohol as a colorless oil, which was used for the next reaction without purification. To a stirred solution of this crude alcohol in acetone (1.71 L) and water (151 mL) were added 2,6-lutidine (36.3 mL, 338 mmol), OsO_4 (861 mg, 3.39 mmol), and 4-methylmorpholine *N*-oxide (29.7 g, 254 mmol) at room temperature. After 2 h at room temperature, $PhI(OAc)_2$ (126 g, 391 mmol) was added with stirring. After 2 h at room temperature, saturated aqueous sodium thiosulfate solution and saturated aqueous $NaHCO_3$ solution were added and the mixture was extracted with hexane. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2.65 kg, hexane/EtOAc=5:1) to afford **61** (55.2 g, 85% for three steps) as white solids: R_f=0.50 (hexane/EtOAc=2:1); mp 41–43 °C (not recrystallized); $[\alpha]_D^{29.0}$ −12.3 (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3453, 3072, 2932, 2859, 1714, 1472, 1428, 1362, 1113, 1077, 824, 742, 704; ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.07 (s, 9H), 2.18 (s, 3H), 2.60 (dd, J=16.9, 4.6 Hz, 1H), 2.64 (dd, J=16.9, 7.4 Hz, 1H), 2.89 (d, J=4.3 Hz, 1H), 3.60 (dd, J=10.0, 6.0 Hz, 1H), 3.64 (dd, J=10.0, 5.1 Hz, 1H), 4.18 (m, 1H), 7.36–7.46 (m, 6H), 7.63–7.66 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 19.2, 26.8 (3C), 30.8, 46.4, 67.0, 68.2, 127.8 (4C), 129.8 (2C), 133.0 (2C), 133.1 (2C), 135.5 (2C), 208.4; LRMS (EI) m/z $(M-{}^t\mathrm{Bu})^+$ 299.1; HRMS (EI-quadrupole) m/z $(M-{}^t\mathrm{Bu})^+$ calcd for $C_{17}H_{19}O_3Si$ 299.1104, found 299.1119.

*4.2.14. (2S,4S)-1-(tert-Butyldiphenylsilyloxy)-4-methylhex-5-ene-2,4-diol (**62**) and (2S,4R)-1-(tert-butyldiphenylsilyloxy)-4-methylhex-5-ene-2,4-diol (**63**).* To a stirred solution of **61** (44.8 g, 0.126 mmol) in THF (630 mL) was added 1.0 M vinylmagnesium bromide in THF (252 mL, 0.252 mmol) at 0 °C. After 15 min at room temperature, saturated aqueous NH_4Cl solution was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.0 kg, hexane/EtOAc=5:1) to afford **62** (15.8 g, 33%), **63** (14.7 g, 30%) as colorless syrups and **61** (11.0 g, 23%) as colorless solids. Compound **62**: R_f=0.63 (hexane/EtOAc=2:1); $[\alpha]_D^{29.1}$ +11.0 (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3424, 2859, 1640, 1462, 1428, 1391, 1364, 1113, 924, 824, 741, 702; ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.06 (s, 9H), 1.25 (s, 3H), 1.50 (m, 1H), 1.69 (dd, J=14.3, 10.8 Hz, 1H), 2.91 (d, J=2.3 Hz, 1H), 3.49 (dd, J=10.0, 7.1 Hz, 1H), 3.56 (dd, J=10.0, 4.0 Hz, 1H), 3.82 (br s, 1H), 3.97 (m, 1H), 5.13 (dd, J=10.6, 1.7 Hz, 1H), 5.36 (dd, J=17.2, 1.7 Hz, 1H), 5.86 (dd, J=17.2, 10.6 Hz, 1H), 7.37–7.46 (m, 6H), 7.63–7.66 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 19.2, 26.8 (3C), 29.8, 42.7, 68.0, 70.4, 73.5, 112.6, 127.8 (4C), 129.9 (2C), 132.9 (2C), 133.0 (2C), 135.5 (2C), 144.1; LRMS (EI) m/z $(M-{}^t\mathrm{Bu})^+$ 327.1; HRMS (EI-quadrupole) m/z $(M-{}^t\mathrm{Bu})^+$ calcd for $C_{19}H_{23}O_3Si$ 327.1417, found 327.1408. Compound **63**: R_f=0.55 (hexane/EtOAc=2:1); $[\alpha]_D^{29.1}$ −1.83 (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3383, 2931, 2859, 1472, 1428, 1391, 1363, 1113, 824, 758, 740, 703; ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.07 (s, 9H), 1.35 (s, 3H), 1.54 (dd,

J=14.6, 2.9 Hz, 1H), 1.65 (dd, J=14.6, 10.0 Hz, 1H), 3.03 (br s, 1H), 3.21 (br s, 1H), 3.55 (dd, J=10.1, 7.2 Hz, 1H), 3.60 (dd, J=10.1, 4.3 Hz, 1H), 4.09 (m, 1H), 5.01 (dd, J=10.9, 1.1 Hz, 1H), 5.22 (dd, J=17.4, 1.1 Hz, 1H), 5.91 (dd, J=17.4, 10.9 Hz, 1H), 7.36–7.46 (m, 6H), 7.64–7.67 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 19.2, 26.8 (3C), 26.9, 42.9, 68.2, 69.7, 72.7, 111.3, 127.8 (4C), 129.9 (2C), 133.1 (2C), 135.5 (4C), 145.6; LRMS (EI) m/z (M−^{t}Bu)$^+$ 327.1; HRMS (EI-quadrupole) m/z (M−^{t}Bu)$^+$ calcd for $C_{19}H_{23}O_3Si$ 327.1417, found 327.1408.

*4.2.15. ((2R,4S,6S)-6-Methyl-2-phenyl-6-vinyl-1,3-dioxan-4-yl) methanol (**64**).* To a stirred solution of **62** (13.5 g, 35.1 mmol) in CH_2Cl_2 (70.0 mL) were added benzaldehyde dimethylacetal (7.98 mL, 52.5 mmol) and *p*-toluenesulfonic acid (665 mg, 3.51 mmol) at room temperature. After 2 h at room temperature, the mixture was filtered through a short column of silica gel (30.0 g, hexane/EtOAc=5:1). The filtrate was concentrated under reduced pressure to give a crude dioxane as a yellow oil, which was used for the next reaction without purification. To a solution of this crude dioxane in THF (170 mL) was added 1.0 M TBAF in THF (52.5 mL, 52.5 mmol) at 0 °C. After 2 h at room temperature, saturated aqueous NH_4Cl solution was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (400 g, hexane/EtOAc=5:1) to afford **64** (5.90 g, 72% for two steps) as a colorless syrup: R_f=0.35 (hexane/EtOAc=2:1); $[\alpha]_D^{26.6}$ +47.3 (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3444, 3036, 2976, 2928, 2877, 1454, 1404, 1366, 1217, 1140, 1085, 1060, 1004, 926, 757; ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.38 (s, 3H), 1.77 (d, J=17.2, 13.5 Hz, 1H), 1.80 (dd, J=13.5, 8.5 Hz, 1H), 2.05 (br s, 1H), 3.62 (dd, J=11.6, 6.5 Hz, 1H), 3.69 (br d, J=11.6 Hz, 1H), 4.07 (m, 1H), 5.25 (d, J=17.8 Hz, 1H), 5.36 (dd, J=11.2, 0.6 Hz, 1H), 5.75 (s, 1H), 5.92 (dd, J=17.8, 11.2 Hz, 1H), 7.32–7.41 (m, 3H), 7.50–7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 30.9, 35.0, 65.8, 74.0, 75.4, 96.1, 116.2, 126.2 (2C), 128.3 (2C), 128.8, 138.6, 141.7; LRMS (EI) m/z (M)$^+$ 234.1; HRMS (EI-quadrupole) m/z (M)$^+$ calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1234.

*4.2.16. From alkynyl alcohol **65** to **64**.* To a stirred solution of **65**[40] (21.0 mg, 0.114 mmol) in THF (0.570 mL) was added $LiAlH_4$ (8.7 mg, 0.22 mmol) at room temperature. After 2 h, saturated aqueous potassium sodium tartrate solution (0.570 mL) was added at 0 °C and the mixture was warmed to room temperature. After 2 h at room temperature, water was added and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude alcohol, which was used for the next reaction without purification. To a solution of this crude alcohol in CH_2Cl_2 (0.570 mL) were added benzaldehyde dimethylacetal (0.173 mL, 1.14 mmol) and *p*-toluenesulfonic acid (21.6 mg, 0.114 mmol mmol) at room temperature. After 3 h at room temperature, saturated aqueous $NaHCO_3$ solution was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.0 g, hexane/EtOAc=5:1) to afford **64** (17.6 mg, 66% for two steps) as a colorless syrup. The ^{1}H and ^{13}C NMR spectra of this compound were identical with those of **64** obtained from **62**.

*4.2.17. Ethyl (3Z)-2-[(tert-butyldimethylsilyloxy)-((2R,4S,6S)-6-methyl-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl]-3-iodoacrylate (**66**) and ethyl (3Z)-2-[(tert-butyldimethylsilyloxy)-(phenyl)methyl]-3-iodoacrylate (**67**).* To a stirred solution of **64** (20.0 mg, 0.0852 mmol) in CH_2Cl_2 (0.133 mL) and DMSO (0.0806 mL) was added (i-Pr)$_2$EtN (1.10 mL, 0.596 mmol) and SO_3·pyridine (54.2 mg, 0.340 mmol) at room temperature. After 2 h, water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude aldehyde **58** as a yellow oil, which was used for the next reaction without purification. To a stirred solution of magnesium iodide (71.1 mg, 0.256 mmol) in CH_2Cl_2 (0.426 mL) was added a solution of the crude aldehyde **58** in CH_2Cl_2 (0.085 mL) at 0 °C. After 5 min, ethyl propiolate (0.0261 mL, 0.256 mmol) was added at 0 °C. After 18 h at room temperature, saturated aqueous sodium thiosulfate solution and saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude ester as an orange oil, which was used for the next reaction without purification. To a stirred solution of this crude ester in dry CH_2Cl_2 (0.426 mL) were added 2,6-lutidine (0.0137 mL, 0.128 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.0293 mL, 0.111 mmol) at room temperature. After 2 h, saturated aqueous NH_4Cl solution was added and the mixture was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.50 g, hexane/EtOAc=20:1) to afford a 1.3:1 inseparable mixture (judged by ^{1}H NMR spectrum) of **66** (8.8 mg, 18% for three steps) as a colorless syrup and **67** (13.3 mg, 35% for three steps) as a colorless syrup. *Major isomer of* **66**: R_f=0.82 (hexane/EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.26 (t, J=7.1 Hz, 3H), 1.35 (s, 3H), 1.57 (dd, J=13.2, 12.0 Hz, 1H), 1.86 (dd, J=13.2, 2.3 Hz, 1H), 4.05 (ddd, J=12.0, 6.3, 2.3 Hz, 1H), 4.08–4.22 (m, 2H), 4.62 (dd, J=6.3, 1.1 Hz, 1H), 5.28 (d, J=17.2 Hz, 1H), 5.35 (dd, J=11.2, 0.9 Hz, 1H), 5.67 (s, 1H), 5.88 (dd, J=17.7, 11.2 Hz, 1H), 6.94 (d, J=1.2 Hz, 1H), 7.28–7.35 (m, 3H), 7.44–7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −5.1, −5.0, 14.0, 18.2, 25.6 (3C), 31.0, 33.4, 61.2, 75.6, 75.9, 76.4, 83.0, 96.1, 116.2, 126.3 (2C), 128.0 (2C), 128.5, 138.8, 141.7, 145.2, 166.3. *Minor isomer of* **66**: R_f=0.82 (hexane/EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.05 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.24 (t, J=7.1 Hz, 3H), 1.36 (s, 3H), 1.73 (dd, J=13.5, 11.8 Hz, 1H), 1.94 (dd, J=13.5, 2.3 Hz, 1H), 3.88 (ddd, J=11.8, 5.7, 2.3 Hz, 1H), 4.08–4.22 (m, 2H), 4.58 (dd, J=5.7, 1.1 Hz, 1H), 5.19 (d, J=17.7 Hz, 1H), 5.32 (d, J=11.2 Hz, 1H), 5.64 (s, 1H), 5.87 (dd, J=17.7, 11.2 Hz, 1H), 7.07 (d, J=1.5 Hz, 1H), 7.28–7.35 (m, 3H), 7.44–7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −5.0, −4.9, 14.0, 18.2, 25.8 (3C), 31.0, 34.2, 61.2, 75.7, 75.9, 76.1, 83.3, 96.1, 116.2, 126.2 (2C), 128.0 (2C), 128.5, 138.7, 141.7, 145.9, 166.2. *Mixture of two isomers of* **66**: IR (neat, cm^{-1}) 2955, 2930, 2886, 2857, 1723, 1472, 1462, 1391, 1367, 1307, 1280, 1255, 1216, 1189, 1127, 1058, 1005, 859, 838, 780, 756, 699; LRMS (EI) m/z (M−^{t}Bu)$^+$ 515.1; HRMS (EI-quadrupole) m/z (M−^{t}Bu)$^+$ calcd for $C_{21}H_{28}O_5ISi$ 515.0751, found 515.0745. Compound **67**: R_f=0.87 (hexane/EtOAc=5:1); IR (neat, cm^{-1}) 2955, 2930, 2857, 1724, 1471, 1367, 1306, 1257, 1183, 1113, 1096, 1057, 861, 838, 778, 699; ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ −0.14 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.22 (t, J=7.2 Hz, 3H), 4.11–4.21 (m, 2H), 5.52 (d, J=1.5 Hz, 1H), 7.06 (d, J=1.5 Hz, 1H), 7.23–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −5.2, −4.9, 14.0, 18.1, 25.7 (3C), 61.1, 76.3, 82.9, 127.0 (2C), 127.9 (2C), 128.3, 140.8, 147.5, 166.0; LRMS (EI) m/z (M−^{t}Bu)$^+$ 389.8; HRMS (EI-quadrupole) m/z (M−^{t}Bu)$^+$ calcd for $C_{14}H_{18}ISiO_3$ 389.0070, found 389.0076.

*4.2.18. Methyl (3Z)-2-[(tert-butyldimethylsilyloxy)-((2R,4S,6S)-6-methyl-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl]-3-iodoacrylate (**68**) and methyl (3Z)-2-[(tert-butyldimethylsilyloxy)-(phenyl) methyl]-3-iodoacrylate (**69**).* To a stirred solution of **64** (200 mg, 0.852 mmol) in CH_2Cl_2 (1.33 mL) and DMSO (0.806 mL) were added

(i-Pr)$_2$EtN (11.0 mL, 5.96 mmol) and SO$_3$·pyridine (542 mg, 3.40 mmol) at room temperature. After 2 h at room temperature, water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude aldehyde **58** as yellow oil, which was used for the next reaction without purification. To a stirred suspension of magnesium (103 mg, 2.56 mmol) in Et_2O (0.853 mL) was added iodine (325 mg, 2.56 mmol) at room temperature. After 3 h at room temperature, a solution of the crude aldehyde **58** in CH_2Cl_2 (1.33 mL) was added at −20 °C. After 5 min, methyl propiolate (0.215 mL, 2.56 mmol) was added at −20 °C. After 18 h at room temperature, saturated aqueous sodium thiosulfate solution and saturated aqueous $NaHCO_3$ solution were added and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude ester as an orange oil, which was used for the next reaction without purification. To a stirred solution of this crude ester in dry CH_2Cl_2 (4.26 mL) were added 2,6-lutidine (0.142 mL, 0.128 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.293 mL, 0.111 mmol) at room temperature. After 2 h, saturated aqueous NH_4Cl solution was added and the mixture was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (40.0 g, hexane/EtOAc=20:1) to afford a 1.2:1 inseparable mixture (judged by ^{1}H NMR spectrum) of **68** (200 mg, 85% for three steps) and **69** (trace) as colorless syrups. *Major isomer of* **68**: R_f=0.82 (hexane/EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.33 (s, 3H), 1.57 (dd, J=13.2, 12.3 Hz, 1H), 1.85 (dd, J=13.2, 2.3 Hz, 1H), 3.65 (s, 3H), 4.03 (ddd, J=11.8, 6.0, 2.3 Hz, 1H), 4.66 (dd, J=6.0, 1.1 Hz, 1H), 5.26 (d, J=18.6 Hz, 1H), 5.34 (dd, J=10.3, 0.8 Hz, 1H), 5.65 (s, 1H), 5.87 (m, 1H), 6.97 (d, J=1.1 Hz, 1H), 7.28−7.34 (m, 3H), 7.43−7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −5.1, −4.9, 18.1, 25.6 (3C), 31.0, 33.1, 51.8, 75.6, 76.3, 76.4, 83.2, 96.2, 116.2, 126.2 (2C), 128.0 (2C), 128.6, 138.7, 141.8, 145.1, 166.7. *Minor isomer of* **68**: R_f=0.82 (hexane/EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.04 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.35 (s, 3H), 1.71 (dd, J=13.5, 12.4 Hz, 1H), 1.94 (dd, J=13.5, 2.3 Hz, 1H), 3.66 (s, 3H), 3.83 (ddd, J=11.8, 5.9, 2.3 Hz, 1H), 4.57 (dd, J=6.0, 1.5 Hz, 1H), 5.18 (d, J=18.6 Hz, 1H), 5.31 (d, J=10.3 Hz, 1H), 5.63 (s, 1H), 5.86 (dd, J=18.6, 10.3 Hz, 1H), 7.11 (d, J=1.5 Hz, 1H),7.28−7.34 (m, 3H), 7.43−7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −5.1, −4.9, 18.1, 25.8 (3C), 31.0, 34.5, 51.8, 75.66, 75.73, 76.4, 83.8, 96.0, 116.2, 126.4 (2C), 128.0 (2C), 128.5, 138.7, 141.7, 145.9, 166.6. *Mixture of two isomers of* **68**: IR (neat, cm^{-1}) 2954, 2930, 2858, 1729, 1460, 1435, 1401, 1364, 1308, 1281, 1257, 1199, 1126, 1058, 1005, 839, 780, 755, 699; LRMS (EI) m/z (M−^{t}Bu)$^+$ 501.0; HRMS (EI-quadrupole) m/z (M−^{t}Bu)$^+$ calcd for $C_{20}H_{26}O_5ISi$ 501.0595, found 501.0566. Compound **69**: R_f=0.85 (hexane/EtOAc=5:1); IR (neat, cm^{-1}) 2953, 2930, 2857, 1728, 1471, 1455, 1434, 1313, 1257, 1198, 1173, 1114, 1058, 838, 779, 757, 699; ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ −0.14 (s, 3H), −0.05 (s, 3H), 0.86 (s, 9H), 3.71 (s, 3H), 5.53 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 7.25−7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.0) δ −5.2, −4.9, 18.1, 25.7 (3C), 51.7, 76.3, 83.4, 127.0 (2C), 128.0, 128.3 (2C), 140.8, 147.5, 166.4; LRMS (EI) m/z (M−^{t}Bu)$^+$ 375.0; HRMS (EI-quadrupole) m/z (M−^{t}Bu)$^+$ calcd for $C_{13}H_{16}ISiO_3$ 374.9914, found 374.9907.

*4.2.19. (5S,3Z)-4-Hydroxy-5-((S)-2-hydroxy-2-methylbut-3-en-1-yl)-3-(iodomethylene)dihydrofuran-2(3H)-one (**70**).* To a stirred solution of **64** (1.00 g, 4.26 mmol) in CH_2Cl_2 (6.67 mL) and DMSO (4.03 mL) were added (i-Pr)$_2$EtN (55.0 mL, 29.8 mmol) and SO$_3$·pyridine (2.71 g, 17.0 mmol) at room temperature. After 2 h at room temperature, water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude aldehyde **58** as a yellow oil, which was used for the next reaction without purification. To a stirred suspension of magnesium (513 mg, 21.3 mmol) in Et_2O (14.2 mL) was added iodine (2.70 g, 21.3 mmol) at room temperature. After 3 h at room temperature, a solution of the crude aldehyde **58** in CH_2Cl_2 (20.3 mL) was added at −20 °C. After 5 min, methyl propiolate (2.15 mL, 25.6 mmol) was added at −20 °C. After 18 h at room temperature, saturated aqueous sodium thiosulfate solution and saturated aqueous $NaHCO_3$ solution were added and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude ester as an orange oil, which was used for the next reaction without purification. To a stirred solution of this crude ester in MeOH (7.99 mL) was added *p*-toluenesulfonic acid (30.2 mg, 0.159 mmol) at room temperature. After 2 h at room temperature, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20.0 g, hexane/EtOAc=5:1) to afford a 1.1:1 inseparable mixture (judged by ^{1}H NMR spectrum) of **70** (714 mg, 51% for three steps) as a colorless syrup. *Major isomer of* **70**: R_f=0.56 (hexane/EtOAc=1:2); ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.41 (s, 3H), 2.03 (dd, J=14.6, 5.1 Hz, 1H), 2.22 (dd, J=14.6, 8.9 Hz, 1H), 2.26 or 2.28 (br s, 1H), 3.89 (br s, 1H), 4.61 (ddd, J=8.9, 5.1, 4.9 Hz, 1H), 4.87 (br d, J=4.9 Hz, 1H), 5.14 (d, J=11.1 Hz, 1H), 5.29 (d, J=17.4 Hz, 1H), 5.98 (dd, J=17.4, 11.1 Hz, 1H), 7.83 (s, J=1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 27.2, 38.7, 72.2, 72.4, 78.0, 95.0, 112.6, 137.8 or 138.2, 144.3, 167.0. *Minor isomer of* **70**: R_f=0.56 (hexane/EtOAc=1:2); ^{1}H NMR (500 MHz, $CDCl_3$, TMS=0.00) δ 1.42 (s, 3H), 1.95 (dd, J=14.3, 8.6 Hz, 1H), 2.12 (dd, J=14.3, 4.9 Hz, 1H), 2.26 or 2.28 (br s, 1H), 4.08 (br s, 1H), 4.33 (ddd, J=8.6, 6.9, 4.9 Hz, 1H), 4.54 (br d, J=6.9 Hz, 1H), 5.16 (d, J=10.5 Hz, 1H), 5.31 (d, J=17.5 Hz, 1H), 6.00 (dd, J=17.5, 10.5 Hz, 1H), 7.60 (d, J=2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ 27.1, 44.1, 72.8, 77.9, 80.4, 90.8, 112.8, 137.8 or 138.2, 145.0, 166.2. *Mixture of two isomers of* **70**: IR (neat, cm^{-1}) 3406, 2971, 2930, 1755, 1626, 1451, 1413, 1378, 1349, 1265, 1164, 1116, 1084, 993, 929, 845, 820, 756, 658; LRMS (EI) m/z (M)$^+$ 324.0; HRMS (EI-quadrupole) m/z (M)$^+$ calcd for $C_{10}H_{13}IO_4$ 323.9859, found 323.9851.

*4.2.20. (4R,5S,3Z)-4-(tert-Butyldimethylsilyloxy)-5-((S)-2-hydroxy-2-methylbut-3-en-1-yl)-3-(iodomethylene)dihydrofuran-2(3H)-one (**57**) and (4S,5S,3Z)-4-(tert-butyldimethylsilyloxy)-5-((S)-2-hydroxy-2-methylbut-3-en-1-yl)-3-(iodomethylene)dihydrofuran-2(3H)-one (**71**).* To a stirred solution of **70** (20.0 mg, 0.0617 mmol) in dry CH_2Cl_2 (0.309 mL) were added 2,6-lutidine (0.0130 mL, 0.123 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.019 mL, 0.0736 mmol) at −78 °C. After 30 min, saturated aqueous NH_4Cl solution was added and the mixture was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.50 g, hexane/EtOAc=5:1) to afford **57** (12.9 mg, 48%) as a colorless syrup and **71** (11.7 mg, 44%) as a colorless syrup. Compound **57**: R_f=0.57 (hexane/EtOAc=2:1); $[\alpha]_D^{27.3}$ −13.1 (*c* 1.80, $CHCl_3$); IR (neat, cm^{-1}) 3473, 2957, 2929, 2857, 1764, 1628, 1463, 1376, 1363, 1260, 1153, 1119, 1089, 863, 839, 779; ^{1}H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.12 (s, 6H), 0.91 (s, 9H), 1.35 (s, 3H), 1.84 (dd, J=14.9, 10.0 Hz, 1H), 1.93 (dd, J=14.9, 2.9 Hz, 1H), 2.23 (br s, 1H), 4.28 (ddd, J=10.0, 5.1, 2.9 Hz, 1H), 4.48 (dd, J=5.1, 1.7 Hz, 1H), 5.15 (dd, J=10.9, 0.8 Hz, 1H), 5.34 (dd, J=17.2, 0.8 Hz, 1H), 5.90 (dd, J=17.2, 10.9 Hz, 1H), 7.45 (d, J=1.7 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$, $CDCl_3$=77.00) δ −4.3, −4.2, 17.9, 25.6 (3C), 28.7, 44.3, 72.5, 77.6, 80.9, 90.9, 113.2, 138.6, 143.5, 165.9; LRMS (EI) m/z $(M-{}^tBu)^+$ 381.0; HRMS (EI-quadrupole) m/z $(M-{}^tBu)^+$ calcd for $C_{12}H_{18}IO_4Si$ 381.0019, found 381.0004. Compound **71**: R_f=0.53 (hexane/EtOAc=2:1); $[\alpha]_D^{27.2}$ +3.7 (*c* 1.76, $CHCl_3$); IR (neat, cm^{-1}) 3456, 2958, 2929, 2857, 1764, 1727, 1630, 1462, 1378, 1261, 1163, 1120, 1074, 994, 837, 779; ^1H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.35 (s, 3H), 1.88 (dd, *J*=15.5, 8.9 Hz, 1H), 1.94 (dd, *J*=15.5, 3.2 Hz, 1H), 2.12 (br s, 1H), 4.57 (ddd, *J*=8.9, 5.5, 3.2 Hz, 1H), 4.78 (d, *J*=5.5 Hz, 1H), 5.12 (d, *J*=10.6 Hz, 1H), 5.33 (d, *J*=17.2 Hz, 1H), 5.90 (dd, *J*=17.2, 10.6 Hz, 1H), 7.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −4.6, −4.4, 18.1, 25.6 (3C), 28.7, 40.1, 72.2, 74.5, 78.2, 90.7, 112.8, 138.9, 144.2, 166.4; LRMS (EI) m/z $(M-{}^tBu)^+$ 381.0; HRMS (EI-quadrupole) m/z $(M-{}^tBu)^+$ calcd for $C_{12}H_{18}IO_4Si$ 381.0019, found 381.0004.

*4.2.21. (4R,5S,3Z)-4-(tert-Butyldimethylsilyloxy)-3-((R)-3-(2,2-dimethoxyethyl)-4-methylpent-4-en-1-ylidene)-5-((S)-2-hydroxy-2-methylbut-3-en-1-yl)dihydrofuran-2(3H)-one (**72**).* To a stirred solution of **50** (20.0 mg, 0.0456 mmol) and 1.00 M hexane solution of **51** (0.273 mL, 0.273 mmol) in dry Et_2O (0.351 mL) were added at −78 °C 1.58 M pentane solution of ^{t}BuLi (0.115 mL, 0.182 mmol) and dry THF (0.351 mL). After 10 min at −78 °C, the resulting suspension was warmed to room temperature. After 30 min at room temperature, 3.0 M aqueous K_3PO_4 (0.0910 mL, 0.274 mmol) was added and then a solution of **57** (23.1 mg, 0.0912 mmol) and $PdCl_2$(dppf) (3.7 mg, 0.00456 mmol) in DMF (0.456 mL) was added at room temperature. After 3 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane/EtOAc=5:1) to afford **72** (11.3 mg, 53%) as a colorless syrup: R_f=0.24 (hexane/EtOAc=2:1); $[\alpha]_D^{27.3}$ −18.7 (*c* 0.50, $CHCl_3$); IR (neat, cm^{-1}) 3453, 2953, 2931, 2858, 1758, 1677, 1645, 1463, 1448, 1374, 1254, 1179, 1127, 1091, 1005, 940, 893, 861, 839, 779; ^1H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.088 (s, 3H), 0.092 (s, 3H), 0.89 (s, 9H), 1.33 (s, 3H), 1.65 (s, 3H), 1.68−1.71 (m, 2H), 1.81 (dd, *J*=14.6, 10.3 Hz, 1H), 1.89 (dd, *J*=14.6, 2.6 Hz, 1H), 2.37 (m, 1H), 2.40 (br s, 1H), 2.80 (br t, *J*=7.0 Hz, 2H), 3.29 (s, 3H), 3.31 (s, 3H), 4.27 (ddd, *J*=10.3, 5.1, 2.6 Hz, 1H), 4.35 (dd, *J*=6.5, 4.8 Hz, 1H), 4.37 (m, 1H), 4.76 (br s, 1H), 4.81 (br s, 1H), 5.15 (dd, *J*=10.6, 1.1 Hz, 1H), 5.34 (dd, *J*=17.2, 1.1 Hz, 1H), 5.89 (dd, *J*=17.2, 10.6 Hz, 1H), 6.23 (ddd, *J*=7.4, 7.1, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −4.3, −4.2, 17.9, 18.2, 25.6 (3C), 28.9, 30.8, 35.8, 42.9, 44.7, 52.5, 53.1, 72.6, 75.4, 82.1, 102.8, 112.9, 113.1, 128.7, 143.6, 144.9, 145.8, 167.3; LRMS (EI) m/z $(M)^+$ 468.3; HRMS (EI-quadrupole) m/z $(M)^+$ calcd for $C_{25}H_{44}O_6Si$ 468.2907, found 468.2908.

*4.2.22. (R)-3-((Z)-2-((4R,5S)-4-(tert-Butyldimethylsilyloxy)-5-((S)-2-hydroxy-2-methylbut-3-en-1-yl)-2-oxodihydrofuran-3(2H)-ylidene)ethyl)-4-methylpent-4-enal (**36**).* To a stirred solution of **72** (9.0 mg, 0.019 mmol) in acetone (0.096 mL) was added *p*-toluenesulfonic acid (0.4 mg, 0.002 mmol) at room temperature. After 1 h at room temperature, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.1 g, hexane/EtOAc=5:1) to afford **36** (4.2 mg, 52%) as a colorless syrup: R_f=0.69 (hexane/EtOAc=1:2); $[\alpha]_D^{26.6}$ −10.1 (*c* 0.50, $CHCl_3$); IR (neat, cm^{-1}) 3443, 3075, 2958, 2929, 2857, 1755, 1726, 1679, 1462, 1452, 1376, 1260, 1170, 1094, 1031, 861, 839, 779; ^1H NMR (500 MHz, $CDCl_3$, solvent residual peak=7.26) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.33 (s, 3H), 1.69 (br s, 3H), 1.81 (dd, *J*=14.6, 10.0 Hz, 1H), 1.89 (dd, *J*=14.6, 2.5 Hz, 1H), 2.36 (br s, 1H), 2.49 (m, 1H), 2.56 (m, 1H), 2.81−2.87 (m, 3H), 4.29 (ddd, *J*=10.0, 5.1, 2.5 Hz, 1H), 4.39 (m, 1H), 4.79 (s, 1H), 4.84 (br s, 1H), 5.15 (dd, *J*=10.6, 1.1 Hz, 1H), 5.34 (dd, *J*=17.2, 1.1 Hz, 1H), 5.90 (dd, *J*=17.2, 10.6 Hz, 1H), 6.21 (m, 1H), 9.69 (dd, *J*=2.3, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$=77.00) δ −4.3 (2C), 17.9, 19.0, 25.6 (3C), 28.8, 30.5, 40.9, 44.7, 46.9, 72.6, 75.3, 82.2, 113.1, 113.2, 129.7, 143.55, 143.60, 145.0, 167.3, 201.3; LRMS (EI) m/z $(M-{}^tBu)^+$ 365.1; HRMS (EI-quadrupole) m/z $(M-{}^tBu)^+$ calcd for $C_{19}H_{29}O_5Si$ 365.1784, found 365.1763.

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Supplementary data

These data include synthetic procedure of **19**, experiments for Table 1, Schemes 4 and 5, determination of % ee and absolute configuration of **42**, and ^1H and ^{13}C NMR spectra for all new compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.076.

References and notes

1. Kamel, H. N.; Fronczek, F. R.; Fischer, N. H.; Slattery, M. *Tetrahedron Lett.* **2004**, *45*, 1995–1997.
2. Kamel, H. N.; Ding, Y.; Li, X.-C.; Ferreira, D.; Fronczek, F. R.; Slattery, M. *J. Nat. Prod.* **2009**, *72*, 900–905.
3. Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 429–440.
4. (a) Kashman, Y.; Bodner, M.; Finer-Moore, J. S.; Clardy, J. *Experientia* **1980**, *36*, 891–892; (b) Braekman, J. C.; Daloze, D.; Tursch, B.; Hull, S. E.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Experientia* **1980**, *36*, 893.
5. (a) Anjaneyulu, A. S. R.; Venkateswara Rao, G.; Prakash, C. V. S. *Indian J. Chem., Sect. B* **1994**, *33*, 1165–1169; (b) Venkateswarlu, Y.; Ramesh, P.; Reddy, P. S.; Jamil, K. *Phytochemistry* **1999**, *52*, 1275–1277.
6. Matsuda, Y.; Endo, Y.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2011**, *76*, 6258–6263.
7. Ramesh, P.; Reddy, N. S.; Rao, T. P.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 1019–1021.
8. In this manuscript (except Experimental section), the carbon numbering system used in Ref. 1 was employed.
9. We rename the compound **7** as 'africene oxide'. The original name is 'epoxyafricanane'.[7]
10. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568; (c) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723–6737; (d) Seidel, G.; Fürstner, A. *Chem. Commun.* **2012**, 2055–2070.
11. For the synthesis of the model epoxide **19**, see Supplementary data. Although the relative configuration of **19** was not determined, we used one stereoisomer.
12. (a) Ide, M.; Yasuda, M.; Nakata, M. *Synlett* **1998**, 936–938; (b) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491–2499.
13. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.
14. (a) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440–7441; (b) Toshima, K.; Ohta, K.; Ohashi, A.; Nakamura, T.; Nakata, M.; Tatsuta, K.; Matsumura, S. *J. Am. Chem. Soc.* **1995**, *117*, 4822–4831.
15. Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2257–2259.
16. Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.
17. Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306–1308.
18. Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 3950–3952.
19. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647–2650.
20. Recent review, see: Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674.
21. Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767–4770.
22. (a) Li, G.; Wei, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823–826; (b) Chen, D.; Timmons, C.; Liu, J.; Headley, A.; Li, G. *Eur. J. Org. Chem.* **2004**, 3330–3335; (c) Chen, D.; Guo, L.; Saibabu Kotti, S. R. S.; Li, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1757–1762.
23. Wei, H.-X.; Chen, D.; Xu, X.; Li, G.; Paré, P. W. *Tetrahedron: Asymmetry* **2003**, *14*, 971–974.
24. (a) Senapati, B. K.; Hwang, G.-S.; Lee, S.; Ryu, D. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 4398–4401; (b) Lee, S. I.; Jang, J. H.; Hwang, G.-S.; Ryu, D. H. *J. Org. Chem.* **2013**, *78*, 770–775.
25. Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808–3809.
26. Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498–1499.

27. The % ee and absolute configuration were determined by the conversion of the compound **42** to the chiral acetyl mandelate, see Supplementary data. See also: Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villiéras, J. *Tetrahedron Lett.* **1998**, *39*, 1759–1762.
28. Futatsugi, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1484–1487.
29. (a) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992–9993; (b) Paddon-Row, M. N.; Kwan, L. C. H.; Willis, A. C.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7013–7017.
30. Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321–1329.
31. In the case of α-substituted-α,β-unsaturated aldehyde (no α-hydrogen atom, e. g., methacrolein), the % ee of the coupling product would be expected better than that of our case. For example, see Ref. 24b. Furthermore, without the catalyst **41a**–**c**, this reaction gave only trace amounts of the coupling product.
32. Reilly, M. K.; Rychnovsky, S. D. *Org. Lett.* **2010**, *12*, 4892–4895.
33. Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.
34. (a) Lavallée, J.-F.; Spino, C.; Ruel, R.; Hogan, K. T.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406–1426; (b) Mori, K.; Fukamatsu, K. *Liebigs Ann. Chem.* **1992**, 489–493; (c) Pattenden, G.; Winne, J. M. *Tetrahedron Lett.* **2010**, *51*, 5044–5047; (d) Takita, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 2068–2070.
35. (a) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885–7892; (b) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4737–4739.
36. Judging from ^{1}H and ^{13}C NMR spectra of an inseparable mixture of **37**+**52** (and **53**+**54**), it looks like a single isomer because the C1 chiral center is far from the C11 chiral center. Therefore, we could not determine the diastereomer ratio.
37. Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9–12.
38. Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Chem.—Eur. J.* **2002**, *8*, 1621–1636.
39. Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552–1555.
40. Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 1731–1733.
41. Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
42. Wei, H.-X.; Hu, J.; Purkiss, D. W.; Paré, P. W. *Tetrahedron Lett.* **2003**, *44*, 949–952.