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Total Synthesis of 10-Isocyano-4-cadinene and Its Stereoisomers and Evaluations of Antifouling Activities

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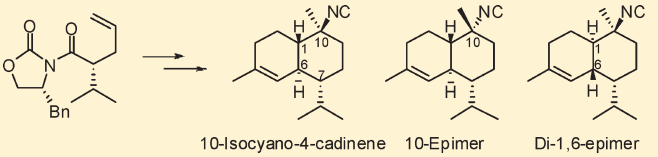
Supporting Information

ABSTRACT: The first enantioselective total synthesis of 10-isocyano-4-cadinene, a marine sesquiterpene isolated from nudibranchs of the family *Phyllidiidae*, and determination of its absolute stereochemistry were achieved. 10-Isocyano-4-cadinene is expected to be a novel nontoxic antifouling agent. In the synthesis, intermolecular Diels–Alder reaction and samarium diiodide induced Barbier-type cyclization were employed as key steps. The absolute configuration of 10-isocyano-4-cadinene was determined as (1*S*,6*S*,7*R*,10*S*) by comparison of the optical rotations between natural and synthetic samples. In addition, the authors successfully synthesized 10-*epi*- and di-1,6-*epi*-10-isocyano-4-cadinene through the same synthetic pathway. Antifouling activities against *Balanus amphitrite* with the cadinenes were also evaluated.



INTRODUCTION

10-Isocyano-4-cadinene (**1**), a marine sesquiterpene isolated by Okino et al.[1] from nudibranchs of the family *Phyllidiidae* along with other sesquiterpenes such as 10-isocyano-4-amorphene (**2**), 2-isocyanotrachyopsane (**3**), 1,7-epidioxy-5-cadinene (**4**), and axisonitrile-3 (**5**), exhibits potent antifouling activity[2] against the larvae of the barnacle *Balanus amphitrite* (EC_{50} = 0.14 μg/mL) (Figure 1). It was revealed that the isonitrile group at the quaternary carbon center is especially important for the antifouling activity.[3] Cadinene **1** is expected to be a novel lead compound for nontoxic antifouling agents. As a fouling inhibitor, tributyltin (TBT)[4] has been widely used in ships' hulls and fishing nets since the early 1960s. Unfortunately, due to the toxicity of TBT, the marine environment has been seriously compromised. For example, TBT-exposed oysters have abnormal shell development, brittle shells, poor weight gain, and imposex.[5] To prevent pollution of the ocean environment, the marine environment protection committee of the International Maritime Organization (IMO) has prohibited the use of organotin compounds since 2008. Since the use of TBT was restricted in 1992 in Japan, Japanese ships have been commonly coated with cuprous oxide paints to prevent the settlement of fouling organisms. However, the use of cuprous oxide and other copper compounds has also been reported to cause environmental contamination.[6]

As structural features, **1** has four continuous stereocenters, including a quaternary carbon center with an isonitrile group. Although the relative stereochemistry of **1** was assigned as shown in Figure 1 using 1D and 2D NMR experiments, the absolute configuration has not been determined. We have achieved the first enantioselective total synthesis of **1**. In a previous letter, we reported the determination of the absolute configuration of **1** through the total synthesis of (+)-**1** and (−)-**1**.[7] In the synthesis, an intermolecular Diels–Alder reaction and a samarium diiodide (SmI_2)-induced Barbier-type reaction were employed as key steps. The absolute configuration of **1** was unambiguously determined to be (1*S*,6*S*,7*R*,10*S*) on the basis of the total synthesis. Antifouling activities against *Balanus amphitrite* with both enantiomers of **1** were also evaluated. Moreover, we successfully synthesized 10-*epi*- and di-1,6-*epi*-10-isocyano-4-cadinene to examine the structure–activity relationship of the

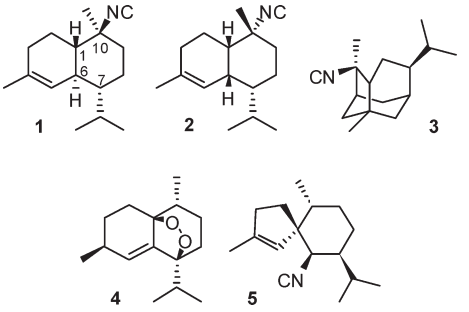


Figure 1. Sesquiterpenes from nudibranchs of the Family *Phyllidiidae*.

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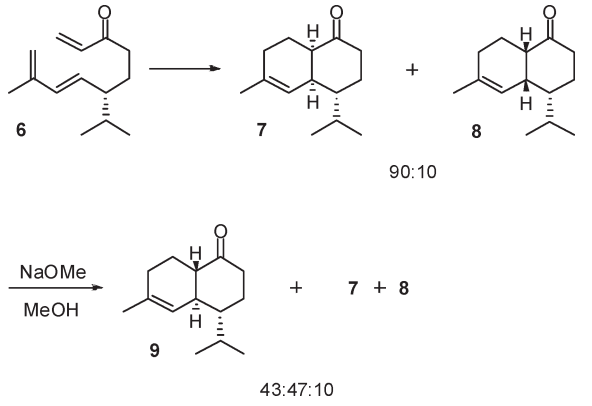
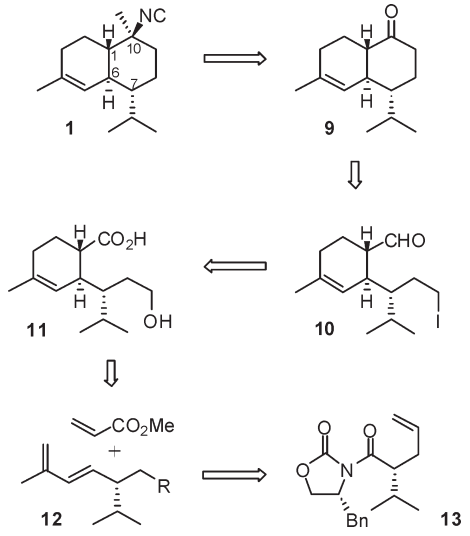
Scheme 1. Intramolecular Diels–Alder Reaction of (±)-Trienone 6



Scheme 2. Retrosynthetic Analysis of 10-Isocyano-4-cadinene (1)



cadinenes. In this article, we describe the full details of the total synthesis of **1** and its isomers and evaluation of their antifouling activities.

RESULTS AND DISCUSSION

Retrosynthetic Analysis of 10-Isocyano-4-cadinene (1). We envisioned the construction of the *trans* relationship between C1 and C6 by intermolecular Diels–Alder reaction[8] followed by equilibrium of the resultant mixture under basic conditions because it is known that *cis*-decalin frameworks are selectively formed through the corresponding intramolecular Diels–Alder reaction.[9] For a typical example, the intramolecular Diels–Alder reaction of the (±)-trienone **6** afforded a mixture of the (±)-*cis*-decalins **7** and **8** in a ratio of 90:10 (**7**:**8**) (Scheme 1).[9b] The mixture of **7** and **8** was isomerized by NaOMe in MeOH, forming an inseparable mixture of **7**, **8**, and the (±)-*trans*-decalin **9** in a ratio of 43:47:10 (**9**:**7**:**8**). With this strategy in mind, retrosynthetic analysis of **1** shown in Scheme 2 was planned. The

Scheme 3. Synthesis of Diene 18

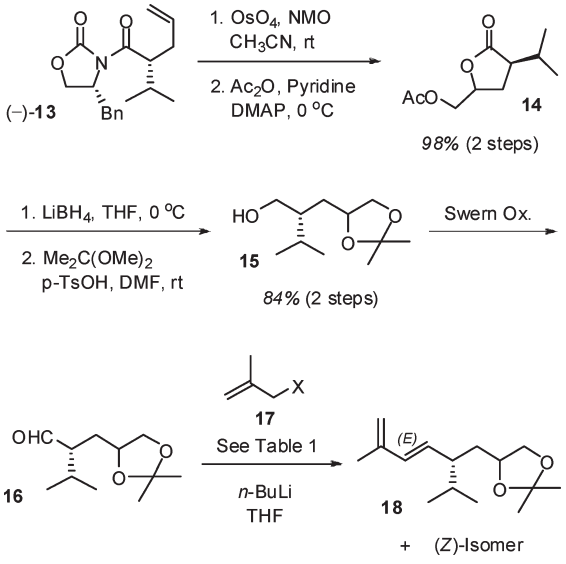


Table 1. Optimization for Installation of *E*-Olefin 18

entry	X	yield (%)[a]	*E*:*Z*
1	PPh_3CI (**17a**)	46	80:20
2	$POPh_2$ (**17b**)	45	100:0
3	$PO(OEt)_2$ (**17c**)	84	100:0

[a] Isolated yield in 2 steps from the alcohol **15**.

functional groups at C10 of **1** would be installed with the ketone **9** at a later stage of the synthesis. To construct the cyclohexane ring of **9**, Barbier-type cyclization induced by SmI_2 would be applied to the aldehyde **10**, which was derived from the carboxylic acid **11**. As mentioned above, the *trans* relationship at C1 and C6 in **11** would be constructed by an intermolecular Diels–Alder reaction with the diene **12** and methyl acrylate, followed by isomerization. The diene **12** would be synthesized from the known imide **13**.

Syntheses of the Intermolecular Diels–Alder Reaction Precursors 12. The total synthesis commenced with the known imide **13**,[10] prepared via Evans alkylation with allyl bromide (Scheme 3). After OsO_4 oxidation of the olefin moiety followed by spontaneous lactonization of the resultant diol, acetylation of the primary alcohol gave the acetate **14**, and the chiral auxiliary was recovered.[10b] The acetate **14** was converted into the alcohol **15** through $LiBH_4$ reduction[11] and subsequent selective acetonide protection of the 1,2-diol moiety, which was then subjected to Swern oxidation to provide the aldehyde **16**. For the intermolecular Diels–Alder reaction, the installation of the *E*-diene moiety was required because a preliminary study indicated that only the *E*-olefin reacted with the dienophile to afford the Diels–Alder adducts. The optimization for the *E*-selective olefination is shown in Table 1. Attempted olefination of **16** with (2-methyl-2-propenyl)triphenylphosphonium chloride (**17a**)[12b,c] led to a 46% yield (based on the alcohol **15**) of the diene (*E*)-**18** and minor amounts of (*Z*)-**18** in a ratio of 80:20 (*E*:*Z*) (entry 1). When the reaction of **16** was carried out using (2-methyl-2-propenyl)-diphenylphosphine oxide (**17b**),[12a,e] only the *E*-diene

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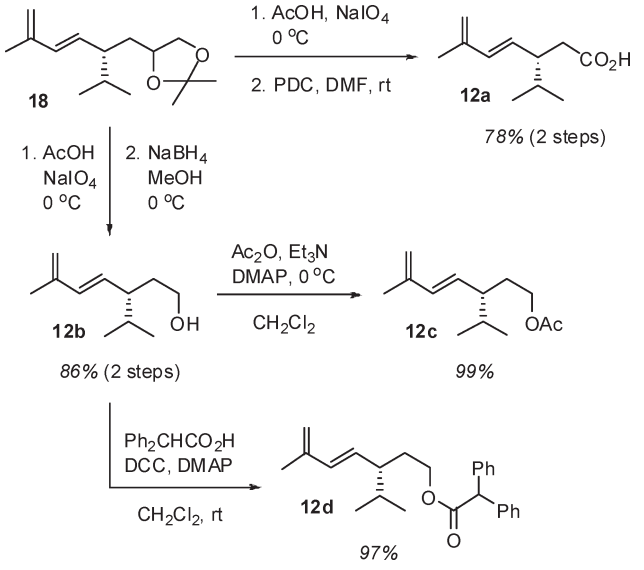
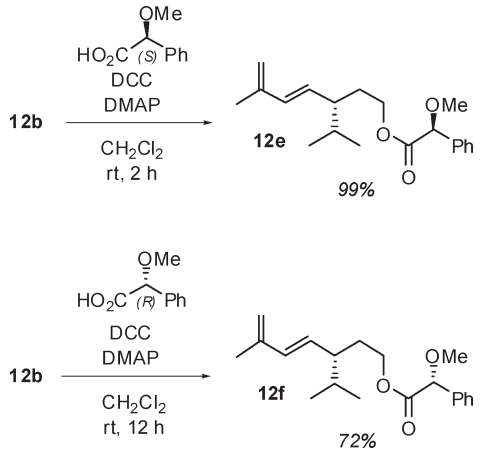
Scheme 4. Synthesis of Intermolecular Diels–Alder Reaction Precursor 12



Scheme 5. Synthesis of Esters 12e and 12f

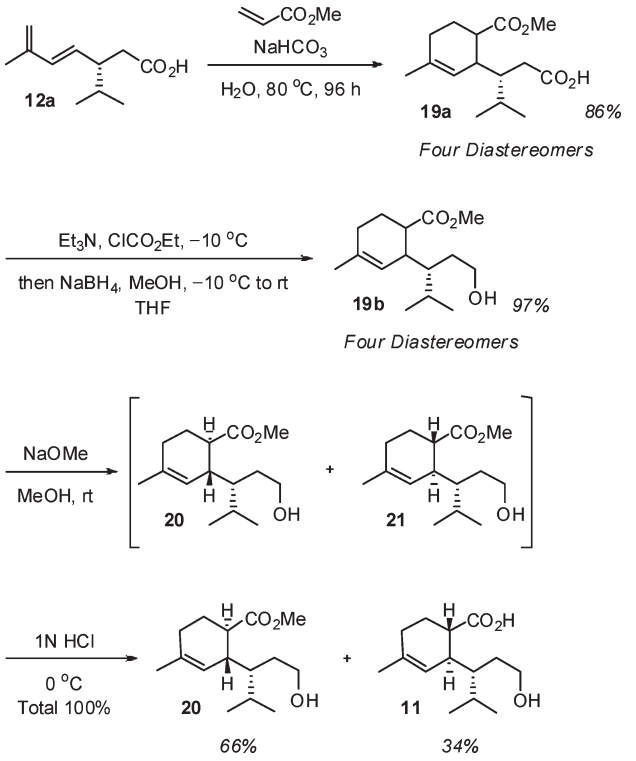


was selectively obtained in 45% yield in 2 steps (entry 2). Horner–Wadsworth–Emmons reaction of **16** with diethyl 2-methyl-2-propenyl phosphonate (**17c**), according to the protocol reported by Wang et al.,[9m,12d,12f] cleanly proceeded to afford only (*E*)-**18** in good yield (84% based on **15**) (entry 3).

As illustrated in Scheme 4, the intermolecular Diels–Alder reaction precursors **12a**–**12d** were synthesized from **18**. The (*E*)-diene **18** was converted into the aldehyde by one-pot deprotection of the acetonide group and oxidative treatment with $NaIO_4$.[13] The carboxylic acid **12a** was prepared by PDC oxidation of the resultant aldehyde.[14] The alcohol **12b** was synthesized by $NaBH_4$ reduction of the aldehyde. Subsequent esterification of **12b** with acetic anhydride or diphenylacetic acid afforded the esters **12c** or **12d**, respectively.

In order to confirm the optical purity of **12b**, esterification of **12b** with (*S*)- or (*R*)-*O*-methylmandelic acid[15] was carried out to give the esters **12e** or **12f**, respectively, as sole products

Scheme 6. Intermolecular Aqueous Diels–Alder Reactions of Carboxylic Acid 12a, Successive Epimerization, and Selective Hydrolysis



(Scheme 5). The ^1H NMR spectrum of **12e** was not identical to that of **12f**, indicating that epimerization did not occur under the strong basic conditions required in the Horner–Wadsworth–Emmons reaction.

Intermolecular Diels–Alder Reaction of Diene 12. We first investigated the intermolecular Diels–Alder reaction in water between the carboxylic acid **12a** and methyl acrylate. Aqueous Diels–Alder reactions were reported previously by Grieco et al.[16] during the total synthesis of vernolepin.[16a] The reaction of **12a** under basic conditions at 80 °C for 96 h afforded the adduct **19a** in 86% yield as a mixture of four diastereomers (Scheme 6). After the selective reduction of the carboxylic acid of **19a**, the resultant mixture **19b** was equilibrated with NaOMe (25 equiv to **19b**) in MeOH (0.08 M of substrate) to a mixture of the two *trans*-esters **20** and **21**. The desired ester **21** was hydrolyzed with complete selectivity by the slow addition of 1 M HCl to the MeOH solution at 0 °C to provide the easily separable mixture of the desired carboxylic acid **11** and the unhydrolyzed ester **20** (**11**:**20** = 1:2). Separation of the diastereomers was essential for the total synthesis. After extensive studies, we found the best procedure described above. For example, treatment of **19b** (four diastereomers) with NaOMe (25 equiv to **19b**) in dilute MeOH solution (0.02 M of substrate) and neutralization with 1 M HCl afforded a mixture of **20** and **21** without hydrolysis of the methyl ester. Attempted separation of **20** and **21** by silica gel chromatography failed. Moreover, when the treatment of **19b** with NaOMe (25 equiv to **19b**), followed by neutralization with 1 M HCl, was conducted in concentrated MeOH solution (0.16 M of substrate), both **20** and **21** were hydrolyzed.

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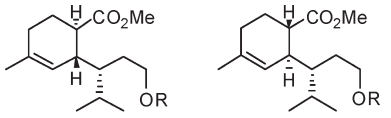
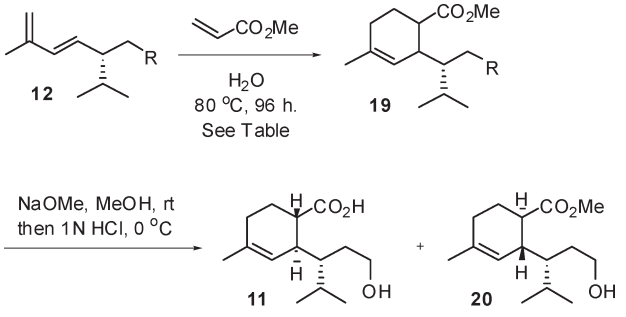


Figure 2. Structures of hydroxyesters **20** and **21** and siloxyesters **22** and **23**.

Table 2. Examination of Intermolecular Aqueous Diels–Alder Reactions

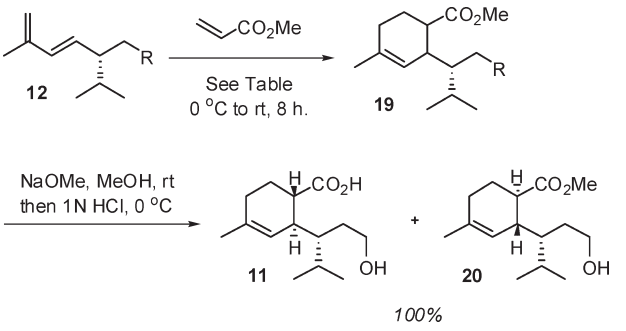


entry	diene	yield (%)[a]	ratio of **11**:**20**
1	**12b**	78	1:2
2[b]	**12b**	11	1:2
3	**12c**	32	1:2
4[b]	**12c**	45	1:2
5	**12d**	44	1:1
6	**12e**	40	1:1
7	**12f**	22	1:1

[a] isolated yield. [b] $Yb(OTf)_3$ was added as Lewis acid.

We also examined the influence of the OH group in the stereoselective hydrolysis and found that intramolecular H-bonding plays an important role. As expected, when 1 M HCl was added to a MeOH solution (0.08 M of substrate) of the hydroxyester **21**[17] and NaOMe (25 equiv to **21**) at 0 °C, hydrolysis of the methyl ester group smoothly occurred to afford the carboxylic acid **11** in almost quantitative yield (Figure 2). In stark contrast, when the neutralization was carried out using the siloxyester **23**[17] under the exact same conditions, **23** was quantitatively recovered without any hydrolysis of the methyl ester moiety. Furthermore, the same treatment of the 1:1 mixture of the siloxyesters **22**[17] and **23** resulted in complete recovery of the starting materials **22** and **23** without any cleavage of the methyl ester group.[18] Apparently, the OH group of **21** enhances the reactivity of **21** toward hydrolysis of its ester group. On the other hand, IR spectra of **20** and **21** were measured in dilute CCl_4 solutions (0.01 M, 0.005, and 0.0025 M, Supporting Information). Although the intramolecular H-bonding OH absorption peak is appreciably weaker than the free OH absorption peak in the IR spectrum of **20**, it is stronger than the free OH absorption peak in the IR spectrum of **21**. Therefore, it seems feasible that intramolecular H-bonding between the OH and C=O groups of **21** effectively accelerates the hydrolysis of the methyl ester moiety.

Table 3. Examination of Intermolecular Diels–Alder Reactions Using Lewis Acids



entry	diene	Lewis acid	solvent	yield(%)[a]	ratio of **11**:**20**
1	**12c**	$BF_3 \cdot OEt_2$	toluene	0[b]	
2	**12c**	$ZnCl_2$	toluene	0[b]	
3	**12c**	Me_3Al	toluene	0[c]	
4	**12c**	Me_2AlCl	toluene	0[c]	
5	**12c**	Et_2AlCl	toluene	0[c]	
6	**12c**	$MeAlCl_2$	toluene	51	2:1
7	**12c**	$MeAlCl_2$	CH_2Cl_2	11	2:1
8	**12c**	$MeAlCl_2$	benzene	52	2:1
9	**12c**	$MeAlCl_2$	xylene	70	2:1
10	**12b**	$MeAlCl_2$	xylene	0[c]	
11	**12d**	$MeAlCl_2$	xylene	36	1:1.5
12	**12e**	$MeAlCl_2$	xylene	0[c]	
13	**12f**	$MeAlCl_2$	xylene	0[c]	

[a] Isolated yield. [b] No reaction. [c] Complex mixture.

Intermolecular aqueous Diels–Alder reactions between the various dienes **12b**–**12f** and methyl acrylate were investigated. In Table 2, isolated yields of Diels–Alder adducts **19b**–**19f** and the ratios between desired **11** and unhydrolyzed **20** obtained after the equilibration and the following selective hydrolysis are shown. Diels–Alder reaction of the alcohol **12b** afforded the corresponding adducts **19b** in 78% isolated yield, and desired **11** was obtained as the minor product in a ratio of 1:2 (**11**:**20**) (entry 1). When $Yb(OTf)_3$ was added as the Lewis acid, the adduct **19a** was obtained in 11% yield (entry 2). The acetate **12c** is less effective for aqueous Diels–Alder reaction, and a low yield (32%) of **19c** and a stereoselectivity ratio of 1:2 (**11**:**20**) were observed (entry 3). By the addition of $Yb(OTf)_3$, the intermolecular reaction of **12c** resulted in 45% isolated yield of **19c** and a selectivity of 1:2 (**11**:**20**) (entry 4). Although intermolecular reactions with **12d**–**12f** afforded **11** and **20** in a ratio of 1:1, isolated yields of these adducts **19d**–**19f** were low (22–44%) (entries 5–7).

Next, we investigated the intermolecular Diels–Alder reaction of the dienes **12b**–**12f** with methyl acrylate in organic solvent in the presence of Lewis acids[19] (Table 3). Among various Lewis acids ($BF_3 \cdot OEt_2$, $ZnCl_2$, Me_3Al, Me_2AlCl, Et_2AlCl, and $MeAlCl_2$) examined in toluene with **12c**, only $MeAlCl_2$ provided the Diels–Alder adducts **19c** in 51% yield (entries 1–6). Similar to the aqueous Diels–Alder reactions, the mixture of the adducts (4 diastereomers) was equilibrated with NaOMe in MeOH to two *trans*-diastereomers **20** and **21**. The desired product **11** was obtained as the major product in a 2:1 (**11**:**20**) ratio after diastereoselective hydrolysis of the methyl ester group of **21** by

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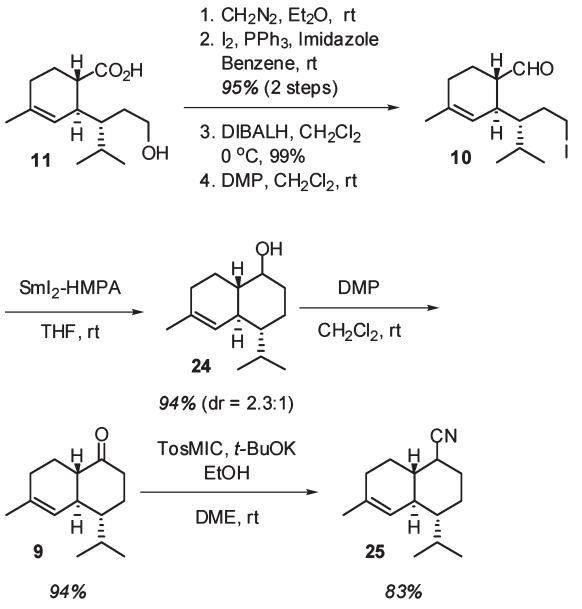
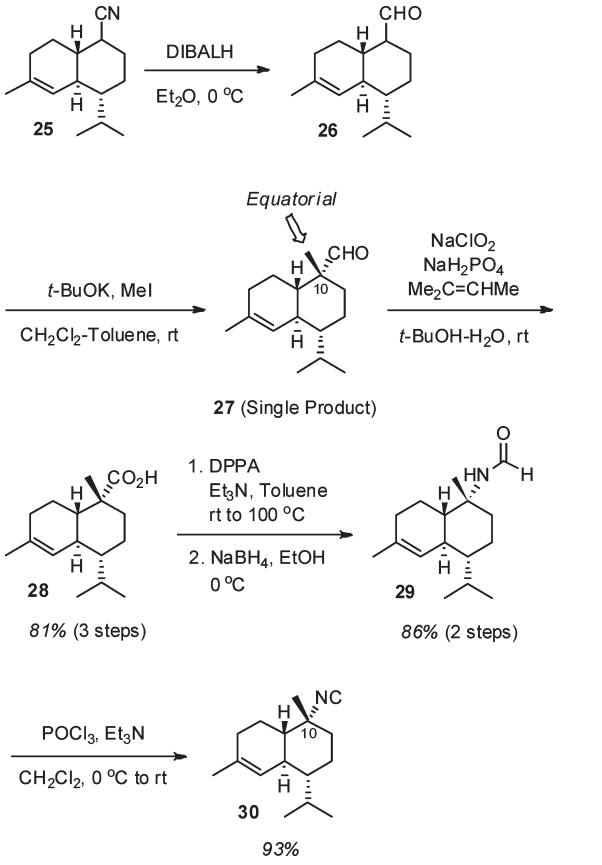
Scheme 7. Construction of *trans*-Decalin Skeleton via SmI_2-Mediated Cyclization



Scheme 8. Synthesis of 10-*epi*-10-Isocyano-4-cadinene (30)



adding 1 M HCl to the MeOH solution (entry 6). Screening of solvents in the presence of $MeAlCl_2$ revealed that xylene was the best for yield (70%), although the selectivity was only 2:1 (**11**:**20**) (entries 7−9). Therefore, the optimized conditions for the Diels−Alder reaction were found to be those in entry 9. Intermolecular Diels−Alder reactions with other dienes **12b** and **12d**−**12f** were examined under the optimized conditions and resulted in low yields of the adducts or formation of complex mixtures (entries 10−13).

As mentioned so far, we found that the intermolecular Diels−Alder reaction using $MeAlCl_2$ in xylene gave the desired carboxylic acid **11** as the major product. Natural **1** was synthesized from **11**. Since the intermolecular aqueous Diels−Alder reaction afforded the unhydrolyzed ester **20** as the major product, **20** was used toward the synthesis of di-1,6-*epi*-10-isocyano-4-cadinene to explore the structure−activity relationships of the diastereomers. As described in this section, the observed stereocomplementarity is highly advantageous because it enhances the possibilities for application to divergent syntheses of products with complementary stereochemistry.

Synthesis of 10-*epi*-10-Isocyano-4-cadinene (30). We turned our attention to the construction of the right cyclohexane ring and the quaternary carbon center at C10 (Scheme 7). The carboxylic acid **11** was transformed to the cyclization precursor **10** in a 4-step reaction sequence: (1) esterification with CH_2N_2, (2) iodination of the primary alcohol, (3) DIBALH reduction of the ester to the alcohol, and (4) oxidation with Dess−Martin periodinane.[20] The treatment of **10** with SmI_2 in the presence of HMPA afforded the alcohol **24** in 94% isolated yield,[21] which was then oxidized with Dess−Martin periodinane. To install the quaternary carbon center, the ketone **9** was first converted into the nitrile **25** with *p*-toluenesulfonylmethyl isocyanide (TosMIC).[9l,22] The nitrile **25** was next reduced to the aldehyde **26**, which was successfully methylated with MeI in the presence of KO*t*-Bu to afford **27** as a single diasteromer (Scheme 8).[23] In contrast, direct methylation of **25** under various conditions resulted in a low yield or complex mixture.[9l] At this stage, the stereochemistry at C10 could not be assigned. The conversion of **27** into **1** allowed the stereochemistry to be assigned. Thus, Pinnick oxidation[24] of **27** led to the carboxylic acid **28**, which was subjected to Curtius rearrangement using DPPA[9l,25] to afford the isocyanate. The isocyanato group was transformed to the isonitrile group in 2 steps: $NaBH_4$ reduction of the isocyanate to the formamide **29** and dehydration. Unfortunately, the ^1H NMR spectrum of synthetic **30** was not identical to that of natural **1**. From the NOESY spectrum, **30** was found to be the 10-epimer of **1**.[26] Therefore, an alternative procedure for the construction of C10 stereochemistry was required.

Synthesis of 10-Isocyano-4-cadinene (1). The α-alkylation of aldehyde **26** with MeI proceeded from the *equatorial* orientation.[23] Thus, we planned to construct an *axial* methyl group in C10 by the following sequence: (1) introduction of an *equatorial* hydroxyl methyl group with protecting group by the alkylation of **26**, (2) reduction of the aldehyde to the *axial* methyl group, and (3) deprotection followed by oxidation. As expected, the alkylation of **26** with *p*-methoxybenzyl chloromethyl ether **31**[27] successfully afforded the PMB ether **32**, which was reduced under Wolff−Kishner conditions[28] to afford the PMB ether **33** as a single diastereomer (Scheme 9). The PMB ether **33** was converted into the aldehyde by removal of the PMB group with DDQ,[29] followed by Dess−Martin oxidation. The aldehyde group was converted into an isonitrile group by a 4-step reaction sequence identical to that shown in the synthesis of **30**: (1) Pinnick oxidation, (2) Curtius rearrangement of the carboxylic acid **34** with DPPA, (3) $NaBH_4$ reduction of the isocyanate, and (4) dehydration of 10-formamide-4-cadinene (**35**)[30] with $POCl_3$

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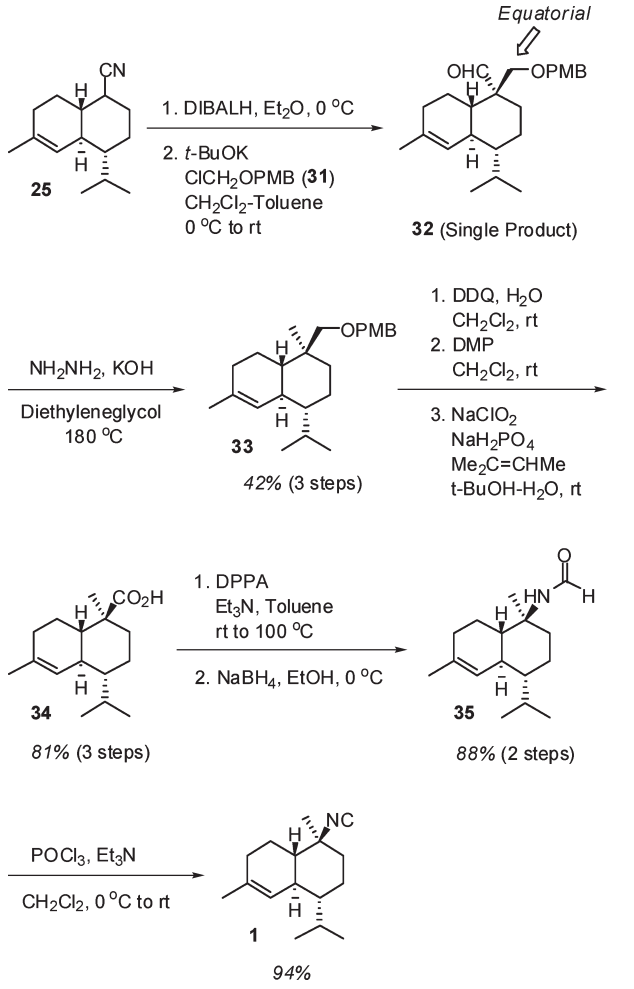
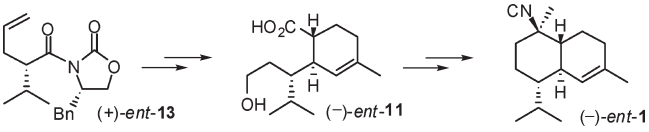
Scheme 9. Synthesis of (+)-10-Isocyano-4-cadinene (1)



Scheme 10. Synthesis of (−)-10-Isocyano-4-cadinene (*ent*-1)



to achieve the total synthesis of 10-isocyano-4-cadinene (**1**). All data (^{1}H and ^{13}C NMR, MS, and IR) of the synthetic **1** were completely identical with those of the natural sample. The optical rotation of synthetic (+)-**1**, $[\alpha]^{23}_D$ +59.8 (*c* 0.65, $CHCl_3$), is similar to that of the natural product, $[\alpha]^{23}_D$ +63.6 (*c* 0.60, $CHCl_3$).[1] Additionally, we synthesized the enantiomer, (−)-10-isocyano-4-cadinene (*ent*-**1**), from (+)-imide *ent*-**13** via (−)-carboxylic acid *ent*-**11** by the use of the same synthetic procedure (Scheme 10). The optical rotation of (−)-*ent*-**1**, $[\alpha]^{23}_D$ −58.2 (*c* 0.68, $CHCl_3$), is opposite in sign to that of the natural product. Therefore, the absolute configuration of (+)-**1** is unambiguously established as (1*S*,6*S*,7*R*,10*S*).

Syntheses of Stereoisomers. We performed the enantioselective synthesis of di-1,6-*epi*-10-isocyano-4-cadinene (**43**) in a similar manner in order to explore the structure−activity relationships of the cadinene diastereomers (Scheme 11). The SmI_2-induced Barbier-type cyclization reaction of the aldehyde **36**, prepared from ester **20** in 3 steps, afforded the alcohol **37** in 91% yield. The alcohol **37** was converted into the aldehyde in 3 steps. The methyl group at C10 was introduced using MeI and *t*-BuOK. The stereochemistry of **40** was unambiguously confirmed by a NOESY spectrum of the alcohol **44** synthesized from **40** by $NaBH_4$ reduction (Scheme 12).[31] Pinnick oxidation of **40** afforded the carboxylic acid **41**. The carboxylic acid **41** was converted to (+)-di-1,6-*epi*-10-isocyano-4-cadinene (**43**) in a 3-step sequence.

We then synthesized the enantiomers, (+)-10-*epi*-10-isocyano-4-cadinene (*ent*-**30**) and (−)-di-1,6-*epi*-10-isocyano-4-cadinene (*ent*-**43**), from (+)-imide *ent*-**13** by the use of the same synthetic procedure (Scheme 13).

Antifouling Activities with the Cadinenes. With 10-isocyano-4-cadinene (**1**) and its two diastereomers **30** and **43** in hand, we evaluated their biological activities along with the synthetic intermediates, **24**, **9**, and **25**, and the enantiomers of **1**, **30**, and **43**, prepared from *ent*-(+)-**13** via the same synthetic scheme. The activities were evaluated as EC_{50} (50% effective concentration) values against cyprid larvae of the barnacle *Balanus amphitrite* exposed to each compound for 48 h. The results are shown in Table 4. Interestingly, (+)-**1** and (−)-**1** exhibited slightly different EC_{50} values, which both corresponded closely to that of the natural sample. Furthermore, both **30** and **43** exhibited potent activities without regard to stereochemistry, although they were less active than **1**. In addition, **1** showed 100% inhibition at 1.0 μg/mL, whereas **30** and **43** inhibited 54−88% of larval metamorphosis. These results suggested that configurational differences in **1**, **30**, and **43** affected the antifouling activity against the barnacle *Balanus amphitrite*. Among the synthetic intermediates tested, **24**-ax, **24**-eq, and **9** showed activities similar to that of $CuSO_4$ (EC_{50} 0.19 μg/mL), which is used as a fouling inhibitor. However, most larvae exposed to **24**-ax, **24**-eq, and **9** floated on the surface of the test seawater. The high rate of floating larvae resulted in a low EC_{50} value. The effects of these intermediates should be considered to be different from the antifouling activities of the isocyano compounds. The nitriles **25**-ax and **25**-eq were revealed to be much less potent.

■ CONCLUSION

In summary, the total synthesis of 10-isocyano-4-cadinene was achieved by intermolecular Diels−Alder reaction and SmI_2-induced Barbier-type reaction as the key steps. The absolute configuration of natural 10-isocyano-4-cadinene was determined as (1*S*,6*S*,7*R*,10*S*). In the course of the synthesis, we successfully synthesized10-*epi*- and di-1,6-*epi*-10-isocyano-4-cadinene in a diastereoselective manner. With (+)- and (−)-10-isocyano-4-cadinenes, their diastereomers, and intermediates, we evaluated the antifouling activities against cyprid larvae of the barnacle *Balanus amphitrite* and revealed that both enantiomers of 10-isocyano-4-cadinene exhibited potent activity. These results indicate that the absolute configuration of the cadinenes had little effect on the antifouling activity against the barnacle *Balanus amphitrite* and lead us to investigate the structure−activity relationship in more detail.

■ EXPERIMENTAL SECTION

General Methods. The optical rotations were determined with a polarimeter. The melting points were determined using melting point

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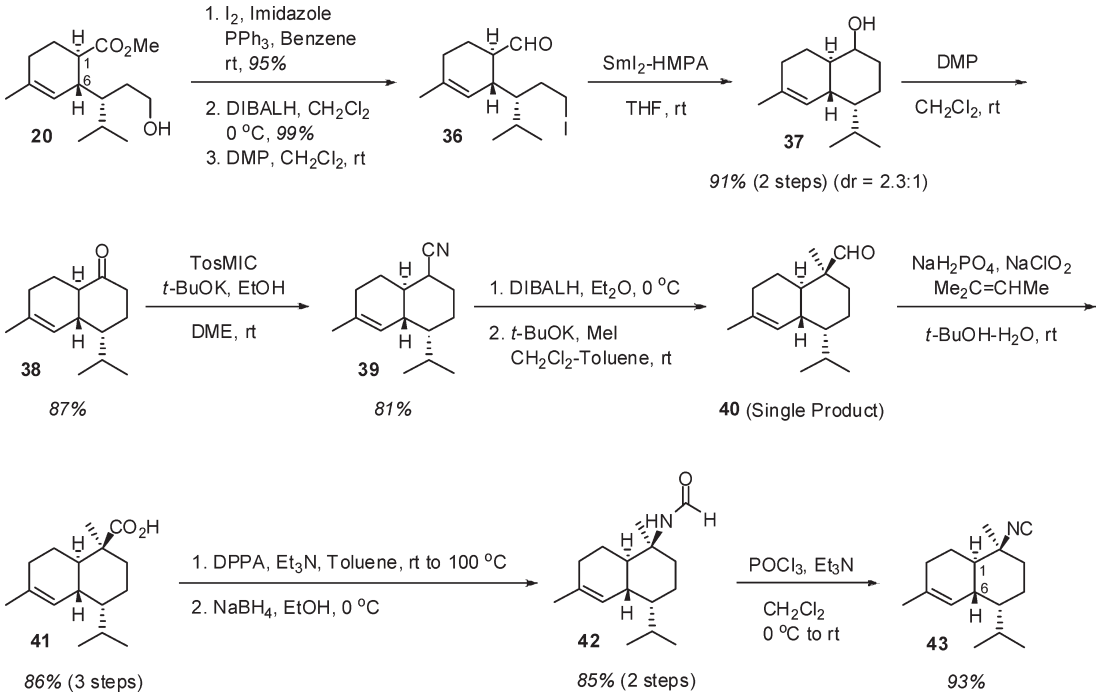
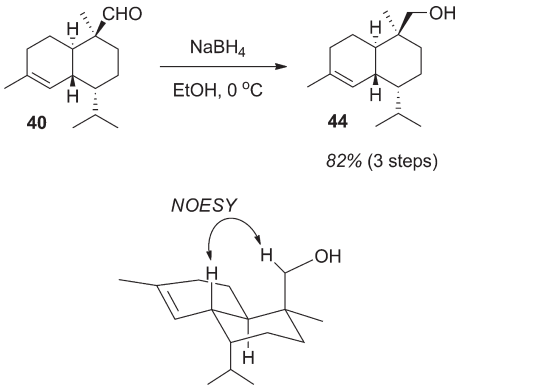
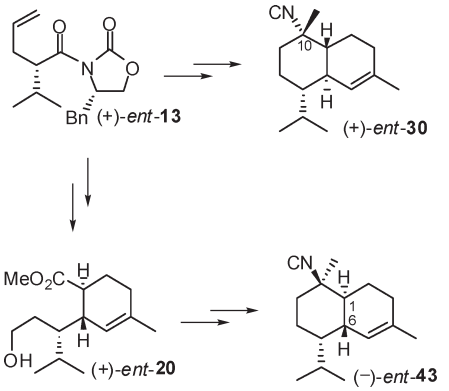
Scheme 11. Synthesis of Di-1,6-*epi*-10-isocyano-4-cadinene (43)



Scheme 12. Confirmation of Stereochemistry of Alcohol 44



Scheme 13. Synthesis of (+)-10-*epi*-10-Isocyano-4-cadinene (*ent*-30) and (−)-Di-1,6-*epi*-10-isocyano-4-cadinene (*ent*-43)



apparatus. The IR spectra were recorded using IR spectrometer using a NaCl cell or KBr disk. Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometer (^{1}H and ^{13}C). Chemical shifts were reported in ppm downfield from the peak of Me_4Si (TMS) used as the internal standard. Splitting patterns are designed as "s, d, t, q, and m", indicating "singlet, doublet, triplet, quartet, and multiplet" respectively. Tetrahydrofuran (THF) and ether were distilled from Na metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), iodomethane (MeI), and hexamethylphosphoramide (HMPA) were distilled from CaH_2. All commercially obtained reagents were used as received. Analytical and preparative TLC was carried out using precoated, glass-backed silica gel plates. The column chromatography was performed using 230−400 mesh silica.

Imide (13)[10]**.** Evans alkylation of (*R*)-3-(3-methylbutanoyl)-4-benzyloxazolidin-2-one was performed using the previously described procedure[1] to afford **13** as a colorless oil: $[\alpha]^{23}_D$ = −65.4 (*c* 0.67, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +66.3 (*c* 0.71, $CHCl_3$); IR (neat) 3064, 3022, 2958, 2914, 2866, 1776, 1694, 1639, 1603, 1495, 1452, 1383, 1347, 1289, 1232, 1207, 1124, 1099, 1074, 1050, 1000, 916, 839, 762, 746, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (6H, d, *J* = 6.8 Hz), 2.01 (1H, octet, *J* = 6.8 Hz), 2.34−2.54 (2H, m), 2.64 (1H, dd, *J* = 10.2, 13.4 Hz), 3.31 (1H, dd, *J* = 3.2, 13.4 Hz), 3.86 (1H, m), 4.10−4.17 (2H, m), 4.69 (1H, m), 5.02 (1H, d, *J* = 10.2 Hz), 5.10 (1H, dd, *J* = 1.4, 17.1 Hz), 5.82 (1H, m), 7.20−7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 20.9, 30.3, 33.7, 38.1, 48.2, 55.7, 65.7, 116.8, 127.2, 128.8, 129.3, 135.44, 135.50, 153.1, 175.6; EI-MS *m*/*z* 301 (M^+); HR EI-MS *m*/*z* 301.1677 (M^+, calcd for $C_{18}H_{23}NO_3$ 301.1678).

Acetate (14)[10b]**.** To a solution of **13** (19.8 g, 65.8 mmol) in CH_3CN (165 mL) were added NMO (50.0% in H_2O, 30.8 mL, 132 mmol) and OsO_4 (0.020 M in H_2O, 32.9 mL, 0.658 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 15 h, quenched with saturated aqueous Na_2SO_3, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and

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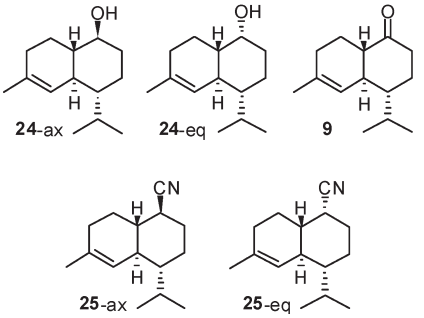
Table 4. Biological Activities of Synthetic (+)- and (−)-10-Isocyano-4-cadinene, its Stereoisomers and the Synthetic Intermediates

compound	EC_{50} (μg/mL)[a]	compound	EC_{50} (μg/mL)[a]
natural (+)-**1**[b]	0.14	**24**-ax	0.31
synthetic (+)-**1**	0.06	**24**-eq	0.38
ent-(−)-**1**	0.08	**9**	0.26
(−)-**30**	0.21	**25**-ax	4.36
ent-(+)-**30**	0.40	**25**-eq	1.48
(+)-**43**	0.16	$CuSO_4$[b]	0.27
ent-(−)-**43**	0.20		

[a] EC_{50}(μg/mL): Antifouling Activities against *Balanus amphitrite*. [b] Reference.[1]



concentrated under reduced pressure. The crude lactone was used immediately for the next step.

The lactone was dissolved in pyridine (18 mL) and cooled to 0 °C. Ac_2O (31.0 mL, 329 mmol) and DMAP (80.3 mg, 0.658 mmol) were added to the solution under Ar atmosphere. The mixture was stirred for 2 h at 0 °C, quenched with MeOH (26 mL) at 0 °C, diluted with EtOAc, and washed with saturated aqueous $CuSO_4$, H_2O, and saturated aqueous $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 10:90) to give **14** (12.9 g, 64.5 mmol, 98% in 2 steps) as a colorless oil in a 1:1 ratio of two diastereomers: IR (neat) 2956, 2870, 1770, 1740, 1643, 1466, 1369, 1339, 1234, 1166, 1120, 1075, 1043, 972, 843, 796, 746, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94, 1.05 (each 1.5H, d, J = 7.1 Hz), 0.95, 1.04 (each 1.5H, d, J = 6.8 Hz), 1.79 (0.5H, dt, J = 10.2, 12.2 Hz), 2.01−2.32 (2.5H, m), 2.10 (3H, s), 2.64 (1H, m), 4.11 (0.5H, d, J = 12.2 Hz), 4.13 (0.5H, dd, J = 1.7, 12.2 Hz), 4.26 (0.5H, dd, J = 3.6, 12.2 Hz), 4.34 (0.5H, dd, J = 2.9, 12.2 Hz), 4.57 (0.5H, m), 4.67 (0.5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 18.3, 20.3, 20.5, 20.66, 20.73, 25.86, 25.93, 27.6, 28.8, 45.1, 46.2, 64.9, 65.6, 74.9, 75.2, 170.3, 170.4, 177.0, 177.8; FAB-MS m/z 201 (M^+ + H); HR FAB-MS m/z 201.1140 (M^+ + H, calcd for $C_{10}H_{17}O_4$ 201.1127).

Alcohol (15). Compound **14** (5.32 g, 26.6 mmol) was dissolved in THF (53 mL) under Ar atmosphere and cooled to 0 °C. $LiBH_4$ (2.90 g, 133 mmol) was added to the solution. The mixture was stirred for 15 min, warmed to room temperature, and stirred for 12 h. The reaction was slowly quenched with 1 N HCl (140 mL) at 0 °C, filtered through a Celite pad, washed with THF, and concentrated under reduced pressure to obtain the crude triol, which was directly reacted in the following reaction.

To a solution of the triol in DMF (24 mL) were added 2,2-dimethoxypropane (11.1 mL, 90.4 mmol) and p-TsOH·H_2O (2.53 g, 13.3 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 15 h, quenched with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 10:90) provided **15** (4.54 g, 22.4 mmol, 84% in 2 steps) as a colorless oil in a 3:2 mixture of two diastereomers: IR (neat) 3426, 2950, 2866, 1464, 1368, 1247, 1216, 1159, 1058, 923, 863, 791 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88, 0.90, 0.94 (total 6H, d, J = 6.8 Hz), 1.36, 1.37, 1.43 (total 6H, each s), 1.44−1.61 (1.6H, m), 1.61−1.88 (2.4H, m), 2.28 (0.6H, t, J = 5.8 Hz), 3.03 (0.4H, dd, J = 5.0, 7.9 Hz), 3.47−3.72 (3H, m), 4.02−4.20 (1.4H, m), 4.25 (0.6H, quintet, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 19.6, 19.9, 20.1, 25.7, 25.9, 26.89, 26.91, 28.2, 30.3, 32.5, 33.8, 43.4, 45.7, 63.9, 64.8, 69.7, 70.0, 74.0, 76.2, 108.8, 109.2; FAB-MS m/z 203 (M^+ + H); HR FAB-MS m/z 203.1654 (M^+ + H, calcd for $C_{11}H_{23}O_3$ 203.1647).

Phosphonate (17c)[12d,f]. A mixture of triethyl phosphite (19.3 g, 31.6 mmol) and 3-chloro-2-methylpropene (31.6 g, 348 mmol) was heated at reflux for 9 days at 130 °C. Evaporation of the remaining 3-chloro-2-methylpropene afforded **17c** (6.07 g, 31.6 mmol) as a colorless oil, which was directly employed in the next reaction: IR (neat) 3470, 3072, 2978, 2904, 1645, 1475, 1443, 1389, 1283, 1250, 1161, 1096, 1055, 1027, 963, 893, 859, 837, 795, 769, 736, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (6H, t, J = 7.2 Hz), 1.88 (3H, s), 2.56 (1H, s), 2.61 (1H, s), 4.05−4.18 (4H, m), 4.88 (1H, d, J = 5.1 Hz), 4.94 (1H, d, J = 3.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.39, 16.45, 23.62, 23.64, 34.7, 36.1, 61.78, 61.85, 115.2, 115.3, 136.0, 136.1; EI-MS m/z 192 (M^+); HR EI-MS m/z 192.0910 (M^+, calcd for $C_8H_{17}O_3P$ 192.0915).

Diene (18). DMSO (5.68 mL, 80.0 mmol) was added at −78 °C under Ar atmosphere to a solution of oxalyl chloride (3.49 mL, 40.0 mmol) in CH_2Cl_2 (95 mL). After 15 min of stirring, a solution of **15** (2.89 g, 14.3 mmol) in CH_2Cl_2 (29 mL) was added dropwise. After stirring for 50 min, the white suspension was treated with Et_3N (14.9 mL, 107 mmol). The reaction was allowed to warm to room temperature and stirred for 1 h. Saturated aqueous NH_4Cl was added to the solution, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the resulting crude aldehyde was used directly in the next reaction.

To a solution of **17c** (8.24 g, 42.9 mmol) in THF (65 mL) was added *n*-BuLi (2.64 M in hexane, 16.2 mL, 42.9 mmol) dropwise at −78 °C under Ar atmosphere. After 30 min of stirring, HMPA (14.9 mL, 85.7 mmol) was added dropwise. A solution of the aldehyde in THF (20 mL) was next added dropwise. The mixture was gradually warmed to room temperature over 3 h, stirred for 12 h, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 3:97) provided **18** (2.86 g, 12.0 mmol, 84% in 2 steps) as a colorless oil in a 3:2 ratio of two diastereomers: IR (neat) 3076, 2952, 2866, 1606, 1452, 1367, 1242, 1217, 1159, 1109, 1062, 969, 882, 826, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84, 0.88 (each 1.2H, d, J = 6.8 Hz), 0.85, 0.89 (each 1.8H, d, J = 6.8 Hz), 1.33, 1.40 (each 1.8H, brs), 1.33, 1.40 (each 1.2H, brs), 1.40−1.70 (2H, m), 1.70−1.89 (1.4H, m), 1.83 (3H, brs), 2.08 (0.6H, m), 3.40−3.53 (1H, m), 3.93−4.09 (2H, m), 4.88 (2H, brs), 5.36 (0.6H, dd, J = 10.0, 15.6 Hz), 5.43 (0.4H, dd, J = 9.2, 15.6 Hz), 6.05 (0.4H, d, J = 15.6 Hz), 6.13 (0.6H, d, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 18.9, 19.0, 20.5, 20.6, 25.8, 27.0, 27.1, 32.4, 32.6, 36.4, 37.0, 46.35, 46.44, 69.4, 70.0, 74.6, 75.0, 108.1, 108.3, 114.7, 114.8, 131.47, 131.52, 134.0, 134.4, 141.6; EI-MS m/z 238 (M^+), 223 (M^+ − CH_3); HR EI-MS m/z 238.1937 (M^+, calcd for $C_{15}H_{26}O_2$ 238.1933).

Carboxylic Acid (12a). To a solution of **18** (2.17 g, 9.10 mmol) in 80% AcOH aqueous (446 mL) was slowly added $NaIO_4$ (4.87 g, 22.8 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 4 h at room temperature, diluted with H_2O, extracted with EtOAc, washed

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with 15% NaOH aqueous solution and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde was employed directly in the next reaction.

To a solution of the crude aldehyde in DMF (13 mL) was added PDC (6.85 g, 18.2 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 15 h at room temperature, quenched with H_2O, filtered with a Celite pad, washed with Et_2O, extracted with Et_2O, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane/CH_3CO_2H, 10:89:1) to give **12a** (1.29 g, 7.10 mmol, 78% in 2 steps) as a colorless oil: $[\alpha]^{23}_D = -9.9$ (*c* 2.00, $CHCl_3$), enantiomer $[\alpha]^{23}_D = +9.8$ (*c* 2.22, $CHCl_3$); IR (neat) 3076, 2954, 2868, 1707, 1607, 1436, 1409, 1384, 1368, 1294, 1260, 1165, 1100, 1033, 967, 884, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87, 0.90 (each 3H, d, J = 6.8 Hz), 1.70 (1H, m), 1.82 (3H, s), 2.33 (1H, dd, J = 8.5, 13.9 Hz), 2.44 (1H, m), 2.51 (1H, dd, J = 5.1, 13.9 Hz), 4.89 (2H, s), 5.47 (1H, dd, J = 8.5, 15.6 Hz), 6.15 (1H, d, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 18.9, 20.5, 31.8, 37.7, 45.4, 115.2, 129.9, 134.4, 141.7, 179.3; EI-MS m/z 182 (M^+); HR EI-MS m/z 182.13054 (M^+, calcd for $C_{11}H_{18}O_2$ 182.13068).

Alcohol (12b). To a solution of **18** (32.6 g, 137 mmol) in 80% aqueous AcOH (685 mL) was added $NaIO_4$ (73.3 g, 343 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 4 h at room temperature, diluted with H_2O, and extracted with EtOAc. The combined organic layers were washed with 15% NaOH aqueous solution and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde was used directly in the next reaction.

A solution of the aldehyde in MeOH (274 mL) was cooled to 0 °C under Ar atmosphere. After $NaBH_4$ (2.59 g, 68.5 mmol) was added to this solution, the mixture was stirred for 30 min, quenched with saturated aqueous NH_4Cl, and concentrated *in vacuo*. The aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to afford **12b** (19.8 g, 118 mmol, 86% in 2 steps) as a colorless oil: $[\alpha]^{23}_D = +15.5$ (*c* 2.03, MeOH), enantiomer $[\alpha]^{23}_D = -15.3$ (*c* 2.11, MeOH); IR (neat) 3350, 3074, 2950, 2866, 1606, 1464, 1452, 1383, 1366, 1257, 1165, 1047, 969, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85, 0.90 (each 3H, d, J = 6.8 Hz), 1.40−1.70 (3H, m), 1.76 (1H, m), 1.84 (3H, s), 1.99 (1H, m), 3.52−3.71 (2H, m), 4.88 (2H, s), 5.44 (1H, dd, J = 9.5, 15.6 Hz), 6.13 (1H, d, J = 15.6 Hz); ^1H NMR (C_6D_6, 400 MHz) δ 0.83, 0.89 (each 3H, d, J = 6.6 Hz), 1.36−1.62 (2H, m), 1.70 (1H, m), 1.76 (3H, s), 2.01 (1H, m), 3.40−3.67 (2H, m), 4.88, 4.92 (each 1H, s), 5.39 (1H, dd, J = 9.5, 15.6 Hz), 6.16 (1H, d, J = 15.6 Hz); ^{13}C NMR (C_6D_6, 100 MHz) δ 19.7, 20.0, 21.7, 33.4, 36.6, 47.1, 61.9, 115.6, 133.1, 135.3, 142.7; EI-MS m/z 168 (M^+), 153 ($M^+ - CH_3$); HR EI-MS m/z 168.1520 (M^+, calcd for $C_{11}H_{20}O$ 168.1514).

Acetate (12c). To a solution of **12b** (6.06 g, 36.0 mmol) in CH_2Cl_2 (120 mL) were added Et_3N (20.0 mL, 144 mmol), Ac_2O (6.80 mL, 72.0 mmol), and DMAP (220 mg, 1.80 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 30 min at 0 °C, diluted with CH_2Cl_2, washed with brine and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification over silica gel column chromatography (EtOAc/hexane, 5:95) afforded **12c** (7.50 g, 35.6 mmol, 99%) as a colorless oil: $[\alpha]^{23}_D = +7.7$ (*c* 4.74, $CHCl_3$), enantiomer $[\alpha]^{23}_D = -7.9$ (*c* 4.74, $CHCl_3$); IR (neat) 3076, 2952, 2866, 1739, 1606, 1464, 1384, 1365, 1235, 1037, 969, 884, 807 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85, 0.89 (each 3H, d, J = 6.8 Hz), 1.49−1.69 (2H, m), 1.81 (1H, m), 1.83 (3H, s), 1.96 (1H, m), 2.03 (3H, s), 3.97 (1H, m), 4.08 (1H, m), 4.88 (2H, s), 5.39 (1H, dd, J = 9.2, 15.6 Hz), 6.08 (1H, d, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 19.0, 20.5, 20.9, 31.2, 32.2, 46.2, 63.3, 114.7, 131.1, 134.3, 141.6, 170.8; EI-MS m/z 210 (M^+); HR EI-MS m/z 210.1617 (M^+, calcd for $C_{13}H_{22}O_2$ 210.1620).

Ester (12d). To a solution of **12b** (96.9 mg, 0.576 mmol) in CH_2Cl_2 (12 mL) were added diphenylacetic acid (183 mg, 0.864 mmol), DMAP (141 mg, 1.15 mmol), and DCC (297 mg, 1.44 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 2 h, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to give **12d** (203 mg, 0.560 mmol, 97%) as a colorless oil: $[\alpha]^{23}_D = +18.3$ (*c* 2.00, $CHCl_3$), enantiomer $[\alpha]^{23}_D = -17.6$ (*c* 4.48, $CHCl_3$); IR (neat) 3058, 3022, 2952, 2864, 1733, 1602, 1494, 1451, 1383, 1365, 1347, 1304, 1271, 1226, 1185, 1148, 1080, 1029, 1007, 971, 883, 742, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80, 0.83 (each 3H, d, J = 6.8 Hz), 1.46−1.62 (2H, m), 1.75−1.89 (2H, m), 1.80 (3H, s), 4.03, 4.17 (each 1H, m), 4.82, 4.86 (each 1H, s), 5.01 (1H, s), 5.33 (1H, dd, J = 9.5, 15.6 Hz), 5.95 (1H, d, J = 15.6 Hz), 7.20−7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 19.1, 20.6, 31.1, 32.2, 46.0, 57.3, 64.0, 114.8, 127.1, 128.48, 128.54, 128.6, 131.1, 134.6, 138.67, 138.70, 141.7, 172.3; EI-MS m/z 362 (M^+); HR EI-MS m/z 362.2237 (M^+, calcd for $C_{25}H_{30}O_2$ 362.2246).

Ester (12e). To a solution of **12b** (22.9 mg, 0.136 mmol) in CH_2Cl_2 (2.7 mL) were added (*S*)-(+)-methoxyphenyl acetic acid (33.9 mg, 0.204 mmol), DMAP (33.2 mg, 0.272 mmol), and DCC (70.2 mg, 0.340 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 2 h, diluted with EtOAc, washed with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to afford **12e** (42.7 mg, 0.135 mmol, 99%) as a colorless oil; $[\alpha]^{23}_D = +88.6$ (*c* 1.63, $CHCl_3$), enantiomer $[\alpha]^{23}_D = -83.2$ (*c* 1.03, $CHCl_3$); IR (neat) 3072, 3025, 2952, 2918, 2866, 2820, 1747, 1603, 1492, 1452, 1383, 1367, 1256, 1197, 1172, 1116, 1074, 1028, 1010, 969, 883, 802, 730, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78, 0.82 (each 3H, d, J = 6.8 Hz), 1.43−1.60 (2H, m), 1.72−1.83 (2H, m), 1.78 (3H, s), 3.41 (3H, s), 4.00 (1H, m), 4.13 (1H, m), 4.75 (1H, s), 4.77 (1H, s), 4.84 (1H, s), 5.28 (1H, dd, J = 9.5, 15.6 Hz), 5.80 (1H, d, J = 15.6 Hz), 7.30−7.40 (3H, m), 7.41−7.47 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 19.0, 20.6, 31.1, 32.1, 45.9, 57.3, 63.9, 82.6, 114.8, 127.1, 128.5, 128.6, 130.8, 134.6, 136.4, 141.6, 170.5; EI-MS m/z 316 (M^+); HR FAB-MS m/z 339.1952 (M^+ + Na, calcd for $C_{20}H_{28}O_3Na$ 339.1936).

Ester (12f). To a solution of **12b** (68.9 mg, 0.409 mmol) in CH_2Cl_2 (8.2 mL) were added (*R*)-(−)-methoxyphenyl acetic acid (102 mg, 0.614 mmol), DMAP (99.9 mg, 0.818 mmol), and DCC (211 mg, 1.02 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 12 h, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to yield **12f** (93.2 mg, 0.294 mmol, 72%) as a colorless oil; $[\alpha]^{23}_D = -19.4$ (*c* 1.92, $CHCl_3$), enantiomer $[\alpha]^{23}_D = +18.8$ (*c* 2.50, $CHCl_3$); IR (neat) 3070, 3024, 2952, 2868, 2820, 1746, 1641, 1605, 1492, 1452, 1383, 1366, 1347, 1256, 1197, 1174, 1113, 1073, 1027, 1006, 970, 884, 799, 729, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.77, 0.79 (each 3H, d, J = 7.2 Hz), 1.42−1.53 (2H, m), 1.70−1.79 (2H, m), 1.80 (3H, s), 3.41 (3H, s), 4.01 (1H, m), 4.16 (1H, m), 4.74 (1H, s), 4.83 (1H, s), 4.86 (1H, s), 5.31 (1H, dd, J = 9.1, 15.6 Hz), 5.96 (1H, d, J = 15.6 Hz), 7.30−7.40 (3H, m), 7.41−7.46 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 18.9, 20.5, 31.1, 32.0, 45.7, 57.3, 63.9, 82.6, 114.8, 127.1, 128.5, 128.6, 130.9, 134.6, 136.3, 141.6, 170.4; EI-MS m/z 316 (M^+); HR EI-MS m/z 316.2045 (M^+, calcd for $C_{20}H_{28}O_3$ 316.2039).

Carboxylic Acid (11) and Ester (20). To a solution of **12a** (181 mg, 0.995 mmol) in H_2O (1.00 mL) was $NaHCO_3$ (100 mg, 1.19 mmol) at room temperature. After the mixture was stirred for 30 min, methyl acrylate (0.718 mL, 7.96 mmol) was added. The mixture was warmed to 80 °C and stirred for 96 h. The mixture was diluted with 1 N HCl at room temperature, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 10:90) to yield

colorless oil **19a** (230 mg, 0.859 mmol, 86%) as a mixture of four diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80, 0.85, 0.89, 0.92, 0.97 (total 6H, each d, J = 6.8 Hz), 1.68−2.37 (8H, m), 2.38−2.48, 2.49−2.58, 2.60−2.72, 2.72−2.84 (total 2H, each m), 3.64, 3.66, 3.69, 3.71 (total 3H, each s), 5.18, 5.26, 5.31, 5.41 (total 1H, each s).

To a solution of **19a** (746 mg, 2.78 mmol) in THF (28 mL) was added dropwise Et_3N (0.504 mL, 3.61 mmol) at −10 °C under Ar atmosphere. Ethyl chloroformate (0.345 mL, 3.61 mmol) was added. After 10 min of stirring, $NaBH_4$ (841 mg, 22.2 mmol) was added. After MeOH (18.5 mL) was slowly added, the mixture was warmed to room temperature and stirred for 30 min. The mixture was adjusted with 1 N HCl to pH 7, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 10:90) to give colorless oil **19b** (683 mg, 2.68 mmol, 97%) as a mixture of four diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78, 0.83, 0.866, 0.874, 0.878, 0.883, 0.92, 0.93 (total 6H, d, J = 6.8 Hz), 1.27 (1H, m), 1.37−2.10 (6H, m), 1.66, 1.68 (total 3H, each s), 2.37, 2.47−2.58, 2.62−2.82 (total 2H, each m), 3.50−3.67 (2H, m), 3.66, 3.68, 3.69 (total 3H, each s), 5.22, 5.33, 5.47 (total 1H, each s).

Na (1.62 g, 70.4 mmol) was slowly dissolved in MeOH (28 mL) at room temperature under Ar atmosphere. To the mixture was added dropwise a solution of **19b** (358 mg, 1.41 mmol) in MeOH (7.1 mL). The mixture was stirred for 24 h, slowly quenched with 1 N HCl to pH 1 at 0 °C, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 20:80) to afford **11** (113 mg, 0.471 mmol, 33%) and **20** (240 mg, 0.994 mmol, 67%) as colorless oils: **11**: $[\alpha]^{23}_D$ = +20.2 (*c* 0.53, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −21.4 (*c* 0.70, $CHCl_3$); IR (neat) 3010, 2950, 2868, 1700, 1449, 1432, 1409, 1384, 1365, 1293, 1259, 1239, 1191, 1045, 1009, 893, 875, 811, 771, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83, 0.89 (each 3H, d, J = 6.8 Hz), 1.35 (1H, m), 1.48 (1H, m), 1.63−1.82 (4H, m), 1.67 (3H, s), 1.88−2.11 (3H, m), 2.55 (1H, dt, J = 2.2, 10.1 Hz), 2.62 (1H, m), 3.63−3.80 (2H, m), 5.33 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 23.4, 23.7, 26.4, 27.7, 29.1, 30.2, 39.2, 42.2, 43.3, 61.4, 121.3, 133.3, 181.0; FAB-MS m/z 239 (M^+ − H); HR FAB-MS m/z 239.1642 (M^+ − H, calcd for $C_{14}H_{23}O_3$ 239.1647). **20**: $[\alpha]^{23}_D$ = −34.2 (*c* 5.56, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +34.4 (*c* 5.02, $CHCl_3$); IR (neat) 3428, 2948, 2866, 1733, 1432, 1370, 1261, 1239, 1191, 1160, 1045, 1011, 936, 872, 811 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91, 0.92 (each 3H, d, J = 6.8 Hz), 1.37−1.58 (2H, m), 1.62−1.85 (3H, m), 1.66 (3H, s), 1.85−2.10 (3H, m), 2.37 (1H, dt, J = 2.7, 10.2 Hz), 2.68 (1H, d, J = 10.2 Hz), 2.78 (1H, brs), 3.48−3.69 (2H, m), 3.68 (3H, s), 5.22 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 21.2, 23.7, 26.5, 29.3, 30.9, 32.2, 38.9, 43.3, 44.8, 51.5, 63.0, 121.2, 134.6, 176.7; EI-MS m/z 254 (M^+), 236 ($M^+ - H_2O$); HR EI-MS m/z 254.1881 (M^+, calcd for $C_{15}H_{26}O_3$ 254.1882).

Preparation of diazomethane. To a solution of KOH (6.08 g) in Et_2O (76 mL) and H_2O (15 mL) was slowly added 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) (1.24 g, 5.16 mmol) at 0 °C. After 30 min of stirring, the organic layers were directly employed as a solution of CH_2N_2 in Et_2O in the following reaction.

Ester (22). To a solution of **11** (12.7 mg, 52.7 μmol) in MeOH (11 μL) was added CH_2N_2 in Et_2O (0.78 mL) at room temperature under Ar atmosphere. The mixture was stirred for 2 h at room temperature and concentrated under reduced pressure. The crude ester **21** was directly employed in the next reaction.

To a solution of **21** in CH_2Cl_2 (0.11 mL) were added Et_3N (8.81 μL, 63.2 μmol), DMAP (0.40 mg, 3.16 μmol), and TBSCl (8.70 mg, 58.0 μmol) under Ar atmosphere. The mixture was stirred for 24 h, quenched with saturated aqueous $NaHCO_3$ and saturated aqueous NH_4Cl, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to afford **22** (19.2 mg, 52.2 μmol, 99% in 2 steps) as a colorless oil: $[\alpha]^{23}_D$ = +26.5 (*c* 0.66, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −24.4 (*c* 0.85, $CHCl_3$); IR (neat) 2948, 2924, 2852, 1734, 1461, 1433, 1384, 1360, 1306, 1255, 1221, 1188, 1158, 1095, 1022, 932, 835, 808, 775, 662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05 (6H, s), 0.82, 0.87 (each 3H, d, J = 6.8 Hz), 0.89 (9H, s), 1.19, 1.48 (eacn 1H, m), 1.54−1.65 (2H, m), 1.69−1.99 (4H, m), 1.65 (3H, s), 2.50−2.58 (2H, m), 3.50−3.65 (2H, m), 3.66 (3H, s), 5.33 (1H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.2, 18.7, 23.1, 23.8, 25.8, 26.0, 26.1, 28.0, 28.9, 31.1, 40.3, 42.7, 43.3, 51.4, 62.9, 122.4, 133.3, 176.6; EI-MS m/z 368 (M^+); HR EI-MS m/z 368.2746 (M^+, calcd for $C_{21}H_{40}O_3$ Si 368.2747).

Ester (23). To a solution of **20** (72.6 mg, 0.285 mmol) in CH_2Cl_2 (0.57 mL) were added Et_3N (47.7 μL, 0.342 mmol), DMAP (2.09 mg, 17.1 μmol), and TBSCl (47.3 mg, 0.314 mmol) under Ar atmosphere. The mixture was stirred for 24 h, quenched with saturated aqueous $NaHCO_3$ and saturated aqueous NH_4Cl, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to afford **23** (0.104 g, 0.282 mmol, 99%) as a colorless oil: $[\alpha]^{23}_D$ = −40.3 (*c* 1.49, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +39.9 (*c* 1.58, $CHCl_3$); IR (neat) 2948, 2924, 2852, 1734, 1467, 1432, 1383, 1367, 1307, 1254, 1218, 1189, 1159, 1094, 1042, 1028, 1008, 937, 915, 833, 812, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (6H, s), 0.89 (9H, s), 0.90, 0.91 (each 3H, d, J = 7.0 Hz), 1.32−1.51 (2H, m), 1.58−1.84 (3H, m), 1.65 (3H, s), 1.84−2.05 (3H, m), 2.33 (1H, dt, J = 2.7, 9.7 Hz), 2.68 (1H, m), 3.54 (2H, t, J = 7.3 Hz), 3.66 (3H, s), 5.22 (1H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1, 18.6, 20.4, 21.3, 23.9, 26.1, 26.9, 29.5, 30.8, 32.3, 38.6, 43.0, 44.8, 51.5, 63.4, 121.7, 134.1, 176.5; EI-MS m/z 368 (M^+); HR EI-MS m/z 368.2742 (M^+, calcd for $C_{21}H_{40}O_3$ Si 368.2747).

Carboxylic Acid (11) and Ester (20). To a solution of methyl acrylate (5.85 mL, 64.8 mmol) in xylene (54.2 mL) was added $MeAlCl_2$ (1.0 M in hexane, 23.8 mL, 23.8 mmol) dropwise at 0 °C under Ar atmosphere. A solution of **12c** (2.28 g, 10.8 mmol) in xylene (54 mL) was next added dropwise. The mixture was stirred for 3 h at 0 °C and gradually warmed to room temperature over 5 h. The mixture was quenched with saturated aqueous NH_4Cl. After the two layers were separated, the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to give the Diels−Alder adduct **19c** (2.24 g, 7.56 mmol, 70%) as a colorless oil, which was a mixture of four diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77, 0.78, 0.83, 0.85, 0.87, 0.88, 0.93, 0.94 (total 6H, d, J = 6.8 Hz), 1.18−2.12 (10H, m), 1.66, 1.68 (total 3H, each s), 2.03, 2.038, 2.042, 2.05 (total 3H, each s), 2.15−2.42, 2.42−2.89 (total 2H, each m), 3.65, 3.66, 3.67, 3.68 (total 3H, each s), 3.91−4.14 (2H, m), 5.21, 5.31, 5.34, 5.40 (total 1H, each s).

NaOMe solution was prepared by adding Na metal (9.32 g, 405 mmol) in small pieces to MeOH (160 mL) at room temperature. The mixture was stirred until the metal was completely consumed. To the mixture was added a solution of **19c** (4.80 g, 16.2 mmol) in MeOH (41 mL). The mixture was stirred for 24 h, slowly quenched with 1 N HCl to pH 1 at 0 °C, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 20:80) to give **11** (2.60 g, 10.8 mmol, 67%) and **20** (1.37 g, 5.40 mmol, 33%) as colorless oils.

Ester (45). To a solution of **11** (764 mg, 3.18 mmol) in MeOH (0.10 mL) was added CH_2N_2 in Et_2O (47 mL) at room temperature under Ar atmosphere. The mixture was stirred for 2 h at room temperature and concentrated under reduced pressure. The crude ester **21** was directly employed in the next reaction.

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A solution of **21** in benzene (18 mL) was cooled to 0 °C under Ar atmosphere. Then imidazole (325 mg, 4.78 mmol), triphenylphosphine (1.25 g, 4.78 mmol), and I_2 (2.26 g, 8.90 mmol) were added to the solution. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous Na_2SO_3. After the two layers were separated, the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to give **45** (1.10 g, 3.02 mmol, 95% in 2 steps) as a colorless oil: $[\alpha]^{23}_D$ = +43.8 (*c* 1.81, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −43.9 (*c* 2.11, $CHCl_3$); IR (neat) 2948, 2918, 2864, 1731, 1684, 1432, 1381, 1364, 1308, 1258, 1189, 1160, 1103, 1055, 1030, 843, 802, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82, 0.90 (each 3H, d, *J* = 6.8 Hz), 1.24 (1H, m), 1.67 (3H, s), 1.68−2.05 (7H, m), 2.50 (1H, t, *J* = 11.5 Hz), 2.59 (1H, brs), 3.12 (1H, q, *J* = 8.6 Hz), 3.29 (1H, dt, *J* = 5.1, 9.3 Hz), 3.70 (3H, s), 5.29 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.5, 19.2, 23.2, 23.8, 26.4, 27.7, 29.1, 32.6, 39.6, 43.4, 47.6, 51.7, 121.5, 133.9, 176.4; EI-MS *m*/*z* 364 (M^+), 237 (M^+−I); HR EI-MS *m*/*z* 364.0901 (M^+, calcd for $C_{15}H_{25}IO_2$ 364.0900).

Alcohol (46). A solution of **45** (880 mg, 2.42 mmol) in CH_2Cl_2 (8.1 mL) was cooled to 0 °C under Ar atmosphere. DIBALH (1.01 M in toluene, 4.78 mL, 4.83 mmol) was added dropwise to the solution. The mixture was stirred for 1 h, quenched with MeOH (0.97 mL) and trace of H_2O at 0 °C, filtered through a Celite pad, washed with CH_2Cl_2, and concentrated *in vacuo*. Purification over silica gel column chromatography (EtOAc/hexane, 10:90) yielded **46** (807 mg, 2.40 mmol, 99%) as a colorless oil: $[\alpha]^{23}_D$ = +37.7 (*c* 3.84, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −37.9 (*c* 3.89, $CHCl_3$); IR (neat) 3334, 3035, 2950, 2918, 2866, 2724, 1722, 1669, 1463, 1446, 1432, 1384, 1365, 1264, 1238, 1167, 1048, 1021, 974, 937, 877, 848, 806 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82, 0.90 (each 3H, d, *J* = 6.8 Hz), 1.38 (1H, m), 1.49−2.04 (10H, m), 1.65 (3H, s), 3.15 (1H, q, *J* = 9.3 Hz), 3.27 (1H, dt, *J* = 5.4, 9.3 Hz), 3.54 (1H, dd, *J* = 7.0, 10.6 Hz), 3.63 (1H, dd, *J* = 5.0, 10.6 Hz), 5.27 (1H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.5, 18.3, 22.9, 23.91, 23.94, 27.8, 28.0, 32.3, 37.3, 38.1, 47.3, 65.4, 121.9, 134.1; EI-MS *m*/*z* 336 (M^+); HR EI-MS *m*/*z* 336.0950 (M^+, calcd for $C_{14}H_{25}IO$ 336.0951).

Preparation of THF Solution of SmI_2-HMPA. To a slurry of Sm metal powder (1.50 g, 9.98 mmol) in THF (50 mL) was added CH_2I_2 (0.450 mL, 5.60 mmol) at room temperature under Ar atmosphere, and the mixture was stirred overnight. HMPA (3.89 mL, 22.4 mmol) was added, and the initially blue solution turned deep purple. The resulting solution was directly used to effect the following reductive cyclization.

Alcohol (24-ax and 24-eq). To a solution of **46** (623 mg, 1.85 mmol) in CH_2Cl_2 (19 mL) was added Dess−Martin periodinane (DMP) (1.95 g, 4.63 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldehyde **9** was directly used in the next step.

After a solution of **9** in THF (19 mL) was degassed by freeze treatment, a 0.100 M THF-HMPA solution of SmI_2 (55.5 mL, 5.55 mmol) was added at room temperature under Ar atmosphere. The mixture was stirred for 30 min and quenched with saturated aqueous $NaHCO_3$. After the two layers were separated, the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to give **24**-eq (254 mg, 1.22 mmol, 66% in 2 steps) as white crystals and **24**-ax (109 mg, 0.522 mmol, 28% in 2 steps) as a colorless oil. **24**-eq: mp 99−102 °C; $[\alpha]^{23}_D$ = +37.3 (*c* 2.80, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −37.9 (*c* 2.84, $CHCl_3$); IR (KBr) 3414, 3048, 3006, 2948, 2912, 2852, 1701, 1664, 1453, 1384, 1366, 1353, 1335, 1314, 1283, 1238, 1226, 1187, 1157, 1138, 1112, 1091, 1054, 1028, 1012, 989, 978, 955, 906, 884, 855, 835, 805, 793 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74, 0.91 (each 3H, d, *J* = 6.8 Hz), 0.98−1.34 (5H, m), 1.56−1.72 (3H, m), 1.66 (3H, s), 1.92−2.08 (3H, m), 2.10−2.24 (2H, m), 3.24 (1H, dt, *J* = 4.4, 10.3 Hz), 5.50 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1, 21.6, 22.7, 24.0, 25.4, 26.1, 30.2, 35.6, 41.2, 45.8, 47.5, 74.2, 121.5, 134.9; EI-MS *m*/*z* 208 (M^+), 190 ($M^+ - H_2O$); HR EI-MS *m*/*z* 208.1824 (M^+, calcd for $C_{14}H_{24}O$ 208.1827). **24**-ax: $[\alpha]^{23}_D$ = −9.3 (*c* 4.73, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +9.3 (*c* 4.93, $CHCl_3$); IR (neat) 3364, 3044, 3000, 2950, 2952, 2862, 1684, 1462, 1447, 1388, 1368, 1333, 1297, 1212, 1188, 1138, 1118, 1094, 1074, 1054, 979, 951, 927, 886, 860, 792, 758, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79, 0.91 (each 3H, d, *J* = 6.8 Hz), 1.02 (1H, m), 1.18−1.67 (7H, m), 1.66 (3H, s), 1.83−2.25 (5H, m), 3.85 (1H, d, *J* = 2.0 Hz), 5.56 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3, 18.5, 21.5, 23.9, 26.2, 27.0, 30.8, 33.4, 35.8, 44.2, 46.8, 70.6, 122.5, 134.3; EI-MS *m*/*z* 208 (M^+) 190 ($M^+ - H_2O$); HR EI-MS *m*/*z* 208.1823 (M^+, calcd for $C_{14}H_{24}O$ 208.1827).

Ketone (9). DMP (1.08 g, 2.55 mmol) was added to a solution of **24** (213 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to give **9** (198 mg, 0.959 mmol, 94%) as white crystals: mp 28−31 °C; $[\alpha]^{23}_D$ = −84.1 (*c* 4.48, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +87.3 (*c* 4.90, $CHCl_3$); IR (KBr) 3040, 3004, 2952, 2922, 2864, 2826, 2720, 1712, 1451, 1429, 1367, 1313, 1291, 1259, 1234, 1204, 1185, 1143, 1065, 1030, 1015, 971, 954, 941, 902, 874, 847, 830, 803, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78, 0.99 (each 3H, d, *J* = 6.8 Hz), 1.36−1.60 (4H, m), 1.69 (3H, s), 1.90−2.47 (8H, m), 5.55 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0, 21.6, 21.9, 23.8, 25.4, 26.4, 29.7, 41.1, 44.3, 46.0, 51.1, 121.3, 135.7, 212.7; EI-MS *m*/*z* 206 (M^+); HR EI-MS *m*/*z* 206.1679 (M^+, calcd for $C_{14}H_{22}O$ 206.1671).

Nitrile (25-eq and 25-ax). To a solution of **9** (195 mg, 0.943 mmol) in DME (4.7 mL) were added EtOH (0.155 mL, 2.64 mmol) and *p*-toluenesulfonylmethyl isocyanide (TosMIC) (331 mg, 1.70 mmol). After *t*-BuOK (359 mg, 3.21 mmol) was slowly added at 5−10 °C to the solution, the mixture was warmed to room temperature and stirred for 1 h. The mixture was quenched with H_2O, neutralized with 1 N HCl to pH 7, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to afford **25** (170 mg, 0.784 mmol, 83%) as a colorless oil in a 1:1 mixture of two diastereomers. A part of the mixture was further separated by HPLC (Mightysil Si-60, 4.6 × 250 mm, EtOAc/hexane, 2:98, flow rate 1.0 mL/min). **25**-eq: $[\alpha]^{23}_D$ = +44.0 (*c* 0.71, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −43.5 (*c* 0.71, $CHCl_3$); IR (neat) 3048, 3006, 2952, 2920, 2860, 2824, 2230, 1729, 1664, 1443, 1383, 1365, 1325, 1289, 1259, 1185, 1167, 1100, 1045, 987, 962, 902, 878, 852, 805, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74, 0.91 (each 3H, d, *J* = 7.0 Hz), 0.98−1.13 (2H, m), 1.29−1.44 (2H, m), 1.51−1.82 (3H, m), 1.67 (3H, s), 1.89−2.30 (6H, m), 5.49 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0, 21.3, 23.7, 23.8, 26.0, 28.4, 30.1, 30.3, 35.0, 42.5, 42.7, 45.5, 120.7, 122.1, 135.3; EI-MS *m*/*z* 217 (M^+); HR EI-MS *m*/*z* 217.1830 (M^+, calcd for $C_{15}H_{23}N$ 217.1831). **25**-ax: $[\alpha]^{23}_D$ = −52.4 (*c* 0.80, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +56.7 (*c* 0.61, $CHCl_3$); IR (neat) 3048, 3006, 2952, 2922, 2864, 2228, 1734, 1661, 1447, 1383, 1368, 1285, 1256, 1187, 1139, 1102, 1047, 951, 875, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ0.82, 0.92 (each 3H, d, *J* = 7.1 Hz), 1.03 (1H, dt, *J* = 2.9, 11.4 Hz), 1.32−1.50 (2H, m), 1.52−1.83 (4H, m), 1.67 (3H, s), 1.90−2.27 (5H, m), 2.83 (1H, brs), 5.53 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3, 21.1, 21.5, 23.9, 26.2, 28.58, 28.64, 29.1, 30.2, 34.0,

39.1, 41.0, 46.4, 120.6, 121.1, 134.6; EI-MS m/z 217 (M^+); HR EI-MS m/z 217.1833 (M^+, calcd for $C_{15}H_{23}N$ 217.1831).

Carboxylic Acid (28). To a solution of **25** (80.0 mg, 0.368 mmol) in Et_2O (1.5 mL) was slowly added DIBALH (0.743 mL, 0.736 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 15 min, quenched with 1 N HCl, and stirred for 30 min. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde **26** was employed directly in the next reaction.

To a solution of **26** in toluene (5.3 mL) and CH_2Cl_2 (5.3 mL) was added *t*-BuOK (288 mg, 2.57 mmol) at 0 °C under Ar atmosphere. The mixture was warmed to room temperature and stirred for 10 min. After the mixture was cooled to 0 °C, MeI (0.688 mL, 11.0 mmol) was slowly added. The mixture was warmed to room temperature and stirred for 15 h. The mixture was diluted with H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde **27** was employed directly in the next reaction.

To a solution of **27** in *t*-BuOH (4.9 mL) and H_2O (2.6 mL) were added NaH_2PO_4 (221 mg, 1.84 mmol) and 2-methyl-2-butene (0.526 mL, 4.97 mmol). After 30 min, $NaClO_2$ (208 mg, 1.84 mmol) was slowly added. The mixture was stirred for 1 h at room temperature, diluted with saturated aqueous NaCl, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 10:90) to afford **28** (74.6 mg, 0.298 mmol, 81% in 3 steps) as white crystals: mp 66−69 °C; $[\alpha]^{23}_D$ = −15.0 (*c* 0.77, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +15.7 (*c* 0.95, $CHCl_3$); IR (KBr) 2950, 2928, 2910, 2864, 1695, 1464, 1454, 1405, 1384, 1317, 1266, 1229, 1190, 1145, 1044, 934, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.77, 0.90 (each 3H, d, J = 6.8 Hz), 0.92−1.77 (7H, m), 1.26 (3H, s), 1.67 (3H, s), 1.83−2.07 (3H, m), 2.07−2.22 (2H, m), 5.51 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 21.4, 24.0, 24.2, 26.2, 26.3, 31.5, 38.3, 38.6, 45.3, 47.2, 49.0, 122.8, 134.4, 182.7; EI-MS m/z 250 (M^+); HR EI-MS m/z 250.1927 (M^+, calcd for $C_{16}H_{26}O_2$ 250.1933).

Formamide (29). To a solution of **28** (32.3 mg, 0.129 mmol) in toluene (1.8 mL) were added diphenylphosphorylazide (DPPA) (33.3 μL, 0.154 mmol) and Et_3N (21.6 μL, 0.154 mmol) at room temperature under Ar atmosphere. After 30 min, the mixture was warmed to 100 °C, stirred for 1 h, and concentrated *in vacuo*. The crude isocyanate was employed directly in the next reaction.

To a solution of the isocyanate in EtOH (2.6 mL) was added $NaBH_4$ (29.3 mg, 0.774 mmol) at 0 °C under Ar atmosphere. The mixture was warmed to room temperature, stirred for 3 h, diluted with H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 30:70) to give **29** (27.4 mg, 0.110 mmol, 85% in 2 steps) as white crystals: mp 99−102 °C; $[\alpha]^{23}_D$ = −47.5 (*c* 0.60, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +48.3 (*c* 0.77, $CHCl_3$); IR (KBr) 3326, 3266, 2942, 2928, 2856, 2743, 1670, 1652, 1525, 1506, 1445, 1386, 1364, 1304, 1245, 1228, 1152, 1045, 883, 805, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78, 0.92 (each 3H, d, J = 6.6 Hz), 1.05 (1H, m), 1.11−1.32 (2H, m), 1.40, 1.49 (total 3H, each s), 1.53 (1H, m), 1.67 (3H, s), 1.73−2.08 (6H, m), 2.18 (1H, m), 2.74 (1H, dd, J = 2.9, 10.4 Hz), 5.50, 5.52 (total 1H, each s), 5.11, 5.77 (total 1H, each s), 8.14, 8.23 (total 1H, each d, J = 1.7, 12.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3, 19.4, 19.8, 21.4, 21.5, 22.9, 23.0, 23.8, 25.6, 26.2, 27.9, 29.8, 30.8, 31.1, 36.0, 37.7, 37.9, 40.4, 46.6, 46.7, 48.6, 49.1, 53.7, 55.5, 121.6, 122.0, 134.5, 134.6, 160.5, 163.1; FAB-MS m/z 250 (M^+ + H); HR FAB-MS m/z 250.2168 (M^+ + H, calcd for $C_{16}H_{28}NO$ 250.2171).

Isonitrile (30). To a solution of **29** (21.0 mg, 84.2 μmol) in CH_2Cl_2 (8.4 mL) were added dropwise $POCl_3$ (23.1 μL, 0.253 mmol) and Et_3N (0.106 mL, 0.758 mmol) at 0 °C under Ar atmosphere. After 30 min, the mixture was warmed to room temperature, stirred for 1 h, quenched with cooled water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:99) to yield **30** (18.1 mg, 78.3 μmol, 93%) as a colorless oil: $[\alpha]^{23}_D$ = −22.3 (*c* 0.56, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +23.7 (*c* 0.63, $CHCl_3$); IR (neat) 724, 794, 871, 886, 941, 1010, 1046, 1069, 1100, 1127, 1150, 1191, 1210, 1251, 1270, 1300, 1367, 1382, 1448, 1461, 1663, 2122, 2866, 2950, 3070 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82, 0.92 (each 3H, d, J = 6.8 Hz), 0.96−1.14 (2H, m), 1.33−1.83 (5H, m), 1.41 (3H, s), 1.62 (3H, s), 1.88−2.10 (4H, m), 2.18 (1H, m), 5.51 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3, 20.1, 21.5, 23.2, 23.8, 26.2, 27.8, 30.5, 38.0, 39.8, 46.2, 47.3, 60.5 (as a triplet), 121.6, 134.3, 154.2 (as a triplet); EI-MS m/z 231 (M^+), 216 ($M^+ - CH_3$); HR EI-MS m/z 231.1972 (M^+, calcd for $C_{16}H_{25}N$ 231.1987).

Sulfide (47)[27]**.** After a solution of NaI (3.61 g, 24.1 mmol) and NaH (55%, 2.10 g, 48.2 mmol) in THF (27 mL) was cooled to 0 °C under Ar atmosphere, (4-methoxyphenyl)methanol (3.00 mL, 24.1 mmol) was added dropwise to the solution. The mixture was warmed to room temperature and stirred for 1 h. Chloromethyl methyl sulfide (1.99 mL, 24.1 mmol) was added at 0 °C. The mixture was stirred for 12 h at room temperature, quenched with H_2O, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 5:95) provided **47** (4.54 g, 22.9 mmol, 95%) as a colorless oil: IR (neat) 2990, 2950, 2914, 2830, 1610, 1582, 1510, 1461, 1439, 1379, 1299, 1246, 1172, 1108, 1059, 1035, 957, 909, 818, 760, 729, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.18 (3H, s), 3.80 (3H, s), 4.55 (2H, s), 4.66 (2H, s), 6.88, 7.28 (each 2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 55.3, 69.0, 74.0, 113.8, 129.4, 129.7, 159.2; EI-MS m/z 198 (M^+); HR EI-MS m/z 198.0713 (M^+, calcd for $C_{10}H_{14}O_2S$ 198.0715).

Chloride[27]**.** To a solution of **47** (4.64 g, 23.4 mmol) in CH_2Cl_2 (59 mL) was dropwise added SO_2Cl_2 (2.41 mL, 25.7 mmol) at −78 °C under Ar atomosphere. The resulting solution of crude **31** was directly used to the following step.

PMB Ether (33). DIBALH (0.99 M in toluene, 0.901 mL, 0.892 mmol) was added to a solution of **25** (96.9 mg, 0.446 mol) in Et_2O (1.5 mL) at 0 °C under Ar atmosphere. The mixture was stirred for 15 min, quenched with 1 N HCl, stirred for another 30 min, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde **26** was immediately employed in the next reaction.

A solution of **26** in toluene (6.4 mL) and CH_2Cl_2 (6.4 mL) was cooled to 0 °C under Ar atmosphere. After *t*-BuOK (350 mg, 3.12 mmol) was added to the solution, the mixture was stirred for 10 min at room temperature. A solution of **31** (1.00 g, 5.35 mmol) in toluene (6.4 mL) and CH_2Cl_2 (6.4 mL) was added dropwise at 0 °C. The mixture was gradually warmed to room temperature over 2 h, quenched with H_2O, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the resulting residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to give the PMB ether **32**.

To a solution of the PMB ether **32** in diethylene glycol (18 mL) were added KOH (450 mg, 8.03 mmol) and $NH_2NH_2 \cdot H_2O$ (0.546 mL, 11.2 mmol) at room temperature under Ar atmosphere. The mixture was heated at 180 °C for 2 h, diluted with EtOAc, washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 1:99) provided **33** (67.0 mg, 0.187 mmol, 42% in 3 steps) as a colorless oil: $[\alpha]^{23}_D$ = +7.9 (*c* 1.24, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −7.9 (*c* 1.27, $CHCl_3$); IR (neat) 3060, 2950, 2924, 2850, 2720, 1728, 1611, 1582, 1510, 1461, 1453, 1364, 1299, 1245, 1206, 1170, 1091, 1038, 884, 875, 821, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75 (3H, s), 0.78, 0.90 (each 3H, d, J = 6.8 Hz), 0.97 (1H, m), 1.07−1.70 (6H, m), 1.65 (3H, s), 1.78−2.00 (4H, m), 2.14 (1H, m), 3.07, 3.26 (each 1H, d, J = 8.8 Hz), 3.81 (3H, s), 4.38, 4.46

(each 1H, d, J = 12.0 Hz), 5.53 (1H, s), 6.87, 7.24 (each 2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 16.2, 19.8, 21.6, 23.7, 24.0, 26.3, 31.3, 36.1, 37.0, 37.5, 43.2, 46.9, 55.3, 72.8, 78.5, 113.5, 123.1, 128.7, 131.1, 134.2, 158.7; EI-MS m/z 356 (M^+); HR EI-MS m/z 356.2717 (M^+, calcd for $C_{24}H_{36}O_2$ 356.2715).

Carboxylic Acid (34). To a solution of **33** (7.10 mg, 19.9 μmol) in CH_2Cl_2 (2.0 mL) were added H_2O (0.10 mL) and DDQ (6.80 mg, 29.9 μmol) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude alcohol was immediately employed in the next step.

DMP (21.0 mg, 49.8 μmol) was added to a solution of the alcohol in CH_2Cl_2 (2.0 mL) at room temperature under Ar atmosphere. The mixture was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. After the two layers were separated, and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldehyde was directly used in the following reaction.

To a solution of the aldehyde in *t*-BuOH (0.27 mL) and H_2O (0.13 mL) were added NaH_2PO_4 (11.9 mg, 99.5 μmol) and 2-methyl-2-butene (28.5 μL, 0.269 mmol) at room temperature. After 30 min of stirring, $NaClO_2$ (11.2 mg, 99.5 μmol) was slowly added for 30 min. The mixture was diluted with saturated aqueous NaCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 10:90) to afford **34** (4.00 mg, 16.0 μmol, 81% in 3 steps) as a colorless oil: $[\alpha]^{23}_D$ = +36.2 (c 0.92, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −39.4 (c 0.91, $CHCl_3$); IR (neat) 2950, 2924, 2910, 2864, 1695, 1463, 1451, 1404, 1383, 1286, 1257, 1239, 1202, 1190, 1120, 1070, 1045, 949, 906, 871, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79, 0.92 (each 3H, d, J = 6.8 Hz), 1.04−1.44 (4H, m), 1.12 (3H, s), 1.47−2.11 (7H, m), 1.66 (3H, s), 2.18 (1H, m), 5.52 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 15.3, 19.6, 21.5, 24.0, 26.0, 26.2, 31.1, 36.8, 37.1, 44.1, 46.4, 46.6, 122.1, 134.6, 184.0; EI-MS m/z 250 (M^+); HR EI-MS m/z 250.1935 (M^+, calcd for $C_{16}H_{26}O_2$ 250.1933).

Formamide (10-Formamido-4-cadinene) (35). To a solution of **34** (8.70 mg, 34.8 μmol) in toluene (0.99 mL) were added diphenylphosphoryl azide (DPPA) (9.00 μL, 41.7 μmol) and Et_3N (5.80 μL, 41.7 μmol) at room temperature under Ar atmosphere. The mixture was stirred for 30 min, heated to 100 °C, stirred for 1 h, filtered, and concentrated *in vacuo*. The crude isocyanate was used immediately in the next reaction.

After a solution of the isocyanate in EtOH (0.70 mL) under Ar atmosphere was cooled to 0 °C, $NaBH_4$ (3.90 mg, 0.104 mmol) was added to the solution. The reaction was stirred for 3 h at room temperature, diluted with H_2O, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 30:70) to afford **35** (7.60 mg, 30.4 μmol, 88% in 2 steps) as a colorless oil: $[\alpha]^{23}_D$ = +28.4 (c 0.66, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −22.3 (c 0.71, $CHCl_3$); IR (neat) 3278, 3050, 2950, 2918, 2848, 1675, 1664, 1535, 1463, 1451, 1384, 1313, 1259, 1192, 1152, 1127, 1071, 1046, 876 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77, 0.78, 0.91, 0.92 (total 6H, each d, J = 6.8 Hz), 0.99−1.38 (3H, m), 1.22, 1.26 (total 3H, each s), 1.49−1.67 (2H, m), 1.67 (3H, s), 1.76−2.26 (7H, m), 5.16, 5.74 (total 1H, each brs), 5.49 (1H, s), 8.07, 8.28 (total 1H, each d, J = 12.5 and 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2, 18.9, 19.1, 20.8, 21.6, 23.1, 23.5, 23.8, 26.07, 26.11, 30.96, 31.05, 37.5, 38.6, 38.8, 41.9, 45.8, 46.3, 46.4, 49.1, 55.8, 57.4, 121.8, 122.2, 134.5, 134.8, 160.2, 162.6; FAB-MS m/z 250 (M^+ + H); HR FAB-MS m/z 250.2166 (M^+ + H, calcd for $C_{16}H_{28}NO$ 250.2171).

Isonitrile (10-Isocyano-4-cadinene) (1). After **35** (6.30 mg, 25.3 μmol) was dissolved in CH_2Cl_2 (2.5 mL) and cooled to 0 °C under Ar atmosphere, $POCl_3$ (6.90 μL, 75.8 μmol) and Et_3N (31.7 μL, 0.228 mmol) were added to the solution, and the mixture was stirred for 30 min. The reaction was stirred for 1 h at room temperature, quenched with cooled H_2O, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification over silica gel column chromatography (EtOAc/hexane, 1:99) gave **1** (5.50 mg, 23.8 μmol, 94%) as a colorless oil: $[\alpha]^{23}_D$ = +59.8 (c 0.65, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −58.2 (c 0.68, $CHCl_3$); IR (neat) 3052, 2922, 2864, 2729, 2122, 1733, 1464, 1452, 1381, 1259, 1210, 1170, 1152, 1127, 1080, 1043, 1012, 955, 908, 884, 871, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.76, 0.91 (each 3H, d, J = 6.8 Hz), 1.01−1.19 (2H, m), 1.19−1.41 (2H, m), 1.30 (3H, s), 1.54−1.78 (2H, m), 1.68 (3H, s), 1.83 (1H, m), 1.95−2.22 (5H, m), 5.46 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2, 20.2, 20.4, 21.5, 23.8, 23.9, 26.0, 30.8, 38.0, 40.7, 46.3, 48.1, 60.8 (as a triplet), 121.1, 135.2, 151.8 (as a triplet); EI-MS m/z 231 (M^+), 216 (M^+−CH_3); HR EI-MS m/z 231.1975 (M^+, calcd for $C_{16}H_{25}N$ 231.1987).

Ester (48). To a solution of **20** (1.20 g, 4.72 mmol) in benzene (19 mL) were added imidazole (482 mg, 7.08 mmol), triphenylphosphin (1.86 g, 7.08 mmol), and I_2 (3.35 g, 13.2 mmol) at 0 °C under Ar atmosphere. The mixture was warmed to room temperature, stirred for 1 h, quenched with saturated aqueous Na_2SO_3, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to afford **48** (1.63 g, 4.48 mmol, 95%) as a colorless oil: $[\alpha]^{23}_D$ = −65.2 (c 2.77, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +66.3 (c 2.90, $CHCl_3$); IR (neat) 3034, 2950, 2868, 2824, 1732, 1461, 1432, 1368, 1209, 1259, 1235, 1189, 1160, 1093, 1056, 1032, 942, 906, 880, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91, 0.93 (each 3H, d, J = 6.8 Hz), 1.66 (3H, s), 1.66−1.84 (5H, m), 1.87−2.08 (3H, m), 2.32 (1H, dt, J = 2.9, 10.0 Hz), 2.68 (1H, m), 3.15 (2H, m), 3.68 (3H, s), 5.18 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.8, 20.3, 21.2, 23.8, 26.7, 29.3, 30.1, 34.1, 38.4, 44.8, 48.6, 51.6, 121.2, 134.9, 176.3; EI-MS m/z 364 (M^+), 237 (M^+−I); HR EI-MS m/z 364.0898 (M^+, calcd for $C_{15}H_{25}IO_2$ 364.0899).

Alcohol (49). To a solution of **48** (1.46 g, 4.01 mmol) in CH_2Cl_2 (13 mL) was added dropwise DIBALH (0.99 M in toluene) (8.10 mL, 8.02 mmol) at 0 °C under Ar atmosphere. After 1 h of stirring, MeOH (1.60 mL) and a trace of H_2O were added dropwise at 0 °C. The mixture was filtered with a Celite pad, washed with CH_2Cl_2, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to afford **49** (1.33 g, 3.97 mmol, 99%) as a colorless oil; $[\alpha]^{23}_D$ = −38.8 (c 3.00, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = +38.2 (c 3.20, $CHCl_3$); IR (neat) 3338, 3024, 2950, 2918, 2866, 2697, 1463, 1440, 1432, 1383, 1365, 1232, 1171, 1051, 1026, 935, 846, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91, 0.92 (each 3H, d, J = 6.8 Hz), 1.21−1.35 (2H, m), 1.35−1.65 (3H, m), 1.66 (3H, s), 1.69−2.01 (5H, m), 2.07 (1H, m), 3.10−3.26 (2H, m), 3.48 (1H, ddd, J = 1.2, 6.6, 10.5 Hz), 3.71 (1H, dd, J = 3.7, 10.5 Hz), 5.19 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.1, 20.4, 20.6, 24.0, 25.0, 28.7, 30.1, 33.9, 37.1, 39.3, 47.7, 65.7, 121.9, 134.2; EI-MS m/z 336 (M^+); HR EI-MS m/z 336.0950 (M^+, calcd for $C_{14}H_{25}IO$ 336.0950).

Alcohol (37-eq and 37-ax). To a solution of **49** (930 mg, 2.77 mmol) in CH_2Cl_2 (28 mL) was added DMP (2.34 g, 5.54 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde **36** was employed directly in the next reaction.

A solution of **36** in THF (28 mL) was degassed by freeze treatment, and a 0.100 M THF-HMPA solution of SmI_2 (83.1 mL, 8.31 mmol) was added at room temperature under Ar atmosphere. The mixture was

stirred for 30 min, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to afford **37**-eq (368 mg, 1.76 mmol, 64% in 2 steps) and **37**-ax (158 mg, 0.756 mmol, 27% in 2 steps) as colorless oils: **37**-eq: $[\alpha]^{23}_D$ = +24.8 (*c* 2.85, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −23.4 (*c* 2.77, $CHCl_3$); IR (neat) 3328, 2946, 2922, 2864, 2714, 1705, 1451, 1383, 1361, 1293, 1238, 1179, 1153, 1110, 1055, 1031, 992, 978, 919, 892, 866, 839, 816, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90, 0.93 (each 3H, d, *J* = 6.6 Hz), 1.16 (1H, m), 1.23−1.55 (5H, m), 1.63 (3H, s), 1.75−2.10 (6H, m), 2.21 (1H, dd, *J* = 2.7, 10.0 Hz), 3.27 (1H, dt, *J* = 4.9, 10.0 Hz), 5.27 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 23.3, 23.5, 26.1, 26.5, 27.9, 29.8, 31.1, 40.9, 44.28, 44.33, 75.4, 126.9, 130.7; EI-MS *m*/*z* 208 (M^+), 190 ($M^+ - H_2O$); HR EI-MS *m*/*z* 208.1827 (M^+, calcd for $C_{14}H_{24}O$ 208.1827). **37**-ax: $[\alpha]^{23}_D$ = +47.8 (*c* 1.54, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −47.3 (*c* 1.60, $CHCl_3$); IR (neat) 3408, 2948, 2912, 2864, 2714, 1711, 1662, 1452, 1383, 1365, 1305, 1259, 1234, 1179, 1132, 1100, 1053, 1000, 979, 960, 924, 890, 848, 814, 766, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89, 0.92 (each 3H, d, *J* = 6.6 Hz), 0.99−1.77 (8H, m), 1.61 (3H, s), 1.77−1.96 (3H, m), 2.02 (1H, m), 2.55 (1H, m), 3.86 (1H, s), 5.27 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 23.6, 23.7, 24.0, 25.8, 26.7, 29.3, 30.3, 37.7, 38.4, 44.9, 70.5, 128.1, 130.3; EI-MS *m*/*z* 208 (M^+) 190 ($M^+ - H_2O$); HR EI-MS *m*/*z* 208.1825 (M^+, calcd for $C_{14}H_{24}O$ 208.1827).

Ketone (38). To a solution of **37** (520 mg, 2.50 mmol) in CH_2Cl_2 (25 mL) was added DMP (2.63 g, 6.24 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 3:97) provided **38** (450 mg, 2.18 mmol, 87%) as a colorless oil: $[\alpha]^{23}_D$ = +155 (*c* 2.03, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −158 (*c* 2.00, $CHCl_3$); IR (neat) 3012, 2950, 2918, 2864, 2826, 2716, 1709, 1451, 1431, 1384, 1360, 1335, 1318, 1291, 1232, 1213, 1152, 1174, 1110, 1037, 1012, 935, 881, 854, 830, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00, 1.02 (each 3H, d, *J* = 6.8 Hz), 1.42 (1H, m), 1.61 (1H, m), 1.64 (3H, s), 1.72 (1H, m), 1.88−2.18 (5H, m), 2.29 (1H, m), 2.36−2.51 (3H, m), 5.34 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 22.4, 23.2, 23.5, 26.3, 28.8, 29.4, 37.9, 43.8, 45.9, 46.4, 125.8, 132.0, 212.4; EI-MS *m*/*z* 206 (M^+); HR EI-MS *m*/*z* 206.1668 (M^+, calcd for $C_{14}H_{22}O$ 206.1671).

Nitrile (39). To a solution of **38** (195 mg, 0.943 mmol) in DME (4.7 mL) were added EtOH (0.155 mL, 2.64 mmol) and *p*-toluenesulfonylmethyl isocyanide (TosMIC) (331 mg, 1.70 mmol). After the mixture was cooled to 5−10 °C, *t*-BuOK (359 mg, 3.21 mmol) was slowly added. The mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with H_2O, neutralized with 1 N HCl to pH 7, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to give **39** (166 mg, 0.764 mmol, 81%) as a colorless oil in a 1:1 mixture of two diastereomers: IR (neat) 2956, 2928, 2864, 2832, 2724, 2230, 1706, 1451, 1384, 1363, 1321, 1302, 1263, 1180, 1161, 1122, 1101, 1046, 1015, 987, 919, 891, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89, 0.90, 0.927, 0.931 (each 1.5H, d, *J* = 6.6 Hz), 1.04 (0.5H, m), 1.14−2.26 (11.5H, m), 1.63 (3H, s), 2.48, 2.88 (each 0.5H, m), 5.22, 5.25 (each 0.5H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 22.7, 23.3, 23.4, 23.51, 23.54, 24.8, 25.7, 26.2, 26.3, 28.6, 28.8, 28.9, 29.7, 34.2, 34.3, 35.6, 36.1, 42.1, 44.0, 44.1, 45.9, 120.9, 122.1, 126.3, 126.6, 130.9, 131.3; EI-MS *m*/*z* 217 (M^+); HR EI-MS *m*/*z* 217.1834 (M^+, calcd for $C_{15}H_{23}N$ 217.1831).

Carboxylic Acid (41). To a solution of **39** (340 mg, 1.56 mmol) in Et_2O (5.2 mL) was added DIBALH (3.16 mL, 3.13 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 15 min, quenched with 1 N HCl, and stirred for 30 min. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde was employed directly in the next reaction.

To a solution of aldehyde in toluene (22 mL) and CH_2Cl_2 (22 mL) was added *t*-BuOK (1.22 g, 10.9 mmol) at 0 °C under Ar atmosphere. The mixture was warmed to room temperature and stirred for 10 min. After the reaction was cooled to 0 °C, MeI (2.91 mL, 46.8 mmol) was slowly added. The mixture was warmed to room temperature, stirred for 15 h, diluted with H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture of the crude aldehyde **40** was employed directly in the next reaction.

To a solution of **40** in *t*-BuOH (21 mL) and H_2O (10 mL) were added NaH_2PO_4 (0.936 mg, 7.80 mmol) and 2-methyl-2-butene (2.23 mL, 21.7 mmol). After 30 min of stirring, $NaClO_2$ (0.882 mg, 7.80 mmol) was slowly added. The mixture was stirred for 1 h, diluted with saturated aqueous NaCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 10:90) yielded **41** (316 mg, 1.26 mmol, 86% in 3 steps) as white crystals: mp 104−107 °C; $[\alpha]^{23}_D$ = +79.0 (*c* 1.11, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −76.3 (*c* 1.00, $CHCl_3$); IR (KBr) 3500, 2963, 2930, 2910, 2864, 2820, 1696, 1488, 1464, 1446, 1404, 1375, 1320, 1288, 1270, 1212, 1150, 1067, 945, 903, 889, 823, 786, 670, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88, 0.92 (each 3H, d, *J* = 6.6 Hz), 0.92−1.66 (5H, m), 1.25 (3H, s), 1.61 (3H, s), 1.66−2.02 (6H, m), 2.66 (1H, m), 5.22 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 23.6, 23.8, 24.5, 26.0, 26.2, 26.3, 31.0, 33.6, 41.2, 42.2, 44.5, 45.6, 127.7, 130.7, 182.9; EI-MS *m*/*z* 250 (M^+); HR EI-MS *m*/*z* 250.1937 (M^+, calcd for $C_{16}H_{26}O_2$ 250.1933).

Formamide (42). To a solution of **41** (230 mg, 0.919 mmol) in toluene (26 mL) were added diphenylphosphorylazide (0.237 mL, 1.10 mmol) and Et_3N (0.154 mL, 1.10 mmol) at room temperature under Ar atmosphere. After stirring for 30 min, the mixture was warmed to 100 °C, stirred for 1 h, filtered, and concentrated *in vacuo*. The crude isocyanate was employed directly in the next reaction.

To a solution of isocyanate in EtOH (18 mL) was added $NaBH_4$ (313 mg, 8.27 mmol) at 0 °C under Ar atmosphere. The mixture was warmed to room temperature and stirred for 3 h. The mixture was diluted with H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 30:70) to afford **42** (195 mg, 0.781 mmol, 85% in 2 steps) as a colorless oil: $[\alpha]^{23}_D$ = +98.0 (*c* 0.97, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −99.9 (*c* 0.99, $CHCl_3$); IR (neat) 3306, 3044, 2940, 2926, 2864, 2756, 1666, 1528, 1444, 1386, 1300, 1258, 1226, 1191, 1161, 1101, 1065, 1033, 955, 931, 911, 858, 814, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90, 0.927, 0.933 (total 6H, each d, *J* = 6.6 Hz), 1.21 (1H, m), 1.31−2.07 (9H, m), 1.40, 1.50 (total 3H, each s), 1.62 (3H, s), 2.30 (1H, dt, *J* = 2.5, 11.6 Hz), 2.47 (1H, td, *J* = 3.3, 14.1 Hz), 5.22, 5.24 (total 1H, each s), 5.23, 5.88 (total 1H, each brs), 8.13, 8.23 (total 1H, each d, *J* = 1.7, 12.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.69, 22.73, 22.8, 23.3, 23.4, 23.6, 23.7, 24.7, 25.3, 25.5, 26.0, 27.8, 29.7, 30.2, 30.4, 31.4, 36.0, 40.5, 40.7, 42.2, 42.9, 44.3, 44.6, 54.2, 56.0, 127.1, 127.4, 130.8, 130.9, 160.7, 163.3; FAB-MS *m*/*z* 272 (M^+ + Na); HR FAB-MS *m*/*z* 272.1986 (M^+ + Na, calcd for $C_{16}H_{27}NONa$ 272.1990).

Isonitrile (43). To a solution of **42** (21.0 mg, 84.2 μmol) in CH_2Cl_2 (8.4 mL) were added dropwise $POCl_3$ (23.1 μL, 0.253 mmol) and Et_3N (0.106 mL, 0.758 mmol) at 0 °C under Ar atmosphere. After stirring for 30 min, the mixture was warmed to room temperature, stirred for 1 h, quenched with cooled water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 1:99) provided **43** (18.1 mg, 78.3 μmol, 93%) as a colorless oil: $[\alpha]^{23}_D$ = +108 (*c* 0.80, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −107 (*c* 0.92, $CHCl_3$); IR (neat) 3050, 2940, 2866, 2828, 2721, 2122, 1640, 1452, 1381, 1363, 1302, 1273, 1250, 1232,

1191, 1152, 1127, 1105, 1067, 1005, 956, 930, 893, 864, 841, 815, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89, 0.94 (each 3H, d, J = 6.8 Hz), 1.41−1.63 (4H, m), 1.43 (3H, s), 1.68−1.84 (4H, m), 1.63 (3H, s), 1.88−2.09 (3H, m), 2.50 (1H, m), 5.24 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8, 23.2, 23.4, 23.6, 25.4, 26.3, 27.7, 30.0, 35.8, 40.7, 41.0, 44.2, 61.5 (as a triplet), 126.9, 130.3, 153.8 (as a triplet); EI-MS m/z 231 (M^+), 216 ($M^+ - CH_3$); HR EI-MS m/z 231.1987 (M^+, calcd for $C_{16}H_{25}N$ 231.1987).

Alcohol (44). To a solution of crude aldehyde **40** (theoretical 0.106 mmol) in MeOH (0.21 mL) was added $NaBH_4$ (12.0 mg, 0.318 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 30 min at 0 °C, quenched with saturated aqueous NH_4Cl, concentrated *in vacuo*, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to give **44** (20.5 mg, 86.9 μmol, 82% in 3 steps) as a colorless oil: $[\alpha]^{23}_D$ = +64.1 (c 0.29, $CHCl_3$), enantiomer $[\alpha]^{23}_D$ = −66.9 (c 0.30, $CHCl_3$); IR (neat) 3364, 2948, 2922, 2862, 2727, 1708, 1467, 1452, 1383, 1314, 1292, 1188, 1157, 1123, 1067, 1030, 981, 939, 921, 889, 843, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88, 0.92 (each 3H, d, J = 6.7 Hz), 0.99 (3H, s), 1.10−1.28 (3H, m), 1.33−1.59 (4H, m), 1.60 (3H, s), 1.66 (1H, m), 1.79−2.00 (4H, m), 2.37 (1H, m), 3.46, 3.75 (each 1H, d, J = 10.9 Hz), 5.22 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 23.5, 23.78, 23.81, 25.1, 25.5, 26.2, 30.2, 31.4, 37.3, 41.1, 42.4, 45.1, 64.8, 128.1, 130.7; EI-MS m/z 236 (M^+); HR EI-MS m/z 236.2140 (M^+, calcd for $C_{16}H_{28}O$ 236.2140).

Antifouling Assay[1,3a]. Adult barnacles, *Balanus amphitrite*, attached to bamboo poles were procured from oyster farms in Lake Hamana, Shizuoka, and maintained in an aquarium at 20 °C by feeding on *Artemia salina* nauplii. Broods released I−II stage nauplii upon immersion in seawater after being dried overnight. Nauplii thus obtained were cultured in 80% filtered seawater (filtered seawater diluted to 80% by deionized water) including penicillin G (20 μg/mL, ICN Biochemical) and streptomycin sulfate (30 μg/mL, Wako Pure Chemical Industries, Ltd.) at 25 °C by feeding with the diatom *Chaetoceros gracillis* (about 40 × 10^4 cells/mL). Larvae reached the cyprid stage in 5 days. The cyprids were collected, then stored at 4 °C until use.

Test samples were dissolved in ethanol. Aliquots of the solution were supplied to wells of 24-well polystyrene tissue culture plates and air-dried. To each well were added 2 mL of 80% filtered seawater and six 1-day-old cyprids. Four wells were used for each concentration. The plates were kept in the dark for 48 h at 25 °C, and the number of larvae that attached, metamorphosed, died, or did not settle were counted under a microscope. Each concentration was repeated 3 times. The antifouling activity of compounds was expressed as an EC_{50} value, which indicated the concentration that reduces the larval settlement to 50% of the control. The EC_{50} values were calculated by a probit analysis.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Okino, T.; Yoshimura, E.; Hirota, H.; Fusetani, N. *Tetrahedron* **1996**, *52*, 9447–9454.

(2) (a) Okino, T.; Yoshimura, E.; Hirota, H.; Fusetani, N. *Tetrahedron Lett.* **1995**, *36*, 8637–8640. (b) Hirota, H.; Tomono, Y.; Fusetani, N. *Tetrahedron* **1996**, *52*, 2359–2368. (c) Okino, T.; Yoshimura, E.; Hirota, H.; Fusetani, N. *J. Nat. Prod.* **1996**, *59*, 1081–1083. (d) Clare, A. S. *Biofouling* **1996**, *9*, 211–229. (e) Garson, M. J.; Simpson, J. S. *Nat. Prod. Rep.* **2004**, *21*, 164–179.

(3) (a) Kitano, Y.; Ito, T.; Suzuki, T.; Nogata, Y.; Shinshima, K.; Yoshimura, E.; Chiba, K.; Tada, M.; Sakaguchi, I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2251–2255. (b) Kitano, Y.; Yokoyama, A.; Nogata, Y.; Shinshima, K.; Yoshimura, E.; Chiba, K.; Tada, M.; Sakaguchi, I. *Biofouling* **2003**, *19*, 187–192. (c) Nogata, Y.; Kitano, Y.; Yoshimura, E.; Shinshima, K.; Sakaguchi, I. *Biofouling* **2004**, *20*, 87–91. (d) Kitano, Y.; Nogata, Y.; Shinshima, K.; Yoshimura, E.; Chiba, K.; Tada, M.; Sakaguchi, I. *Biofouling* **2004**, *20*, 93–100.

(4) Evans, S. M. *Biofouling* **1999**, *14*, 117–129.

(5) Horiguchi, T.; Shiraishi, H.; Shimizu, M.; Yamazaki, S.; Morita, M. *Mar. Pollut. Bull.* **1995**, *31*, 402–405.

(6) (a) Armstrong, E.; Boyd, K. G.; Burgess, J. G. *Biotechnol. Annu. Rev.* **2000**, *6*, 221–241. (b) Negri, A. P.; Smith, D. S.; Webster, N. S.; Heyward, A. J. *Mar. Pollut. Bull.* **2002**, *44*, 111–117.

(7) Nishikawa, K.; Shirokura, Y.; Nakahara, H.; Nogata, Y.; Yoshimura, E.; Umezawa, T.; Okino, T.; Matsuda, F. *Org. Lett.* **2010**, *12*, 904–907.

(8) (a) Vig, O. P.; Chugh, O. P.; Matta, K. L. *Indian J. Chem.* **1970**, *8*, 29–32. (b) Kitahara, T.; Kurata, H.; Matsuoka, T.; Mori, K. *Tetrahedron* **1985**, *41*, 5475–5485.

(9) (a) Vig, O. P.; Trehan, I. R.; Kumar, R. *Indian J. Chem., Sect. B* **1977**, *15B*, 319–321. (b) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992–3993. (c) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1982**, *47*, 337–342. (d) Katayama, M.; Marumo, S. *Tetrahedron Lett.* **1983**, *24*, 1703–1706. (e) Vig, O. P.; Sharma, M. L.; Kiran, S.; Singh, J. *Indian J. Chem., Sect. B* **1983**, *22B*, 746–748. (f) Mori, K.; Waku, M. *Tetrahedron* **1984**, *40*, 305–309. (g) Parker, K. A.; Farmar, J. G. *J. Org. Chem.* **1986**, *51*, 4023–4028. (h) Davidson, B. S.; Plavcan, K. A.; Meinwald, J. *J. Org. Chem.* **1990**, *55*, 3912–3917. (i) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989–8992. (j) Tashiro, T.; Bando, M.; Mori, K. *Synthesis* **2000**, 1852–1862. (k) White, R. D.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1825–1827. (l) Miyaoka, H.; Shida, H.; Yamada, N.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2002**, *43*, 2227–2230. (m) White, R. D.; Keaney, G. F.; Slown, C. D.; Wood, J. L. *Org. Lett.* **2004**, *6*, 1123–1126.

(10) (a) Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Synlett* **1999**, 744–746. (b) Rüeger, H.; Stutz, S.; Spindler, F.; Maibaum, J. *Tetrahedron Lett.* **2000**, *41*, 10085–10089.

(11) Herbert, C. B.; Choi, Y. M.; Narasimhan, S. *Inorg. Chem.* **1981**, *20*, 4454–4456.

(12) (a) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029–4032. (b) Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723–2728. (c) Low, C. M. R. *Synlett* **1991**, 123–124. (d) Probst, M. F.; Modro, A. M.; Modro, T. A. *Can. J. Chem.* **1997**, *75*, 1131–1135. (e) Cramer, C. J.; Harmate, M.; Rashataakhon, P. *J. Org. Chem.* **2001**, *66*, 5641–5644. (f) Wang, Y.; West, F. G. *Synthesis* **2002**, 99–103.

(13) Dureault, A.; Tranchepain, I.; Depezay, J. C. *Synthesis* **1987**, 491–493.

(14) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402.

(15) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem.—Eur. J.* **2005**, *11*, 5509–5522.

(16) (a) Yoshida, K.; Grieco, P. A. *J. Org. Chem.* **1984**, *49*, 5257–5260. (b) Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, *42*, 2847–2853. (c) Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 1975–1978.

(17) The carboxylic acid **11** was converted into **23** via **21** by the following sequence of reactions: (1) esterification of **11** with CH_2N_2, (2) protection of the OH group of **21** with *t*-$BuMe_2SiCl$, (3) protection of the hydroxyester **20** with *t*-$BuMe_2SiCl$ to produce **22**.

(18) As a matter of course, in each case of the hydroxyester **20** and the siloxyester **22**, cleavage of the methyl ester group did not take place when subjecting these substrates to the same neutralization conditions.

(19) (a) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402–7403. (b) Schürer, S. C.; Blechert, S. *Synlett* **1999**, 1879–1882. (c) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543–1546. (d) Halvorsen, G. T.; Roush, W. R. *Org. Lett.* **2007**, *9*, 2243–2246.

(20) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(21) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216–7227. (b) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 2944–2956. (c) Tamiya, H.; Goto, K.; Matsuda, F. *Org. Lett.* **2004**, *6*, 545–549.

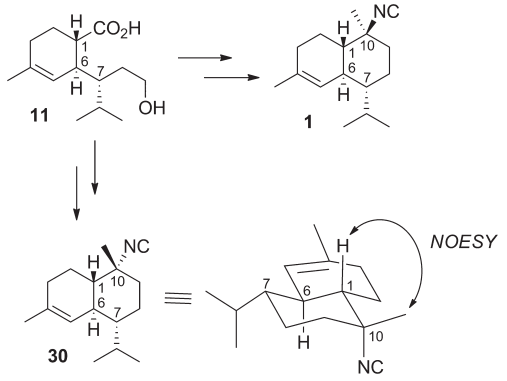
(22) Oldenziel, O. H.; van Leusen, A. M. *Tetrahedron Lett.* **1973**, *14*, 1357–1360.

(23) α-Alkylation of **26** took place in the equatorial orientation in a completely stereoselective manner. For similar equatorial alkylations, see: (a) Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1967**, *32*, 689–696. (b) Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1969**, *34*, 142–152. (c) Vishnumuthy, K.; Cheung, E.; Scheffer, J. R.; Scott, C. *Org. Lett.* **2002**, *4*, 1071–1074.

(24) (a) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574–5576. (b) Kuroda, C.; Kasahara, T.; Akiyama, K.; Amemiya, T.; Kunishima, T.; Kimura, Y. *Tetrahedron* **2002**, *58*, 4493–4504.

(25) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Díaz, C. G. *Synlett* **2000**, 1561–1564.

(26) Natural (+)-10-isocyano-4-cadinene (**1**) was synthesized from the carboxylic acid **11**. Obviously, the absolute configurations in isonitrile **30**, prepared from **11**, are identical to those of **1** at C1, C6, and C7. In the 2D-NOESY spectrum of **30**, an NOE correlation was observed between C1-H and C10-Me. Therefore, the stereochemistry of **30** at C10 was opposite to that of **1**.



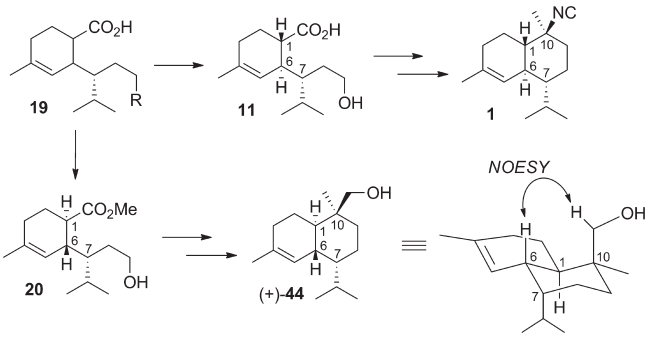
(27) *p*-Methoxybenzyl chloromethyl ether **31** was prepared from *p*-anisylalcohol. (a) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762–763. (b) Gómez, C.; Maciá, B.; Lillo, V. J.; Yus, M. *Tetrahedron* **2006**, *62*, 9832–9839.

(28) (a) Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y. *J. Org. Chem.* **2003**, *68*, 3476–3479. (b) Shimazawa, R.; Suzuki, T.; Dodo, K.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3291–3294.

(29) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.

(30) 10-Formamide-4-cadinene (**35**), a natural product isolated from the sponge *Acanthella cavernosa*, exhibits antifouling activity against the larvae of the barnacle *Balanus amphirite* (EC_{50} 0.50 μg/mL). All data (^1H and ^{13}C NMR, MS) of the synthetic **35** were completely identical with those in the literature. Nogata, Y.; Yoshimura, E.; Shinshima, K.; Kitano, Y.; Sakaguchi, I. *Biofouling* **2003**, *19*, 193–196.

(31) On the basis of the ^1H NMR spectra of the ester **20** and carboxylic acid **11**, it was found that **20** has a *trans* relationship at C1 and C6, opposite to that of **11**. Since **11** led to natural (+)-**1**, the absolute stereochemistry of alcohol **44**, synthesized from **20**, was determined at C1, C6, and C7. In the 2D-NOESY experiment on **44**, an NOE correlation was found between C6-H and C10-CH_2OH. Therefore, the absolute configuration of (+)-**44** was unambiguously established as (1*R*,6*R*,7*R*,10*S*).



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