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Total synthesis of mycestericin A and its 14-epimer

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ABSTRACT

The total synthesis of mycestericin A (**1**) and its 14-epimer **34** is described herein. The Overman rearrangement of an allylic trichloroacetimidate derived from L-tartrate generated a tetra-substituted carbon with nitrogen and subsequent stereoselective transformations afforded the highly functionalized left-half segment, vinyl iodide. Cross-coupling of the vinyl iodide with a chiral organometallic species synthesized from D-tartrate under the Negishi or Suzuki–Miyaura coupling conditions, followed by deprotection, completed the total synthesis of **1**. The 14-epimer of mycestericin A was also synthesized, and a comparison of $[\alpha]_D$ values of peracetyl γ-lactone derivatives of mycestericin A and its 14-epimer as well as degradation studies of **1** and **34** fully confirmed the proposed absolute structure of mycestericin A.

1. Introduction

Mycestericin A (**1**) is a member of mycestericins produced by *Mycelia sterilia* and has been reported to have a potent immunosuppressive activity.[1] A structural elucidation study revealed that the structure of mycestericin A is similar to that of myriocin, a well-known immunosuppressant and serine palmitoyltransferase (SPT) inhibitor, possessing an intriguing α-substituted α-amino acid structure,[2] although mycestericin A has another *E*-olefin between C-12 and C-13 and one distal (*R*)-allylic alcohol function at C-14 (Fig. 1).[1a] The stereochemistry at C-14 was determined using the benzoate CD chirality method of an *N*-acetyl-14-*O*-benzoyl derivative of mycestericin A γ-lactone, which was prepared from natural **1**.[1a] Mycestericin A and its congeners have been reported to have comparable IC_{50} values to that of myriocin in the nanomolar range in the mouse allogeneic mixed lymphocyte reaction.[1] Due to their potent biological properties such as immunosuppressive, antifungal, and SPT inhibitory activities,[3] naturally occurring molecules of this type, including myriocin,[2] sphingofungins,[4] sulfamisterins,[5] and mycestericins,[1] as well as their derivatives are expected to be promising lead compounds for novel therapeutic agents based on their ability to modulate sphingolipid biosynthesis.[6] These interesting biological findings as well as architecturally novel structures have stimulated a number of synthetic efforts, including total syntheses and synthetic approaches to generate natural products possessing α-substituted α-amino acid structures.[7–11]

To date, however, there has been no reported study of the synthesis of mycestericin A, which possesses the most complicated structure in the mycestericin family. In this paper, we present the first report of the total synthesis of mycestericin A and its 14-epimer from tartrates, and the confirmation of the proposed absolute structure of the natural product.[12]

2. Results and discussion

2.1. Retrosynthesis

Our previous success with the total synthesis of myriocin,[9e,10h] sphingofungin E,[10h] and lactacystin,[13] from aldohexoses suggested that the Overman rearrangement[14,15] on chiral scaffolds would effectively generate the tetra-substituted carbon with nitrogen. This idea involves disconnection of the carbon framework in **1** into the highly functionalized left-half segment, vinyl iodide **2** or **3**, and the hydrophobic right-half segment, organometallic species **4**, possessing an (*E*,*R*)-allylic alcohol function (Fig. 2). The well-established Pd-catalyzed coupling reaction of **2** or **3** with **4** was expected to stereoselectively construct the carbon backbone with two *E*-olefins in **1**. We planned to prepare the left-half segment **2** or **3** from homoallyl alcohol **6**, which was thought to arise by the stereoselective allylation of aldehyde **7**. The Overman rearrangement of chiral allylic trichloroacetimidate **8** would install a tetra-substituted carbon with nitrogen in **7**, generating a precursor of α-substituted α-amino acid. For the preparation of imidate **8**, L-tartrate was chosen

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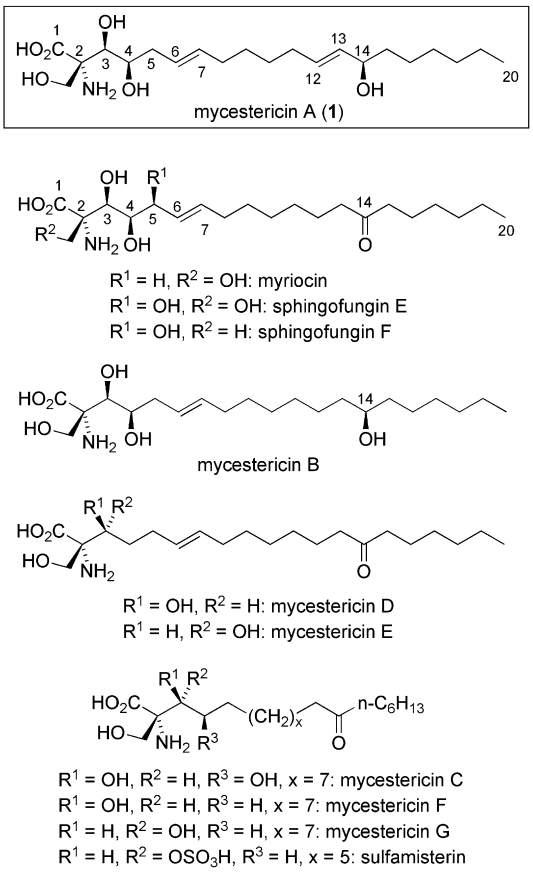


Figure 1. Structures of mycestericin A and related natural products.

as a homochiral starting material. On the other hand, the counterpart **4**, which would be generated from alkyl iodide **5**, was planned to be synthesized from D-tartrate by the *E*-selective carbon-elongation reaction.

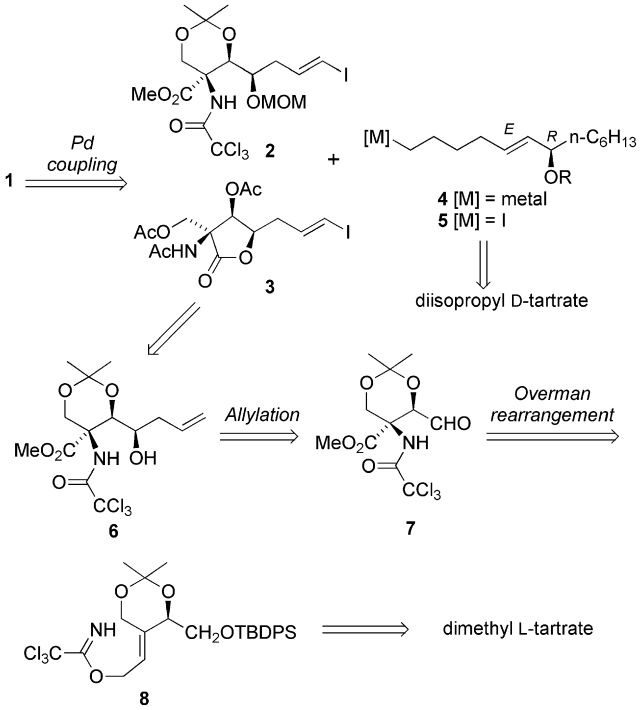
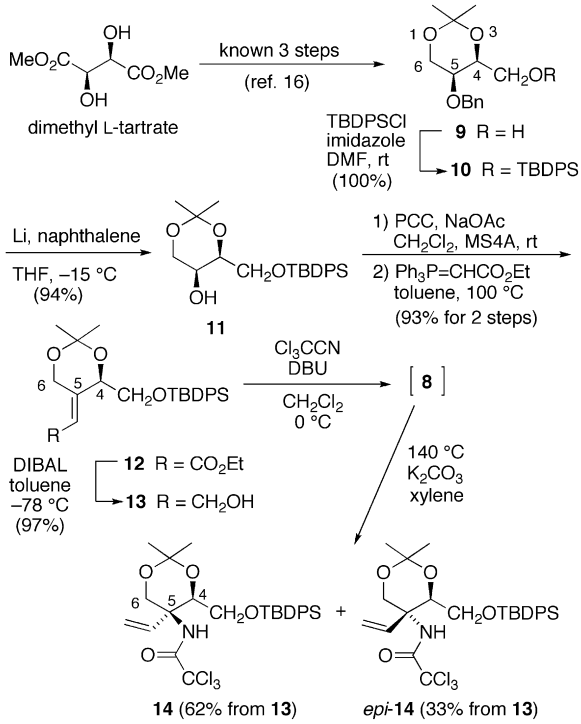


Figure 2. Retrosynthetic route to mycestericin A. MOM=–CH_2OMe, TBDPS=–$SiPh_2(t\text{-}Bu)$.

2.2. Preparation of the highly functionalized left half, vinyl iodide 2

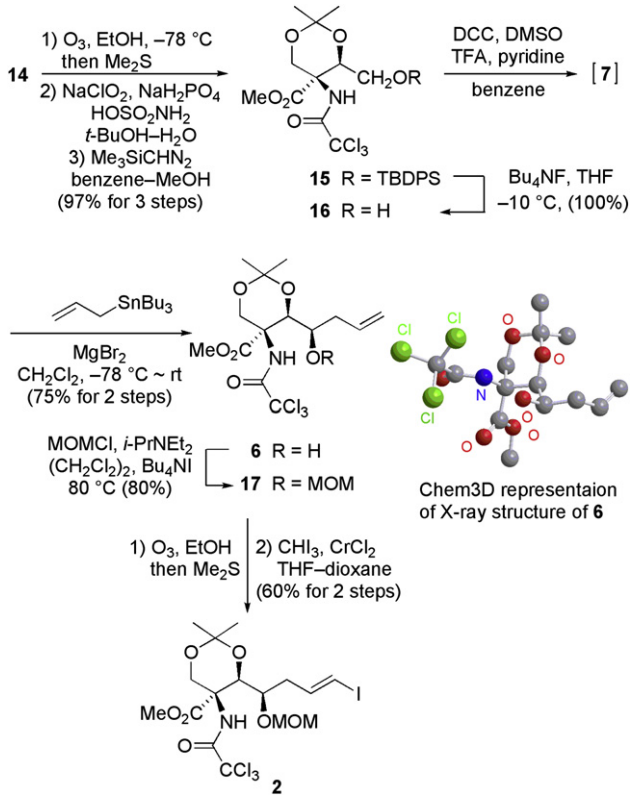
The synthesis of **2** commenced with the known acetonide **9**[16] prepared from dimethyl L-tartrate in a three-step reactions[11e] with a 31% overall yield (Scheme 1). After protection of the primary hydroxy group in **9**, the *O*-benzyl group in **10** was removed to give **11** with a 94% yield from **9**. PCC oxidation of **11**, followed by the Wittig reaction generated **12** as the single isomer (93% for two steps). The *E*-geometry of **12** was confirmed by the observed NOE between a vinyl proton and H-4. The reduction of **12** with DIBAL generated allyl alcohol **13** with a yield of 97%. The treatment of **13** with trichloroacetonitrile and DBU produced trichloroacetimidate **8**, which, without purification, was heated in xylene in the presence of K_2CO_3[17] in a sealed tube at 140 °C for 48 h. Due to Overman rearrangement, this reaction provided **14**[18] and its epimer, *epi*-**14**, with isolated yields of 62% and 33%, respectively. Although the observed stereoselectivity in the Overman rearrangement of **8** was moderate (**14**:*epi*-**14**=1.9:1), the relatively short-step synthesis of **14** from **9** with acceptable overall yields led us to employ this approach for the total synthesis. At this stage, the structure of **14** could not be fully determined but was later confirmed by X-ray analysis of the more advanced compound **6** (vide infra).



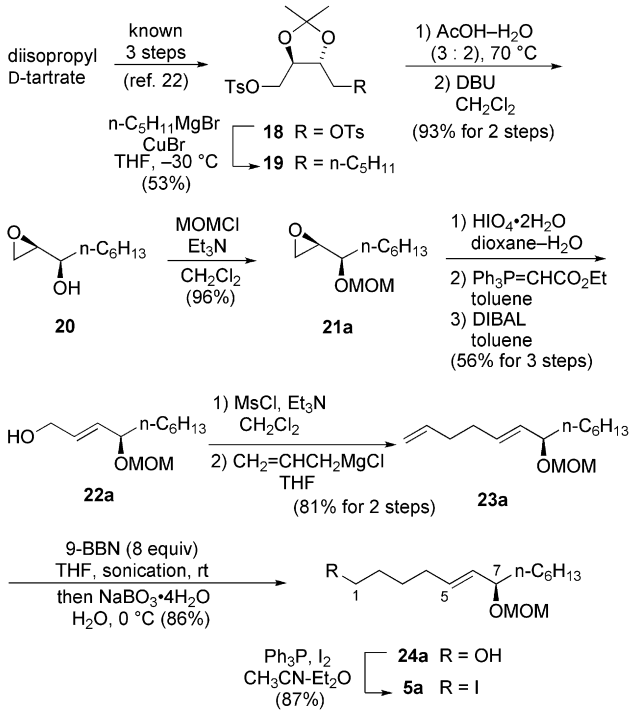
Scheme 1. Bn=–CH_2Ph, PCC=pyridinium chlorochromate, MS4A=molecular sieves 4 Å, DIBAL=$[(CH_3)_2CHCH_2]_2AlH$.

The transformation of rearranged product **14** to generate **2** was next examined (Scheme 2). Ozonolysis of **14**, followed by further oxidation and esterification produced **15** with a 97% yield. Removal of the *O*-silyl protecting group resulted in **16** (100% yield). Pfitzner–Moffatt oxidation of **16** gave aldehyde **7**, which, without purification, was reacted with allyl tributyltin in the presence of $MgBr_2$ in CH_2Cl_2[19] to stereoselectively generate an allylated product, homoallyl alcohol **6**, as the sole product in 75% yield from **16**.

The chelation control (between an aldehyde-carbonyl and an α-ether oxygen) was expected to favor the formation of **6**, the structure of which has been unambiguously assigned by a single crystal X-ray analysis.[20] The hydroxy group in **6** was protected as a methoxymethyl ether to give **17** (80% yield). Ozonolysis of **17**,



Scheme 2. DCC=*N*,*N*′-dicyclohexylcarbodiimide, TFA=CF_3CO_2H.



Scheme 3. 9-BBN=9-borabicyclo[3.3.1]nonane, Ms=–SO_2Me.

followed by the Takai reaction[21] with CHI_3 in the presence of $CrCl_2$ in THF/1,4-dioxane provided (*E*)-vinyl iodide (**2**) with a 60% yield as a geometrically pure compound after chromatographic purification.

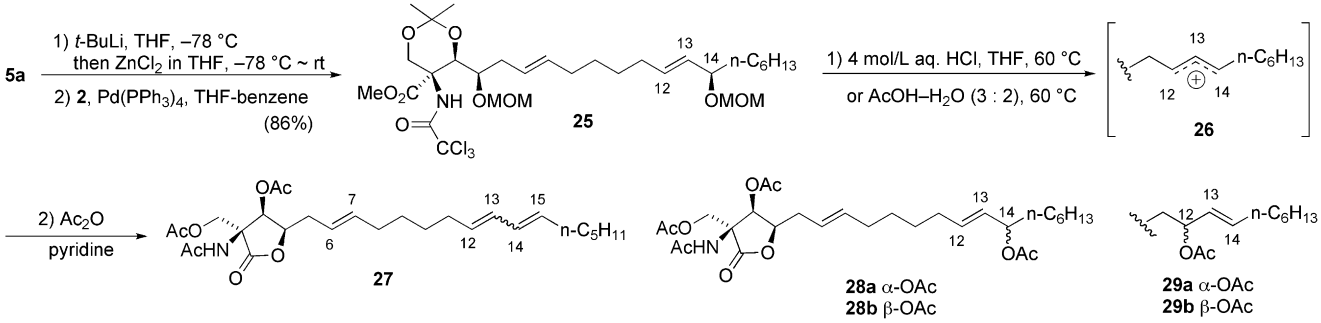
2.3. Synthesis of the hydrophobic right-half segment

The counterpart for the coupling reaction, a precursor of organometallic species, iodide **5a**, was synthesized from D-tartrate (Scheme 3). The known di-*O*-tosylate[22] **18**, prepared from diisopropyl D-tartrate with an 86% overall yield, was treated with *n*-pentylmagnesium bromide in the presence of CuBr to afford **19** in 53% yield. After deprotection of the acetonide group, the product was converted into epoxide **20** (93% yield), whose hydroxy group was protected as an MOM ether to give **21a** (96% yield).

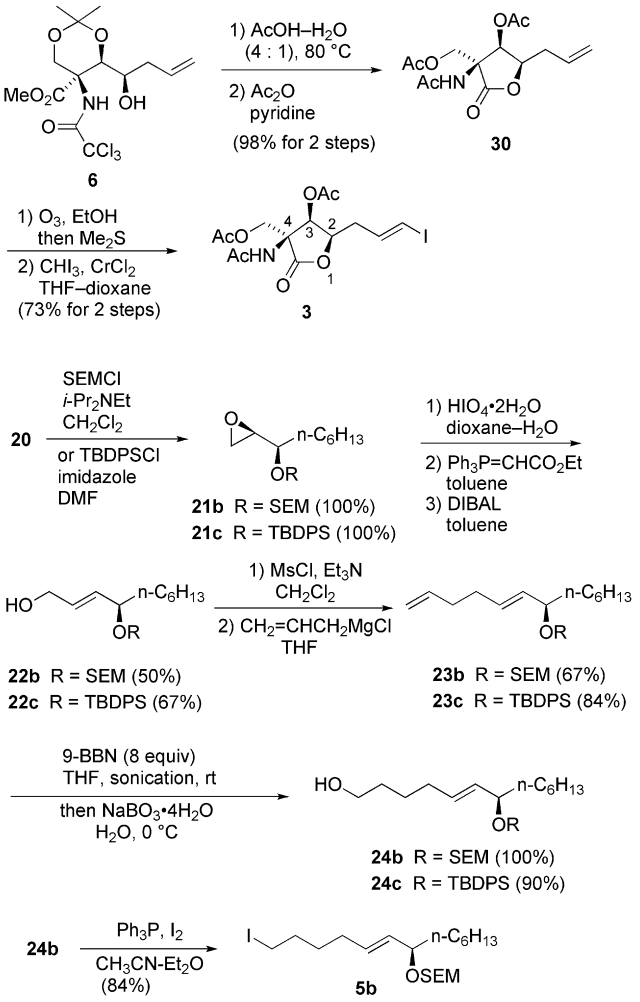
Oxidative cleavage of the epoxide group in **21a** with HIO_4[23] generated the corresponding aldehyde, which was then reacted with the stabilized Wittig reagent to afford an inseparable mixture of *E*-olefin and its *Z*-isomer (*E*:*Z*=6.5:1). DIBAL reduction of the mixture followed by chromatographic separation gave geometrically pure *E*-allyl alcohol **22a** in 55% isolated yield from **21a**. The primary hydroxy group in **22a** was transformed into *O*-mesylate, which was then reacted with allylmagnesium chloride[24] to provide **23a** in 81% yield. Hydroboration of **23a** with excess 9-BBN (8 equiv to **23a**) followed by oxidation provided primary alcohol **24a**, whose hydroxy function was replaced with iodide, to give **5a**,[18] a precursor for the coupling reaction, with a 75% yield.

2.4. Attempted synthesis of 1 via the Negishi coupling reaction

Having established the procedure for the preparation of both counterparts for the coupling reaction, we subsequently explored the conditions of the Negishi cross-coupling reaction,[25] which has been utilized for the total synthesis of myriocin and sphingofungin F by Ham et al.[9f,10i] The reaction of iodide **5a** with *t*-BuLi at −78 °C followed by treatment with $ZnCl_2$ generated an alkyl zinc species. This was then reacted with vinyl iodide **2** in the presence of $Pd(PPh_3)_4$ to generate the coupling product, fully protected mycestericin A (**25**), in 86% yield (Scheme 4). The treatment of **25** with aqueous HCl at 60 °C removed all the protecting groups, however, the concomitant elimination of a methoxymethyloxy or hydroxy function at C-14 (mycestericin A numbering) also occurred and, after acetylation, γ-lactone-diene **27**[26] was obtained. On the



Scheme 4.



Scheme 5. SEM=–$CH_2OCH_2CH_2SiMe_3$.

other hand, the reaction of **25** with aqueous acetic acid followed by acetylation afforded a γ-lactone, which is expected to possess the structure of **28b** (49% yield). The ^{1}H NMR data of the synthetic γ-lactone were very similar to those reported for the lactone **28b** derived from natural mycestericin A[1a] and the FABMS data also supported its structure. However, in the ^{13}C NMR of the synthetic γ-lactone, in addition to a set of four signals (δ 123.2, 128.6, 134.0, and 135.0 ppm) due to olefinic carbons whose chemical shifts are in good agreement with those of the authentic **28b**, an extra four signals (δ 123.1, 128.1, 134.4, and 134.6 ppm) of olefinic carbons, whose intensities were almost same as those of the former four signals, were observed. These results revealed that the synthetic γ-lactone is an inseparable mixture of diastereomers. The most plausible products of the acid hydrolysis of **25**, followed by acetylation, are **28a**,**b** and **29a**,**b**, which would be formed via the allyl cation intermediate **26**. The attempted deprotection of **25** with TMSBr, which was reported to be effective for the clean deprotection of an allylic MOM ethers,[27] also resulted in the formation of a mixture of **28a**,**b** and **29a**,**b**. These results clearly showed that the allylic alcohol moiety in **25** is unexpectedly labile under the acidic conditions used, prompting us to devise an improved route to **1**.

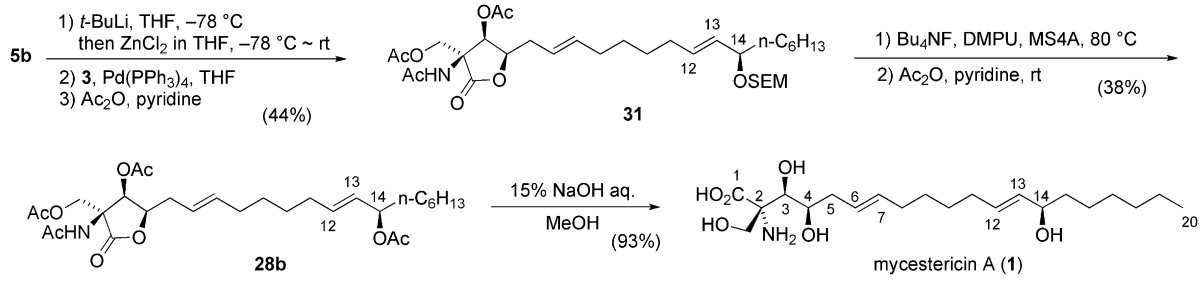
2.5. The alternative approach to 1: completion of the total synthesis

To avoid the formation of the allyl cation **26**, a coupling reaction of substrates possessing protecting groups that could be removed under basic conditions was next explored (Scheme 5). For this purpose, compound **6** was converted into γ-lactone **30** (98% yield) by treatment with aqueous acetic acid at 70 °C followed by acetylation. Ozonolysis of **30** and subsequent Takai reaction generated a new left-half segment, vinyl iodide **3**, as a single *E*-isomer after chromatographic purification with a yield of 73%. On the other hand, for the preparation of the right-half segment, the alcohol function in epoxide **20** was protected as a 2-(trimethylsilyl)ethoxymethyl (SEM) group to give **21b** (100% yield). Then, the same reaction sequence as employed for the conversion of **21a** to **5a** was applied to **21b** to provide **5b**[18] with a 28% overall yield from **21b**. Another right-half segment **23c**, possessing a TBDPS protecting group, was also synthesized from **20** (56% overall for six steps) following the same reaction sequence. Although epoxide **20** could also be transformed into its OTBS and OTES derivatives, it was found that the periodate oxidation of the epoxides possessing OTBS and OTES groups resulted in the decomposition of the substrates.

The Negishi coupling of **5b**-derived alkyl zinc with γ-lactone **3**, followed by acetylation, successfully provided **31** (44% yield; Scheme 6). Compound **31** was treated with anhydrous Bu_4NF and MS4A in *N*,*N*-dimethyl propylene urea (DMPU)[28] at 80 °C and then acetylated. Under these reaction conditions, the SEM protecting group was successfully removed without formation of an allyl cation to generate tetraacetyl mycestericin A γ-lactone (**28b**) as a single isomer (38% yield). The spectral data (^{1}H and ^{13}C NMR) as well as the $[\alpha]_D$ value of the synthetic **28b** were identical with those reported for γ-lactone obtained from natural mycestericin A.[1a] Finally, alkaline hydrolysis of **28b** followed by ion-exchange resin (IRC-76) treatment furnished mycestericin A (**1**) in 93% yield. The $[\alpha]_D$ value {$[\alpha]_D^{21}$ −8.6 (*c* 0.45, MeOH); lit.[1a] $[\alpha]_D^{25}$ −8.5 (*c* 0.50, MeOH)} and spectroscopic data showed good concordance with those reported for the natural product.[1a] Thus, the first total synthesis of mycestericin (**1**) has been achieved.

2.6. The second-generation total synthesis via the Suzuki–Miyaura coupling

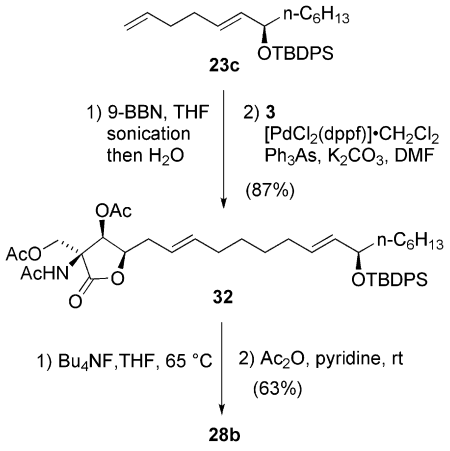
As described in the previous section, mycestericin A (**1**) was successfully synthesized using Negishi coupling as the key reaction. However, the yield of the coupling reaction (44%) was not satisfactory and, furthermore, the final deprotection also resulted in



Scheme 6. DMPU=*N*,*N*-dimethyl propylene urea.

a poor yield (38%). The low yield of the Negishi coupling may be due to the presence of base-sensitive functionalities (γ-lactone and acetyl groups) in the left-half segment (**3**), which might have undergone attack by an excess of organozinc or organolithium reagents. The harsh basic reaction conditions for the deprotection of the OSEM group would have induced the decomposition of the substrate and/or product.[29] To improve these crucial steps, the Suzuki–Miyaura method[30] of coupling γ-lactone **3** with an organoborane derived from the alkene **23c** possessing OTBDPS group was next investigated. The *B*-alkyl Suzuki–Miyaura coupling procedure has been successfully employed in the total synthesis of sphingofungins E and F by Trost,[10d] and sphingofungin E by Nakamura and Shiozaki.[10g]

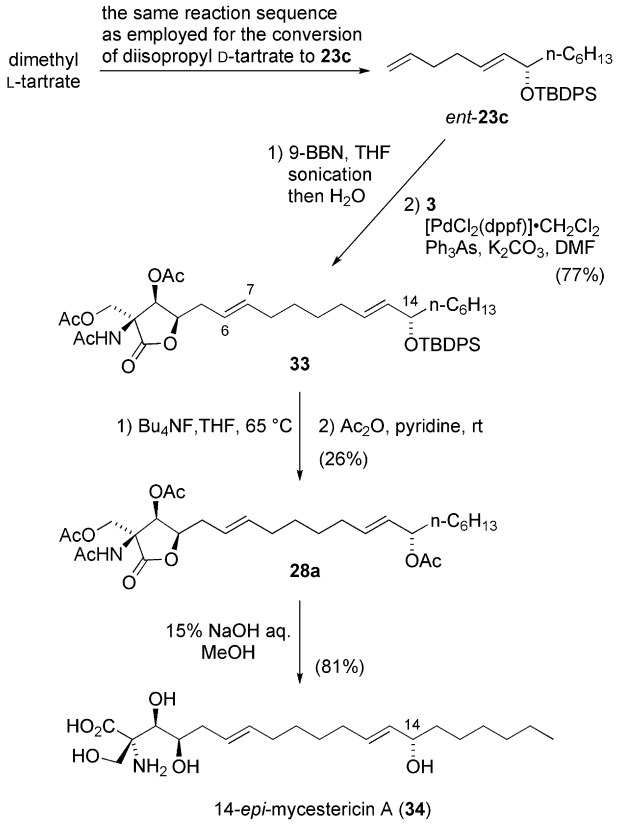
Hydroboration of **23c** with excess 9-BBN followed by H_2O quench produced the corresponding organoborane, which was then reacted with **3** in the presence of $PdCl_2\cdot$dppf, Ph_3As, and K_2CO_3 in DMF (Scheme 7). To our delight, under these reaction conditions, coupling product **32** was obtained with a yield of 87%. The use of Ph_3As was found to be essential for a higher yield; the similar reaction in the absence of Ph_3As gave **32** in 58% yield.[31] Although the treatment of **32** with Bu_4NF in THF at room temperature resulted in recovery of the starting material, the reaction performed at 65 °C generated **28b** in 63% yield after acetylation. By use of the Suzuki–Miyaura coupling reaction, the overall yield of mycestericin A was much improved (4.3% yield from **9** using the Negishi coupling approach compared to 14.0% yield from **9** with the Suzuki–Miyaura approach).



Scheme 7.

2.7. Total synthesis of 14-*epi*-mycestricin A (34): confirmation of the stereochemistry at C-14 of the natural product

As described in the Introduction, the C-14 stereochemistry of mycestericin A had been determined by way of the benzoate CD chirality method for the *N*-acetyl-14-*O*-benzoyl derivative of mycestericin A γ-lactone.[1a] To confirm the stereochemistry at C-14 by the synthetic method, synthesis of 14-epimer of mycestericin A was next investigated. For this purpose, the enantiomer of diene **23c** (*ent*-**23c**) was synthesized starting from dimethyl L-tartrate by a similar reaction sequence to that employed for the conversion of diisopropyl D-tartrate to **23c** (Scheme 8).[32] The *B*-alkyl Suzuki–Miyaura coupling of an organoborane generated from *ent*-**23c** with vinyl iodide **3** afforded the coupling product **33** in 77% yield. Deprotection of the OTBDPS group and subsequent acetylation provided 14-*epi*-tetraacetyl mycestericin A γ-lactone (**28a**) in 26% yield. Alkaline hydrolysis of **28a**, followed by ion-exchange resin (IRC-76) treatment, resulted in an 81% yield of 14-*epi*-mycestericin A (**34**).



Scheme 8.

The ^1H and ^{13}C NMR spectra of **28a** and **34** were quite similar to those of **28b** and **1**, respectively, and we were unable to detect any notable differences between the NMR spectra of **28a** and **28b** and those between **34** and **1**. Fortunately, it was found that the $[\alpha]_D$ values of these compounds displayed some differences as shown in Table 1. The relatively large differences in $[\alpha]_D$ values between **28b** and **28a** (Table 1, entries 1–3) allowed us to clearly distinguish these two compounds, assigning the stereochemistry at C-14 in natural mycestericin A as *R*.

Table 1
$[\alpha]_D$ values of compounds **28b**, **28a**, **1**, and **34**

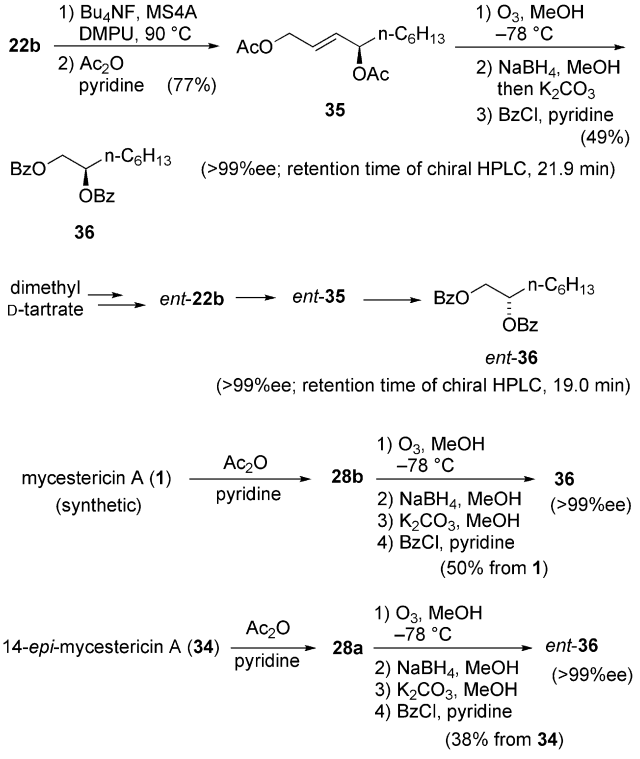
Entry	Compound	Source	$[\alpha]_D$	Measurement conditions
1	**28b**	From natural product	+58.4[a]	25 °C, *c* 0.5, $CHCl_3$
2	**28b**	Synthetic	+58.2	21 °C, *c* 0.41, $CHCl_3$
3	**28a**	Synthetic	+30.0	21 °C, *c* 0.22, $CHCl_3$
4	**1**	Natural product	−8.5[a]	25 °C, *c* 0.5, MeOH
5	**1**	Synthetic	−8.6	21 °C, *c* 0.45, MeOH
6	**34**	Synthetic	−5.0	20 °C, *c* 0.15, MeOH

[a] Ref. 1a.

2.8. Degradation studies of mycestericin A (1) and its 14-epimer (34)

It is a possible that the allylic hydroxy functions at C-14 in compounds **1** and **34** might undergo partial epimerization during the synthetic or purification process via an allyl cation intermediate and it is now understood that such epimerization cannot be detected by ^1H nor ^{13}C NMR analyses. To confirm the stereochemical purities at C-14 in final compounds **1** and **34**, studies of their degradation were conducted (Scheme 9). In the preparation of reference compounds (**36** and *ent*-**36**) for HPLC analyses, compound **22b** was converted into diacetate **35** (77% yield). Ozonolysis

of **35** (reductive workup with $NaBH_4$), followed by the removal of *O*-acetyl groups and subsequent O-benzoylation, produced authentic **36** in 49% yield. A similar reaction sequence was applied to *ent*-**22b** to give *ent*-**36**. The chiral HPLC analyses (DAICEL CHIRALCEL OJ-H, 4.6 mm ID×250 mm, *i*-PrOH/hexane=1:300, flow rate=0.8 mL/min) of **36** (retention time: 21.9 min) and *ent*-**36** (retention time: 19.0 min) revealed that the optical purities of both compounds were >99% ee. Next, the degradation reactions of synthetic mycestericin A (**1**) and its 14-epimer (**34**) were performed. Treatment of **1** with Ac_2O/pyridine gave tetraacetyl mycestericin A γ-lactone (**28b**), whose ozonolysis (reductive workup with $NaBH_4$) followed by basic methanolysis and subsequent benzoylation provided a dibenzoate in 50% overall yield after chromatographic separation. The same reaction sequence was applied to 14-*epi*-mycestericin A (**34**) to afford a dibenzoate via **28a** in 38% overall yield. The ^1H NMR spectra of these dibenzoates were totally identical to those of **36**. The chiral HPLC analyses of degradation products clearly showed that the dibenzoate derived from mycestericin A (**1**) is **36** with >99% ee, whereas the dibenzoate obtained from 14-*epi*-mycestericin A (**34**) is *ent*-**36** with >99% ee. From these experiments it was confirmed that no epimerization at C-14 had occurred during the synthetic and purification processes for the preparation of **1** and **34**, and our final products (**1** and **34**) were both diastereomerically homogeneous.



Scheme 9. Bz=–C(O)Ph.

3. Conclusion

In summary, the first total synthesis of mycestericin A (**1**) from dimethyl L-tartrate has been achieved via an efficient route (24 steps and 4.3% overall yield). The synthesis of 14-*epi*-mycestericin A (**34**), comparison of the $[\alpha]_D$ values of their γ-lactone derivatives (**28b** and **28a**), and the degradation studies of **1** and **34** fully confirmed the proposed absolute structure of the natural product, including the stereochemistry at the distal C-14 hydroxy group. This work has also provided a new synthetic pathway for the synthesis of highly oxygenated α-substituted α-amino acid derivatives with potent biological activities utilizing readily available tartrates.

4. Experimental

4.1. General

Melting points were determined on a Mitamura-Riken micro hot stage and were not corrected. Optical rotations were recorded using a sodium lamp (589 nm) with a JASCO DIP-370 instrument with 1 dm tube and values of $[\alpha]_D$ are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared (IR) spectra were measured with a JASCO FT/IR-200 spectrometer. ^1H NMR spectra were recorded at 300 MHz on a JEOL Lambda 300 or on a Varian MVX-300 spectrometers for solutions in $CDCl_3$, unless otherwise noted. Chemical shifts are reported as δ values in parts per million. Abbreviations used are: b (broad peak), s (singlet), d (doublet), t (triplet), q (quartet) and m (complex multiplet). ^{13}C NMR spectra were recorded at 75 MHz on a JEOL Lambda 300 spectrometer for solutions in $CDCl_3$, unless otherwise noted. Chemical shifts are reported as δ values in parts per million. Mass spectra are measured by a JEOL GC Mate spectrometer with EI (70 eV) or FAB mode. Organic extracts were dried over solid anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. Column chromatography was carried out with silica gel (Merck Kieselgel 60 F_{254}; 230–400 mesh) for purification. Preparative TLC (PLC) was performed with Merck PLC plate (Kieselgel 60 F_{254}, 0.5 mm thickness).

4.2. Synthesis of the left-half segment

*4.2.1. {[(4S,5S)-5-(Benzyloxy)-2,2-dimethyl-1,3-dioxan-4-yl]methoxy}-(tert-butyl)-diphenylsilane (**10**).* To a solution of [(4*S*,5*S*)-5-(benzyloxy)-2,2-dimethyl-1,3-dioxan-4-yl]methanol[16,11e] (**9**) (1.34 g, 5.31 mmol) in DMF (18 mL) at room temperature were added imidazole (545 mg, 8.01 mmol) and TBDPSCl (1.90 mL, 7.31 mmol). After being stirred at room temperature for 20 h, the reaction mixture was diluted with brine, and products were extracted with EtOAc. The organic layer was washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (100 g silica gel, 1:20–1:10 EtOAc/hexane as an eluent) to afford **10** (2.61 g, 100%) as a colorless syrup: $[\alpha]_D^{25}$ +15.3 (*c* 0.89, $CHCl_3$); IR (neat) 3450, 2990, 2940, 2875, 1455, 1385, 1200, 1120, 1080, 1055, 1025 cm^{-1}; ^1H NMR δ 1.06 (9H, s), 1.39, 1.40 (each 3H, 2s), 3.43 (1H, ddd, *J*=1.4, 2.0, 3.9 Hz), 3.71 (1H, ddd, *J*=3.9, 9.0, 9.0 Hz), 3.89 (1H, dd, *J*=2.0, 12.9 Hz), 3.94–4.02 (3H, m), 4.56 and 4.72 (each 1H, 2d, *J*=11.9 Hz), 7.25–7.46 (11H, m), 7.63–7.68 (4H, m); ^{13}C NMR δ 19.1, 19.4, 27.1, 29.2, 62.2, 63.0, 69.7, 71.6, 72.3, 98.7, 127.7, 127.9, 128.0, 128.5, 129.8, 129.9, 133.7, 133.8, 135.8, 135.8, 138.6; HRMS (FAB) *m*/*z* calcd for $C_{30}H_{38}O_4SiNa$ $(M+Na)^+$ 513.2437, found: *m*/*z* 513.2452.

*4.2.2. (4S,5S)-4-[(tert-Butyldiphenylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxan-5-ol (**11**).* To a solution of naphthalene (1.02 g, 7.96 mmol) in THF at −10 °C was added Li (37 mg, 5.3 mmol), and the mixture was stirred at −10 °C for 30 min. To this mixture −10 °C under Ar was added a solution of **10** (261 mg, 0.532 mmol) in THF (5.6 mL). After being stirred at −10 °C for 3.5 h, the reaction mixture was quenched by addition of EtOH (2 mL) and then diluted with EtOAc. The organic layer was washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (50 g silica gel, 1:40–1:3 EtOAc/hexane as an eluent) to afford **11** (200 mg, 94%) as a colorless syrup: $[\alpha]_D^{22}$ +15.6 (*c* 1.52, $CHCl_3$); IR ν_{max} (neat) 3480, 2995, 2960, 2930, 2860, 1470, 1425, 1365, 1275, 1230, 1200, 1130, 1110, 1065 cm^{-1}; ^1H NMR δ 1.06 (9H, s), 1.40 and 1.43 (each 3H, 2s), 2.76 (1H, d, *J*=10.2 Hz), 3.63 (1H, dddd, *J*=1.5, 1.5, 2.7, 10.2 Hz), 3.68 (1H, dd, *J*=5.1, 9.8 Hz), 3.85 (1H, dd, *J*=2.7, 12.2 Hz), 3.87 (1H, dd, *J*=7.1, 9.8 Hz), 3.95 (1H, ddd, *J*=1.5, 5.1, 7.1 Hz), 4.05 (1H, dd, *J*=1.5, 12.2 Hz), 7.34–7.46 (6H, m), 7.65–7.74 (4H, m); ^{13}C NMR δ 18.6, 19.4, 27.0, 29.6, 63.7, 66.2, 72.4, 99.1, 127.9, 129.9, 133.4, 133.7, 135.8, 135.9; HRMS (FAB) *m*/*z* calcd for

$C_{23}H_{33}O_4Si$, $(M+H)^+$ 401.2148, found: 401.2145. Anal. Calcd for $C_{23}H_{32}O_4Si$: C, 68.83; H, 8.05. Found: C, 68.83; H, 7.98.

*4.2.3. (2E)-Ethyl 2-{(4R)-4-[(tert-butyldiphenylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxan-5-ylidene}acetate (**12**).* To the mixture of **11** (1.04 g, 2.60 mmol) and MS 4 Å (800 mg) in CH_2Cl_2 (40 mL) was added a suspension of PCC (1.96 g, 9.10 mmol), NaOAc (1.49 g, 18.2 mmol), and MS 4 Å (800 mg) in CH_2Cl_2 (40 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was partially concentrated and then diluted with Et_2O. The insoluble material was removed by filtration through a pad of Celite. The filtrate was concentrated to give a crude ketone (929 mg) as a yellow syrup, which was used for next reaction without further purification. To a solution of the crude ketone (929 mg) in toluene (27 mL) was added $Ph_3P{=}CHCO_2Et$ (2.70 g, 7.80 mmol), and the mixture was stirred at 100 °C for 12 h. The mixture was concentrated to give a residue, which was purified by column chromatography (50 g silica gel, 1:20 EtOAc/toluene as an eluent) to afford **12** (1.14 g, 93% for two steps) as a colorless syrup: $[\alpha]_D^{22}$ −52.4 (*c* 0.70, $CHCl_3$); IR ν_{max} (neat) 2990, 2935, 2860, 1715, 1415, 1370, 1210, 1150, 1115 cm^{-1}; ^1H NMR δ 1.06 (9H, s), 1.27 (3H, t, *J*=7.3 Hz), 1.35 and 1.36 (each 3H, 2s), 3.83 (1H, dd, *J*=5.9, 10.5 Hz), 3.90 (1H, dd, *J*=5.6, 10.5 Hz), 4.15 (2H, q, *J*=7.3 Hz), 4.41 (1H, ddd, *J*=2.0, 5.6, 5.9 Hz), 4.61 (1H, ddd, *J*=2.0, 3.9, 17.8 Hz), 5.02 (1H, dd, *J*=2.0, 17.8 Hz), 5.78 (1H, dd, 1H, *J*=2.0, 3.9 Hz) 7.34–7.46 (6H, m), 7.64–7.71 (4H, m); ^{13}C NMR δ 14.4, 19.4, 24.4, 25.3, 27.0, 60.3, 61.9, 65.0, 71.7, 100.3, 112.6, 127.9, 127.9, 129.9, 133.5, 135.8, 135.8, 158.9, 166.1; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{37}O_5Si$, $(M+H)^+$ 469.2410, found: 469.2407. Anal. Calcd for $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74. Found: C, 69.19; H, 7.54.

*4.2.4. (2E)-2-{(4R)-4-[(tert-Butyldiphenylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxan-5-ylidene}ethanol (**13**).* To a solution of **12** (4.09 g, 8.73 mmol) in toluene (80 mL) at −78 °C was added DIBAL (1.01 M solution in toluene, 21.6 mL, 21.8 mmol) dropwise under Ar. After being stirred at −78 °C for 1 h, to the reaction mixture at −78 °C was added acetone (10 mL), and the mixture was further stirred at 0 °C for 10 min. The reaction mixture was diluted with EtOAc, and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent gave a residue, which was purified by column chromatography (150 g silica gel, 1:3 EtOAc/hexane as an eluent) to afford **13** (3.62 g 97%) as a colorless syrup: $[\alpha]_D^{21}$ −40.4 (*c* 1.75, $CHCl_3$); IR ν_{max} (neat) 3400, 2930, 2860, 1475, 1425, 1380, 1370, 1225, 1135, 1115, 1080, 1010 cm^{-1}; ^1H NMR δ 1.07 (9H, s), 1.36 and 1.41 (each 3H, 2s), 3.82 (1H, dd, *J*=6.1, 10.7 Hz), 3.92 (1H, dd, *J*=4.9, 10.7 Hz), 4.00–4.17 (2H, m), 4.27 and 4.36 (each 1H, 2d, *J*=14.4 Hz), 4.41 (1H, ddd, *J*=1.7, 4.9, 6.1 Hz), 5.49 (1H, dt, *J*=1.7 and 6.1 Hz), 7.34–7.46 (6H, m), 7.66–7.74 (4H, m); ^{13}C NMR δ 19.4, 23.5, 26.6, 27.0, 58.3, 59.4, 65.7, 72.1, 99.9, 121.4, 127.8, 127.8, 129.8, 129.9, 133.7, 133.8, 135.8, 135.9, 138.2; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{34}O_4SiNa$, $(M+Na)^+$ 449.2124, found: 449.2126.

*4.2.5. N-{(4R,5S)-4-[(tert-Butyldiphenylsilyloxy)methyl]-2,2-dimethyl-5-vinyl-1,3-dioxan-5-yl}-2,2,2-trichloroacetamide (**14**) and its (4R,5R)-isomer (epi-**14**).* To a solution of **13** (741 mg, 1.74 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added DBU (26.0 μL, 0.17 mmol) and trichloroacetonitrile (0.440 mL, 4.34 mmol), and the mixture was stirred at 0 °C for 10 min. The reaction mixture was concentrated to give a residue, which was passed through a short column of silica gel (8 g, 1:5 EtOAc/hexane containing 1% Et_3N as an eluent) to afford crude imidate **8** (961 mg) as a pale yellow syrup. A mixture of crude **8** (961 mg) and K_2CO_3 (48 mg) in *o*-xylene (96 mL) was heated in a sealed tube at 140 °C for 48 h. The reaction mixture was concentrated to give a residue, which was purified by column chromatography (50 g silica gel, 1:20 EtOAc/hexane) to afford first, **14** (615 mg, 62% from **12**) as a colorless syrup. Further elution gave *epi*-**14** (327 mg, 33% from **12**) as a crystalline residue. Data for **14**: $[\alpha]_D^{21}$ +12.6 (*c* 1.20, $CHCl_3$); IR ν_{max} (neat) 3400, 2930, 2860, 1720, 1515, 1505, 1425, 1380, 1200, 1140, 1115 cm^{-1}; ^1H NMR δ 1.08 (9H, s), 1.47 and 1.48 (each 3H, 2s), 3.80 (1H, d, *J*=11.9 Hz), 3.80–3.91 (2H, m), 3.94 (1H, dd, *J*=2.2, 10.2 Hz), 4.31 (1H, d, *J*=11.9 Hz), 5.16 (1H, d, *J*=17.5 Hz), 5.28 (1H, d, *J*=11.2 Hz), 5.78 (1H, dd, *J*=11.2, 17.5 Hz), 7.32–7.48 (6H, m), 7.64–7.74 (5H, m); ^{13}C NMR δ 18.5, 19.4, 27.0, 29.2, 58.3, 63.0, 64.2, 75.8, 92.9, 99.5, 116.9, 127.7, 127.7, 129.8, 133.1, 133.3, 135.7, 135.8, 161.2; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{35}Cl_3NO_4Si$, $(M+H)^+$ 570.1401, found: 570.1398. Anal. Calcd for $C_{27}H_{34}NO_4Cl_3Si$: C, 56.79; H, 6.00; N, 2.45. Found: C, 56.61; H, 6.29; N, 2.45. Data for *epi*-**14**: mp 77.6–79.0 °C; $[\alpha]_D^{25}$ +1.8 (*c* 0.47, $CHCl_3$); IR (neat) 3340, 2915, 1860, 1730, 1510, 1430, 1240, 1200, 1100, 1055 cm^{-1}; ^1H NMR δ 1.11 (9H, s), 1.38 and 1.51 (each 3H, 2s), 3.66 (1H, dd, *J*=3.9, 10.2 Hz), 3.88 (1H, dd, *J*=8.3, 10.2 Hz), 4.12 (1H, d, *J*=11.7 Hz), 4.19 (1H, dd, *J*=3.9, 8.3 Hz), 4.61 (1H, d, *J*=11.7 Hz), 5.36 (1H, d, *J*=17.6 Hz), 5.41 (1H, d, *J*=11.0 Hz), 6.25 (1H, dd, *J*=11.0, 17.6 Hz), 7.34–7.48 (6H, m), 7.58–7.66 (4H, m), 7.70 (1H, br s); ^{13}C NMR δ 18.9, 19.5, 27.3, 28.6, 58.5, 65.3, 66.1, 72.8, 99.3, 115.9, 127.9, 130.1, 132.7, 132.7, 132.8, 135.5, 161.3; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{35}Cl_3NO_4Si$, $(M+H)^+$ 570.1401, found: 570.1392. Anal. Calcd for $C_{27}H_{34}NO_4Cl_3Si$: C, 56.79; H, 6.00; N, 2.45. Found: C, 56.99; H, 6.12; N, 2.30.

Starting from diisopropyl D-tartrate, an enantiomer of **14** (*ent*-**14**) was synthesized by the similar procedures as described for the preparation of **14** from dimethyl L-tartrate. Optical purities of **14** and *ent*-**14** were determined to be >99% ee by chiral HPLC analyses [DAICEL CHIRALCEL OD-H, 4.6 mm ID×250 mm, *i*-PrOH/hexane=1:15, flow rate=0.8 mL/min, UV (254 nm) detection]: retention time for **14**, 6.0 min; for *ent*-**14**, 7.2 min.

*4.2.6. Methyl (4R,5S)-4-[(tert-butyldiphenylsilyloxy)methyl]-2,2-dimethyl-5-(2,2,2-trichloroacetamido)-1,3-dioxane-5-carboxylate (**15**).* Ozone was introduced into a solution **14** (375 mg, 0.657 mmol) in EtOH (6.6 mL) at −78 °C for 25 min. After confirming the complete consumption of the starting material (TLC analysis), excess ozone was removed with a stream of Ar gas. To the reaction mixture was added Me_2S (0.48 mL, 6.6 mmol) at −78 °C and the mixture was stirred at room temperature for 5 h. The resulting mixture was diluted with EtOAc and washed with brine, and dried. Removal of the solvent gave a crude aldehyde (400 mg) as a pale yellow syrup. To a solution of the crude aldehyde (400 mg) in *t*-BuOH (4.4 mL) and H_2O (4.4 mL) were added $NaH_2PO_4{\cdot}2H_2O$ (206 mg, 1.32 mmol), $HOSO_2NH_2$ (192 mg, 1.98 mmol), and $NaClO_2$ (239 mg, 2.64 mmol). After being stirred at room temperature for 15 h, the reaction mixture was diluted with 20 wt% aqueous $Na_2S_2O_3$ solution, and products were extracted with $CHCl_3$ five times. The combined organic layers were dried and concentrated to give a crude carboxylic acid (540 mg) as a white solid. To a solution of the crude carboxylic acid in MeOH (1.7 mL) and benzene (6.6 mL) at 0 °C was added (trimethylsilyl)diazomethane (2.0 M solution in Et_2O, 0.43 mL, 0.86 mmol), and the mixture was stirred at room temperature for 1.5 h. Removal of the solvent gave a residue, which was purified by column chromatography (15 g silica gel, 1:5 EtOAc/hexane) to afford **15** (382 mg, 97%) as a colorless syrup: $[\alpha]_D^{20}$ +16.7 (*c*, $CHCl_3$); IR ν_{max} (neat) 3410, 2955, 2930, 1740, 1715, 1505, 1430, 1385, 1255, 1200, 1115, 1060 cm^{-1}; ^1H NMR δ 1.08 (9H, s), 1.47 and 1.49 (each 3H, 2s), 3.72 (3H, s), 3.79 (1H, dd, *J*=4.4, 11.5 Hz), 3.96 (1H, dd, *J*=3.9, 11.5 Hz), 4.20 (1H, dd, *J*=3.9, 4.4 Hz), 4.27 and 4.34 (each 1H, 2d, *J*=12.4 Hz), 7.34–7.45 (6H, m), 7.65–7.71 (4H, m), 7.86 (br s, 1H, NH); ^{13}C NMR δ 18.9, 19.6, 27.2, 28.9, 53.1, 60.9, 62.9, 63.7, 73.0, 92.3, 99.9, 127.9, 127.9, 130.1, 133.2, 133.2, 135.9, 161.8, 168.6; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{35}Cl_3NO_6Si$, $(M+H)^+$ 602.1300, found: 602.1285.

*4.2.7. Methyl (4R,5S)-2,2-dimethyl-4-(hydroxymethyl)-5-(2,2,2-trichloroacetamido)-1,3-dioxane-5-carboxylate (**16**).* To a solution of **15** (382 mg, 0.633 mmol) in THF (6.3 mL) was added Bu_4NF (1.0 M

solution in THF, 1.10 mL, 1.10 mmol) at −15 °C. After being stirred at −15 °C for 1 h, the reaction mixture was diluted with EtOAc, and washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (6 g silica gel, 1:2–1:1 EtOAc/hexane as an eluent) to afford **16** (231 mg, 100%) as a crystalline residue: mp 57.3–58.9 °C; $[\alpha]_D^{28}$ +38.1 (*c* 1.20, $CHCl_3$); IR ν_{max} (neat) 3570, 3480, 3300, 1735, 1715, 1655, 1520, 1390, 1260, 1205, 1125, 1085 cm^{-1}; ^1H NMR δ 1.46 and 1.53 (each 3H, 2s), 2.38 (1H, br s), 3.76–3.84 (1H, m), 3.77 (3H, s), 3.90 (1H, dd, *J*=3.4, 12.4 Hz), 4.15 (1H, dd, *J*=3.2, 3.4 Hz), 4.34 (2H, s), 8.60 (br s, 1H, NH); ^{13}C NMR δ 19.2, 28.8, 53.3, 61.4, 62.3, 62.8, 71.4, 92.4, 100.0, 162.1, 168.9; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{17}Cl_3NO_6$, $(M+H)^+$ 364.0122, found: 364.0123.

*4.2.8. Methyl (4R,5S)-2,2-dimethyl-4-[(R)-1-hydroxybut-3-enyl]-5-(2,2,2-trichloroacetamido)-1,3-dioxane-5-carboxylate (**6**).* To a solution of **16** (249 mg, 0.683 mmol) in benzene (6.8 mL) at room temperature were added pyridine (0.055 mL, 0.68 mmol), TFA (0.026 mL, 0.34 mmol), DMSO (3.4 mL), and DCC (561 mg, 2.72 mmol). After being stirred at room temperature for 5 h, the reaction mixture was diluted with Et_2O, and washed successively with water and brine, and dried. The organic layer was concentrated to give crude aldehyde **7** (589 mg), which was used for the next reaction without further purification. To a solution of $MgBr_2$ (0.068 mL, 1.37 mmol) in CH_2Cl_2 (7.0 mL) at room temperature was added a solution of crude aldehyde **7** (589 mg) in CH_2Cl_2 (6.6 mL) via a cannula under Ar. The mixture was stirred at −78 °C for 10 min. To this mixture at −78 °C was added allyl tributyltin (0.32 mL, 1.02 mmol). After stirring at −78 °C for 15 min, the cooling bath was removed, and the resulting mixture was stirred at ambient temperature for 25 h. The reaction mixture was diluted with 1 M aqueous HCl solution at 0 °C, and products were extracted with EtOAc. The organic layer was washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (25 g silica gel, 1:30 EtOAc/toluene as an eluent) to give **6** (207 mg, 75%) as a crystalline residue: mp 98.2–99.2 °C (from EtOAc); $[\alpha]_D^{22}$ +56.1 (*c* 1.04, $CHCl_3$); IR ν_{max} (neat) 3580, 3305, 1750, 1710, 1540, 1385, 1245, 1200 cm^{-1}; ^1H NMR δ 1.44 and 1.47 (each 3H, 2s), 2.26 (1H, ddd, *J*=7.1, 7.1, 13.9 Hz), 2.35–2.45 (2H, m), 3.76 (3H, s), 3.89 (1H, ddd, *J*=1.0, 7.1, 16.1 Hz), 3.94 (1H, d, *J*=1.0 Hz), 4.36 (1H, d, *J*=12.4 Hz), 4.45 (1H, d, *J*=12.4 Hz), 5.11 (1H, d, *J*=16.8 Hz), 5.13 (1H, d, *J*=8.5 Hz), 5.68 (1H, m), 9.22 (1H, br s); ^{13}C NMR δ 19.4, 28.1, 39.2, 53.1, 62.3, 62.4, 69.9, 70.8, 92.3, 99.9, 119.2, 132.8, 162.0, 169.1; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{21}Cl_3NO_6$, $(M+H)^+$ 404.0434, found: 404.0428. Anal. Calcd for $C_{14}H_{20}NO_6Cl_3$: C, 41.55; H, 4.98; N, 3.46. Found: C, 41.66; H, 4.99; N, 3.48.

*4.2.9. Methyl (4R,5S)-2,2-dimethyl-4-[(R)-1-(methoxymethoxy)but-3-enyl]-5-(2,2,2-trichloroacetamido)-1,3-dioxane-5-carboxylate (**17**).* To a solution of **6** (25 mg, 0.062 mmol) in $(CH_2Cl)_2$ (1 mL) at room temperature were added *i*-Pr_2NEt (0.12 mL, 0.68 mmol), MOMCl (0.028 mL, 0.37 mmol), and tetrabutylammonium chloride (2.5 mg, 0.007 mmol). After stirring at room temperature for 17 h, the reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent gave a residue, which was purified by column chromatography (1 g silica gel, 1:7 EtOAc/hexane as an eluent) to afford **17** (22 mg, 79%) as a colorless syrup: $[\alpha]_D^{30}$ +88.9 (*c* 0.77, $CHCl_3$); IR ν_{max} (neat) 3365, 2995, 2955, 1730, 1715, 1515, 1505, 1385, 1260, 1200 cm^{-1}; ^1H NMR δ 1.46 and 1.49 (each 3H, 2s), 2.44–2.54 (2H, m), 3.43 (3H, s), 3.72–3.80 (1H, m), 3.78 (3H, s), 4.08 (1H, d, *J*=1.0 Hz), 4.25 and 4.54 (each 1H, 2d, *J*=12.2 Hz), 4.78 and 4.82 (each 1H, 2d, *J*=7.1 Hz), 5.11 (1H, d, *J*=16.1 Hz), 5.12 (1H, d, *J*=10.2 Hz), 5.58–5.64 (1H, m), 8.73 (1H, br s); ^{13}C NMR δ 18.8, 29.1, 35.4, 53.1, 56.7, 62.4, 62.5, 71.1, 76.7, 92.7, 96.5, 100.2, 119.1, 133.1, 161.3, 168.8; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{25}Cl_3NO_7$, $(M+H)^+$ 448.0697, found: 448.0686. Anal. Calcd for $C_{16}H_{24}NO_7Cl_3$: C, 42.83; H, 5.39; N, 3.12. Found: C, 43.00; H, 5.51; N, 3.02.

*4.2.10. Methyl (4R,5S)-2,2-dimethyl-4-[(R,E)-4-iodo-1-(methoxymethoxy)but-3-enyl]-5-(2,2,2-trichloroacetamido)-1,3-dioxane-5-carboxylate (**2**).* Ozone was introduced into a solution of **17** (32 mg, 0.071 mmol) in EtOH (2 mL) at −78 °C for 1.5 min. After purging of excess ozone with a stream of Ar gas, to the reaction mixture at −78 °C was added Me_2S (0.052 mL, 0.71 mmol), and the resulting mixture was stirred at room temperature for 5 h. The mixture was diluted with EtOAc and washed with brine, and dried. Removal of the solvent gave a crude aldehyde (35 mg) as a pale yellow syrup. To a suspension of $CrCl_2$ (349 mg, 2.84 mmol) in THF (3.5 mL) and 1,4-dioxane (3.5 mL) at 0 °C under Ar was added a solution of the crude aldehyde (35 mg) and CHI_3 (335 mg, 0.85 mmol) in THF (3.5 mL) via a cannula. After being stirred at room temperature for 20 h, the reaction was quenched by the addition of H_2O (1 mL). The resulting mixture was diluted with Et_2O and washed successively with 30 wt % aqueous $Na_2S_2O_3$ solution and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (1.5 g, silica gel, 1:5 EtOAc/hexane as an eluent) to afford **2** (28 mg, 60% from **17**) as a colorless syrup: $[\alpha]_D^{30}$ +61.0 (*c* 0.82, $CHCl_3$); IR ν_{max} (neat) 3370, 2915, 2850, 1730, 1715, 1515, 1380, 1260, 1150 cm^{-1}; ^1H NMR δ 1.46 and 1.49 (each 3H, 2s), 2.42–2.60 (2H, m), 3.42 (3H, s), 3.75–3.83 (1H, m), 3.81 (3H, s), 4.01 (1H, d, *J*=1.0 Hz), 4.26 and 4.54 (each 1H, 2d, *J*=12.2 Hz), 4.77 and 4.80 (each 1H, 2d, *J*=7.1 Hz), 6.15 (1H, d, *J*=14.4 Hz), 6.40 (1H, ddd, *J*=6.8, 8.3, 14.4 Hz), 8.64 (1H, br s); ^{13}C NMR δ 18.5, 29.0, 38.0, 53.1, 56.6, 62.1, 62.2, 71.5, 75.8, 78.4, 96.8, 100.1, 100.5, 140.6, 161.1, 168.5; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{24}Cl_3INO_7$, $(M+H)^+$ 573.9664, found: 573.9650.

*4.2.11. (2R,3R,4S)-4-Acetamido-4-(acetoxymethyl)-2-allyl-5-oxotetrahydrofuran-3-yl acetate (**30**).* A solution of **6** (185 mg, 0.457 mmol) in AcOH (16 mL) and H_2O (4 mL) was stirred at 80 °C for 11 h. The reaction mixture was concentrated to give a residue, which was dissolved in pyridine (6 mL) and Ac_2O (5 mL). After stirring at room temperature for 9 h, the reaction mixture was concentrated to give a residue, which was purified by column chromatography (4 g silica gel, 1:5–2:3 EtOAc/hexane as an eluent) to give **30** (141 mg, 98%) as a colorless syrup: $[\alpha]_D^{22}$ +71.4 (*c* 0.63, $CHCl_3$). IR ν_{max} (neat) 3350, 3270, 3050, 2930, 1780, 1755, 1750, 1670, 1540, 1375, 1230, 1185, 1050, 1030 cm^{-1}; ^1H NMR δ 2.03, 2.05 and 2.10 (each 3H, 3s), 2.37–2.56 (2H, m), 4.50 (2H, s, 2H), 4.77 (1H, td, *J*=4.9, 8.3 Hz), 5.13–5.21 (2H, m), 5.75–5.89 (2H, m), 6.07 (1H, br s); ^{13}C NMR δ 20.3, 20.5, 22.7, 33.2, 62.6, 62.8, 72.0, 80.9, 118.8, 132.0, 168.9, 169.4, 170.1, 172.2; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{19}NO_7$, $(M+H)^+$ 314.1240, found: 314.1242.

*4.2.12. (2R,3R,4S)-4-Acetamido-4-(acetoxymethyl)-2-[(E)-3-iodoallyl]-5-oxotetrahydrofuran-3-yl acetate (**3**).* Ozone was introduced into a solution of **30** (113 mg, 0.361 mmol) in EtOH (10 mL) at −78 °C for 10 min. After confirming the complete consumption of the starting material (TLC analysis), excess ozone was removed with a stream of Ar gas. To the reaction mixture was added Me_2S (0.30 mL, 4.1 mmol) at −78 °C and the mixture was stirred at 0 °C for 6 h. The reaction mixture was concentrated to give a residue, which was diluted with EtOAc. The organic layer was washed with brine, and dried. Removal of the solvent left a crude aldehyde (115 mg). To a suspension of $CrCl_2$ (442 mg, 3.60 mmol) in dioxane (6.0 mL) under Ar at 0 °C was added a THF solution (3.0 mL) of the crude aldehyde (115 mg) and CHI_3 (433 mg, 1.10 mmol) via a cannula. After stirring at room temperature for 1.5 h, the reaction was quenched by addition of 20 wt % aqueous $Na_2S_2O_3$ solution (20 mL), and then diluted with EtOAc. The organic layer was washed successively with 20 wt % aqueous $Na_2S_2O_3$ solution, H_2O and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (3 g silica gel,

1:2–2:1 EtOAc/hexane as an eluent) to give first, the *Z*-isomer of **3** (20 mg, 13%) as a colorless syrup. Further elution afforded **3** (115 mg, 73%) as a crystalline residue. Data for **3**: mp 58.0–58.9 °C; $[\alpha]_D^{24}$ +83.5 (*c* 0.93, $CHCl_3$); IR ν_{max} (KBr disk) 3350, 3050, 1780, 1755, 1750, 1680, 1540, 1375, 1230, 1185, 1050, 1030 cm^{-1}; ^1H NMR δ 2.03, 2.06 and 2.12 (each 3H, 3s), 2.38–2.56 (2H, m), 4.49 (2H, s), 4.77 (1H, ddd, *J*=4.9, 8.6, 8.6 Hz), 5.75 (1H, d, *J*=4.9 Hz), 5.99 (1H, br s), 6.27 (1H, ddd, *J*=1.2, 1.2, 14.4 Hz), 6.55 (ddd, 1H, *J*=7.1, 7.1, 14.4 Hz); ^{13}C NMR δ 20.8, 21.1, 23.1, 35.9, 62.6, 63.8, 72.3, 79.5, 79.8, 140.1, 169.7, 170.2, 170.5, 170.7; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{18}NO_7INa$, $(M+Na)^+$ 462.0026, found: 462.0031. Data for *Z*-isomer of **3**: $[\alpha]_D^{19}$ +67.1 (*c* 0.24, $CHCl_3$); IR ν_{max} (neat) 3350, 3050, 1780, 1755, 1750, 1680, 1540, 1375, 1230, 1185, 1050 cm^{-1}; ^1H NMR δ 2.03, 2.09 and 2.10 (each 3H, 3s), 2.51–2.68 (2H, m), 4.50 (2H, s), 4.84 (1H, ddd, *J*=4.6, 5.2, 5.2 Hz), 5.79 (1H, d, *J*=4.6 Hz), 6.06 (1H, br s), 6.31 (1H, ddd, *J*=6.8, 6.8, 7.2 Hz), 6.46 (1H, ddd, *J*=1.5, 1.5, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.6, 22.6, 34.5, 62.4, 62.9, 71.8, 86.3, 134.8, 169.0, 169.5, 170.3, 172.0; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{19}NO_7I$, $(M+H)^+$ 440.0206, found: 440.0214.

4.3. Synthesis of the right-half segment

*4.3.1. [(4R,5R)-2,2-Dimethyl-5-hexyl-1,3-dioxolan-4-yl]methanol 4-methylbenzenesulfonate (**19**).* To a suspension of CuBr (1.30 g, 9.03 mmol) in THF (30 mL) at 0 °C under Ar was added *n*-pentylmagnesium bromide (1.5 M solution in Et_2O, 34.4 mL, 51.6 mmol), and the mixture was cooled to −30 °C. To this suspension was added a THF solution (22 mL) of [(4*R*,5*R*)-2,2-dimethyl-5-hexyl-1,3-dioxolan-4-yl]-4,5-dimethanol 4,5-bis(4-methylbenzenesulfonate)[22] (**18**) (6.09 g, 12.9 mmol). After being stirred for 19 h at −30 °C, the reaction mixture was diluted with 1 M aqueous HCl solution (30 mL) at −30 °C, and products were extracted with EtOAc. The organic layer was washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent gave a residue, which was purified by column chromatography (150 g silica gel, 1:10 EtOAc/hexane as an eluent) to afford **19** (2.55 g, 53%) as a colorless syrup: $[\alpha]_D^{21}$ +19.9 (*c* 1.44, $CHCl_3$); IR ν_{max} (neat) 2935, 2855, 1370, 1190, 1180, 1100, 980 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=6.9 Hz), 1.24–1.58 (10H, m), 1.29 and 1.35 (each 3H, 2s), 2.45 (3H, s), 3.74–3.82 (2H, m), 4.05 (1H, dd, *J*=4.1, 10.5 Hz), 4.11 (1H, dd, *J*=3.7, 10.5 Hz), 7.34 and 7.79 (each 2H, 2d, *J*=8.0 Hz); ^{13}C NMR δ 14.2, 21.8, 22.7, 26.0, 26.9, 27.5, 29.4, 31.8, 33.2, 69.4, 78.0, 78.4, 109.5, 128.2, 130.0, 132.9, 145.2; HRMS (EI) *m*/*z* calcd for $C_{19}H_{30}O_5S$, $(M)^+$ 370.1814, found: 370.1820.

*4.3.2. (R)-1-[(R)-Oxiran-2-yl]heptan-1-ol (**20**).* A solution of **19** (6.50 g, 17.5 mmol) in AcOH (80 mL) and H_2O (20 mL) was heated at 70 °C for 13 h. The reaction mixture was concentrated to give a crude diol (6.12 g) as a crystalline residue, which was dissolved in CH_2Cl_2 (88 mL). To this solution at room temperature was added DBU (7.35 mL, 49.1 mmol), and the resulting mixture was stirred at room temperature for 2 h. After addition of saturated aqueous NH_4Cl solution (40 mL), the reaction mixture was diluted with EtOAc, and washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (65 g silica gel, 1:15–1:4 EtOAc/hexane as an eluent) to give **20** (2.58 g, 93%) as a colorless syrup: $[\alpha]_D^{23}$ −3.6 (*c* 2.51, $CHCl_3$); IR ν_{max} (neat) 3440, 3955, 2930, 2860, 1730, 1460, 1255, 1085, 980 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7.1 Hz), 1.20–1.67 (10H, m), 1.82 (1H, br s), 2.72 (1H, dd, *J*=2.7, 4.9 Hz), 2.82 (1H, dd, *J*=4.1, 4.9 Hz), 2.98 (1H, ddd, *J*=2.7, 4.1, 5.0 Hz), 3.44 (1H, dt, *J*=5.0, 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 25.4, 29.4, 31.8, 34.4, 45.3, 55.7, 71.9; HRMS (FAB) *m*/*z* calcd for $C_9H_{19}O_2$, $(M+H)^+$ 159.1385, found: 159.1394.

*4.3.3. (R)-2-[(R)-1-(Methoxymethoxy)heptyl]oxirane (**21a**).* To a solution of **20** (66 mg, 0.42 mmol) in $(CH_2Cl)_2$ (2 mL) at room temperature were added *i*-Pr_2NEt (0.72 mL, 4.16 mmol) and MOMCl (0.16 mL, 2.1 mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution. Products were extracted with EtOAc, and the organic layer was washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (1.6 g silica gel, 1:5 EtOAc/hexane as an eluent) to give **21a** (81 mg, 96%) as a colorless syrup: $[\alpha]_D^{24}$ +47.0 (*c* 0.73, $CHCl_3$); IR ν_{max} (neat) 2930, 2860, 1470, 1155, 1100 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=6.8 Hz), 1.21–1.67 (10H, m), 2.53 (1H, dd, *J*=2.7, 4.9 Hz), 2.78 (1H, dd, *J*=4.4, 4.9 Hz), 2.98 (1H, ddd, *J*=2.7, 4.4, 7.1 Hz), 3.26 (1H, td, *J*=6.1, 7.1 Hz), 3.40 (3H, s), 4.66 and 4.88 (each 1H, 2d, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.8, 25.6, 29.5, 31.9, 32.5, 44.1, 54.9, 55.8, 78.2, 95.7; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{22}O_3Na$, $(M+Na)^+$ 225.1467, found: 225.1482.

*4.3.4. (R)-2-{(R)-1-[(2-(Trimethylsilyl)ethoxy)methoxy]heptyl}oxirane (**21b**).* To a solution of **20** (2.30 g, 14.3 mmol) in CH_2Cl_2 (65 mL) at room temperature were added *i*-Pr_2NEt (9.90 mL, 56.8 mmol) and SEMCl (5.00 mL, 28.4 mmol). After stirring at room temperature for 7 h, the reaction mixture was diluted with EtOAc and washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (150 g silica gel, 1:50–1:30 EtOAc/hexane as an eluent) to give **21b** (4.20 g, 100%) as a colorless syrup: $[\alpha]_D^{26}$ +52.0 (*c* 1.44, $CHCl_3$); IR ν_{max} (neat) 2960, 2930, 2860, 1470, 1380, 1250, 1100 cm^{-1}; ^1H NMR δ 0.01 (9H, s), 0.84–0.98 (5H, m), 1.20–1.70 (10H, m), 2.52 (1H, dd, *J*=2.7, 4.9 Hz), 2.75 (1H, dd, *J*=4.9, 4.9 Hz), 2.96 (1H, ddd, *J*=2.7, 4.9, 6.8 Hz), 3.28 (1H, td, *J*=6.8, 7.1 Hz), 3.58 and 3.70 (each 1H, 2dt, *J*=7.1, 10.0 Hz), 4.71 and 4.88 (each 1H, 2d, *J*=6.8 Hz); ^{13}C NMR δ −1.3, 14.2, 18.2, 22.7, 25.6, 29.5, 31.9, 32.5, 43.9, 54.9, 65.4, 77.8, 93.9; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{33}O_3Si$, $(M+H)^+$ 289.2199, found: 289.2195.

*4.3.5. tert-Butyl{(R)-1-[(R)-oxyran-2-yl]heptyloxy}diphenylsilane (**21c**).* To a solution of **20** (257 mg, 1.63 mmol) in DMF (6.4 mL) at 0 °C were added imidazole (664 mg, 9.75 mmol) and TBDPSCl (1.25 mL, 4.88 mmol). After being stirred at room temperature for 6.5 h, the reaction mixture was diluted with EtOAc and washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (40 g silica gel, 1:100–1:75 EtOAc/hexane as an eluent) to give **21c** (644 mg, 100%) as a colorless syrup: $[\alpha]_D^{20}$ −17.5 (*c* 0.49, $CHCl_3$); IR ν_{max} (neat) 2960, 2930, 2860, 1470, 1430, 1100, 1070, 930 cm^{-1}; ^1H NMR δ 0.82 (3H, t, *J*=6.8 Hz), 1.01–1.30 (17H, m), 1.45–1.52 (2H, m), 2.46 (1H, dd, *J*=2.8, 4.9 Hz), 2.71 (1H, dd, *J*=4.1, 4.9 Hz), 3.05 (1H, ddd, *J*=2.8, 4.1, 6.6 Hz), 3.35 (1H, td, *J*=6.1, 6.6 Hz), 7.34–7.45 (6H, m), 7.67–7.73 (4H, m); ^{13}C NMR δ 14.0, 19.4, 22.5, 24.8, 27.0, 29.0, 31.6, 34.7, 44.8, 55.7, 75.2, 127.4, 127.4, 129.5, 134.0, 134.3, 136.0; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{37}O_2Si$, $(M+H)^+$ 397.2563, found: 397.2562.

*4.3.6. (R,E)-4-(Methoxymethoxy)dec-2-en-1-ol (**22a**).* To a solution of **21a** (581 mg, 2.87 mmol) in 1,4-dioxane (14 mL) at room temperature was added a solution of $HIO_4 \cdot 2H_2O$ (1.50 g, 6.60 mmol) in H_2O (2.9 mL). After being stirred at room temperature for 14 h, the reaction mixture was diluted with EtOAc and washed with brine, and dried. Removal of the solvent gave a crude aldehyde (571 mg). To a solution of the crude aldehyde (571 mg) in toluene (28 mL) was added $Ph_3P{=}CHCO_2Et$ (1.70 g, 4.90 mmol), and the resulting mixture was stirred at 60 °C for 15 h. The reaction mixture was concentrated to give a residue, which was purified by column of silica gel (20 g, 1:100 EtOAc/hexane as an eluent) to afford a geometrical mixture (*E*/*Z*=ca. 6.5:1) of an ethyl ester (588 mg, 79%) as a yellow syrup. To a solution of the crude ethyl ester (588 mg, 2.28 mmol) in toluene (11 mL) was added at −78 °C under Ar dropwise DIBAL (0.99 M solution in toluene, 12.4 mL, 12.4 mmol), and the mixture was stirred at −78 °C for 20 min. The reaction mixture was quenched by addition of acetone (1.5 mL) at −78 °C. After stirring at

0 °C for 10 min, to the mixture was added $Na_2SO_4 \cdot 10H_2O$ (2 g) and the whole mixture was further stirred at room temperature for 4 h. The insoluble material was removed by filtration through Celite, and the filtrate was concentrated to give a residue, which was purified by column chromatography (10 g silica gel, 1:8 EtOAc/hexane as an eluent) to afford first, *Z*-isomer of compound **22a** (54 mg, 9% from **21a**) as a colorless syrup: $[\alpha]_D^{23}$ +106.4 (*c* 0.58, $CHCl_3$); IR ν_{max} (neat) 3420, 2930, 2860, 1470, 1155, 1130 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=6.6 Hz), 1.19–1.69 (10H, m), 2.43 (1H, dd, *J*=4.4, 7.1 Hz), 3.37 (3H, s), 4.01 (1H, ddd, *J*=1.2, 6.1, 7.1 Hz), 4.26–4.42 (2H, m), 4.53 and 4.73 (each 1H, 2d, *J*=7.1 Hz), 5.36 (1H, ddd, *J*=1.2, 9.8, 11.0 Hz), 5.88 (1H, dddd, *J*=1.0, 6.1, 8.0, 11.0 Hz); ^{13}C NMR δ 14.3, 22.8, 25.5, 29.4, 32.0, 35.6, 55.4, 58.3, 70.6, 93.6, 132.4, 132.7; HRMS (FAB) *m*/*z* calcd for $C_{12}H_{24}O_3Na$, $(M+Na)^+$ 239.1624, found: 239.1618. Further elution afforded **22a** (345 mg, 56% from **21a**) as a colorless syrup: $[\alpha]_D^{23}$ +89.5 (*c* 0.51, $CHCl_3$); IR ν_{max} (neat) 3420, 2930, 2860, 1470, 1155, 1095 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=6.6 Hz), 1.22–1.68 (11H, m), 3.63 (3H, s), 4.01 (1H, ddd, *J*=6.8, 6.8, 7.8 Hz), 4.14–4.17 (2H, m), 4.52 and 4.69 (each 1H, 2d, *J*=6.8 Hz), 5.55 (1H, bdd, *J*=7.8, 15.6 Hz), 5.81 (1H, btd, *J*=5.4, 15.6 Hz); ^{13}C NMR δ 14.3, 22.8, 25.6, 29.4, 32.0, 35.8, 55.6, 63.1, 76.5, 93.9, 131.8, 132.1; HRMS (FAB) *m*/*z* calcd for $C_{12}H_{24}O_3Na$, $(M+Na)^+$ 239.1624, found: 239.1630. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.60; H, 11.21.

*4.3.7. (R,E)-4-{[(Trimethylsilyl)methoxy]ethoxy}dec-2-en-1-ol (**22b**).* By the similar reaction conditions as described for the preparation of **22a** from **21a**, compound **21b** (304 mg, 1.05 mmol) was converted into **22b** (168 mg, 53%) and *Z*-isomer of **22b** (22 mg, 7%). Data for *Z*-isomer of **22b**: colorless syrup; $[\alpha]_D^{28}$ +104.0 (*c* 1.90, $CHCl_3$); IR ν_{max} (neat) 3420, 2955, 2930, 2860, 1250, 1100, 1060 cm^{-1}; ^1H NMR δ 0.01 (9H, s), 0.84–1.00 (5H, m), 1.20–1.70 (10H, m), 2.47 (1H, br s), 3.53 and 3.71 (each 1H, 2dt, *J*=7.1, 10.0 Hz), 3.98 (1H, ddd, *J*=1.0, 6.1, 12.9 Hz), 4.32 (1H, ddd, *J*=1.0, 8.3, 12.9 Hz), 4.42 (1H, dt, *J*=6.3 and 10.0 Hz), 4.61 and 4.74 (each 1H, 2d, *J*=7.1 Hz), 5.35 (1H, dddd, *J*=1.0, 1.0, 10.0, 11.0 Hz), 5.89 (1H, ddd, *J*=6.1, 8.3, 11.0 Hz); ^{13}C NMR δ −1.4, 14.2, 18.1, 22.7, 25.5, 29.4, 31.9, 35.6, 58.2, 65.1, 70.7, 91.7, 132.4, 132.7; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{35}O_3Si$, $(M+H)^+$ 303.2356, found: 303.2353. Data for **22b**: colorless syrup; $[\alpha]_D^{27}$ +86.4 (*c* 2.43, $CHCl_3$); IR ν_{max} (neat) 3400, 2930, 2860, 1460, 1380, 1250, 1100, 1060 cm^{-1}; ^1H NMR δ 0.02 (9H, s), 0.85–0.96 (5H, m), 1.20–1.70 (11H, m), 3.51 and 3.73 (each 1H, 2dt, *J*=7.1, 10.0 Hz), 4.04 (1H, dt, *J*=5.9, 7.8 Hz), 4.15 (2H, dd, *J*=1.2, 5.3 Hz), 4.60 and 4.69 (each 1H, 2d, *J*=7.1 Hz), 5.55 (1H, dddd, *J*=1.2, 1.2, 7.8, 15.6 Hz), 5.81 (1H, td, *J*=5.3, 15.6 Hz); ^{13}C NMR δ −1.3, 14.2, 18.3, 22.8, 25.6, 29.4, 32.0, 35.8, 63.1, 65.2, 76.2, 92.1, 131.9, 132.0; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{35}O_3Si$, $(M+H)^+$ 303.2356, found: 303.2356.

*4.3.8. (R,E)-4-(tert-Butyldiphenylsilyloxy)dec-2-en-1-ol (**22c**).* By the similar reaction conditions as described for the preparation of **22a** from **21a**, compound **21c** (1.00 g, 2.52 mmol) was converted into **22c** (692 mg, 67%) and its *Z*-isomer (49 mg, 5%). Data for *Z*-isomer of **22c**: colorless syrup; $[\alpha]_D^{19}$ −24.4 (*c* 0.595, $CHCl_3$); IR ν_{max} (neat) 3300, 2960, 2930, 2860, 1470, 1430, 1100, 1080 cm^{-1}; ^1H NMR δ 0.86 (3H, t, *J*=6.7 Hz), 1.05 (9H, s), 1.18–1.29 (9H, m), 1.39–1.66 (2H, m) 3.58–3.69 (2H, m), 4.35 (1H, td, *J*=7.3, 8.7 Hz), 5.33 (1H, td, J_{2-1}=6.8, 11.2 Hz), 5.49 (1H, dd, *J*=8.7, 11.2 Hz), 7.34–7.47(6H, m), 7.66–7.71 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.3, 22.6, 24.8, 26.9, 29.2, 31.8, 38.2, 58.6, 69.4, 127.4, 127.5, 128.1, 129.6, 129.7, 134.2, 134.3, 135.9, 136.1; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{39}O_2Si$, $(M+H)^+$ 411.2719, found: 411.2713. Data for **22c**: colorless syrup; $[\alpha]_D^{21}$ +5.9 (*c* 0.66, MeOH); IR ν_{max} (neat) 3300, 2960, 2930, 2860, 1470, 1430, 1100, 1080, 970 cm^{-1}; ^1H NMR δ 0.86 (3H, t, *J*=6.9 Hz), 1.07 (9H, s), 1.11–1.59 (11H, m), 3.90 (2H, dd, *J*=1.2, 5.6 Hz), 4.18 (1H, dt, *J*=6.1, 6.3 Hz), 5.40 (1H, td, *J*=5.6, 15.4 Hz), 5.56 (1H, tdd, *J*=1.2, 6.1, 15.4 Hz), 7.33–7.54 (6H, m), 7.65–7.70 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.3, 22.6, 24.7, 27.0, 29.2, 31.8, 37.9, 63.1, 73.9, 127.3, 127.5, 129.1, 129.4, 129.5, 134.4, 134.7, 135.9, 136.1; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{38}O_2SiNa$, $(M+Na)^+$ 433.2539, found: 433.2550.

*4.3.9. (R,E)-7-(Methoxymethoxy)trideca-1,5-diene (**23a**).* To a solution of **22a** (339 mg, 1.57 mmol) in CH_2Cl_2 (8 mL) at 0 °C were added Et_3N (0.440 mL, 3.16 mmol) and MsCl (0.220 mL, 2.84 mmol). After stirring at 0 °C for 30 min, the reaction was quenched by addition of 1 M aqueous HCl solution (2 mL) at 0 °C. The resulting mixture was diluted with EtOAc and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent gave a crude mesylate (502 mg). To a solution of the crude mesylate (502 mg) in THF (16 mL) under Ar at room temperature was added allylmagnesium chloride (2.0 M solution in THF, 2.75 mL, 5.50 mmol), and the mixture was stirred at 50 °C for 10 h. The reaction was quenched by addition of 1 M aqueous HCl solution (5 mL) at 0 °C. The mixture was diluted with EtOAc and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (10 g silica gel, 1:15 EtOAc/hexane as an eluent) to afford **23a** (307 mg, 81%) as a colorless syrup: $[\alpha]_D^{23}$ +99.1 (*c* 0.92, $CHCl_3$); IR ν_{max} (neat) 2930, 2860, 1470, 1115, 1095, 1040 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7.1 Hz), 1.21–1.66 (10H, m), 2.12–2.15 (4H, m), 3.35 (3H, s), 3.92 (1H, td, *J*=6.3, 8.3 Hz), 4.48 and 4.71 (each 1H, 2d, *J*=6.6 Hz), 4.96 (1H, d, *J*=10.2 Hz), 5.01 (1H, d, *J*=18.5 Hz), 5.26 (1H, dd, *J*=8.3, 15.3 Hz), 5.60 (1H, td, *J*=6.3, 15.3 Hz), 5.72–5.86 (1H, m); ^{13}C NMR δ 14.3, 22.8, 25.7, 29.4, 31.8, 32.0, 33.6, 35.9, 55.5, 76.9, 93.4, 115.0, 130.8, 133.7, 138.3; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{28}O_2Na$, $(M+Na)^+$ 263.1987, found: 263.1982.

*4.3.10. (R,E)-Trimethyl{[2-(trideca-1,5-dien-7-yloxy)ethoxy]methyl}-silane (**23b**).* By the similar reaction conditions as described for the preparation of **23a** from **22a**, compound **22b** (954 mg, 3.16 mmol) was converted into **23b** (691 mg, 67%): colorless syrup; $[\alpha]_D^{27}$ +98.4 (*c* 0.74, $CHCl_3$); IR ν_{max} (neat) 2960, 2930, 2860, 1640, 1380, 1250, 1100, 1060 cm^{-1}; ^1H NMR δ 0.02 (9H, s), 0.85–0.96 (5H, m), 1.20–1.65 (10H, m), 2.12–2.15 (4H, m), 3.49 and 3.73 (each 1H, 2dt, *J*=6.6, 9.5 Hz), 3.94 (1H, dt, *J*=6.3, 6.8 Hz), 4.57 and 4.70 (each 1H, 2d, *J*=6.8 Hz), 4.96 (1H, dd, *J*=2.0, 11.0 Hz), 5.01 (1H, dd, *J*=2.0, 18.1 Hz), 5.26 (1H, dd, *J*=8.3, 15.4 Hz), 5.55–5.66 (1H, m), 5.72–5.86 (1H, m); ^{13}C NMR δ −1.3, 14.2, 18.3, 22.8, 25.7, 29.4, 31.8, 32.0, 33.6, 35.9, 65.1, 76.8, 91.7, 115.0, 130.9, 133.4, 138.2; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{39}O_2Si$, $(M+H)^+$ 327.2719, found: 327.2712.

*4.3.11. (R,E)-tert-Butyldiphenyl(trideca-1,5-dien-7-yloxy)silane (**23c**).* By the similar reaction conditions as described for the preparation of **23a** from **22a**, compound **22c** (217 mg, 0.527 mmol) was converted into **23c** (192 mg, 84%): colorless syrup; $[\alpha]_D^{26}$ +21.8 (*c* 0.75, $CHCl_3$); IR ν_{max} (neat) 2960, 2930, 2860, 1470, 1430, 1100, 1070, 970 cm^{-1}; ^1H NMR δ 0.85 (3H, t, *J*=6.8 Hz), 1.05 (9H, s), 1.10–1.55 (10H, m), 1.97–1.99 (4H, m), 4.06 (1H, ddt, J_{7-6}=1.0, 7.1, 7.1 Hz), 4.91 (1H, ddd, *J*=1.0, 2.2, 10.1 Hz), 4.96 (1H, ddd, *J*=1.0, 2.2, 17.1 Hz), 5.23 (1H, td, *J*=5.6, 15.4 Hz), 5.39 (1H, dd, *J*=7.1, 15.4 Hz), 5.67–5.80 (1H, m), 7.31–7.44 (6H, m), 7.64–7.70 (4H, m); ^{13}C NMR δ 14.1, 19.3, 22.6, 24.8, 27.1, 29.2, 31.5, 31.8, 33.3, 38.1, 74.7, 114.5, 127.2, 127.4, 129.3, 129.4, 130.1, 133.4, 134.71, 134.74, 136.0, 136.1, 138.3; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{43}OSi$, $(M+H)^+$ 435.3083, found: 435.3098.

*4.3.12. (R,E)-7-(Methoxymethoxy)tridec-5-en-1-ol (**24a**).* To neat **23a** (135 mg, 0.56 mmol) under Ar at room temperature was added a solution of 9-BBN (0.5 M in THF, 9.0 mL, 4.5 mmol), and the resulting mixture was sonicated (47 kHz, 60 W) in a water bath at ambient temperature for 2 h. To the reaction mixture at 0 °C were added H_2O (9 mL) and $NaBO_3 \cdot 4H_2O$ (2.58 g, 16.8 mmol), and the mixture was further stirred at 0 °C for 17 h. The reaction mixture was diluted with EtOAc and washed with brine, and dried. Removal

of the solvent left a residue, which was purified by column chromatography (15 g silica gel, 1:5 EtOAc/hexane as an eluent) to afford **24a** (124 mg, 86%) as a colorless syrup: $[\alpha]_D^{27}$ +95.2 (*c* 1.05, $CHCl_3$); IR ν_{max} (neat) 3400, 2930, 2860, 1470, 1115, 1095, 1040 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=6.3 Hz), 1.22–1.70 (15H, m), 2.07 (2H, dt, *J*=6.8, 7.1 Hz), 3.35 (3H, s), 3.64 (2H, t, *J*=6.6 Hz), 3.92 (1H, td, *J*=6.6, 8.3 Hz), 4.49 and 4.71 (each 1H, 2d, *J*=6.8 Hz), 5.26 (1H, dd, *J*=8.3, 15.4 Hz), 5.60 (1H, td, *J*=6.8, 15.4 Hz); ^{13}C NMR δ 14.3, 22.8, 25.5, 25.7, 29.4, 32.0, 32.1, 32.4, 35.9, 55.5, 62.9, 77.0, 93.4, 130.7, 134.1; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{30}O_3Na$, $(M+Na)^+$ 281.2093, found: 281.2094.

*4.3.13. (R,E)-7-{[(Trimethylsilyl)methoxy]ethoxy}tridec-5-en-1-ol (**24b**).* By the similar reaction conditions as described for the preparation of **24a** from **23a**, compound **23b** (993 mg, 3.04 mmol) was converted into **24b** (1.17 g, 100%): colorless syrup; $[\alpha]_D^{20}$ +96.1 (*c* 1.45, $CHCl_3$); IR ν_{max} (neat) 3420, 2930, 2860, 1455, 1380, 1250, 1100, 1055 cm^{-1}; ^1H NMR δ 0.02 (9H, s), 0.85–0.99 (5H, m), 1.23–1.62 (15H, m), 2.07 (2H, dtd, *J*=1.5, 6.1, 7.1 Hz), 3.50 (1H, dt, *J*=7.3, 9.5 Hz), 3.64 (2H, t, *J*=6.3 Hz), 3.73 (1H, td, *J*=7.3, 9.5 Hz), 3.94 (1H, td, *J*=5.9, 8.3 Hz), 4.58 and 4.70 (each 1H, 2d, *J*=6.8 Hz), 5.26 (1H, tdd, *J*=1.5, 8.3, 15.4 Hz), 5.60 (1H, td, *J*=7.1, 15.4 Hz); ^{13}C NMR δ −1.3, 14.2, 18.3, 22.8, 25.5, 25.7, 29.4, 32.0, 32.1, 32.4, 35.9, 62.9, 65.1, 76.8, 91.7, 130.8, 133.9; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{41}O_3Si$, $(M+H)^+$ 345.2825, found: 345.2808.

*4.3.14. (R,E)-7-{[(Trimethylsilyl)methoxy]ethoxy}tridec-5-en-1-ol (**24c**).* By the similar reaction conditions as described for the preparation of **24a** from **23a**, compound **23c** (56 mg, 0.014 mmol) was converted into **24c** (53 mg, 90%): colorless syrup; $[\alpha]_D^{26}$ +14.3 (*c* 0.26, $CHCl_3$); IR ν_{max} (neat) 3350, 2960, 2930, 2860, 1470, 1430, 1100 cm^{-1}; ^1H NMR δ 0.83 (3H, t, *J*=7.0 Hz), 1.03 (9H, s), 1.15–1.58 (15H, m), 1.88 (2H, tdd, *J*=1.0, 6.8, 6.8 Hz), 3.56 (2H, t, *J*=6.4 Hz), 4.05 (dt, *J*=6.8, 6.8 Hz), 5.18 (1H, tdd, *J*=1.0, 6.8, 15.5 Hz), 5.36 (1H, tdd, *J*=1.0, 6.8, 15.5 Hz), 7.30–7.41 (6H, m), 7.63–7.67 (4H, m); ^{13}C NMR δ 14.0, 19.3, 22.6, 24.8, 25.2, 27.1, 29.2, 31.8, 32.2, 38.1, 62.8, 74.7, 127.2, 127.4, 129.2, 129.4, 130.6, 133.3, 134.7, 134.8, 135.9, 136.0; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{45}O_2Si$, $(M+H)^+$ 452.3189, found: 452.3198.

*4.3.15. (R,E)-1-Iodo-7-(methoxymethoxy)tridec-5-ene (**5a**).* To a solution of **24a** (172 mg, 0.67 mmol) in CH_3CN (5.0 mL) and Et_2O (1.7 mL) at 0 °C were added imidazole (273 mg, 4.01 mmol), Ph_3P (526 mg, 2.01 mmol), and I_2 (382 mg, 3.01 mmol). After stirring at room temperature for 13 h, the reaction mixture was diluted with hexane (5 mL) and the insoluble material was removed by filtration through a pad of silica gel. The filtrate was concentrated to give a residue, which was purified by column chromatography (20 g silica gel, toluene as an eluent) to afford **5a** (215 mg, 87%) as a colorless syrup: $[\alpha]_D^{26}$ +69.9 (*c* 3.71, $CHCl_3$); IR ν_{max} (neat) 2915, 2855, 1455, 1150, 1095 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=6.8 Hz), 1.24–1.54 (12H, m), 1.82 (2H, m), 2.07 (2H, dt, *J*=6.6, 6.8 Hz), 3.18 (2H, t, *J*=7.1 Hz), 3.36 (3H, s), 3.92 (2H, td, *J*=6.6, 8.0 Hz), 4.50 and 4.70 (each 1H, 2d, *J*=6.6 Hz), 5.27 (1H, dd, *J*=8.0, 15.3 Hz), 5.58 (1H, ddd, *J*=6.6, 6.6, 15.3 Hz); ^{13}C NMR δ 6.8, 14.3, 22.8, 25.7, 29.4, 30.1, 31.3, 32.0, 33.1, 35.9, 55.5, 76.9, 93.5, 131.1, 133.5; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{29}IO_2Na$, $(M+Na)^+$ 391.1111, found: 391.1108. Anal. Calcd for $C_{15}H_{29}IO_2$: C, 48.92; H, 7.94. Found: C, 48.80; H, 7.94.

*4.3.16. (R,E)-1-Iodo-7-{[(trimethylsilyl)methoxy]ethoxy}tridec-5-ene (**5b**).* By the similar reaction conditions as described for the preparation of **5a** from **24a**, compound **24b** (28 mg, 0.080 mmol) was converted into **5b** (31 mg, 84%): colorless syrup; $[\alpha]_D^{28}$ +70.8 (*c* 1.43, $CHCl_3$); IR ν_{max} (neat) 2955, 2930, 2855, 1460, 1380, 1250, 1100 cm^{-1}; ^1H NMR δ 0.02 (9H, s), 0.85–0.96 (5H, m), 1.24–1.61 (12H, m), 1.82 (2H, tt, *J*=7.1, 7.1 Hz), 2.06 (2H, dt, *J*=6.8, 7.1 Hz), 3.17 (2H, t, *J*=7.1 Hz), 3.49 and 3.75 (each 1H, 2td, *J*=7.1, 9.8 Hz), 3.95 (1H, td, *J*=6.6, 8.1 Hz), 4.58 and 4.69 (each 1H, 2d, *J*=6.8 Hz), 5.26 (1H, tdd, *J*=1.0, 8.1, 15.3 Hz), 5.58 (1H, ddd, *J*=6.8, 6.8, 15.4 Hz); ^{13}C NMR δ −1.3, 6.8, 14.3, 18.3, 22.8, 25.7, 25.7, 29.4, 30.1, 31.2, 32.0, 33.1, 35.9, 65.1, 76.7, 91.7, 131.2, 133.3; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{40}O_2ISi$, $(M+H)^+$ 455.1843, found: 455.1853.

*4.3.17. Determination of optical purities of **5a**, **5b**, and **24c**.* Starting from dimethyl L-tartrate, enantiomers of **5a** (*ent*-**5a**), **5b** (*ent*-**5b**), and **24c** (*ent*-**24c**) were synthesized by the similar reaction procedures. Optical purities of **5a**, *ent*-**5a**, **5b**, *ent*-**5b**, **24c**, and *ent*-**24c** were determined to be all >99% ee by chiral HPLC analyses. Analytical conditions for **5a** and **24c**: [DAICEL CHIRALCEL OD-H, 4.6 mm ID×250 mm, *i*-PrOH/hexane=1:500, flow rate=1.0 mL/min, UV (254 nm) detection]; retention time for **5a**, 5.8 min; for *ent*-**5a**, 5.1 min; retention rime for **24c**, 34.6 min; for *ent*-**24c**, 31.8 min. Analytical conditions for **5b**: [DAICEL CHIRALCEL OD-H, 4.6 mm ID×250 mm, *i*-PrOH/hexane=1:1000, flow rate=1.0 mL/min, UV (254 nm) detection]; retention time for **5b**, 7.0 min; for *ent*-**5b**, 5.0 min.

4.4. Coupling reactions of the left-half segment with the right-half segment and total synthesis of mycestericin A

*4.4.1. Methyl (4R,5S)-4-[(1R,3E,9E,11R)-1,11-bis(methoxymethoxy)-3,9-heptadecadiene-1-yl]-2,2-dimethyl-5-[(2,2,2-trichloroacetyl)-amino]-1,3-dioxane-5-carboxylate (**25**).* To a solution of **5a** (30 mg, 0.082 mmol) in THF (0.2 mL) was added *tert*-BuLi (1.53 M solution in pentane, 0.28 mL, 0.43 mmol) at −78 °C under Ar, and the mixture was stirred for 15 min at −78 °C. To this mixture at −78 °C was added a THF solution of $ZnCl_2$ (1.0 M, 0.13 mL, 0.13 mmol), and the cooling bath was removed. After stirring at ambient temperature for 30 min, the resulting colorless solution of Zn reagent was added to a solution of **2** (11 mg, 0.019 mmol) and $Pd(PPh_3)_4$ (2.3 mg, 0.002 mmol) in THF (0.25 mL) and benzene (0.25 mL) via a cannula at room temperature. After stirring at room temperature for 2 h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (2 mL) at 0 °C, and products were extracted with Et_2O. The organic layer was washed successively with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (1.3 g silica gel, 1:20 EtOAc/toluene as an eluent) to afford **25** (11.3 mg, 86%) as a colorless syrup: $[\alpha]_D^{25}$ +82.6 (*c* 0.21, $CHCl_3$); IR ν_{max} (neat) 3375, 2930, 2855, 1740, 1700, 1520, 1380, 1260, 1200 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=6.8 Hz), 1.24–1.58 (14H, m), 1.45 and 1.50 (each 3H, 2s), 1.95–2.09 (4H, m), 2.39–2.46 (2H, m), 3.36 and 3.45 (each 3H, 2s), 3.70 (1H, ddd, *J*=1.0, 6.1, 8.3 Hz), 3.77 (3H, s), 3.92 (1H, dt, *J*=6.6, 7.8 Hz), 4.08 (1H, d, *J*=1 Hz), 4.25 (1H, d, *J*=12.2 Hz), 4.49 (1H, d, *J*=6.6 Hz), 4.52 (1H, d, *J*=12.2 Hz), 4.71 (1H, d, *J*=6.6 Hz), 4.81 and 4.85 (each 1H, 2d, *J*=7.1 Hz), 5.18–5.30 (2H, m), 5.50 (1H, ddd, *J*=6.8, 6.8, 15.4 Hz), 5.60 (1H, ddd, *J*=6.8, 6.8, 15.4 Hz), 8.54 (1H, br s); ^{13}C NMR δ 14.3, 18.9, 22.8, 25.7, 28.9, 29.1, 29.1, 29.4, 32.1, 32.3, 32.7, 34.1, 35.9, 53.0, 55.5, 56.8, 62.0, 62.7, 66.7, 71.0, 76.9, 77.0, 93.4, 96.5, 100.1, 124.5, 130.5, 134.3, 135.2, 163.7, 169.2; HRMS (FAB) *m*/*z* calcd for $C_{31}H_{52}Cl_3NO_9Na$, $(M+Na)^+$ 710.2605, found: 710.2600.

*4.4.2. N-{(3S,4R,5R)-4-(Acetyloxy)-3-[(acetoxy)methyl]tetrahydro-2-oxo-5-[(2E,8E,10R)-10-[[2-(trimethylsilyl)ethoxy]methoxy]-2,8-hexadecadien-1-yl]-3-furanyl}-acetamide (**31**).* To a solution of **5b** (226 mg, 0.050 mmol) in THF (4.0 mL) was added *tert*-BuLi (1.53 M solution in pentane, 0.65 mL, 1.00 mmol) at −78 °C under Ar, and the mixture was stirred for 15 min at −78 °C. To this mixture at −78 °C was added $ZnCl_2$ (1.0 M solution in THF, 0.50 mL, 0.50 mmol), and the cooling bath was removed. After stirring at ambient temperature for 30 min, the resulting colorless solution of Zn reagent was added to a solution of **3** (56 mg, 0.13 mmol) and $Pd(PPh_3)_4$ (43.7 mg, 0.038 mmol) in THF (5.0 mL) via a cannula at room temperature. After stirring at room temperature for 1.5 h, the reaction was

quenched by addition of saturated aqueous NH_4Cl solution (15 mL) at 0 °C, and products were extracted with Et_2O. The organic layer was washed successively with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried. Removal of the solvent left a residue, which was roughly purified by column chromatography (3 g silica gel, 1:1 EtOAc/hexane as an eluent) to afford crude coupling product. The crude product was dissolved in pyridine (2.0 mL) and Ac_2O (1.0 mL) and the resulting solution was stirred at room temperature for 5 h. The reaction mixture was concentrated to give a residue, which was purified by column chromatography (3 g silica gel, 1:2–1:1 EtOAc/hexane as an eluent) to afford **31** (35.1 mg, 44%) as a colorless syrup: $[\alpha]_D^{24}$ +95.9 (*c* 1.14, $CHCl_3$); IR ν_{max} (neat) 3300, 2950, 2930, 2860, 1790, 1755, 1750, 1680, 1370, 1230, 1055 cm^{-1}; ^1H NMR δ 0.02 (9H, s), 0.83–0.96 (5H, m), 1.20–1.60 (14H, m), 1.92–2.15 (4H, m), 2.02, 2.04 and 2.10 (each 3 H, 3s), 2.31–2.46 (2H, m), 3.50 and 3.72 (each 1H, 2dt, *J*=6.6, 9.8 Hz), 3.94 (1H, dt, *J*=7.1, 7.1 Hz), 4.51 (2H, s), 4.58 and 4.70 (each 1H, 2d, *J*=6.8 Hz), 4.68–4.74 (1H, m), 5.23 (1H, dd, *J*=6.1, 15.3 Hz), 5.40 (1H, ddd, *J*=6.6, 6.6, 15.6 Hz), 5.51–5.63 (2H, m), 5.79 (1H, d, *J*=4.2 Hz), 6.00 (1H, br s); ^{13}C NMR δ −1.3, 14.2, 18.2, 20.5, 20.7, 22.8, 22.9, 25.7, 28.8, 29.3, 32.0, 32.2, 32.3, 32.5, 35.9, 62.8, 72.0, 76.7, 81.7, 91.5, 123.3, 130.4, 134.2, 135.1, 169.0, 169.6, 170.3, 172.6; HRMS (FAB) *m*/*z* calcd for $C_{33}H_{58}NO_9Si$, $(M+H)^+$ 640.3881, found: 640.3878.

*4.4.3. N-{(3S,4R,5R)-4-(Acetyloxy)-5-[(2E,8E,10R)-10-(acetyloxy)-2,8-hexadecadien-1-yl]-3-[(acetyloxy)methyl]tetrahydro-2-oxo-3-furanyl}-acetamide (tetraacetyl mycestericin A γ-lactone) (**28b**).* To a mixture of **31** (2.8 mg, 4.4 μmol) and MS4A (50 mg) at room temperature under Ar was added Bu_4NF (57.3 mg, 0.22 mmol) in *N*,*N*-dimethyl propylene urea (DMPU, 1.0 mL), and the resulting mixture was stirred at 80 °C for 12 h. After cooling, to the reaction mixture at room temperature were added pyridine (1.0 mL) and Ac_2O (0.5 mL). After stirring at room temperature for 15 h, the reaction mixture was poured into H_2O (2 mL), and products were extracted with EtOAc. The organic layer was washed with brine, and dried. Removal of the solvent left a residue, which was purified by preparative TLC (4:1 EtOAc/hexane as an eluent) to afford **28b** (0.9 mg, 38%) as a colorless syrup: $[\alpha]_D^{21}$ +58.2 (*c* 0.41, $CHCl_3$); IR ν_{max} (neat) 3350, 2920, 2855, 1790, 1750, 1725, 1680, 1540, 1460, 1375, 1240, 1030 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7.0 Hz), 1.22–1.40 (12H, m), 1.50–1.66 (2H, m), 1.99–2.05 (4H, m), 2.02, 2.03, 2.05, and 2.10 (each 3 H, 4s), 2.29–2.49 (2H, m), 4.50 and 4.52 (each 1H, 2d, *J*=11.5 Hz), 4.71 (1H, ddd, *J*=4.4, 8.0, 8.0 Hz), 5.17 (1H, dt, *J*=6.8, 6.8 Hz), 5.32–5.44 (2H, m), 5.51–5.71 (2H, m), 5.79 (1H, d, *J*=4.4 Hz), 6.01 (1H, br s); ^{13}C NMR δ 14.0, 20.3, 20.5, 21.4, 22.5, 22.7, 25.2, 28.5, 28.7, 29.0, 31.7, 32.0, 32.2, 32.3, 34.5, 62.6, 62.7, 71.8, 75.0, 81.6, 123.2, 128.6, 134.0, 135.0, 168.8, 169.3, 170.2, 170.4, 172.4; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{46}NO_9$, $(M+H)^+$ 552.3172, found: 552.3181. The spectral data were fully identical with those reported for the authentic sample derived from natural mycestericin A.[1a]

*4.4.4. N-{(3S,4R,5R)-4-(Acetyloxy)-3-[(acetoxy)methyl]tetrahydro-2-oxo-5-[(2E,8E,10R)-10-(tert-butyldimethylsilyloxy)-2,8-hexadecadien-1-yl]-3-furanyl}-acetamide (**32**).* To neat **23c** (25 mg, 0.057 mmol) under Ar at room temperature was added a solution of 9-BBN (0.5 M in THF, 0.91 mL, 0.46 mmol), and the resulting mixture was sonicated (47 kHz, 60 W) in a water bath at ambient temperature for 1 h. To the reaction mixture at 0 °C was added H_2O (0.12 mL), and the mixture was stirred at room temperature for 10 min. The resulting organoborane solution was added to a solution of **3** (6.1 mg, 0.014 mmol) and $AsPh_3$ (0.9 mg, 2.8 μmol) in DMF (1.0 mL) via a cannula at room temperature. To this mixture at room temperature were added K_2CO_3 (7.9 mg, 0.057 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (2.3 mg, 2.8 μmol), and the whole mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with saturated aqueous NH_4Cl solution at 0 °C, and products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous NH_4Cl solution, water and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (0.3 g silica gel, 1:3 EtOAc/hexane as an eluent) to afford **32** (9.0 mg, 87%) as a colorless syrup: $[\alpha]_D^{25}$ +47.2 (*c* 0.94, $CHCl_3$); IR ν_{max} (neat) 3350, 2950, 2930, 2860, 1790, 1755, 1750, 1680, 1540, 1460, 1430, 1370, 1230, 1190, 1110, 1055, 1030 cm^{-1}; ^1H NMR δ 0.84 (3H, t, *J*=6.6 Hz), 1.04 (9H, s), 1.15–1.62 (14H, m), 1.83–2.11 (4H, m), 2.03, 2.04, and 2.09 (each 3H, 3s), 2.34–2.43 (2H, m), 4.05 (1H, ddt, *J*=1.0, 6.8, 6.8 Hz), 4.49 and 4.53 (each 1H, 2d, *J*=13.4 Hz), 4.71 (1H, ddd, *J*=4.6, 8.3, 8.3 Hz), 5.20 (1H, dddd, *J*=1.0, 6.6, 6.6, 15.4 Hz), 5.32–5.43 (2H, m), 5.54 (1H, dddd, *J*=1.0, 6.6, 6.6, 15.4 Hz), 5.79 (1H, d, *J*=4.6 Hz), 6.03 (1H, br s), 7.30–7.42 (6H, m), 7.63–7.68 (4H, m); ^{13}C NMR δ 14.0, 19.3, 20.3, 20.5, 22.6, 22.8, 24.8, 27.1, 28.6, 28.7, 29.3, 31.8, 31.9, 32.2, 32.4, 38.1, 62.6, 62.7, 71.9, 74.7, 81.6, 123.1, 127.2, 127.3, 129.2, 129.4, 130.8, 133.0, 134.7, 135.1, 135.9, 136.0, 168.0, 169.3, 170.1, 172.4; HRMS (FAB) *m*/*z* calcd for $C_{43}H_{62}NO_8Si$, $(M+H)^+$ 748.4244, found: 748.4251.

*4.4.5. Tetraacetyl mycestericin A γ-lactone (**28b**) from **32**.* To a solution of **32** (3.7 mg, 4.9 μmol) in THF (0.7 mL) at room temperature was added Bu_4NF (1.0 M solution in THF, 90 μL, 90 μmol), and the mixture was stirred at 65 °C for 7 h. After cooling, to the resulting mixture were added Ac_2O (0.5 mL) and pyridine (1.0 mL). After stirring at room temperature for 15 h, the reaction mixture was diluted with H_2O at 0 °C, and products were extracted with EtOAc. The organic layer was washed successively with H_2O and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (0.3 g silica gel, 1:2–1:1.5 EtOAc/hexane as an eluent) to give **26b** (1.7 mg, 63%) as a colorless syrup. The $[\alpha]_D$ value and spectral (IR, ^1H and ^{13}C NMR, and MS) data were fully identical with those of **28b** obtained from **31**.

*4.4.6. Mycestericin A (**1**).* To a solution of **28b** (6.8 mg, 1.2 μmol) in MeOH (0.5 mL) at room temperature was added 15% aqueous NaOH solution (0.5 mL). The mixture was stirred at 70 °C for 3 h, and then neutralized with IRC-76 resin (H^+ form) at room temperature. Insoluble materials were removed by filtration and the filtrate was concentrated to give a residue, which was purified by column chromatography [0.3 g silica gel, 1:5–2:5 MeOH/$CHCl_3$ (saturated with H_2O) as an eluent] to afford mycestericin A (**1**) (4.6 mg, 93%) as an amorphous solid: $[\alpha]_D^{21}$ −8.6 (*c* 0.45, MeOH); IR ν_{max} (KBr disk) 3400, 3270, 2920, 2855, 1630, 1460, 1400, 1050, 965 cm^{-1}; ^1H NMR (CD_3OD) δ 0.89 (3H, t, *J*=7.1 Hz), 1.25–1.60 (14H, m), 1.93–2.10 (4H, m), 2.26 (2H, t, *J*=6.8 Hz), 3.77–3.95 (4H, m), 4.00 (1H, d, *J*=11.0 Hz), 5.34–5.47 (2H, m), 5.53 (1H, ddd, *J*=6.8, 6.8, 15.3 Hz), 5.59 (1H, ddd, *J*=6.8, 6.8 15.3 Hz); ^{13}C NMR (CD_3OD) δ 14.4, 23.6, 26.6, 29.97, 30.0, 30.4, 33.0, 33.1, 33.6, 38.5, 38.6, 65.2, 70.5, 71.2, 73.66, 73.74, 126.9, 132.3, 134.57, 134.64, 173.5; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{40}NO_6$, $(M+H)^+$ 402.2856, found: 402.2857. The spectral data were fully identical with those reported for natural mycestericin A.[1a]

4.5. Synthesis of 14-*epi*-mycestericin A

*4.5.1. (S,E)-tert-Butyldiphenyl(trideca-1,5-dien-7-yloxy)silane (*ent*-**23c**).* The same reaction sequence for the preparation of **23c** from diisopropyl D-tartrate was applied to dimethyl L-tartrate to provide *ent*-**23c**: $[\alpha]_D^{26}$ −21.2 (*c* 0.55, $CHCl_3$). The spectral data were fully identical with those of **23c**.

*4.5.2. N-{(3S,4R,5R)-4-(Acetyloxy)-3-[(acetoxy)methyl]tetrahydro-2-oxo-5-[(2E,8E,10S)-10-(tert-butyldimethylsilyloxy)-2,8-hexadecadien-1-yl]-3-furanyl}-acetamide (**33**).* Coupling reaction of *ent*-**23c** (56 mg, 0.13 mmol) with **3** (15 mg, 0.034 mmol) by the similar reaction conditions as described for the reaction of **23c** with **3** afforded **33** (19 mg, 77%) as a colorless syrup: $[\alpha]_D^{25}$ +26.6 (*c* 0.95,

$CHCl_3$); IR ν_{max} (neat) 3350, 2950, 2930, 2860, 1790, 1755, 1750, 1680, 1540, 1460, 1430, 1370, 1230, 1190, 1110, 1055, 1030 cm^{-1}; ^1H NMR δ 0.84 (3H, t, J=6.6 Hz), 1.04 (9H, s), 1.15–1.62 (14H, m), 1.83–2.11 (4H, m), 2.03, 2.04 and 2.09 (each 3H, 3s), 2.29–2.48 (2H, m), 4.05 (ddt, 1H, H-14, J=1, 6.8, 6.8 Hz), 4.49 and 4.53 (each 1H, 2d, J=13.4 Hz), 4.70 (1H, ddd, J=4.6, 8.3, 8.3 Hz), 5.20 (1H, dddd, J=1.0, 6.6, 6.6, 15.4 Hz), 5.32–5.43 (2H, m), 5.54 (1H, dddd, J=1.0, .6.6, 6.6, 15.4 Hz), 5.79 (1H, d, J=4.6 Hz), 6.02 (1H, br s), 7.30–7.43(6H, m), 7.63–7.68 (4H, m); ^{13}C NMR δ 14.1, 19.3, 20.3, 20.5, 22.6, 22.8, 24.8, 27.1, 28.6, 28.7, 29.2, 31.8, 31.9, 32.2, 32.4, 38.1, 62.6, 62.7, 72.0, 74.7, 81.6, 123.1, 127.2, 127.4, 129.3, 129.4, 130.8, 133.1, 134.7, 135.1, 135.9, 136.0, 168.8, 169.4, 170.1, 172.4; HRMS (FAB) m/z calcd for $C_{43}H_{62}NO_8Si$, $(M+H)^+$ 748.4244, found: 748.4248.

*4.5.3. N-{(3S,4R,5R)-4-(Acetyloxy)-5-[(2E,8E,10S)-10-(acetyloxy)-2,8-hexadecadien-1-yl]-3-[(acetyloxy)methyl]tetrahydro-2-oxo-3-furanyl}-acetamide (**28a**).* By the similar reaction conditions employed for the preparation of **28b** from **31**, compound **33** (14 mg, 0.018 mmol) was converted into **28a** (2.6 mg, 26%): colorless syrup; $[\alpha]_D^{21}$ +30.0 (c 0.22, $CHCl_3$); IR ν_{max} (neat) 3350, 2920, 2855, 1790, 1750, 1725, 1680, 1540, 1460, 1375, 1240, 1030 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7.0 Hz), 1.22–1.40 (12H, m), 1.50–1.66 (2H, m), 1.99–2.05 (4H, m), 2.02, 2.03, 2.05, and 2.10 (each 3H, 4s), 2.29–2.49 (2H, m), 4.50 and 4.52 (each 1H, 2d, J=11.5 Hz), 4.72 (1H, ddd, J=4.4, 8.0, 8.0 Hz), 5.17 (1H, dt, J=6.8, 6.8 Hz), 5.32–5.44 (2H, m), 5.51–5.71 (2H, m), 5.79 (1H, d, J=4.4 Hz), 5.99 (1H, br s); ^{13}C NMR δ 14.0, 20.3, 20.5, 21.4, 22.6, 22.8, 25.2, 28.5, 28.7, 29.0, 31.7, 32.0, 32.2, 32.3, 34.5, 62.6, 62.7, 71.9, 75.0, 81.6, 123.2, 128.6, 134.0, 135.0, 168.8, 169.3, 170.2, 170.4, 172.4; HRMS (FAB) m/z calcd for $C_{29}H_{45}NO_9Na$, $(M+Na)^+$ 574.2992, found: 574.2988.

*4.5.4. 14-epi-Mycestericin A (**34**).* By the similar reaction conditions employed for the preparation of **1** from **28b**, compound **28a** (4.3 mg, 7.8 μmol) was converted into **34** (2.5 mg, 81%): amorphous solid; $[\alpha]_D^{21}$ −5.0 (c 0.15, MeOH); IR ν_{max} (KBr disk) 3400, 3270, 2920, 2855, 1630, 1460, 1400, 1050, 965 cm^{-1}; ^1H NMR (CD_3OD) δ 0.89 (3H, br t, J=6.8 Hz), 1.25–1.60 (14H, m), 1.93–2.10 (4H, m), 2.26 (2H, br t, J=6.8 Hz), 3.77–3.95 (4H, m), 4.00 (1H, d, J=11.0 Hz), 5.34–5.64 (4H, m); ^{13}C NMR (CD_3OD) δ 14.4, 23.6, 26.6, 29.95, 30.0, 30.4, 33.0, 33.1, 33.6, 38.5, 38.7, 65.1, 70.5, 71.3, 73.7, 73.8, 126.9, 132.3, 134.59, 134.64 (a signal of the carboxyl carbon could not be detected due to its low intensity); HRMS (FAB) m/z calcd for $C_{21}H_{40}NO_6$, $(M+H)^+$ 402.2856, found: 402.2847.

4.6. Degradation study of mycestericin A and its 14-epimer

*4.6.1. (R,E)-Dec-2-ene-1,4-diyl diacetate (35) and its (S,E)-isomer (ent-**35**).* To a mixture of **22b** (7.2 mg, 0.024 mmol) and MS4A (50 mg) was added TBAF (62 mg, 0.24 mmol) in DMPU (0.4 mL), and the mixture was stirred at 90 °C for 3 h. To the mixture at room temperature were added pyridine (1.5 mL) and Ac_2O (1.0 mL), and the mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with EtOAc, and washed with brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (0.3 g silica gel, 1:15–1:10 EtOAc/hexane as an eluent) to afford **35** (4.7 mg, 77%) as a colorless syrup: $[\alpha]_D^{21}$ +26.5 (c 1.20, $CHCl_3$); IR ν_{max} (neat) 2960, 2930, 2860, 1740, 1460, 1430, 1370, 1240, 1025 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=6.6 Hz), 1.24–1.31 (8H, m), 1.49–1.67 (2H, m), 2.05 and 2.06 (each 3H, 2s), 4.54 (2H, d, J=4.9 Hz), 5.24 (1H, dt, J=6.0, 6.8 Hz), 5.67 (1H, dd, J=6.0, 15.6 Hz), 5.77 (1H, td, J=4.9, 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.9, 21.2, 22.5, 25.0, 29.0, 31.6, 34.2, 64.0, 73.6, 126.3, 132.6, 170.3, 170.6; HRMS (FAB) m/z calcd for $C_{14}H_{25}O_4$, $(M+H)^+$ 257.1753, found: 257.1751.

By the similar reaction conditions as employed for the synthesis of **35** from **22b**, *ent*-**22b** (5.0 mg, 0.016 mmol) was converted into *ent*-**35** (3.2 mg, 75%): $[\alpha]_D^{21}$ −26.6 (c 0.23, $CHCl_3$).

*4.6.2. (R)-Octane-1,2-diyl dibenzoate (**36**) and its (S)-isomer (ent-**36**).* Ozone was introduced into a solution of **35** (13.2 mg, 0.052 mmol) in MeOH (0.8 mL) at −78 °C for 5 min. After confirming the complete consumption of the starting material (TLC analysis), excess ozone was removed with a stream of Ar gas. To the reaction mixture was added $NaBH_4$ (9.8 mg, 0.26 mmol) at −78 °C and the mixture was stirred for 5 min at −78 °C. To this mixture was added K_2CO_3 (36 mg, 0.26 mmol) at −78 °C, and the reaction mixture was stirred at 0 °C for 40 min. The reaction mixture was diluted with saturated aqueous NH_4Cl solution, and products were extracted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl solution, and dried. Removal of the solvent gave a crude diol. To a solution of the crude diol in pyridine (1.0 mL) at 0 °C was added BzCl (46 μL, 0.40 mmol) at 0 °C and the mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with saturated aqueous NH_4Cl solution, and products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous NH_4Cl solution, and saturated aqueous $NaHCO_3$ solution, H_2O and brine, and dried. Removal of the solvent left a residue, which was purified by column chromatography (0.3 g silica gel, 1:40 EtOAc/hexane as an eluent) to afford **36** (9.1 mg, 49% for three steps) as a colorless syrup: $[\alpha]_D^{24}$ +5.4 (c 0.63, $CHCl_3$); IR ν_{max} (neat) 2960, 2930, 2860, 1740, 1710, 1600, 1460, 1315, 1280, 1240, 1110, 1070, 1025 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=6.6 Hz), 1.26–1.51 (8H, m), 1.71–1.92 (2H, m), 4.47 (1H, dd, J=6.6, 11.7 Hz), 4.56 (1H, dd, J=3.4, 11.7 Hz), 5.50 (1H, ddt, J=3.4, 6.6, 7.3 Hz), 7.38–7.47 (4H, m), 7.51–7.58 (2H, m), 7.99–8.07 (4H, m); ^{13}C NMR δ 14.0, 22.5, 25.2, 29.1, 31.0, 31.6, 65.7, 72.3, 128.4, 129.7, 132.95, 133.01, 166.1; Retention time of HPLC [DAICEL CHIRLCEL OJ-H, 4.6 mm ID×250 mm, *i*-PrOH/hexane=1:300, flow rate=0.8 mL/min, UV (254 nm) detection], 21.9 min (>99% ee); HRMS (FAB) m/z calcd for $C_{22}H_{27}O_4$, $(M+H)^+$ 355.1909, found: 355.1904.

By the similar reaction conditions as employed for the synthesis of **36** from **35**, *ent*-**35** (8.5 mg, 0.033 mmol) was converted into *ent*-**36** (5.3 mg, 45%): $[\alpha]_D^{21}$ −6.0 (c 0.15, $CHCl_3$); Retention time of HPLC [DAICEL CHIRLCEL OJ-H, 4.6 mm ID×250 mm, *i*-PrOH/hexane=1:300, flow rate=0.8 mL/min, UV (254 nm) detection], 19.0 min (>99% ee).

*4.6.3. Degradation of synthetic mycestericin A (**1**).* To a solution of mycestericin A (**1**) (2.5 mg, 6.2 μmol) in pyridine (1.5 mL) was added Ac_2O (1.0 mL), and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated to give a residue, which was purified by column chromatography (0.3 g silica gel, 1:2–1:1 EtOAc/hexane as an eluent) to afford tetraacetyl mycestericin A γ-lactone (**28b**) (2.5 mg, 73%) as a colorless syrup. Ozone was introduced into a solution of **28b** (2.5 mg, 4.5 μmol) in MeOH (1.5 mL) at −78 °C for 5 min. After confirming the complete consumption of the starting material (TLC analysis), excess ozone was removed with a stream of Ar gas. To the reaction mixture was added $NaBH_4$ (0.5 mg 13.2 μmol) at −78 °C. After being stirred for 5 min, the reaction was quenched by addition of 1 M aqueous HCl solution (0.1 mL) and diluted with water. Products were extracted with EtOAc. The organic layer was washed with 1 M aqueous HCl solution, and dried. Removal of the solvent left a residue, which was roughly purified by column chromatography (0.1 g silica gel, 1:7 EtOAc/hexane as an eluent). The active fractions were collected and concentrated to give an oil, which was dissolved in MeOH (1.0 mL). To this solution at 0 °C was added K_2CO_3 (1.8 mg, 13.2 μmol). After being stirred for 30 min, the reaction mixture was diluted with saturated aqueous NH_4Cl solution, and products were extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous, and dried. Removal of the solvent gave crude octane-1,2-diol. To a solution of crude octane-1,2-diol in pyridine (1.0 mL) was added BzCl (50 μL, 380 μmol) at 0 °C. The mixture was stirred at room temperature for 13 h. The reaction

mixture was diluted with saturated NH_4Cl aqueous, and products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous NH_4Cl solution, and saturated aqueous $NaHCO_3$ solution, H_2O and brine, and dried. Removal of the solvent left a residue, which was purified by preparative TLC (1:50 EtOAc/hexane, developed three times) to afford **36** (1.1 mg, 50% for four steps) as a colorless syrup: HRMS (FAB) *m*/*z* calcd for $C_{22}H_{27}O_4$, $(M+H)^+$ 355.1909, found: 355.1908. The ^1H NMR spectral data were fully identical with those of **36** prepared from **35**, and chiral HPLC analysis assigned the absolute configuration of **36** prepared from **1** as *R* with >99% ee.

*4.6.4. Degradation of 14-epi-mycestericin A (**34**).* The similar reaction conditions as described for conversion of **1** to **36** were applied to 14-*epi*-mycestericin A (**34**, 1.5 mg, 3.7 mmol) to afford *ent*-**36** (0.5 mg, 38% for four steps) as a colorless syrup: HRMS (FAB) *m*/*z* calcd for $C_{22}H_{27}O_4$, $(M+H)^+$ 355.1909, found: 355.1907. The ^1H NMR spectral data were fully identical with those of **36** prepared from **35**, and chiral HPLC analysis assigned the absolute configuration of *ent*-**36** prepared from **34** as *S* with >99% ee.

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