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Asymmetric Synthesis of the Cytotoxic Marine Natural Product (+)-Awajanomycin and Its C-11 Epimer

Rui Fu,[†] Jian-Liang Ye,*[,†] Xi-Jie Dai,[†] Yuan-Ping Ruan,[†] and Pei-Qiang Huang*[,†,‡]

[†]*Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China, and* [‡]*State Key Laboratory of Bioorganic and Natural Products Chemistry, 354 Fenglin Lu, Shanghai 200032, P. R. China*

pqhuang@xmu.edu.cn

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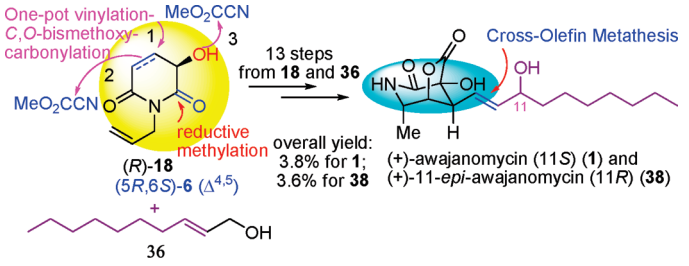

Full details of the convergent synthetic approach to awajanomycin, and the first total syntheses of the marine natural product (+)-awajanomycin (**1**) and its C-11 epimer **38** by an improved 13-step approach, are described. The key elements of the synthetic strategy resided in the use of (*R*)-**18** as the chiral building block to construct the γ-lactone-δ-lactam core **3** and cross-olefin metathesis as the key reaction to couple the latter with the allylic alcohol segment (*R*- or *S*-**4**). The efficient construction of the core **3** was realized by taking advantage of the inherent multiple reactivities of the chiral building block (*R*)-**18**. A highly diastereoselective one-pot transformation of **6** to **26** was achieved in a "one stone four birds" manner. On the other hand, enantioselective synthesis of both enantiomers of the segment **4** has been undertaken by an alternative and more efficient two-step procedure. Both awajanomycin (**1**) and 11-*epi*-awajanomycin **38** have been synthesized with overall yields of 3.8% and 3.6%, respectively. Quantum chemical calculations were undertaken to reveal the low reactivity of compound **27** toward methoxycarbonylation and to get an insight into the favored conformations of the intermediates **25**−**27**. In addition, the geometry of the side product **39** arising from the homocoupling of the allylic alcohol moiety **4** was revised as *E*, and an unusual cyclopropanation reaction was discovered.

Introduction

One of the contemporary trends in drug discovery from natural sources is the investigation of natural products from the marine environment.[1−3] Marine microorganisms,[2] in particular, marine-derived fungi have recently gained attention as important sources of chemically interesting and biologically active secondary metabolites for the development of new pharmaceutical agents.[3] In 2006, Jang and co-workers reported the isolation of (+)-awajanomycin (**1**, Figure 1) from the marine-derived fungus *Acremonium* sp. AWA16-1, collected from sea mud off Awajishima island in Japan.[4] Awajanomycin (**1**) exhibited cytotoxic activity against the

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(2) For two reviews, see: (a) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347–9377. (b) Tan, L. T. *Phytochemistry* **2007**, *68*, 954–968.

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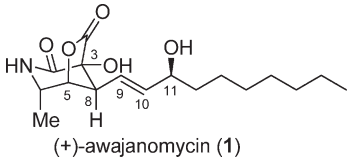


FIGURE 1. Structure of (+)-awajanomycin.

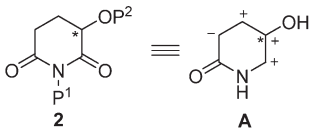
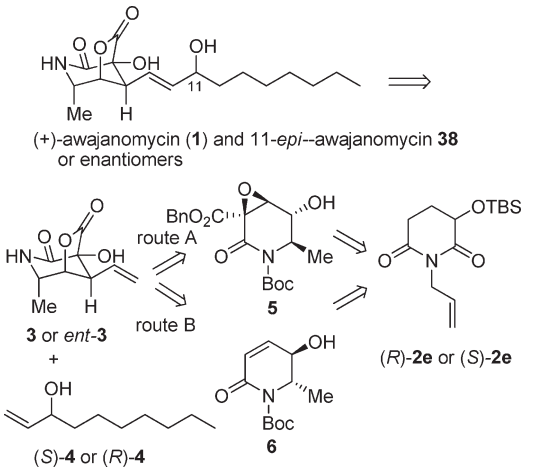


FIGURE 2. Multiple reactivities of the building block **2** displayed by synthon **A**.

A549 cells with an IC_{50} value of 27.5 μg/mL. The structure, including the relative stereochemistry of (+)-awajanomycin (**1**), was elucidated by spectroscopic analysis and chemical methods, while the stereochemistry at C-11 and the absolute configuration of the natural product have not been determined in the original report.

Awajanomycin (**1**) possesses a characteristic γ-lactone-δ-lactam core with a fully substituted 2-piperidinone ring bearing four chiral centers including a quaternary carbon. The intriguing structural features, unknown absolute stereochemistry, and significant cytotoxicity exhibited by awajanomycin make it an attractive and challenging synthetic target.[5,6] In 2009, a racemic synthesis of the core ring system was reported.[5a] Soon after this report, we accomplished the first total synthesis of the unnatural enantiomer of awajanomycin (*ent*-**1**) and established

SCHEME 1



the stereochemistry at C-11 as well as the absolute configuration of the natural product as 3*R*,5*R*,6*S*,8*S*,11*S*.[6] Here, the full account of the strategy is described, and the first total syntheses of the natural (+)-awajanomycin (**1**) and its 11-epimer **38** by an improved approach are reported.

Results and Discussion

In recent years, we have been engaged in the development of protected (*R*)- and (*S*)-glutarimides **2** (Figure 2) as versatile building blocks[7,8] for the asymmetric synthesis of substituted 3-piperidinol-containing alkaloids and pharmaceutically relevant molecules. Taking advantage of the multiple reactivities possessed by these building blocks shown by synthon **A**, methods have been established for alkylation and/or functionalization at any of the six positions of the 3-piperidinol nucleus.[7] On the basis of this methodology, we have demonstrated that the building block **2** can serve as an effective template for the asymmetric construction of awajanomycin bicyclic core in the recent total synthesis of (−)-awajanomycin (*ent*-**1**).

Our retrosynthetic analysis of **1** and its diastereomer is displayed in Scheme 1. The basic strategy was to connect the γ-lactone-δ-lactam core **3** with the lipid side chain **4** by cross-olefin metathesis.[9] For the construction of γ-lactone-δ-lactam moiety **3** and its enantiomer, a chiral relay tactic was envisioned. It was based on the hydroxyl group directed *cis*-diastereoselective vinylation of either α,β-epoxy ester/amide **5**[10] or α,β-unsaturated amide **6**,[11] both of which were accessible from the corresponding enantiomer of the building block **2e**. Thus, from the existing chiral center in the building block **2e**, three other chiral centers could be established in stereocontrolled manners. In this study, more efficient methods, other than the asymmetric

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(6) Fu, R.; Chen, J.; Guo, L.-C.; Ruan, Y.-P.; Huang, P.-Q. *Org. Lett*. **2009**, *11*, 5242–5245.

(7) For an account, see: (a) Huang, P.-Q. *Synlett* **2006**, 1133–1149. For recent examples, see: (b) Wei, B.-G.; Chen, J.; Huang, P.-Q. *Tetrahedron* **2006**, *62*, 190–198. (c) Huang, P.-Q.; Guo, Z.-Q.; Ruan, Y.-P. *Org. Lett*. **2006**, *8*, 1435–1438. (d) Yu, D.-S.; Xu, W.-X.; Liu, L.-X.; Huang, P.-Q. *Synlett* **2008**, 1189–1192. (e) Fu, R.; Du, Yu; Li, Z.-Y.; Xu, W.-X.; Huang, P.-Q. *Tetrahedron* **2009**, *65*, 9765–9771. For an improved procedure for the preparation of (*S*)-glutarimides **2**, see: (f) Ruan, Y.-P.; Wei, B.-G.; Xu, X.-Q.; Liu, G.; Yu, D.-S.; Liu, L.-X.; Huang, P.-Q. *Chirality* **2005**, *17*, 595–599.

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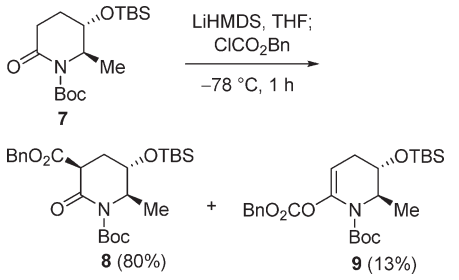
(10) For examples on the hydroxyl group directed ring opening of an epoxide, see: (a) Tius, M. A.; Fauq, A. H. *J. Org. Chem*. **1983**, *48*, 4131–4132. (b) Marshall, J. M.; Cleary, D. G. *J. Org. Chem*. **1986**, *51*, 858–863. (c) Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc*. **1986**, *108*, 1035–1039. (d) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc*. **2000**, *122*, 3830–3838. (e) Makino, K.; Suzuki, T.; Awane, S.; Hara, O.; Hamada, Y. *Tetrahedron Lett*. **2002**, *43*, 9391–9395. (f) Hong, Z.-Y.; Chen, X.-C.; Xu, X.-X. *Tetrahedron Lett*. **2003**, *44*, 485–488. (g) Morokuma, K.; Takahasi, K.; Ishihara, J.; Hatakeyama, S. *Chem. Commun*. **2005**, 2265–2267. (h) Krishna, P. R.; Lopinti, K. *Synlett* **2007**, 1742–1744.

SCHEME 2



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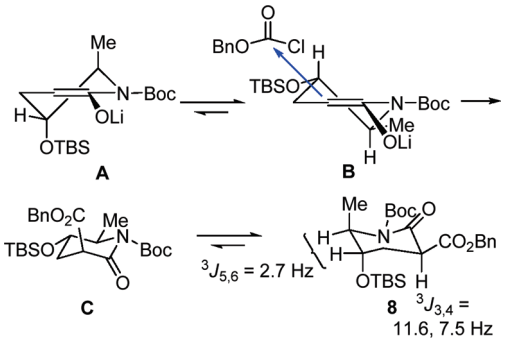
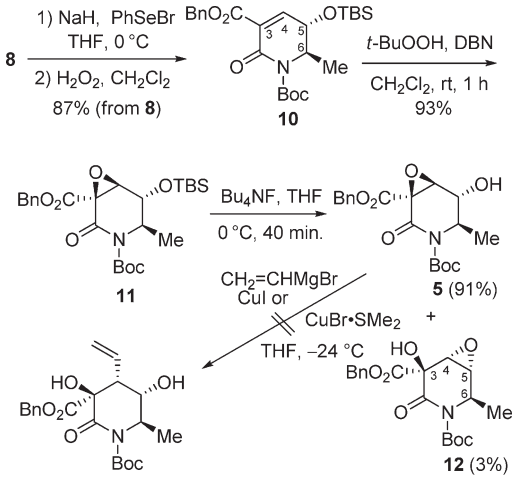


catalytic transfer hydrogenation of the corresponding propargyl alcohol[12] used in our previous synthesis of *ent*-awajanomycin,[6] were exploited for the synthesis of the chiral nonracemic allylic alcohol moiety **4**.

For the synthesis of segment *ent*-**3**, we first investigated route A (cf. Scheme 1). As outlined in Scheme 2, deprotonation of the known *N*-Boc-amide **7**[6] with LiHMDS at −78 °C followed by trapping the resultant enolate with benzyl chloroformate produced smoothly the desired product **8** as a single diastereomer in 80% yield, along with 13% of the *O*-benzyloxycarbonylation product **9**, which showed a characteristic downfield signal of the olefinic proton at δ_H 4.78 (t, J = 3.7 Hz). The stereochemistry at the newly formed stereocenter in **8** was established by NOESY experiments, which implicated that the stereochemical outcome of the reaction was the same with what we previously observed in

SCHEME 4



the benzylation[13a] and opposed to the nonhydroxylated δ-lactam systems.[13b−f]

Formation of the diastereomer **8** could be explained on the basis of the predominant conformer **B**, where the two substituents OTBS and Me were both in favorable equatorial orientations (Scheme 3). Then, a stereoelectronic controlled addition[14] led to **C**, which underwent a fast conformational equilibrium to give **8**.[15] The conformation of **8** was deduced from the small coupling constants between the protons at C-5 and C-6 ($^3J_{5,6}$ = 2.7 Hz) as well as the large coupling constants between the protons at C-3 and C-4 ($^3J_{3,4}$ = 11.6, 7.5 Hz). The preferential axial orientation of protected hydroxyl groups in saturated δ-lactams has been reported.[15]

The carbon−carbon double bond was introduced[16] by successive treatment of compound **8** with NaH and PhSeBr at 0 °C, followed by oxidation of the resultant crude α-phenyl selenide with a 30% aqueous hydrogen peroxide in CH_2Cl_2 and in situ elimination of the resultant selenoxide, which produced compound **10** in 87% yield (Scheme 4). Epoxidation of **10** was performed with *tert*-butyl hydroperoxide (TBHP) in the presence of DBN[17] at rt for 1 h giving stereospecifically the epoxide **11** in 93% yield. The stereochemistry of the epoxide was determined by the observed correlation between H-4 and $SiCH_3$ in the NOESY spectrum, and the stereochemical outcome of the reaction might be attributed to the steric effect of the OTBS group. To carry out a hydroxyl group-directed regio- and diastereoselective epoxide ring-opening reaction,[10] *O*-desilylation was first undertaken. Treatment of a THF solution of **11** with tetrabutylammonium fluoride at 0 °C provided the desired epoxy alcohol **5** in 91% yield, along with 3% of the

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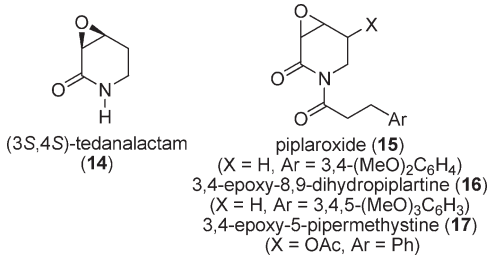


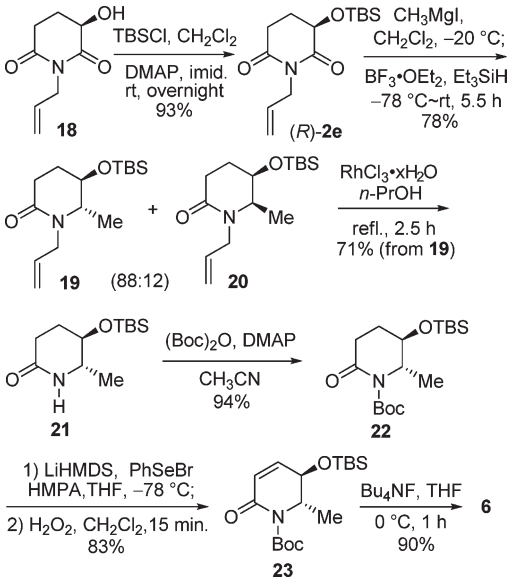
FIGURE 3. Some *cis*-3,4-epoxy-2-piperidone alkaloids.

Payne rearrangement[18] product **12**. It is noteworthy that the partial conversion of the epoxide **5** to **12** was also observed by standing a pure sample of **5** in a refrigerator.

We next investigated the key vinylative ring-opening of epoxide **5** in the hope of obtaining the vinylated product **13**. A literature search revealed that addition of carbon nucleophiles to epoxyesters could take place chemoselectively at either ester[19a,d] or epoxide[19a−c] moiety, and CuI or CuBr·SMe_2-mediated additions of Grignard reagents led to epoxide ring-opening products.[19a−c] For 2,3-epoxypropanoates and their homologues in particular, the regiospecific ring-opening at the β-position can be achieved by various organometallic compounds.[10g,19f,19g] However, all attempts to perform a CuI or CuBr·SMe_2-mediated addition of vinylmagnesium bromide to **5** were unsuccessful. No desired product was isolated, instead, products arising from the addition of the vinyl group to the ester group and the *N*-Boc group were observed. The failure to achieve the chemo- and regio-selective β-vinylation was attributed to the severe steric hindrance of the ring system **5** (vide infra).

In spite of the unsuccessful attempts to serve as an advanced intermediate for the synthesis of (+)-awajanomycin, the enantioselective construction of highly functionalized *cis*-3,4-epoxy-2-piperidone motif **5** is of value in organic synthesis. Such a skeleton is found in some bioactive natural products; however its enantioselective synthesis has been rarely reported.[20] For example, the mother nucleus *cis*-3,4-epoxy-2-piperidone (**14**, tedanalactam) (Figure 3), isolated from sponge *Tedania ignis*[21a] and leaves of *Piper crassinervium* (Piperaceae),[21b] displays promising fungicidal activity. Its *N*-acyl derivative, piplaroxide **15**, is an ant-repellant alkaloid isolated from *Piper tuberculatum*,[22a] 3,4-epoxy-8,9-dihydropiplartine **16** was isolated from the leaves[22b] and twigs of *Piper verrucosum*, and 3,4-epoxy-5-pipermethystine **17** was isolated from roots of the kava shrub

SCHEME 5



(*Piper methysticum*).[22c] In addition, epoxy piperidines have been shown to possess cytotoxicity.[23]

Thus, this approach was abandoned, and we turned to investigate route B (cf. Scheme 1). In view of the synthesis of natural enantiomer (+)-awajanomycin, (*R*)-*N*-allyl-3-hydroxyglutarimide **18** was prepared from D-glutamic acid by following the procedure described for its enantiomer.[7e,f] *O*-Silylation (TBSCl, DMAP, imidazole, CH_2Cl_2, rt, overnight) gave the building block (*R*)-**2e** in 93% yield (Scheme 5). Treatment of (*R*)-**2e** with MeMgI in CH_2Cl_2 at −20 °C produced the C2 and C6 adducts in 90:10 ratio. Without separation, the crude adducts (a regio- and diastereomeric mixture) were subjected to $BF_3\cdot OEt_2$-mediated Et_3SiH reduction (−78 °C to rt, 5.5 h), giving lactam **19** and its diastereomer **20** in an 88:12 ratio with a combined yield of 78%. The high regio- and diastereoselectivities observed for the stepwise reductive methylation of glutarimide derivative **2e** were in contrast with the similar reactions of the *N*-benzyl, *O*-TBS protected malimide, where low regio- and diastereoselectivities (C2/C6 addition = 64:36; dr = 82:18) were obtained.[24] Treatment of the major diastereomer **19** with 5 mol % of $RhCl_3$ hydrate in refluxing *n*-propanol[25] for 2.5 h cleaved the *N*-allyl group to give lactam **21** in 71% yield. During the formation of the *N*-Boc-activated lactam **22**, a remarkable solvent effect[26] was observed. Among the tested solvents (THF, NMP, MeCN, Py, CH_2Cl_2), acetonitrile turned out to be the best [$(Boc)_2O$, DMAP (cat.), MeCN], which afforded **22** in 94% yield. The introduction of a double bond into compound **22** was achieved in 83% yield by phenylselenylation followed by oxidative elimination. Desilylation of compound **23** under standard conditions (TBAF, THF, 0 °C, 1 h) produced the requisite amide (5*R*,6*S*)-**6** in 90% yield.

We then explored the hydroxyl-directed vinylation reaction.[11] Treatment of γ-hydroxy-α,β-unsaturated amide (5*R*,6*S*)-**6** with vinylmagnesium bromide (3.0 equiv) at −78 °C for 1.5 h

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(24) (a) He, B.-Y.; Wu, T.-J.; Yu, X.-Y.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2003**, *14*, 2101–2108. (b) Ye, J.-L.; Huang, P.-Q.; Lü, X. *J. Org. Chem.* **2007**, *72*, 35–42.

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SCHEME 6

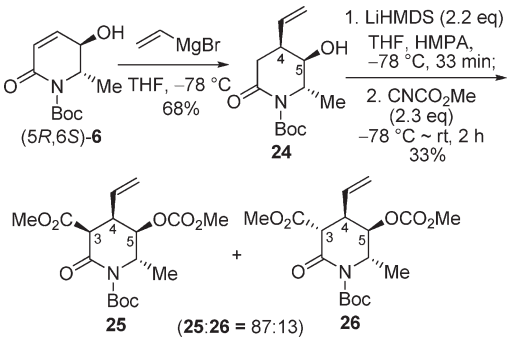
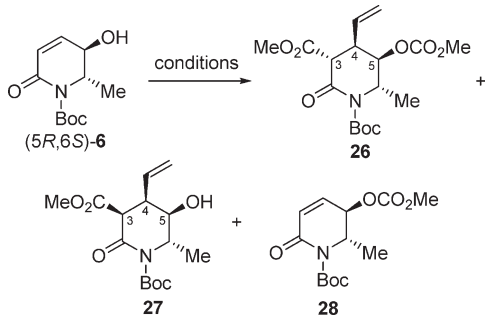


TABLE 1. Conditions Tried for the One-Pot Conversion of 6 into 26



entry	conditions	yield (%)
1	CH_2=CHMgBr (2.5 equiv), $ZnCl_2$ (2.5 equiv), $CNCO_2CH_3$ (3 equiv), HMPA (5 equiv), THF	**28** (73)
2	CH_2=CHMgBr (2.5 equiv), $ZnMe_2$ (2.5 equiv), $CNCO_2CH_3$ (3 equiv), HMPA (5 equiv), THF	**26** (36) + **28** (34)
3	CH_2=CHMgBr (5 equiv), $AlEt_2Cl$ (5 equiv), $CNCO_2CH_3$ (5 equiv), HMPA (5 equiv), CH_2Cl_2	**26** (36)
4	CH_2=CHMgBr (2.5 equiv), $CNCO_2CH_3$ (3 equiv), DMPU (5 equiv), THF	**26** (34) + **27** (19)
5	CH_2=CHMgBr (2.5 equiv), $CNCO_2CH_3$ (3 equiv), HMPA (5 equiv), THF	**26** (49) + **27** (9)

produced the desired 4,5-*cis*-adduct **24** as a single diastereomer in 68% yield (Scheme 6). The stereochemistry at C-4 of **24** was established on the basis of the observed correlations between H-4 and H-5 as well as H-4 and CH_3 in the NOESY spectrum. To our surprise, successive treatment of compound **24** with 2.2 equiv of LHMDS and 2.3 equiv of Mander's reagent ($CNCO_2Me$)[27] gave the concomitantly *C*,*O*-bis-methoxycarbonylated compound **25** and its diastereomer **26** in 33% combined yield with a ratio of 87:13 (determined by ^{1}H NMR). The 3,4-*cis*-stereochemistry for diastereomer **25** was assigned on the basis of the observed correlation between H-3 and H-5 in the NOESY spectrum, while no such a correlation was observed for its diastereomer **26**. Formation of *C*,*O*-bis-methoxycarbonylated compound **25** as the major product is somewhat surprising because the Mander's reagent is known to be a chemoselective *C*-methoxycarbonylation reagent. Although unexpected, it was discovered that compound **25** would be a useful substrate for the subsequent hydroxylation. However, efforts to improve the yields on both steps failed, which prompted us to perform a one-pot transformation of **6** to **25**.

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SCHEME 7

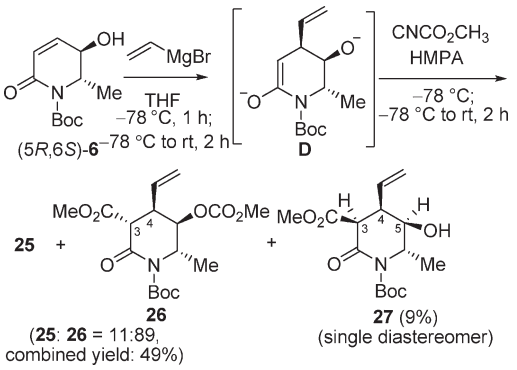
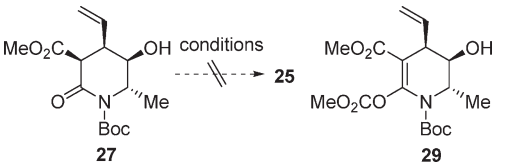


TABLE 2. Conditions Tried for the Conversion of Compound 27 into Compound 25



entry	conditions	yield (%)
1	DMAP, NEt_3, $CNCO_2CH_3$, THF	NR
2	NaH, $CNCO_2CH_3$, THF	NR
3	NaH, $CNCO_2CH_3$, THF, HMPA	NR
4	NaH (2.2 equiv), $ClCO_2CH_3$ (2.1 equiv), THF, HMPA (5 equiv)	**29** (62)

After extensive investigations, including use of organozinc reagents generated from $ZnCl_2$[28] or $ZnMe_2$,[29] or organoaluminum reagent generated from $AlEt_2Cl$[30] (cf. Table 1), we found that use of vinylmagnesium bromide as the vinylation reagent and HMPA as a cosolvent gave the best result (Table 1, entry 5). Thus, compound (5*R*,6*S*)-**6** was successively treated with 2.5 equiv of vinylmagnesium bromide and 3.0 equiv of the Mander's reagent ($CNCO_2Me$) in a mixed THF-HMPA (HMPA: **6** = 5:1 molar ratio) solvent system at −78 °C, then the reaction was warmed to rt and stirred for 2 h. Using this method, *C*,*O*-bis-methoxycarbonylated compounds **25** and **26** were obtained in 49% yield and in 11: 89 diastereomeric ratio (determined by ^{1}H NMR) in favor of the 3,4-*trans*-diastereomer **26**, alongside with compound **27** in 9% yield (Scheme 7). The structures of diastereomer **26** and its 3,4-*cis*-diastereomer **25** were ascertained by comparing with their corresponding enantiomers,[6] and the structure of compound **27** was determined on the basis of analytical and spectroscopic methods including NOESY experiment.

We next tried to transform compound **27** into **25**. However, all attempts to perform *O*-methoxycarbonylation of the hydroxyl group with the Mander's reagent in the presence of either triethylamine or NaH failed (Table 2, entries, 1−3). The starting **27** remained intact. When methyl chloroformate

(28) (a) Dunkerton, L.; Euske, J. M.; Serino, A. J. *Carbohydr. Res*. **1987**, *171*, 89–107. (b) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett*. **2006**, *8*, 4799–4801.

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(30) Rodeschini, V.; Boiteau, J. G.; Weghe, P. V. D.; Tarnus, C.; Eustache, J. *J. Org. Chem*. **2004**, *69*, 357–373.

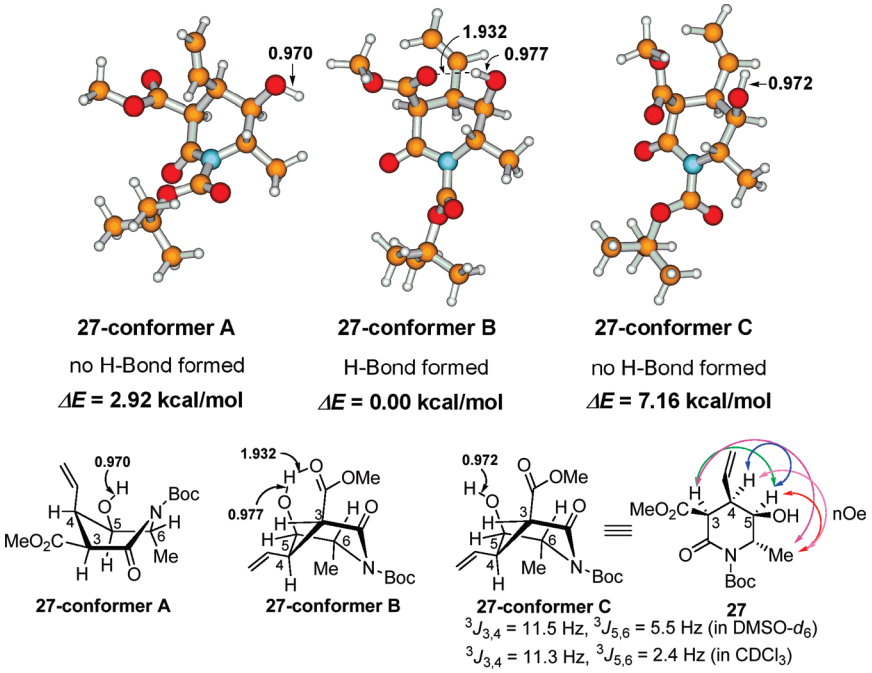


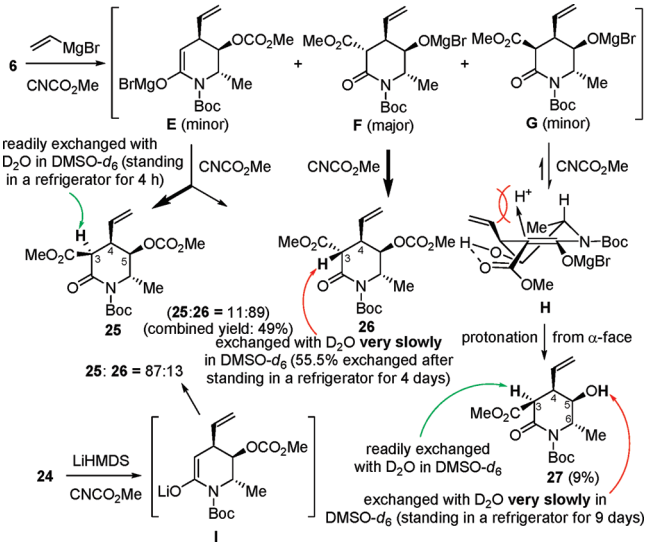
FIGURE 4. B3LYP/6-31G*-optimized geometries and relative energies of three conformers of **27** together with 2D NOESY correlations: no intramolecular hydrogen bond formed (**27**-conformers A, C) and intramolecular hydrogen bond formed (**27**-conformer B). Distances of O−H bonds are given in angstroms.

was used as a methoxycarbonylation reagent, compound **29**[31] was obtained in 62% yield.

The failure to convert compound **27** into compound **25** led us to study the structure of this compound in detail. To this end, quantum chemical calculations at B3LYP/6-31G* level were undertaken, and three stable conformers of **27**, conformers A−C, were located, which all adopt a boat conformation. As observed from Figure 4, the formation of an intramolecular H-bond was indicated by a short distance (1.932 Å) between H (5-OH) and O (3-CO) in **27**-conformer B, which was more stable than the no H-bonding **27**-conformer A by 2.92 kcal/mol, although in the latter case both C3 and C5 substituents disposed the equatorial orientation. In contrast, another non-H-bonding **27**-conformer C, whose C3 and C5 substituents also adopt axial orientation as those of **27**-conformer B, was less stable than **27**-conformer A by 4.24 kcal/mol. In addition, the ^{1}H NMR experiments also provided evidence that a strong intramolecular H-bond existed: the resonance peak of H-3 (δ 4.00) readily exchanged with D_2O in DMSO-d_6, while that of the hydroxyl group at C-5 (δ 7.07) exchanged very slowly. A complete exchange was observed only after standing in a refrigerator for nine days. Consequently, the hydroxyl group was fairly inert to any acylation. The DEPT 90 experiments, which selectively acquired methine carbon resonance, also indicated that H-3 (δ 4.00) exchanged readily with D_2O in DMSO-d_6. The methine C-3 peak was recorded at 52.6 ppm in DMSO- d_6 in DEPT 90 spectrum, while the peak was not shown when D_2O was added. It was suggested that H-3 exchanged with D_2O and the methine C-3 was converted to a quaternary carbon, which cannot be recorded in a DEPT 90 spectrum.

(31) We were unable to purify this compound, which prohibited its full characterization.

SCHEME 8



In contrast with the high acidity of the H-3 of diastereomer **27**, the H-3 of diastereomer **26** was much less acidic: after standing in a refrigerator for 4 days, only 55.5% of the resonance peak of H-3 (δ 3.58) was exchanged with D_2O in DMSO-d_6.

At this stage, we have a clearer image about the mechanism of the reaction (Scheme 8). First, the conjugate addition of vinylmagnesium bromide was followed by the capture of the resultant enolate intermediate with the Mander's reagent, leading to the formations of enolate **E**, and alcolates **F** and **G**, with the conformer **F** as the predominant intermediate. Further reaction of alcolates **F** with Mander's reagent produced the desired **26**, while for alcoholate **G**, due to the high acidity of the H-3, a proton exchange occurred spontaneously

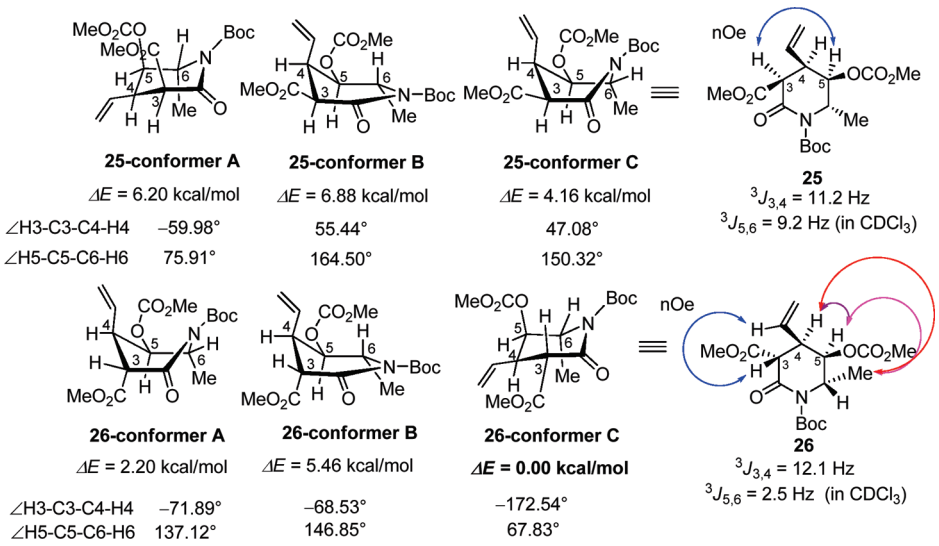
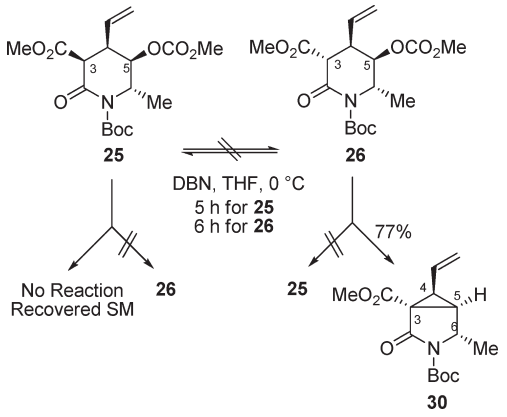


FIGURE 5. B3LYP/6-31G*-optimized conformers and relative energies of **25** and **26** together with 2D NOESY correlations.

SCHEME 9



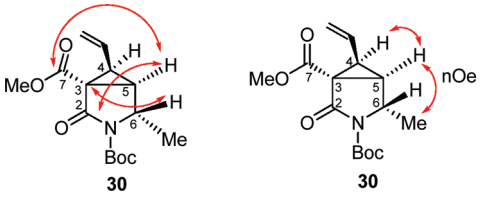


FIGURE 6. 2D HMBC and NOESY correlations of **30**.

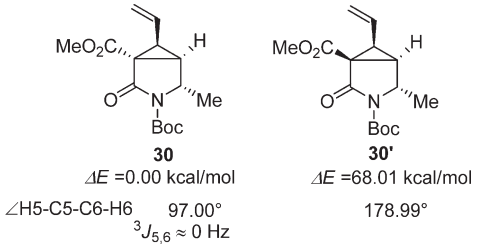


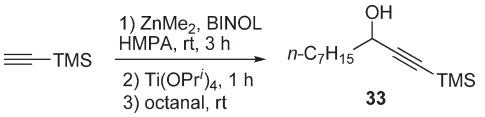
FIGURE 7. B3LYP/6-31G*-optimized geometries and relative energies of **30** (with *R* configuration at C-3) and **30′** (with *S* configuration at C-3).

to give enolate **H**, which was stabilized by the H-bonding. Under the control of both $A^{1,2}$-interaction and stereoelectronic effect, protonation of the intermediated **H** then gave diastereomer **27** as a sole diastereomer. In the case of stepwise vinylation−methoxycarbonylation (cf. Scheme 6), it was possible that methoxycarbonylation first occurred to give lithium enolate **I**, which reacted, via a conformation similar to that displayed in Scheme 3 (conformer **A**), with a second Mander's reagent to give **25** as the major diastereomer. However, for what reason was lithium enolate **I** formed as the primary intermediate in the stepwise manner (Scheme 6) while magnesium alcoholate **F** formed predominantly in the tandem reaction (Scheme 7) remained unclear.

To get an insight into the conformations of the diastereomers **25** and **26**, we also undertook quantum chemical calculations at B3LYP/6-31G* level. As shown in Figure 5, diastereomer **25** prefers a boat conformation with axial H-3, H-5, H-6, and equatorial H-4, which is in agreement with the coupling constant between H-3 and H-4 ($J_{3,4}$ = 11.2 Hz) and H-5 and H-6 ($J_{5,6}$ = 9.2 Hz), while diastereomer **26** preferentially adopts a chair conformation with equatorial H-5, H-6, and axial H-3, H-4, which is in agreement with coupling constant between H-3 and H-4 ($J_{3,4}$ = 12.1 Hz), H-5 and H-6 ($J_{5,6}$ = 2.5 Hz). Diastereomer **26** is more stable than **25** by 4.16 kcal/mol; thus, **26** is the thermodynamically more stable product. Unexpectedly, in an attempt to convert epimer **25** into **26** by treatment of **25** with DBN in THF at 0 °C for 5 h, the expected epimer **26** was not observed; instead, the starting **25** was recovered (Scheme 9). More interestingly, treatment of epimer **26** with DBN in THF at 0 °C for 6 h led to bicyclic product **30** in 77% yields.

The structure of compound **30** was determined by $^1H-^1H$ COSY combined with HSQC, HMBC, and DEPT-135 techniques. The C3−C5 bond formation was confirmed by the connectivities around the quaternary carbon, i.e., C-3/H-6, C-2/H-5 and C-7/H-5, which was established by a HMBC experiment (Figure 6). The NOEs detected between H-4/H-5 and H-5/CH_3 suggested *R* configuration at C-5. However, the relative stereochemistry at C-3 could not be established by NOESY experiments. To tackle this problem, quantum chemical calculations were undertaken once again.

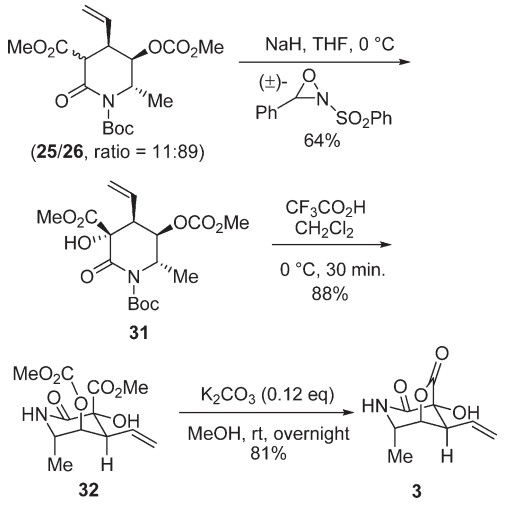
TABLE 3. Asymmetric Addition of Alkynylzinc Reagents to Octanal



entry	alkyne (equiv)	$ZnMe_2$ (equiv)	BINOL (equiv)	$Ti(OPr^i)_4$ (equiv)	solvent	time (h)	yield (%)	% ee (config)
1	4	4	*R* (0.4)	1.0	CH_2Cl_2	5.5	36	86.7 (*S*)
2	4	4	*S* (0.4)	1.0	CH_2Cl_2	30	76	84.5 (*R*)
3	4	4	*R* (1.0)	2.5	CH_2Cl_2	26	70	83.5 (*S*)
4	4	4	*R* (1.0)	2.5	toluene	26	93	77.5 (*S*)
5	6	6	*R* (1.0)	2.5	CH_2Cl_2	26	92	83.2 (*S*)
6	6	$ZnEt_2$, 6	*R* (1.0)	2.5	CH_2Cl_2	18, 0 °C	87	78.4 (*S*)

n-octanal (1.0 molar equiv)

SCHEME 10

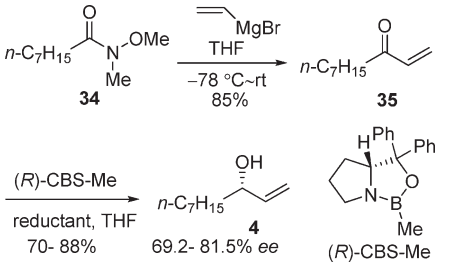


As the computational results showed (Figure 7), **30** (with *R*-configuration at C-3) is more stable than **30′** (with *S*-configuration at C-3) by 68.01 kcal/mol, and in **30**, the H5−C5−C6−H6 dihedral angle is 97.00, which is in agreement with the observed coupling constant ($^3J_{5,6} \approx 0$ Hz).

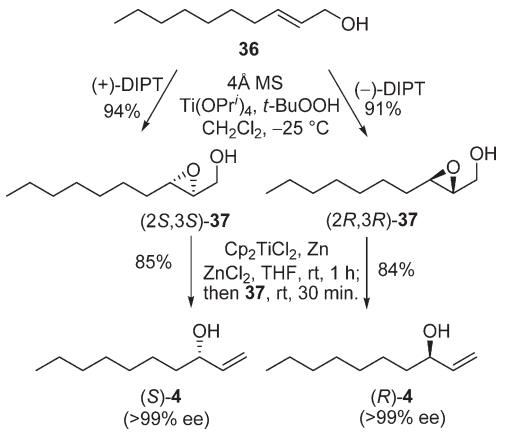
Although the yield of compound **26** was only 49%, taking into account that two C−C bonds and a C−O bond were formed in one-pot, and two adjacent chiral centers were established in a highly *cis*-diastereoselective way, this transformation is both efficient and highly diastereoselective in establishing the C-4 stereogenic center.

As we have demonstrated in the synthesis of (−)-awajanomycin,[6] both diastereomers of compound **26** might be used in the subsequent synthesis of the core structure **3**. Successive treatment of the diastereomeric mixture of compound **26** with sodium hydride and the Davis' oxaziridine[32] in THF at 0 °C afforded compound **31** as a single diastereomer in 64% yield (Scheme 10). Cleavage of the *N*-Boc group by treatment of compound **31** with trifluoroacetic acid in CH_2Cl_2 at 0 °C for 30 min smoothly gave lactam **32** in 88% yields. Finally, stirring a methanolic solution of **32** in the presence of 1.2 equiv of K_2CO_3, as described for its enantiomer[6] afforded the segment **3** in 58% yield. Using only 0.12 molar equiv of K_2CO_3, the yield was significantly improved to 81%. Thus, starting from glutarimide derivative (*R*)-**18**, segment **3** was synthesized in 10 steps with an overall yield of 8.1%, which is a significant improvement when compared to the synthesis of *ent*-**3** (4.9%).[6]

SCHEME 11



SCHEME 12



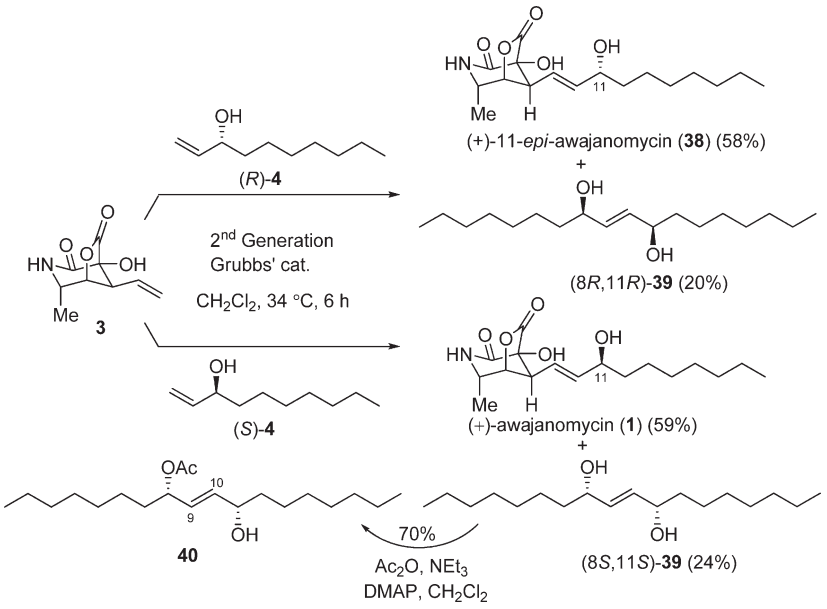
We next focused on the synthesis of the chiral lipid side chain **4**. In our previous synthesis, five steps were required for either enantiomer of **4**,[6] herein we set to explore a more efficient method. We first studied the enantioselective addition of monoprotected ethyne to *n*-octanal.[33] The method of Pu and co-workers was tried.[34] As can be seen from Table 3, only moderate enantioselectivities (78%-87% ee) were obtained.

(32) (a) Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **1999**, *1*, 451–453. (b) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684–685. (c) White, J. D.; Shin, H.; Kim, T. S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, *119*, 2404–2419. (d) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348.

(33) For a recent review on the enantioselective addition of alkyne nucleophiles to carbonyl groups, see: Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983.

(34) (a) Gao, G.; Xie, R.-G.; Pu, L. *Proce. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417–5420. (b) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146. (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886.

SCHEME 13



Other catalytic systems[35,36] were also tried and were shown to be not reactive enough.

We next tried another approach. Vinyl ketone **35** was then prepared from Weinreb amide[37] **34** by reaction with vinylmagnesium bromide. The enantioselective reduction by Corey's method [(*R*)-CBS-Me, $BH_3 \cdot Me_2S$ or $BH_3 \cdot NEt_2Ph$, −78 to +20 °C],[38] however, gave the corresponding allylic alcohol in only 69−82% ee and 70−88% yields (Scheme 11).

Finally, the protocol developed by Yadav and co-workers[39] was attempted. To this end, commercially available *E*-allylic alcohol **36** was subjected to the Sharpless asymmetric epoxidation[40] to give the 2,3-epoxy alcohol (2*S*,3*S*)-**37** in 94% yield (Scheme 12). Titanium(III) [$(C_5H_5)_2TiCl$]-induced regioselective deoxygenation of **37** led smoothly to the formation of (*S*)-dec-1-en-3-ol **4** in 85% yield. The enantiomeric excess of (*S*)-**4** was determined to be >99% by chiral HPLC analysis of its *O*-benzyloyl derivative. Using (−)-DIPT in the Sharpless asymmetric epoxidation, and following the same procedure as that described for (2*S*,3*S*)-**37**, (*R*)-**4** was obtained in 84% yield and >99% ee. In that way, from commercially available *E*-allylic alcohol **36**, (*S*)-**4** and (*R*)-**4** were synthesized in just two steps, respectively, with high overall yields (79.4% and 76.4%) and excellent enantioselctivities (>99% ee).

The stage was set for the key cross-olefin metathesis reaction. In the presence of 20 mol % of Grubbs' second-generation catalyst,[41] the coupling of segment **3** with segment (*R*)-**4** in CH_2Cl_2 at 34 °C for 6 h proceeded smoothly to give 11-*epi*-awajanomycin (**38**) in 58% yield (based on **3**), along with the homocoupling product (8*R*,11*R*)-**39** in 20% yield (based on *R*-**4**) (Scheme 13).

Similarly, the cross-coupling of segment **3** with segment (*S*)-**4** catalyzed by the same catalyst afforded (+)-awajanomycin (**1**) in 59% yield, along with the homocoupling product (8*S*,11*S*)-**39** in 24% yield. It should be mentioned that the reaction in toluene at 70 °C gave poorer yields (22% of **1** and 17% of **39**). The ^1H and ^{13}C NMR spectroscopic data of the two synthetic products (**1** and its C-11 epimer **38**) are in accordance with those of the natural product, which prohibited the identification of the natural product from two synthetic products. By comparing the optical rotation data of the two synthetic diastereomers with that of the natural product [synthetic **1**: $[\alpha]^{20}_D$ +70.9 (*c* 0.6, CH_3OH) [lit. $[\alpha]^{20}_D$ +78 (*c* 0.1, CH_3OH)] for natural product;[4] $[\alpha]^{20}_D$ −70.5 (*c* 0.21, CH_3OH) for its synthetic enantiomer;[6] **38**: $[\alpha]^{20}_D$ +47.5 (*c* 0.52, CH_3OH)], compound **1** was determined as the natural product (+)-awajanomycin (**1**). Through the total synthesis of the natural (+)-**1** and its C-11 epimer **38**, we further confirmed the absolute configuration of the natural (+)-awajanomycin as 3*R*,5*R*,6*S*,8*S*,11*S*.

It should be noted that, in our previous communication,[6] the stereochemistry of the homocoupling products (8*R*,11*R*)-**39** and (8*S*,11*S*)-**39** was assigned as *Z* on the basis of the estimated small coupling constants of the proton at C-9 of the homocoupling products (J = 3.8, 1.9 Hz). Considering that the cross-metathesis of **3** and **4** led to *E*-olefins such as **38** and **1**, the *Z*-geometry previously assigned for the homocoupling products came into question. It should be recognized

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that diol **39** is a C_2-symmetric chiral molecule, the protons at C-9 and C-10 are equivalent, and do not have a coupling constant (it was confirmed by decoupling the proton at C-8). Therefore, it was not possible to determine the geometry of the C−C double bond according to the coupling constant. To tackle this problem, diol **39** was monoacetylated (Ac_2O, NEt_3, DMAP, CH_2Cl_2) to give compound **40**. From the vicinal coupling constant of the protons at C-9 and C-10 of compound **40** ($J_{9,10}$ = 15.6 Hz), the stereochemistry of olefin **40** was determined as *E*. Thus, diols (8*R*,11*R*)-**39** and (8*S*,11*S*)-**39** each possessed a *E*-geometry. The *Z*-geometry previously assigned for the homocoupling products[6] should be revised as *E*, and the observed coupling constants *J* = 3.8, 1.9 Hz should be reassigned to $^3J_{8,9}$ and $^4J_{9,11}$ respectively. This is also proven by the observed absorption at 970 cm^{-1} in the IR spectrum of **39**, which is an indication of an *E*-olefin (990−960 cm^{-1} for *E*-olefins; 725−675 cm^{-1} for *Z*-olefins).

Conclusion

We have reported the first total synthesis of the natural product (+)−awajanomycin (**1**) and its diastereomer (+)−11-*epi*-awajanomycin (**38**). Starting from the building block **18** and *E*-allylic alcohol **36**, the diastereodivergent syntheses of **1** and 11-*epi*-awajanomycin **38** have been achieved both in 13 steps with overall yields of 3.8% and 3.6%, respectively. The low reactivity of compound **27** toward methoxycarbonylation agents has been attributed to the presence of a strong intramolecular H-bond on the basis of both quantum chemical calculations and D_2O exchange experiments. That also used to reveal the favored conformations of the intermediates **25** ∼ **27**, which were helpful to understand the mechanism and stereochemical outcome of the tandem reaction (**6** → **26**). Through this work, the absolute configuration of the natural product was further confirmed, and the geometry of the homocoupling products (8*R*,11*R*)-**39** and (8*S*,11*S*)-**39** have been revised as *E*. Comparing with the route developed for the unnatural (−)-awajanomycin (−)-**1**,[6] the improved synthetic route presented herein was three steps shorter, and the overall yield was improved from 1.9% to 3.8%.

Experimental Section

3-Benzyl 1-*tert*-Butyl (3*S*,5*S*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-6-methyl-2-oxopiperidine-1,3-dicarboxylate (8). To a solution of hexamethyldisilazane (HMDS, 0.26 mL, 1.24 mmol) in THF (3.9 mL) at −78 °C was added *n*-butyllithium (0.47 mL, 2.5 M in hexane, 1.18 mmol). After the mixture was stirred for 20 min at −78 °C, a solution of **7** (203 mg, 0.59 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, and benzyl chloroformate (0.1 mL, 0.65 mmol) was added dropwise. The reaction was stirred for 1 h at this temperature before being quenched with saturated aqueous ammonium chloride solution (1 mL). The mixture was extracted with EtOAc (3 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1:10) to give compound **8** (226 mg, yield 80%) and **9** (37 mg, yield 13%).

Compound **8**: white solid; mp 101−102 °C (EtOAc/PE); $[\alpha]^{20}_D$ −8.0 (*c* 0.97, $CHCl_3$); IR (film) ν_{max} 2949, 2934, 2848, 1735, 1715, 1696, 1291, 1241, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.067 (s, 3H), 0.071 (s, 3H), 0.86 (s, 9H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.50 (s, 9H), 2.05 (dddd, *J* = 13.6, 7.5, 3.6, 2.0 Hz, 1H), 2.37 (ddd, *J* = 13.6, 11.6, 2.7 Hz, 1H), 3.83 (dd, *J* = 11.6, 7.5 Hz, 1H), 3.93 (dt, *J* = 3.6, 2.7 Hz, 1H), 4.20 (qdd, *J* = 6.8, 2.7, 2.0 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.26 (d, *J* = 12.4 Hz, 1H), 7.30−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.9, 17.9, 19.4, 25.6, 27.9, 29.1, 47.5, 58.5, 67.1, 67.8, 83.0, 128.1, 128.2, 128.5, 135.6, 152.8, 167.0, 170.4; MS (ESI, *m*/*z*) 500 (M + Na^+, 100). Anal. Calcd for $C_{25}H_{39}NO_6Si$: C, 62.86; H, 8.23; N, 2.93. Found: C, 62.71; H, 8.43; N, 2.83.

***tert*-Butyl (5*S*,6*R*)-2-(benzyloxycarbonyloxy)-5-(*tert*-butyldimethylsilyloxy)-6-methyl-4,5-dihydropyridine-1(2*H*)-carboxylate (9):** pale yellow oil; $[\alpha]^{20}_D$ −65.4 (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 2949, 2930, 2852, 1704, 1680, 1369, 1330, 1299, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.42 (s, 9H), 2.10 (dd, *J* = 18.4, 3.7 Hz, 1H), 2.30 (ddd, *J* = 18.4, 4.3, 3.7 Hz, 1H), 3.79 (dd, *J* = 4.3, 3.2 Hz, 1H), 4.42 (qd, *J* = 7.0, 3.2 Hz, 1H), 4.78 (t, *J* = 3.7 Hz, 1H), 5.19 (d, *J* = 12.2 Hz, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 7.32−7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, 14.1, 18.0, 25.7, 28.0, 28.3, 55.1, 67.9, 69.7, 80.8, 96.6, 128.2, 128.4 (2C), 134.8, 138.5, 152.4, 152.9; MS (ESI, *m*/*z*) 500 (M + Na^+, 100). Anal. Calcd for $C_{25}H_{39}NO_6Si$: C, 62.86; H, 8.23; N, 2.93. Found: C, 62.76; H, 8.18; N, 2.83.

3-Benzyl 1-*tert*-Butyl (5*S*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-6-methyl-2-oxo-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (10). To a suspension of NaH (91.2 mg, 60% in mineral oil, 2.28 mmol) in THF (7 mL) at 0 °C was added dropwise a solution of **8** (726 mg, 1.52 mmol) in THF (4 mL). After the mixture was stirred for 30 min at 0 °C, a solution of phenylselenyl bromide (424 mg, 1.82 mmol) in THF (4 mL) was added. The reaction was stirred for 1 h at this temperature before being quenched with saturated aqueous ammonium chloride solution (3 mL). The mixture was extracted with EtOAc (6 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (8 mL), and 30% aqueous H_2O_2 solution was added dropwise until the reaction was complete by TLC monitoring. The mixture was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C, extracted with CH_2Cl_2 (6 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:10) to give compound **10** (631 mg, 87%) as a white solid: mp 122−124 °C (PE/EtOAc); $[\alpha]^{20}_D$ +148.7 (*c* 0.94, $CHCl_3$); IR (film) ν_{max} 2953, 2930, 2852, 1723, 1704, 1692, 1291, 1268 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.56 (s, 9H), 4.11 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.51 (qt, *J* = 7.0, 1.8 Hz, 1H), 5.29 (d, *J* = 12.5 Hz, 1H), 5.32 (d, *J* = 12.5 Hz, 1H), 7.13 (dd, *J* = 6.0, 1.8 Hz, 1H), 7.32−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.4, 18.0, 18.1, 25.5, 28.0, 57.1, 66.0, 67.2, 83.3, 128.2 (2C), 128.5, 131.0, 135.5, 142.5, 152.4, 158.6, 163.9; MS (ESI, *m*/*z*) 498 (M + Na^+, 100). Anal. Calcd for $C_{25}H_{37}NO_6Si$: C, 63.13; H, 7.84; N, 2.94. Found: C, 63.59; H, 8.04; N, 2.95.

3-Benzyl 1-*tert*-Butyl (3*S*,4*S*,5*R*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-6-methyl-3,4-epoxy-2-oxopiperidine-1,3-dicarboxylate (11). DBN (0.2 mL, 1.64 mmol) was added to a stirring solution of *tert*-butyl hydroperoxide (TBHP, 0.5 mL, 5.5 M solution in nonane, 2.74 mmol) in CH_2Cl_2 (7.7 mL). After the mixture was stirred at room temperature for 20 min, a solution of **10** (651 mg, 1.37 mmol) in CH_2Cl_2 (6 mL) was added at 0 °C. The reaction was stirred for 2 h at 0 °C before being quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with CH_2Cl_2 (7 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:10) to give compound **11** (629 mg, 94%) as a white solid: mp 112−113 °C (PE/EtOAc); $[\alpha]^{20}_D$ +27.3 (*c* 0.94, $CHCl_3$); IR (film) ν_{max} 2961, 2934, 2856, 1758, 1723, 1272, 1256, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.83 (s, 9H),

1.30 (d, J = 7.1 Hz, 3H), 1.52 (s, 9H), 3.61 (dd, J = 3.1, 2.0 Hz, 1H), 4.22 (dd, J = 3.1, 2.0 Hz, 1H), 4.29 (qt, J = 7.1, 2.0 Hz, 1H), 5.22 (d, J = 12.4 Hz, 1H), 5.37 (d, J = 12.4 Hz, 1H), 7.27−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.9, 17.8, 18.7, 25.4, 25.7, 27.8, 57.5, 57.7, 60.4, 67.6, 83.9, 128.1, 128.3, 128.4, 134.9, 151.9, 163.8, 164.4; MS (ESI, m/z) 514 (M + Na^+, 100). Anal. Calcd for $C_{25}H_{37}NO_7Si$: C, 61.07; H, 7.59; N, 2.85. Found: C, 60.91; H, 7.97; N, 2.80.

3-Benzyl 1-*tert*-Butyl (3*S*,4*S*,5*R*,6*R*)-5-Hydroxy-6-methyl-3,4-epoxy-2-oxopiperidine-1,3-dicarboxylate (5). A 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (0.75 mL, 0.75 mmol) was added to a solution of **11** (184 mg, 0.375 mmol) in THF (1.3 mL) at 0 °C. The reaction mixture was stirred for 1 h and then quenched with saturated aqueous NH_4Cl (2 mL). The mixture was extracted with EtOAc (3 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:1) to give compounds **5** (129 mg, 91%) as a colorless oil and a small amount compounds **12** (5 mg, 3%) as a white solid.

Compound **5**: $[\alpha]^{20}_D$ +3.1 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3471, 2976, 2934, 1758, 1276, 1252, 1155, 1132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 7.1 Hz, 3H), 1.51 (s, 9H), 3.49 (d, J = 5.9 Hz, 1H, OH, D_2O exchangeable), 3.76 (dd, J = 2.9, 1.8 Hz, 1H), 4.23−4.28 (m, 1H), 4.35 (qt, J = 7.1, 1.8 Hz, 1H), 5.26 (s, 2H), 7.28−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 27.8, 57.6 (2C), 60.1, 66.7, 67.9, 84.3, 128.2, 128.4, 128.5, 134.7, 151.8, 163.9, 164.6; MS (ESI, m/z) 400 (M + Na^+, 100). Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.21; H, 6.50; N, 3.60.

3-Benzyl 1-*tert*-butyl (3*S*,4*R*,5*R*,6*R*)-3-hydroxy-6-methyl-4,5-epoxy-2-oxopiperidine-1,3-dicarboxylate (12): white solid; mp 105−106 °C (EtOAc/PE); $[\alpha]^{20}_D$ −63.9 (*c* 1.1, $CHCl_3$); IR (film) ν_{max} 3432, 2976, 2934, 1723, 1272, 1241, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, J = 6.8 Hz, 1H), 1.51 (s, 9H), 3.38 (dd, J = 4.1, 2.4 Hz, 1H), 3.41 (dd, J = 4.1, 1.2 Hz, 1H), 4.24 (s, 1H, OH, D_2O exchangeable), 4.79 (qdd, J = 6.8, 2.4, 1.2 Hz, 1H), 5.31 (d, J = 12.4 Hz, 1H), 5.44 (d, J = 12.4 Hz, 1H), 7.28−7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 27.9, 49.9, 52.1, 52.9, 68.7, 77.5, 84.1, 127.8, 128.4, 128.6, 134.7, 151.6, 165.6, 170.3; MS (ESI, m/z) 400 (M + Na^+, 100). Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.40; H, 6.38; N, 3.60.

(*R*)-1-Allyl-3-(*tert*-butyldimethylsilyloxy)piperidine-2,6-dione (2e). To a solution of (*R*)-*N*-allyl-3-hydroxyglutarimide **18** (2.929 g, 17.3 mmol) prepared from D-glutamic acid by the procedure described for its enantiomer[7e] in CH_2Cl_2 (87 mL) were added successively imidazole (2.353 g, 34.6 mmol), 4-(*N,N*-dimethylamino)pyridine (DMAP) (422 mg, 3.5 mmol), and *tert*-butyldimethylsilyl chloride (3.114 g, 20.8 mmol) at room temperature under N_2. After being stirredat rt overnight, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2 (20 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:12) to give compound **2e** (4.550 g, 93%) as a colorless oil: $[\alpha]^{20}_D$ +31.9 (*c* 1.2, $CHCl_3$); IR (KBr) ν_{max} 2953, 2926, 2856, 1731, 1684, 1334, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.87 (s, 9H), 1.90−2.10 (m, 2H), 2.57 (ddd, J = 17.7, 7.0, 5.8 Hz, 1H), 2.84−2.94 (m, 1H), 4.26−4.33 (m, 3H), 5.05−5.15 (m, 2H), 5.68−5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −4.8, 18.1, 25.5, 26.5, 28.9, 41.6, 69.1, 117.1, 131.8, 171.3, 171.8; MS (ESI, m/z) 306 (M + Na^+, 100). Anal. Calcd for $C_{14}H_{25}NO_3Si$: C, 59.32; H, 8.89; N, 4.94. Found: C, 59.23; H, 8.98; N, 5.06.

(5*R*,6*S*)-1-Allyl-5-(*tert*-butyldimethylsilyloxy)-6-methylpiperidin-2-one (19). To a cooled solution (−20 °C) of compound **2e** (2.963 g, 10.5 mmol) in CH_2Cl_2 (70 mL) was added dropwise a 2.0 M solution of CH_3MgI in Et_2O (15.7 mL, 31.4 mmol). The mixture was stirred at −20 °C for 3 h. A saturated aqueous solution of NH_4Cl (15 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The *N,O*-acetal was used in the next step without further purification.

To a cooled solution (−78 °C) of the above residue (*N,O*-acetal) in CH_2Cl_2 (42 mL) were successively added dropwise Et_3SiH (16.6 mL, 105 mmol) and $BF_3\cdot OEt_2$ (3.9 mL, 31.5 mmol). The mixture was stirred at −78 °C for 3 h and then allowed to warm for ∼2.5 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 2:3) to give compound **19** (2045 mg, 69%) and its diastereomer **20** (267 mg, 9%) (diastereomeric ratio = 88:12).

19 (major diastereomer): colorless oil; $[\alpha]^{20}_D$ −81.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2953, 2930, 2852, 1638, 1470, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.17 (d, J = 6.8 Hz, 3H), 1.69−1.78 (m, 1H), 2.00 (dddd, J = 18.6, 11.9, 6.6, 2.1 Hz, 1H), 2.32 (ddd, J = 17.8, 6.6, 2.1 Hz, 1H), 2.62 (ddd, J = 17.8, 11.9, 7.1 Hz, 1H), 3.32−3.40 (m, 2H), 3.83 (dt, J = 4.4, 2.1 Hz, 1H), 4.64 (ddt, J = 15.6, 4.3, 2.8 Hz, 1H), 5.10 (ddt, J = 10.3, 2.8, 1.6 Hz, 1H), 5.22 (ddt, J = 17.2, 2.8, 1.6 Hz, 1H), 5.72 (dddd, J = 17.2, 10.3, 6.8, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.9, 17.9, 18.5, 24.3, 25.6, 26.8, 46.9, 58.5, 69.0, 116.5, 133.1, 169.0; MS (ESI, m/z) 306 (M + Na^+, 100). Anal. Calcd for $C_{15}H_{29}NO_2Si$: C, 63.55; H, 10.31; N, 4.94. Found: C, 63.21; H, 10.12; N, 5.13.

(5*R*,6*R*)-1-Allyl-5-(*tert*-butyldimethylsilyloxy)-6-methylpiperidin-2-one (20). 20 (minor diastereomer): colorless oil; $[\alpha]^{20}_D$ +54 (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 2949, 2926, 2852, 1642, 1470, 1252, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.18 (d, J = 6.6 Hz, 3H), 1.78 (dddd, J = 17.1, 7.8, 4.4, 3.9 Hz, 1H), 1.88−1.99 (m, 1H), 2.40 (ddd, J = 18.2, 9.4, 7.8 Hz, 1H), 2.53 (ddd, J = 18.2, 7.4, 3.9 Hz, 1H), 3.35−3.43 (m, 1H), 3.45−3.52 (m, 1H), 3.98 (dt, J = 10.6, 4.4 Hz, 1H), 4.48 (ddt, J = 15.4, 4.6, 1.7 Hz, 1H), 5.11−5.14 (m, 1H), 5.15−5.17 (m, 1H), 5.76 (dddd, J = 18.1, 9.3, 6.9, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.7, 13.7, 18.0, 25.4, 25.7, 29.0, 47.4, 55.8, 68.2, 116.8, 133.4, 168.8; MS (ESI, m/z) 306 (M + Na^+, 100). Anal. Calcd for $C_{15}H_{29}NO_2Si$: C, 63.55; H, 10.31; N, 4.94. Found: C, 63.30; H, 10.12; N, 5.11.

(5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-methylpiperidin-2-one (21). To a solution of compound **19** (2.264 g, 8.0 mmol) in *n*-PrOH (16 mL) was added $RhCl_3\cdot xH_2O$ (107 mg, 0.4 mmol). The solution was heated to reflux for 2.5 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: EtOAc/PE 1:1) to give compound **21** (1.383 g, 71%) as a white solid: mp 101−103 °C (PE/EtOAc); $[\alpha]^{20}_D$ −25.3 (*c* 0.97, $CHCl_3$); IR (film) ν_{max} 3198, 3089, 2949, 2929, 2852, 1669, 1459, 1404, 1322, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.14 (d, J = 6.4 Hz, 3H), 1.67−1.78 (m, 1H), 1.83−1.91 (m, 1H), 2.26 (ddd, J = 17.8, 8.8, 6.4 Hz, 1H), 2.45 (dt, J = 17.8, 6.1 Hz, 1H), 3.27 (m, 1H), 3.51 (ddd, J = 9.0, 6.4, 3.1 Hz, 1H), 7.05 (br s, 1H, N*H*, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.5, 17.8, 20.2, 25.6, 27.8, 28.3, 54.8, 70.6, 171.8; MS (ESI, m/z) 266 (M + Na^+, 100). Anal. Calcd for $C_{12}H_{25}NO_2Si$: C, 59.21; H, 10.35; N, 5.75. Found: C, 59.03; H, 10.28; N, 5.74.

***tert*-Butyl (5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-methyl-1-oxopiperidine-1-carboxylate (22).** To a solution of **21** (2.624 g, 10.8 mmol) in MeCN (54 mL) were added di-*tert*-butyl dicarbonate (3.2 mL, 14.0 mmol) and 4-(dimethylamino)pyridine (527 mg, 4.3 mmol). The mixture was stirred at room temperature for 48 h. After concentration, the residue was diluted with

EtOAc (25 mL) and H_2O (15 mL). The resultant solution was extracted with EtOAc (15 mL × 3). The organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:8) to give compound **22** (2.553 g, 94% based on recovered starting material **21**, 700 mg, 26.7%) as a white solid: mp 71−72 °C (PE/EtOAc); $[\alpha]^{20}_D$ +2.5 (*c* 0.93, $CHCl_3$); IR (film) ν_{max} 2953, 2930, 2848, 1766, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.88 (s, 9H), 1.16 (d, J = 6.8 Hz, 3H), 1.52 (s, 9H), 1.68−1.77 (m, 1H), 1.97 (dddd, J = 13.8, 11.3, 7.1, 2.6 Hz, 1H), 2.34 (ddd, J = 17.6, 7.1, 2.4 Hz, 1H), 2.68 (ddd, J = 17.6, 11.3, 7.8 Hz, 1H), 3.83 (dt, J = 3.4, 2.6 Hz, 1H), 4.14 (qdd, J = 6.8, 3.4, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −5.0, 17.8, 19.3, 24.6, 25.5, 27.8, 29.4, 58.3, 68.2, 82.3, 152.7, 170.8; MS (ESI, *m*/*z*) 366 (M + Na^+, 100). Anal. Calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68; N, 4.08. Found: C, 59.42; H, 9.51; N, 4.03.

***tert*-Butyl (5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-methyl-2-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (23).** To a solution of hexamethyldisilazane (HMDS, 2.1 mL, 9.85 mmol) in THF (26 mL) at −78 °C was added *n*-butyllithium (3.8 mL, 2.5 M in hexane, 9.5 mmol). After the mixture was stirred at −78 °C for 20 min, a solution of amide **22** (1.300 g, 3.8 mmol) in THF (6 mL) and HMPA (3.3 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, and phenylselenyl bromide (1.003 g, 4.3 mmol) in THF (6 mL) was added. The mixture was stirred for 1 h at −78 °C before being quenched with a saturated aqueous ammonium chloride solution (5 mL). The mixture was extracted with EtOAc (10 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. After dilution with CH_2Cl_2 (12 mL), a 30% aqueous H_2O_2 solution (1 mL) was added dropwise. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) at 0 °C. The resultant mixture was extracted with CH_2Cl_2 (6 mL × 3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:8) to give compound **23** (1.072 g, 83%) as a white solid: mp 65−67 °C (PE/EtOAc); $[\alpha]^{20}_D$ −182 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2949, 2922, 2856, 1770, 1712, 1291, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.86 (s, 9H), 1.17 (d, J = 7.0 Hz, 3H), 1.53 (s, 9H), 3.96 (dd, J = 5.7, 1.6 Hz, 1H), 4.42 (qt, J = 7.0, 1.6 Hz, 1H), 5.97 (d, J = 9.7 Hz, 1H), 6.51 (ddd, J = 9.7, 5.7, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.5, 17.9, 18.2, 25.5, 27.9, 57.3, 66.4, 82.6, 127.2, 139.0, 152.1, 162.2; MS (ESI, *m*/*z*) 364 (M + Na^+, 100). Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 59.80; H, 8.19; N, 4.05.

***tert*-Butyl (5*R*,6*S*)-5-Hydroxy-6-methyl-2-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (6).** To a solution of compound **23** (1.346 g, 3.95 mmol) in THF (13.2 mL) was added a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (7.9 mL, 7.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. After being quenched with saturated aqueous NH_4Cl (5 mL), the mixture was extracted with EtOAc (10 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:1) to give compound (5*R*,6*S*)-**6** (809 mg, 90%) as a white solid: mp 97.5−98.1 °C (PE/EtOAc); $[\alpha]^{20}_D$ −168 (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 3405, 2976, 1762, 1742, 1396, 1373, 1287, 1248, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3H), 1.53 (s, 9H), 3.17 (d, J = 7.0 Hz, 1H, OH, D_2O exchangeable), 4.01 (dd, J = 5.8, 1.4 Hz, 1H), 4.48 (qt, J = 6.9, 1.4 Hz, 1H), 6.01 (d, J = 9.7 Hz, 1H), 6.70 (ddd, J = 9.7, 5.8, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 28.0, 57.4, 65.9, 83.3, 127.6, 139.3, 152.1, 162.2; MS (ESI, *m*/*z*) 250 (M + Na^+, 100). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.80; H, 8.04; N, 5.96.

***tert*-Butyl (4*S*,5*R*,6*S*)-5-Hydroxy-6-methyl-2-oxo-4-vinylpiperidine-1-carboxylate (24).** To a round-bottomed flask containing a THF solution (6.7 mL) of (5*R*,6*S*)-**6** (110 mg, 0.49 mmol) was added, at −78 °C, a 1.0 M solution of vinylmagnesium bromide (1.5 mL, 1.5 mmol) in THF. The mixture was stirred at −78 °C for 1.5 h and allowed to warm to room temperature for 2 h. The mixture was quenched with a saturated NH_4Cl solution (2 mL) and extracted with EtOAc (4 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE 1:3) to give compound **24** (84.6 mg, 68%) as a colorless oil: $[\alpha]^{20}_D$ +21.8 (*c* 1.6, $CHCl_3$); IR (film) ν_{max} 3332, 2979, 2921, 2848, 1753, 1708, 1250, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.8 Hz, 1H), 1.50 (s, 9H), 2.24 (d, J = 3.4 Hz, 1H, OH, D_2O exchangeable), 2.45 (dd, J = 17.0, 6.0 Hz, 1H), 2.68 (dd, J = 17.0, 12.0 Hz, 1H), 2.77−2.85 (m, 1H), 3.81−3.85 (m, 1H), 4.31 (qd, J = 6.8, 2.6 Hz, 1H), 5.16 (dt, J = 17.2, 1.3 Hz, 1H), 5.22 (dt, J = 10.6, 1.1 Hz, 1H), 5.83 (ddd, J = 17.2, 10.6, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 27.9, 33.7, 37.0, 57.6, 70.5, 83.0, 117.1, 137.1, 152.7, 170.2; MS (ESI, *m*/*z*) 278 (M + Na^+, 100); HRMS calcd for $C_{13}H_{21}NNaO_4$ [M + Na^+] 278.1368, found 278.1366.

1-*tert*-Butyl 3-Methyl (3*S*,4*R*,5*R*,6*S*)-5-(Methoxycarboxy)-6-methyl-2-oxo-4-vinylpiperidine-1,3-dicarboxylate (25). To a solution of hexamethyldisilazane (HMDS, 40 μL, 0.21 mmol) in THF (0.5 mL) at −78 °C was added *n*-butyllithium (80 μL, 2.5 M in hexane, 0.2 mmol). After the mxiture was stirred at −78 °C for 20 min, a solution of amide **24** (22.4 mg, 0.09 mmol) in THF (0.4 mL) and HMPA (80 μL) was added dropwise. After the mixture was stirred at −78 °C for 33 min, methyl cyanoformate (20 μL, 0.21 mmol) was added dropwise at −78 °C. The reaction temperature was allowed to rise to room temperature for 2 h. The mixture was quenched with a saturated $NaHCO_3$ solution (1 mL) and extracted with EtOAc (1 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: EtOAc/PE 1:4) to give compound **25** and its diastereomer **26** (10.6 mg, combined yield: 33%) in 87:13 ratio as determined by ^1H NMR.

A sample of pure major diastereomeric (**25**) was obtained by column chromatography. Major diastereomer (**25**): colorless oil; $[\alpha]^{20}_D$ +26.5 (*c* 0.53, $CHCl_3$); IR (film) ν_{max} 2982, 2957, 1784, 1741, 1699, 1439 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, J = 6.8 Hz, 3H), 1.50 (s, 9H), 3.33−3.43 (m, 1H), 3.48 (d, J = 11.2 Hz, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 4.47 (dq, J = 9.2, 6.8 Hz, 1H), 4.73 (t, J = 9.2 Hz, 1H), 5.07−5.20 (m, 2H), 5.66 (ddd, J = 17.0, 10.2, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 28.0, 48.5, 53.0, 53.4, 53.7, 56.0, 82.9, 83.7, 118.9, 133.8, 151.8, 154.6, 167.0, 169.8; MS (ESI, *m*/*z*) 394 (M + Na^+, 100); HRMS calcd for $C_{17}H_{25}NNaO_8$ [M + Na^+] 394.1478, found 394.1487.

1-*tert*-Butyl 3-Methyl (3*R*,4*R*,5*R*,6*S*)-5-(Methoxycarboxy)-6-methyl-2-oxo-4-vinylpiperidine-1,3-dicarboxylate (26). To a round-bottomed flask containing a THF solution (3 mL) of (5*R*,6*S*)-**6** (100 mg, 0.44 mmol) was added, at −78 °C, a 1.0 M solution of vinylmagnesium bromide (1.1 mL, 1.1 mmol) in THF. The mixture was stirred at −78 °C for 1 h and allowed to warm to room temperature. After the mixture was stirred at room temperature for 2 h, methyl cyanoformate (0.1 mL, 1.3 mmol) in THF (1.4 mL) and HMPA (0.38 mL) was added dropwise at −78 °C. The reaction temperature was allowed to warm to room temperature over 2 h. The mixture was quenched with a saturated $NaHCO_3$ solution (2 mL) and extracted with EtOAc (2 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: EtOAc/PE 1:4) to give compound **26** and its diastereomer **25** (80.8 mg, combined yield:

49%) in an 89:11 ratio (determined by ^{1}H NMR), along with compound **27** (12.8 mg, 9%).

A sample of pure major diastereomeric **26** was obtained by column chromatography. Major diastereomer (**26**): white solid; mp 78−80 °C (PE/EtOAc); $[\alpha]^{20}_D$ +78 (*c* 0.91, $CHCl_3$); IR (film) ν_{max} 2984, 2957, 1754, 1712, 1642, 1447 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J = 6.8 Hz, 3H), 1.50 (s, 9H), 3.27−3.34 (m, 1H), 3.69 (d, J = 12.1 Hz, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 4.44 (qd, J = 6.8, 2.5 Hz, 1H), 4.89 (t, J = 2.5 Hz, 1H), 5.17−5.25 (m, 2H), 5.71 (ddd, J = 17.6, 10.3, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 27.9, 40.1, 52.3, 52.6, 55.1, 55.2, 75.7, 83.9, 119.2, 133.5, 152.3, 154.9, 166.0, 169.3; MS (ESI, *m*/*z*) 394 (M + Na^+, 100); HRMS calcd for $C_{17}H_{25}NNaO_8$ [M + Na^+] 394.1478, found 394.1480.

1-*tert*-Butyl 3-methyl (3*S*,4*R*,5*R*,6*S*)-5-hydroxy-6-methyl-2-oxo-4-vinylpiperidine-1,3-dicarboxylate (27): white solid; mp 140−141 °C (PE/EtOAc); $[\alpha]^{20}_D$ −19.5 (*c* 0.97, $CHCl_3$); IR (film) ν_{max} 3377, 2976, 2926, 1786, 1727, 1677, 1517, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, J = 6.9 Hz, 3H), 1.41 (s, 9H), 3.31−3.41 (m, 1H), 3.51 (d, J = 11.3 Hz, 1H), 3.80 (s, 3H), 3.88−4.00 (m, 1H), 4.29 (dd, J = 9.3, 2.4 Hz, 1H), 4.70 (br s, 1H, OH), 5.23 (d, J = 10.3 Hz, 1H), 5.28 (d, J = 17.2 Hz, 1H), 5.74 (ddd, J = 17.2, 10.3, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 28.3, 46.7, 47.1, 53.0, 53.1, 79.8, 84.5, 120.0, 133.0, 154.9, 167.1, 170.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (d, J = 6.8 Hz, 3H), 1.35 (s, 9H), 3.23−3.30 (m, 1H), 3.65−3.80 (m, 1H), 3.70 (s, 3H), 4.01 (d, J = 11.5 Hz, H-3, readily exchanged with D_2O in DMSO-d_6), 4.23 (dd, J = 9.4, 5.5 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 5.18 (d, J = 17.2 Hz, 1H), 5.81 (ddd, J = 17.2, 10.2, 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H, OH, slowly exchanged with D_2O in DMSO-d_6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.0, 28.3, 47.4, 47.5, 52.7 (2C), 77.9, 83.8, 118.4, 134.7, 154.9, 167.8, 170.6; MS (ESI, *m*/*z*) 336 (M + Na^+, 100); HRMS calcd for $C_{15}H_{23}NNaO_6$ [M + Na^+] 336.1423, found 336.1432.

***tert*-Butyl (5*R*,6*S*)-5-(methoxycarboxy)-6-methyl-2-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (28).** white solid; mp 84.2−85.4 °C (EtOAc/PE); $[\alpha]^{20}_D$ −230 (*c* 0.9, $CHCl_3$); IR (film) ν_{max} 2979, 2933, 1750, 1717, 1296, 1263, 1247, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 7.0 Hz, 1H), 1.52 (s, 9H), 3.80 (s, 3H), 4.63 (qt, J = 7.0, 1.6 Hz, 1H), 4.93 (dd, J = 5.8, 1.6 Hz, 1H), 6.17 (dd, J = 9.7 Hz, 1H), 6.68 (ddd, J = 9.7, 5.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 28.0, 54.0, 55.1, 70.2, 83.4, 130.8, 133.9, 151.9, 154.8, 161.1; MS (ESI, *m*/*z*) 308 (M + Na^+, 100). Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.95; H, 6.37; N, 4.78.

1-*tert*-Butyl 3-Methyl (3*R*,4*S*,5*R*,6*S*)-6-Methyl-2-oxo-4-vinyl-1-azabicyclo[3.1.0]hexane-1,3-dicarboxylate (30). To a solution of compound **26** (45 mg, 0.12 mmol) in THF (2.4 mL) was added DBN (0.03 mL, 0.24 mmol) at 0 °C. After being stirred for 6 h at 0 °C, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatograph on silica gel (eluent: EtOAc/PE 1:4) to give compound **30** (27.7 mg, 77%) as a colorless oil: $[\alpha]^{20}_D$ −34.4 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2973, 2927, 1784, 1753, 1720, 1299, 1254, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, J = 6.3 Hz, 3H), 1.50 (s, 9H), 2.25 (d, J = 8.3 Hz, 1H), 2.79−2.85 (m, 1H), 3.80 (s, 3H), 4.04 (q, J = 6.3 Hz, 1H), 5.28−5.35 (m, 1H), 5.43−5.48 (m, 2H); ^{1}H NMR (100 MHz, $CDCl_3$) δ 21.2, 28.0, 33.8(2C), 38.5, 50.6, 52.8, 83.3, 122.4, 127.5, 149.5, 165.3, 168.3; MS (ESI, *m*/*z*) 318 (M + Na^+, 100); HRMS calcd for $C_{15}H_{21}NNaO_5$ [M + Na^+] 318.1317, found 318.1305.

1-*tert*-Butyl 3-Methyl (3*R*,4*S*,5*R*,6*S*)-3-Hydroxy-5-(methoxycarboxy)-6-methyl-2-oxo-4-vinylpiperidine-1,3-dicarboxylate (31). To a suspension of NaH (66.6 mg, 60% in mineral oil, 1.66 mmol) in THF (6 mL) at 0 °C was added dropwise a solution of **26** (475 mg, 1.28 mmol) in THF (4 mL). After the mixture was stirred for 30 min at 0 °C, a precooled (0 °C) THF (2.8 mL) solution of Davis' oxaziridine (468 mg, 1.79 mmol) was added dropwise. The mixture was stirred for 1 h at 0 °C before being quenched by addition of a saturated aqueous ammonium chloride solution. The mixture was extracted with EtOAc (5 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: EtOAc/PE 1:2) to give compound **31** (316 mg, 64%) as a white solid: mp 79−80 °C (PE/EtOAc); $[\alpha]^{20}_D$ +129.7 (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 3447, 2980, 1754, 1719, 1447, 1373, 1264, 1151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J = 6.8 Hz, 3H), 1.53 (s, 9H), 3.07 (dd, J = 8.2, 2.7 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.26 (s, 1H, OH, D_2O exchangeable), 4.49 (qd, J = 6.8, 2.7 Hz, 1H), 4.90 (t, J = 2.7 Hz, 1H), 5.27−5.33 (m, 2H), 6.00 (ddd, J = 18.2, 10.0, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 27.9, 47.3, 53.0, 55.2, 55.5, 75.9 (2C), 84.0, 120.2, 130.9, 151.8, 154.9, 169.7, 170.1; MS (ESI, *m*/*z*) 410 (M + Na^+, 100); HRMS calcd for $C_{17}H_{25}NNaO_9$ [M + Na^+] 410.1427, found 410.1428.

Methyl (3*R*,4*S*,5R,6*S*)-3-Hydroxy-5-(methoxycarboxy)-6-methyl-2-oxo-4-vinylpiperidine-3-carboxylate (32). To a stirring solution of compound **31** (457.4 mg, 1.18 mmol) in anhydrous CH_2Cl_2 (16.9 mL) was added dropwise trifluoroacetic acid (2.0 mL) at 0 °C. After being stirred for 30 min at 0 °C, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatograph (eluent: EtOAc/PE 6:1) to afford compound **32** (296 mg, 88%) as a white solid: mp 178−180 °C (PE/EtOAc); $[\alpha]^{20}_D$ −41.8 (*c* 1.2, CH_3OH); IR (film) ν_{max} 3354, 1754, 1743, 1677, 1642, 1264 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.6 Hz, 3H), 3.02 (dd, J = 9.8, 4.0 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.73−3.85 (m, 1H), 4.49 (s, 1H, OH, D_2O exchangeable), 4.90 (dd, J = 5.9, 4.0 Hz, 1H), 5.22 (dd, J = 16.9, 1.2 Hz, 1H), 5.29 (dd, J = 9.8, 1.2 Hz, 1H), 5.94 (dt, J = 16.9, 9.8 Hz, 1H), 6.72 (br s, 1H, −CON*H*, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 49.2, 50.3, 52.8, 55.1, 75.9 (2C), 120.8, 130.2, 154.8, 169.2, 170.4; MS (ESI, *m*/*z*) 310 (M + Na^+, 100); HRMS calcd for $C_{12}H_{17}NNaO_7$ [M + Na^+] 310.0903, found 310.0898.

(1*R*,4*S*,5*R*,8*S*)-1-Hydroxy-4-methyl-8-vinyl-6-oxa-3-azabicyclo-[3.2.1]octane-2,7-dione (3). To a solution of compound **31** (234 mg, 0.82 mmol) in CH_3OH (8.2 mL) was added K_2CO_3 (13.6 mg, 0.098 mmol) at room temperature. After being stirred at rt overnight, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatograph (eluent: CH_2Cl_2/CH_3OH = 20:1) to afford compound **3** (130 mg, 81%) as a white solid: mp 164−165 °C (CH_2Cl_2/CH_3OH); $[\alpha]^{20}_D$ +56.0 (*c* 1.3, CH_3OH); IR (film) ν_{max} 3291, 2918, 1789, 1677 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (d, J = 6.8 Hz, 3H), 3.33 (d, J = 5.1 Hz, 1H), 3.70 (qt, J = 6.8, 1.7 Hz, 1H), 4.73 (t, J = 1.7 Hz, 1H), 5.29 (dt, J = 10.6, 1.2 Hz, 1H), 5.37 (dt, J = 17.4, 1.2 Hz, 1H), 5.78 (ddd, J = 17.4, 10.6, 6.7 Hz, 1H), 6.07 (s, 1H, −OH, D_2O exchangeable), 8.25 (br s, 1H, −CON*H*, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.1, 44.8, 51.6, 77.0, 78.9, 119.1, 131.3, 165.8, 172.4; MS (ESI, *m*/*z*) 220 (M + Na^+, 100); HRMS calcd for $C_9H_{11}NNaO_4$ [M + Na^+] 220.0586, found 220.0582.

(2*S*,3*S*)-2,3-Epoxydecan-1-ol (37). To a stirring and cooled (−25 °C) suspension of activated powered 4 Å molecular sieves (950 mg) in anhydrous CH_2Cl_2 (19 mL) were added successively, and under a nitrogen atmosphere, (+)-DIPT (263 mg, 1.12 mmol) in anhydrous CH_2Cl_2 (2 mL) and Ti(OPr-*i*)$_4$ (0.27 mL, 0.9 mmol) in anhydrous CH_2Cl_2 (2 mL). After the mixture was stirred for 15 min, allylic alcohol **36** (700 mg, 4.49 mmol) in anhydrous CH_2Cl_2 (3.3 mL) was added and the stirring continued for 30 min. To the resultant mixture was added slowly TBHP (1.0 mL, 5.5 M solution in nonane, 5.5 mmol). After being stirred at the same temperature for 5 h, the reaction was quenched with an aqueous solution (7.6 mL) containing $FeSO_4$ (2.415 g) and citric acid (760 mg). The mixture was stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4,

filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatograph on silica gel (EtOAc/PE = 1:5) to give compound **37** (725 mg, 94%) as a white solid: mp 51.2−51.3 °C (EtOAc/PE); $[\alpha]^{20}_D$ −34.8 (*c* 1.1, $CHCl_3$) [lit.[40] $[\alpha]^{20}_D$ −36.5 (*c* 2.8, $CHCl_3$)]; IR (film) ν_{max} 3421, 3119, 2951, 2918, 2848, 876, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.20−1.40 (m, 8H), 1.40−1.50 (m, 2H), 1.50−1.65 (m, 2H), 1.68 (dd, *J* = 7.3, 5.6 Hz, 1H, *OH*, D_2O exchangeable), 2.90−2.98 (m, 2H), 3.63 (ddd, *J* = 12.5, 7.3, 4.3 Hz, 1H), 3.91 (ddd, *J* = 12.5, 5.5, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.9, 29.2, 29.3, 31.5, 31.7, 56.0, 58.4, 61.7; MS (ESI, *m*/*z*) 195 (M + Na^+, 100).

(*S*)-Dec-1-en-3-ol (*S*-4). To a red solution of Cp_2TiCl_2 (797 mg, 3.2 mmol) in anhydrous THF (11.5 mL) were added zinc chloride (1.3 mL, 1.0 M in Et_2O, 1.3 mmol) and zinc powder (208 mg, 3.2 mmol). The mixture was stirred for 1 h at room temperature while the solution turned green. To the resultant mixture was added epoxide **37** (110 mg, 0.64 mmol) in anhydrous THF (1.3 mL), and the resultant mixture was stirred for 30 min. The reaction was quenched with aqueous HCl (1.0 M, 2.4 mL), and the mixture was extracted with Et_2O (10 mL × 3). The organic layers were successively washed with water, 10% aqueous $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et_2O/PE (30−60 °C) = 1:6) to give compound (*S*)-**4** (84.3 mg, 85%) as a colorless liquid: $[\alpha]^{20}_D$ +8.2 (*c* 1.2, $CHCl_3$) [lit.[42] $[\alpha]^{25}_D$ +13.0 (neat)]; IR (film) ν_{max} 3339, 2954, 2924, 2854, 1595, 991, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.18−1.41 (m, 10H), 1.42−60 (m, 2H), 1.95 (s, 1H, *OH*, D_2O exchangeable), 4.06 (m, 1H), 5.06 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.18 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.83 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 25.3, 29.2, 29.5, 31.8, 37.0, 73.2, 114.4, 141.3; MS (ESI, *m*/*z*) 179 (M + Na^+, 100).

(*R*)-Dec-1-en-3-ol (*R*-4): $[\alpha]^{20}_D$ −8.2 (*c* 1.6, $CHCl_3$) [lit.[6] $[\alpha]^{25}_D$ −8.2 (*c* 1.1, $CHCl_3$)]; $[\alpha]^{20}_D$ −9.4 (*c* 1.4, CH_2Cl_2) [lit.[43] $[\alpha]^{23}_D$ −9.8 (*c* 0.30, CH_2Cl_2)].

(+)-Awajanomycin (1). To a stirring solution of compound **3** (27.4 mg, 0.139 mmol) and (*S*)-**4** (108.5 mg, 0.695 mmol) in CH_2Cl_2 (1.4 mL) was added Grubbs' second-generation catalyst (23.6 mg, 0.028 mmol). After being stirred at 34 °C for 6 h, the mixture was concentrated under reduced pressure. The residue was purified by column flash chromatography (eluent: EtOAc/PE 5:1) on silica gel to give (+)-awajanomycin (**1**) (26.7 mg, 59%) and homocoupling product (8*S*,11*S*)-**39** (23.5 mg, 24%).

(+)-Awajanomycin (**1**): colorless gum; $[\alpha]^{20}_D$ +70.9 (*c* 0.6, CH_3OH); $[\alpha]^{20}_D$ +70.0 (*c* 0.45, CH_3OH) [lit.[4] $[\alpha]^{25}_D$ +78 (*c* 0.1, CH_3OH)]; IR (film) ν_{max} 3320, 2922, 2847, 1794, 1677, 1246, 1151, 979 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.23−1.31 (m, 10H), 1.33−1.41 (m, 2H), 3.29 (d, *J* = 7.2 Hz, 1H), 3.68 (q, *J* = 6.7 Hz, 1H), 3.92 (m, 1H), 4.62 (s, 1H), 4.72 (d, *J* = 4.9 Hz, 1H, 11-OH, D_2O exchangeable), 5.50 (dd, *J* = 15.6, 7.1 Hz, 1H), 5.76 (dd, *J* = 15.6, 5.6 Hz, 1H), 5.96 (s, 1H, 3-OH, D_2O exchangeable), 8.23 (br s, 1H, N*H*, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 18.1, 22.0, 24.8, 28.6, 29.0, 31.2, 37.2, 43.9; 51.6, 70.2, 77.0, 79.7, 121.2, 138.8, 165.9, 172.5; MS (ESI, *m*/*z*) 348 (M + Na^+, 100); HRMS calcd for $C_{17}H_{27}NNaO_5$ [M + Na^+] 348.1787, found 348.1785.

(8*S*,11*S*,*E*)-Octadec-9-ene-8,11-diol ((8*S*,11*S*)-39): white solid; mp 46−48 °C (PE/EtOAc); $[\alpha]^{20}_D$ +7.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3331, 2957, 2922, 2852, 1474, 1013, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.9 (t, *J* = 6.9 Hz, 6H), 1.22−1.43 (m, 20H), 1.45−1.62 (m, 4H), 1.81 (br s, 2H, OH, D_2O exchangeable), 4.08−4.14 (m, 2H), 5.68 (dd, *J* = 3.8, 1.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.4, 29.2, 29.5, 31.8, 37.3, 72.5, 133.9; MS (ESI, *m*/*z*) 307 (M + Na^+, 100). Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76. Found: C, 76.23; H, 12.48.

(+)-11-*epi*-Awajanomycin (38). To a stirring solution of compound **3** (32.2 mg, 0.163 mmol) and (*R*)-**4** (127.5 mg, 0.82 mmol) in CH_2Cl_2 (1.6 mL) was added Grubbs' second-generation catalyst (27.3 mg, 0.032 mmol). After being stirred at 34 °C for 6 h, the mixture was concentrated under reduced pressure. The residue was purified by column flash chromatography (eluent: EtOAc/PE 5:1) on silica gel to give (+)-11-*epi*-awajanomycin (**38**) (30.8 mg, 58%) and homocoupling product (8*R*,11*R*)-**39** (23.4 mg, 20%).

(+)-11-*epi*-Awajanomycin (**38**): colorless gum; $[\alpha]^{20}_D$ +47.5 (*c* 0.52, CH_3OH); IR (film) ν_{max} 3320, 2922, 2847, 1794, 1677, 1246, 1151, 979 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.23−1.31 (m, 10H), 1.33−1.41 (m, 2H), 3.29 (d, *J* = 6.8 Hz, 1H), 3.68 (q, *J* = 6.7 Hz, 1H), 3.92 (m, 1H), 4.62 (s, 1H), 4.72 (d, *J* = 4.9 Hz, 1H, 11-OH, D_2O exchangeable), 5.52 (dd, *J* = 15.7, 6.8 Hz, 1H), 5.75 (dd, *J* = 15.6, 5.5 Hz, 1H), 5.96 (s, 1H, 3-OH, D_2O exchangeable), 8.23 (br s, 1H, N*H*, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 18.1, 22.0, 24.9, 28.6, 29.0, 31.2, 37.2, 43.7, 51.6, 70.2, 77.1, 79.6, 121.1, 138.4, 165.9, 172.5; MS (ESI, *m*/*z*) 348 (M + Na^+, 100); HRMS calcd for $C_{17}H_{27}NNaO_5$ [M + Na^+] 348.1787, found 348.1785.

(8*R*,11*R*,*E*)-Octadec-9-ene-8,11-diol ((8*R*,11*R*)-39): $[\alpha]^{20}_D$ −7.7 (*c* 1.0, $CHCl_3$).

(8*S*,11*S*,*E*)-11-Hydroxyoctadec-9-en-8-yl Acetate (40). To a stirring solution of compound (8*S*,11*S*)-**39** (34 mg, 0.12 mmol) and DMAP (7.3 mg, 0.06 mmol) in CH_2Cl_2 (1.2 mL) were added successively Ac_2O (12 μL, 0.126 mmol) and Et_3N (20 μL, 0.144 mmol). After being stirred overnight at rt, the reaction was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1: 9) to give compound **40** (27.3 mg, 70%) as a colorless oil: $[\alpha]^{20}_D$ −22.2 (*c* 0.7, $CHCl_3$); IR (film) ν_{max} 3448, 2954, 2924, 2851, 1738, 1369, 1238, 1016, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 6H), 1.15−1.40 (m, 20H), 1.40−1.70 (m, 5H, 2 × CH_2, OH, D_2O exchangeable), 2.05 (s, 3H), 4.08 (q, *J* = 6.4 Hz, 1H), 5.22 (q, *J* = 6.5 Hz, 1H), 5.58 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.69 (dd, *J* = 15.6, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (2C), 21.3, 22.6, 25.1, 25.3, 29.2 (2C), 29.3, 29.5, 29.7, 31.7, 31.8, 34.4, 37.1, 72.3, 74.2, 128.9, 135.7, 170.4; MS (ESI, *m*/*z*) 349 (M + Na^+, 100); HRMS calcd for $C_{20}H_{38}NaO_3$ [M + Na^+] 349.2719, found 349.2711.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of new compounds; NOESY of some compounds, HMBC of compound **30**, and chiral HPLC chromatograms of the *O*-benzyloyl derivative of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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