Tetrahedron 65 (2009) 10355–10364

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of (−)-amathaspiramide F

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ARTICLE INFO

Article history:
Received 15 September 2009
Received in revised form 14 October 2009
Accepted 14 October 2009
Available online 31 October 2009

Keywords:
Amathaspiramide F
Enolate Claisen rearrangement
α-Acyloxysilane
Heptamethyldisilazane
Tetrabutylammonium dichlorobromate

ABSTRACT

The stereoselective total synthesis of the marine alkaloid, (−)-amathaspiramide F (**1**), was achieved from the α-hydroxy-α-ethynylsilane **2**. The key steps involved in the synthesis were (1) the enolate Claisen rearrangement of the α-acyloxy-α-alkenylsilane for the stereoselective construction of the consecutive C5 and C9 chiral centers of **1** (*erythro* configuration), (2) the construction of aza-spirohemiaminal **28**, and (3) dibromination during the final stage of the total synthesis. The reaction of the (*Z*)-α-acyloxy-α-alkenylsilane **22** possessing the Boc-homoallylglycine ester as the acyloxy group underwent stereoselective enolate Claisen rearrangement to give the desired *erythro* product **23**. On the other hand, the reaction of the α-acyloxy-α-alkenylsilane (*Z*)-**5** having Boc-proline gave the unexpected *threo* product **6**. Oxidative cleavage of the vinylsilane group of **23** followed by treatment with heptamethyldisilazane as the methylamine equivalent gave aza-spirohemiaminal **28**. The problematic regioselective dibromination to **28** was achieved using *n*-Bu_4NBrCl_2.

1. Introduction

Amathaspiramides A–F were isolated from a New Zealand collection of the marine bryozoan *Amathia wilsoni* by Prinsep and Morris in 1999 (Fig. 1).[1] The structural features common to these

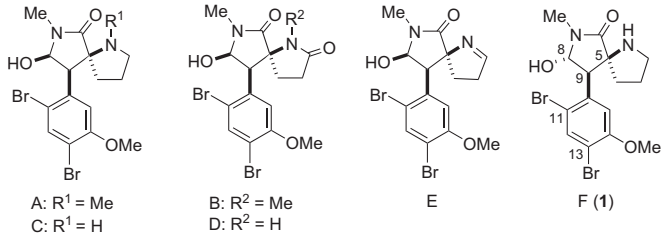

Figure 1. Amathaspiramides.

alkaloids are characterized by a novel aza-spirobicyclic framework that consists of three contiguous chiral centers in which one of the amino groups is attached to the quaternary carbon center, a cyclic hemiaminal moiety, and 11,13-dibrominated aromatic ring (amathaspiramide numbering). Their structures and absolute configurations were determined by the X-ray diffraction analysis of amathaspiramide F (**1**) and extensive NMR studies. Since several natural products containing a cyclic spirolactam or a hemiaminal structure exhibit an important biological activity,[2] amathaspiramides have attracted interest from medicinal chemistry. However, only preliminary biological tests regarding their antimicrobial, antiviral, and cytotoxic activities have been performed for amathaspiramides A–C and E. Amathaspiramide E exhibited a potent antiviral activity (4+, 40 μg/well) against Poliovirus Type-I. Amathaspiramides A and E exhibited moderate cytotoxicity (1+, 40 μg/well) to the BSC-1 cells in addition to a weak antimicrobial activity (1 mm inhibition zone, 60 μg/disk) against the Gram-positive bacterium *Bacillus subtilis* and fungus *Trichophyton mentagrophytes*. Amathaspiramides B and D were inactive against these viruses, cells, bacteria, and fungi. On the other hand, the biological activities of the other congeners have not yet been reported probably due to only minute quantities available from the marine sources. Only two examples for the total synthesis of amathaspiramide F (**1**) have been reported by Trauner and Hughes[3] and our group.[4] Their unique structures together with the unanswered questions surrounding their biological activity prompted us to synthesize these alkaloids. In this report, we describe (1) the stereoselective construction of the consecutive C5 and C9 chiral centers of **1** by the enolate Claisen rearrangement of the α-acyloxy-α-alkenylsilane and (2) the total synthesis of (−)-**1** using this method as the key step.

2. Results and discussion

The optically active α-acyloxy-α-alkenylsilane has received significant attention because of its chirality as well as functional group

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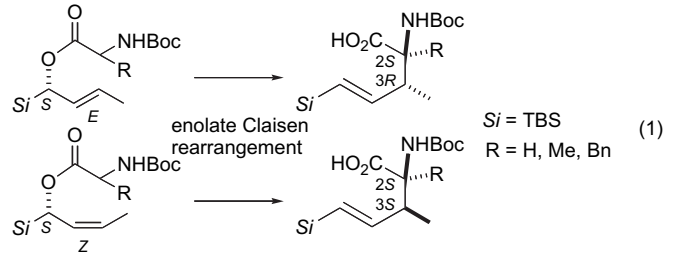
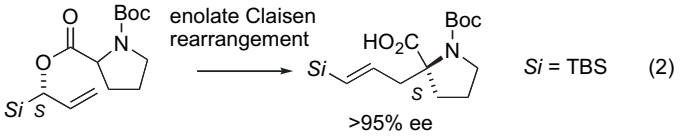
doi:10.1016/j.tet.2009.10.051

transferring properties from the α- to γ-position through a metal-catalyzed cationic rearrangement[5] or an electrocyclic rearrangement with the enolate derived from its acyloxy group.[6] In particular, the $ZnCl_2$-assisted ester-enolate Claisen rearrangement[7] of the α-acyloxy-α-alkenylsilanes having various *N*-protected α-amino acids as the acyloxy group produced the vinylsilane-containing α-substituted α-amino acids with the complete transfer of the original chirality. These results were reported by our previous studies, i.e., (1) the reaction of the (*S*,*E*)- and (*S*,*Z*)-α-acyloxy-α-alkenylsilanes having an *N*-Boc-acyclic amino acid produced the (2*S*,3*R*)- and (2*S*,3*S*)-vinylsilanes, respectively (Eq. 1)[6a–c] and (2) the reaction was also applicable to the (*S*)-α-alkenylsilane having an *N*-Boc-proline to give the optically pure (*S*)-α-substituted proline (Eq. 2).[6d]

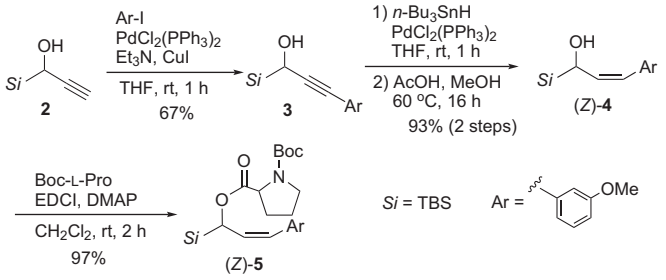




Our plan for the synthesis of **1** was to adopt these methods for the stereoselective construction of the consecutive C5 and C9 chiral centers of **1** as shown in Scheme 1. We chose the (2*S*,3*R*)-*erythro* vinylsilane **B** as the key platform whose oxidative cleavage of the vinylsilane moiety followed by treatment with methylamine would furnish the aza-spirohemiaminal **A**, while the dibromination of **A** leading to a natural product remained uncertain at the planning stage. According to our previous studies in Eqs. 1 and 2, the enolate Claisen rearrangement of the (*S*,*Z*)-α-acyloxy-α-alkenylsilane **C** or **D** would proceed through a chair-like transition state to afford **B** with the requisite (2*S*,3*R*)-configuration. Thus, we planned two routes (route a via (*S*,*Z*)-**C** and route b via (*S*,*Z*)-**D**) for the synthesis of **B**. Route a can minimize the synthetic sequence although the enolate Claisen rearrangement of the disubstituted olefin-containing α-acyloxysilane **C** with an *N*-protected proline is unprecedented.[8,9] On the other hand, the stereochemical outcome of the rearrangement of the *N*-protected acyclic amino acid ester **D** has been well documented (Eq. 1).[6a–c] We considered that route b, which included the pyrrolidine formation from (2*S*,3*R*)-**E**, would complementarily cover the uncertainties of route a. Both intermediates **C** and **D** would be prepared from the (*S*)-α-hydroxy-α-alkynylsilane **F**, which could be synthesized from the α-hydroxy-α-ethynylsilane **2** by the arylation of its alkyne terminus and subsequent oxidation of the hydroxyl group followed by the enantioselective reduction of the resulting ketone.[10] Since the natural **1** possesses a methoxy group at its *meta* position on the aromatic ring, an electrophilic bromination would occur at its 4′ and 6′ positions based on electronic reasons. Therefore, the methoxy substituted aryl group was employed during the initial stage of these synthetic studies.

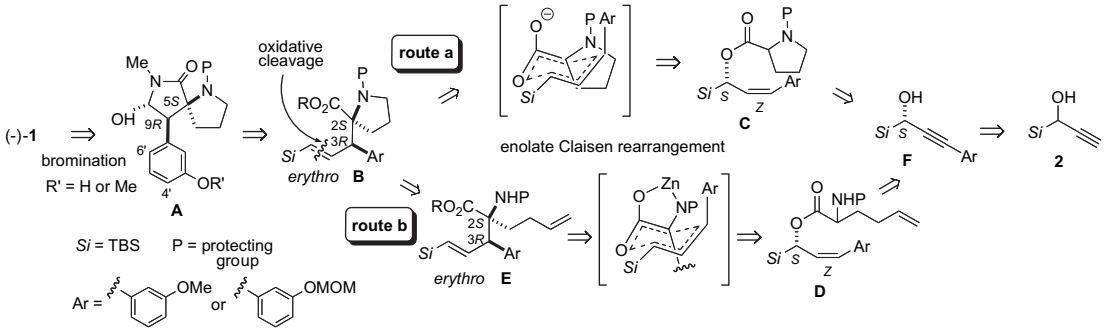
2.1. Synthetic approaches along the line of route a

The synthesis began with the preparation of (*Z*)-α-acyloxy-α-alkenylsilane **5** from the readily available α-hydroxy-α-ethynylsilane **2**[10] (Scheme 2).

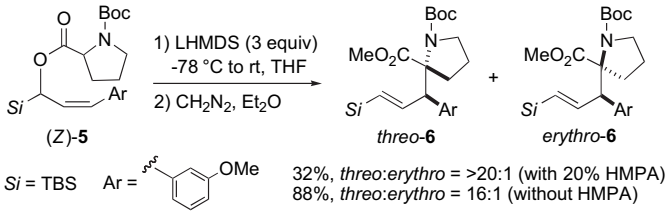


Scheme 2. Synthesis of (*Z*)-**5**.

This compound was prepared in a racemic form for the preliminary examination of the enolate Claisen rearrangement of the disubstituted olefin with *N*-Boc-proline as the acyloxy group. The palladium-catalyzed Sonogashira coupling of **2** with *m*-iodoanisole under standard conditions[11] afforded the desired coupling product **3** in 67% yield. Hydrogenation of **3** to the (*Z*)-olefin **4** using the Lindlar catalyst in several solvents (AcOEt, MeOH, or *n*-hexane) even at high pressure (5 atm) was unsuccessful, resulting in the complete recovery of **3**. The use of Pd/C produced the corresponding alkane. Finally, the conversion of **3** to (*Z*)-**4** was successfully performed by the Pd-catalyzed hydrostanylation followed by treatment with AcOH to give the (*Z*)-olefin **4** (93%, two steps).[12] The esterification of **4** with Boc-L-proline was effected by EDCI in the presence of the catalytic DMAP to give the rearrangement precursor (*Z*)-**5** in 97% yield. The enolate Claisen rearrangement of (*Z*)-**5** under the conditions employed in our previous studies in Eq. 2



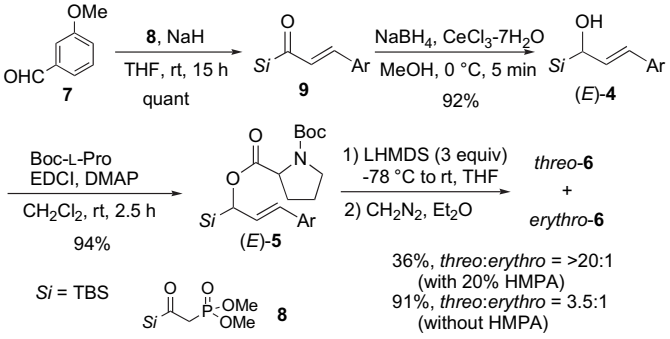
Scheme 1. Synthetic plan.



Scheme 3. Enolate Claisen rearrangement of (*Z*)-**5**.

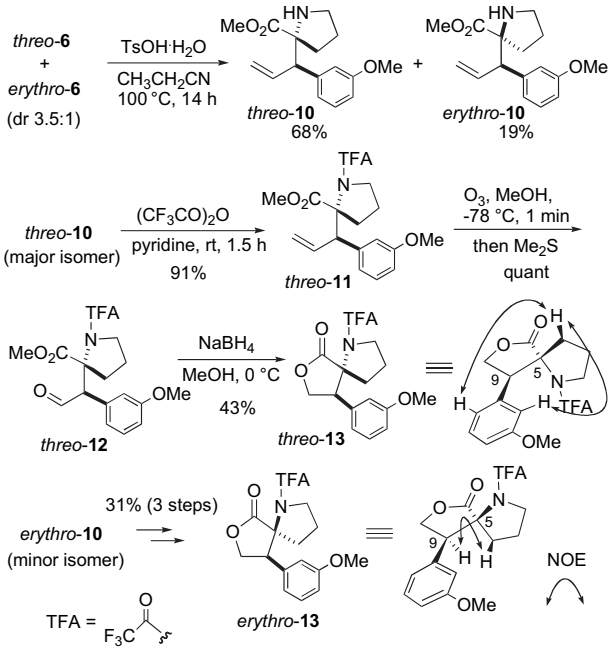
(3 equiv LHMDS in HMPA/THF (1:4) at −78 °C to rt) [6d] gave the rearranged product **6** in 32% yield (Scheme 3). Although the yield was moderate, the diastereoselectivity of this rearrangement was >20:1 (by ^{1}H NMR). The major product either the *threo* or *erythro* isomer was determined by the conversion of **6** to a spirolactone (vide infra, Scheme 5), which revealed that the major isomer was the undesired *threo*-**6**. Without HMPA, the yield increased to 88%, however, the undesired *threo*-**6** was the major product (dr 16:1). These results suggested that the Claisen rearrangement of (*Z*)-**5** did not proceed through the conventional chair-like transition state as shown in Scheme 1. To gain an insight into the enolate Claisen rearrangement of the proline-containing disubstituted olefin, our next attempt was the reaction using an *E*-isomer.

The (*E*)-olefin **5** was prepared from *m*-anisaldehyde (**7**) by the following sequence of reactions (Scheme 4): (1) Horner–Wadsworth–Emmons olefination of **7** with (α-phosphonoacyl)silane **8**,[13] (2) Luche reduction of the resulting (*E*)-silyl ketone **9**,[14] and (3) esterification of the resulting alcohol (*E*)-**4** with Boc-L-Pro (86%, three steps from **7**). However, the enolate Claisen rearrangement of (*E*)-**5** {LHMDS (3 equiv), HMPA/THF (1:4), −78 °C to rt} resulted in the predominant formation of *threo*-**6** in 36% yield (dr >20:1). The *threo* selectivity was decreased to 3.5:1 (91% yield) without HMPA. The 3.5:1 mixture **6**, inseparable by preparative TLC, was converted to the spirolactone **13** for the determination of the relative stereochemistry of **6** (Scheme 5).



Scheme 4. Enolate Claisen rearrangement of (*E*)-**5**.

To avoid the troublesome oxidative cleavage of the vinylsilane,[15] the silyl group of **6** was removed using TsOH to give a mixture of the cyclic amine **10**. Fortunately, the mixture was separable by silica gel column chromatography to give the major isomer-**10** (68%) and the minor isomer-**10** (19%). Each major-**10** and minor-**10** was converted to the corresponding spirolactones major-**13** and minor-**13**, by the following sequence of reactions: (1) protection of the amino group by a trifluoroacetyl (TFA) group, (2) ozonolysis of the olefin **11**, and (3) the reduction of the resulting aldehyde **12** followed by lactonization. The NOE experiments of each spirolactone clearly indicated that the major-**13** possessed the *threo* configuration and the minor-**13** possessed the *erythro* configuration at C5 and C9. These

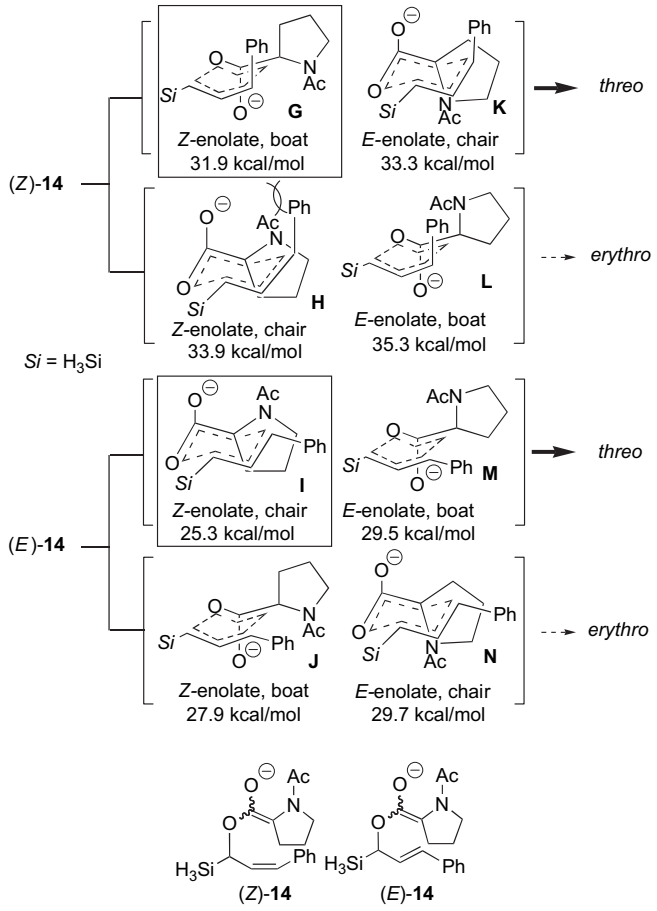


Scheme 5. Determination of relative configuration of *threo*-**6** and *erythro*-**6**.

results suggested that the reaction of (*E*)-**5** proceeded via the conventional chair-like transition state.

In a previous report, we proposed that the enolate Claisen rearrangement of the proline ester with a monosubstituted olefin in the presence of HMPA proceeded through a chair-like transition state with the *Z*-enolate (*Z*/*E*, >98:2) to give the rearrangement product with complete transfer of the original chirality (Eq. 2).[8] However, it was found that the reaction of the disubstituted (*Z*)-olefin **5** produced the undesired isomer *threo*-**6**, suggesting that the reaction did not proceed via the conventional chair-like transition state. To account for the same *threo* selectivity (>20:1) in the enolate Claisen rearrangement of both (*Z*)-**5** and (*E*)-**5** possessing an Ar group at C3, we examined the B3LPY/6-31G* calculations[16] to estimate the activation energy of the enolate Claisen rearrangement using the model enolates (*Z*)-**14** and (*E*)-**14**, where the TBS, *N*-Boc, and Ar groups of **5** were replaced with the H_3Si, *N*-Ac, and Ph groups, respectively (Scheme 6). The calculations were carried out for both the enolates (*Z*)-**14** and (*E*)-**14** with a boat and chair-like transition state (**G**, **H**, **K**, and **L** from (*Z*)-**14** and **I**, **J**, **M**, and **N** from (*E*)-**14**), respectively, while the preferential formation of the monoanionic *Z*-enolate (*Z*/*E*, >98:2) in the presence of HMPA was proposed in our previous studies.[8] According to the calculation of the *Z*-enolate transition state derived from (*Z*)-**14**, the boat-like transition state **G** was found to be more stable (2.0 kcal/mol) than the chair-like **H** probably due to the severe steric repulsion between the Ph group and the *N*-Ac group. Both *E*-enolates with the chair and boat-like transition state structures, **K** and **L**, respectively, showed higher activation energy than that of **G**. These calculations support that (*Z*)-**5** would undergo the enolate Claisen rearrangement via the boat-like **G** to give *threo*-**6** as the major product,[17] which is in good agreement with the experimental result of the high *threo* selectivity (dr >20:1) observed during the conversion of (*Z*)-**5** to *threo*-**6**.

The calculations of the transition state derived from (*E*)-**14** revealed that the chair-like **I** was the most stable transition state form among the other forms, **J**, **M**, and **N**, which agrees with the high *threo* selectivity for the rearrangement of (*E*)-**5** to *threo*-**6** (dr >20:1).[18] These results clearly indicated that the enolate Claisen rearrangement of both the (*Z*)- and the (*E*)-proline-containing α-acyloxy-α-alkenylsilanes **5** gave the undesired *threo*-**6** for the construction of the C5 and C9 stereogenic centers of **1** (route a).

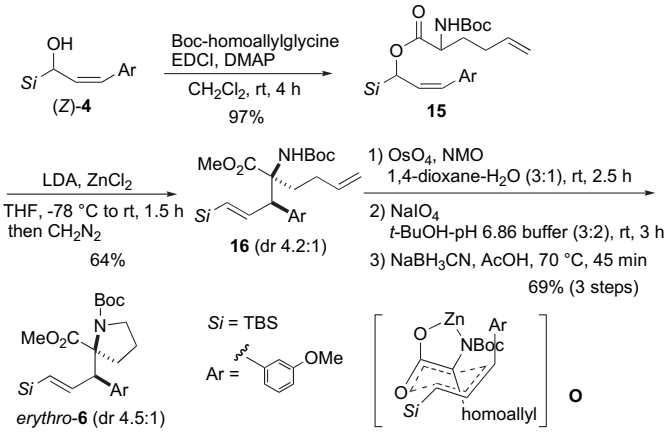


Scheme 6. Activation energies of the enolate Claisen rearrangement of (*Z*)-**14** and (*E*)-**14** by B3LYP/6-31G* calculation.

2.2. Synthetic approaches via route b

Next, we turned our attention to route **b**. We envisioned that the (*S*,*Z*)-α-acyloxy-α-alkenylsilane having the homoallylglycine **D** would undergo the enolate Claisen rearrangement via the chair-like transition state with a dianionic *Z*-enolate to give the (2*S*,3*R*)-*erythro*-**E** (Scheme 1).[6a–c] The rearrangement precursor **15** was prepared by the coupling of (*Z*)-**4** with Boc-homoallylglycine (97%) (Scheme 7). The dianionic enolate Claisen rearrangement of **15** was examined under the established conditions.[6a–c] The treatment of **15** with LDA (3 equiv) and $ZnCl_2$ (1.2 equiv) in THF under −78 °C to rt followed by esterification with CH_2N_2 gave the rearranged product **16** in 64% yield as an inseparable mixture of its diastereomer (dr 4.2:1, by ^1H NMR). The mixture was converted to the desired *erythro*-**6** (dr 4.5:1) by the following sequence of reactions: (1) chemoselective dihydroxylation of the terminal olefin with OsO_4, (2) oxidative cleavage of the resulting diol with $NaIO_4$, and (3) reductive amination with $NaBH_3CN$ in AcOH (67%, three steps from **16**). The ^1H NMR of the resulting *erythro*-**6** was in good agreement with that of the minor isomer **6** synthesized in route a (Scheme 3). Thus, the desired *erythro*-**6** was selectively obtained via route b, which indicated that the $ZnCl_2$-assisted dianionic enolate Claisen rearrangement of **15** preferentially proceeded via the chair-like transition state **O**.

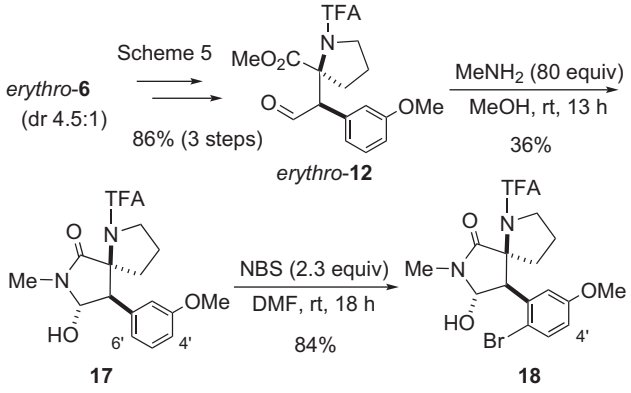
Toward the total synthesis of **1**, the unexploited aza-spirohemiaminal formation and the dibromination of the aromatic group remained to be solved. The preliminary attempts for these transformations are summarized in Scheme 8. The treatment of the diastereomerically pure *erythro*-**12**, prepared from *erythro*-**6** in a manner similar to those of the *threo*-**12** (Scheme 5), with excess



Scheme 7. Synthesis of *erythro*-**6** from (*Z*)-**4**.

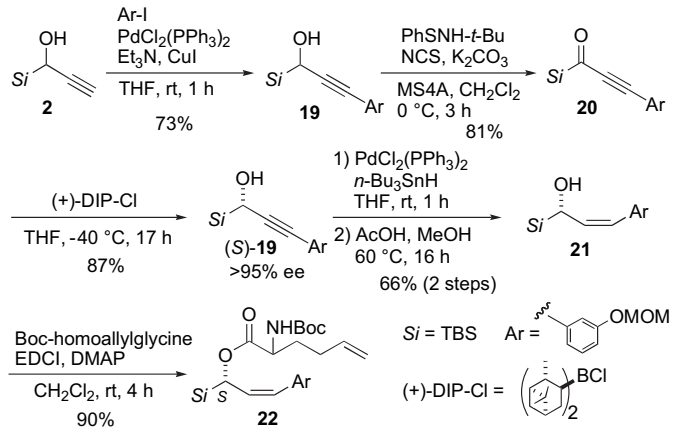
amounts of methylamine in MeOH gave the aza-spirohemiaminal **17**[19] as the exclusive diastereomer in 36% yield. The electrophilic bromination of **17** with NBS (2 equiv) in DMF (rt, 18 h) gave only monobrominated product **18** in 84% yield. However, none of the 4′,6′-dibrominated product was detected even at elevated temperature.[20] The reaction with Br_2 (2 equiv) in CH_2Cl_2 also gave **18** (30%). Numerous attempts for the electrophilic bromination by the addition of TsOH, AcOH or SiO_2 were unsuccessful.[21] These results suggested that the highly reactive phenol is necessary to accomplish the dibromination reaction on the aromatic ring instead of the methoxybenzene moiety of **17**.

To generate the phenol moiety during the late stage of the total synthesis, the methoxymethyl (MOM) group was chosen for its protecting group because this group can be readily removed under



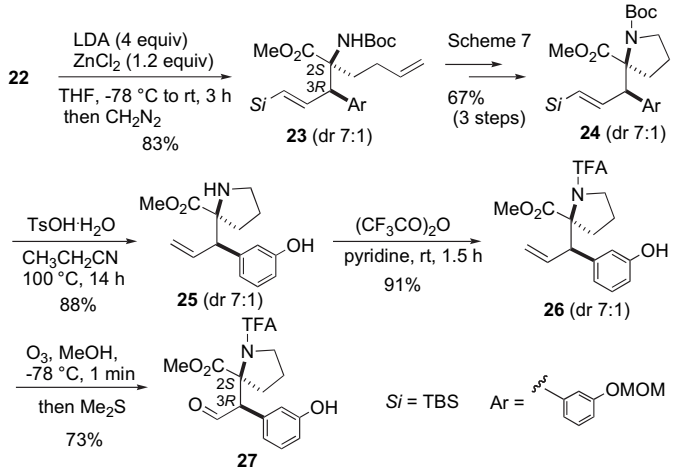
Scheme 8. Synthesis of **18** from *erythro*-**6**.

mild acidic conditions. Toward the enantioselective synthesis of **1** via route b, we synthesized the enolate Claisen precursor (*S*,*Z*)-**22** in an optically active form (Scheme 9). The α-hydroxysilane **19** was prepared by the Sonogashira coupling of **2** with MOM-protected 3-iodophenol (73%). The oxidation of **19** using Jones reagent or other chromium reagents was accompanied by a significant loss of the TBS group to give the silyl ketone **20** in moderate yields. On the other hand, Mukaiyama's oxidation (NCS and catalytic PhSNH-*t*-Bu) afforded **20** in 81% yield without any loss of the TBS group.[22] The enantioselective reduction of **20** by (+)-DIP-Cl[23] gave the optically pure (*S*)-α-hydroxy-α-alkynylsilane **19** (87%, >95% ee). The (*S*,*Z*)-olefin **21** was prepared by the Pd-catalyzed hydrostanylation of (*S*)-**19** followed by the acidic treatment (66%, two steps). The esterification of **21** with racemic Boc-homoallylglycine was effected by EDCI and DMAP to give the (*S*,*Z*)-α-acyloxysilane **22** in 90% yield. The enolate Claisen rearrangement of (*S*,*Z*)-**22** {LDA (4 equiv),



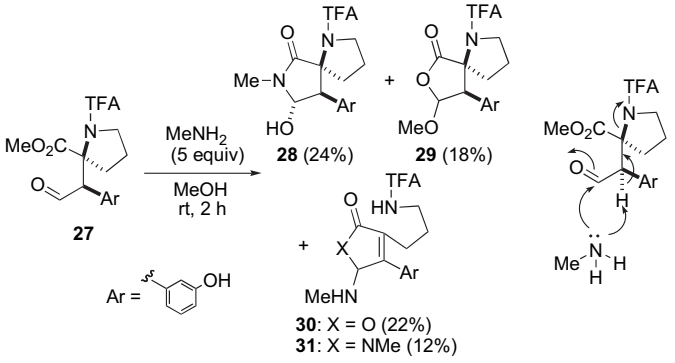
Scheme 9. Synthesis of **22**.

$ZnCl_2$ (1.2 equiv), THF, −78 °C to rt, 3 h, then CH_2N_2} smoothly proceeded to give the desired (2*S*,3*R*)-isomer **23** as an inseparable mixture of its diastereomer[24] (83%, dr 7:1) (Scheme 10).[25] The mixture was converted to the α-substituted proline **24** in a manner similar to the preparation of *erythro*-**6** as shown in Scheme 7 (67%, three steps). The treatment of **24** with TsOH gave the protection-free phenol derivative **25** in 88% yield. Re-protection of the resulting amino group with a TFA group gave **26** (91%), which, upon ozonolysis, afforded the aldehyde **27**. The minor diastereomer was separated at this stage by flash silica gel chromatography to give the diastereomerically pure (2*S*,3*R*)-**27** (73%).

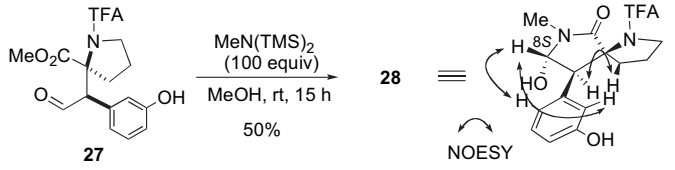


Scheme 10. Synthesis of **27** from **22**.

The final approach to amathaspiramide F was the construction of the aza-spirohemiaminal and the dibromination. The aldehyde **27** was subjected to an excess amount of methylamine in MeOH to give the desired spirohemiaminal **28** as the exclusive diastereomer. However, the yield was moderate (32%) as observed in the preparation of **17** (Scheme 8). Thus, we examined the control experiments of this transformation as follows: the treatment with 5 equiv of methylamine gave a mixture of products consisting of the desired **28** (24%), spirolactone **29**[26] (18%), butenolide **30** (22%), and lactam **31** (12%) (Scheme 11).[27] Further treatment of each product under the same reaction conditions remained unchanged. Presumably, the side products **30** and **31** were produced by the retro-Michael reaction in which methylamine attacked the proton attached to the α-position (Scheme 11). We considered that the sterically bulky heptamethyldisilazane instead of methylamine would prevent the undesired β-elimination reaction. In fact, the treatment of **27** with excess heptamethyldisilazane gave **28** in 50% yield and was reproducible (Scheme 12). The lactam **31** was the only byproduct (12%) isolated from the reaction mixture. The relative stereochemistry of **28** including the hydroxy group at C8 was assigned as shown in Scheme 12 based on its NOE experiments.

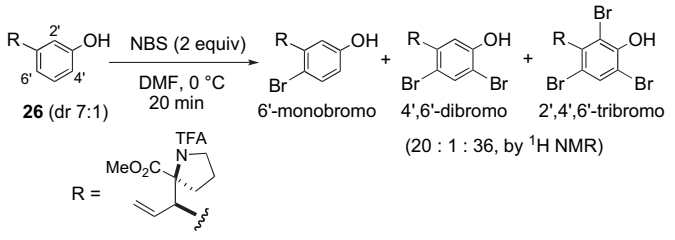


Scheme 11. Construction of aza-spirohemiaminal by $MeNH_2$.



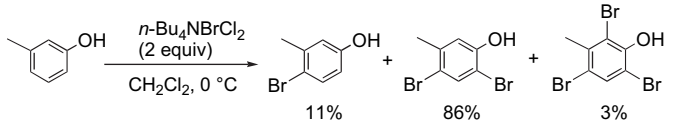
Scheme 12. Construction of aza-spirohemiaminal by $MeN(TMS)_2$.

Prior to the dibromination of **28**, we attempted the dibromination using **26** as a model substrate. However, the ^1H NMR of the reaction mixture indicated that the bromination of **26** with NBS (2 equiv) in DMF at 0 °C afforded a mixture of the 6′-mono- and 2′,4′,6′-tribrominated products as the major products. Only a detectable amount of the desired 4′,6′-dibrominated product was produced (Scheme 13). Increasing amounts of NBS (3 equiv) afforded the 2′,4′,6′-tribrominated product as the exclusive product. Using Br_2 and changing the solvent and temperature, the reaction gave the same products as that of NBS.[28]



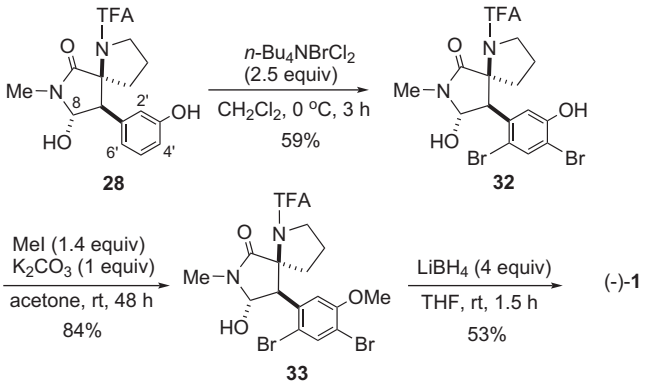
Scheme 13. Bromination of **26** using NBS.

Upon careful survey of the literature regarding electrophilic bromination, Negoro et al. reported that tetrabutylammonium dichlorobromate (n-Bu_4NBrCl_2) is an effective reagent for the electrophilic *o*,*p*-dibromination of phenols as a mild source of bromonium chloride (Scheme 14).[29] Thus, we examined the



Scheme 14. Dibromination of 3-methylphenol using n-Bu_4NBrCl_2.

dibromination using Negoro's conditions. The reaction of **28** with *n*-Bu_4NBrCl_2 (2.5 equiv) in CH_2Cl_2 smoothly proceeded to give the desired 4′,6′-dibrominated product **32** in 59% yield (Scheme 15) accompanied by a trace amount of the 6′-monobrominated product. Finally, etherification of the phenol moiety of **32** (MeI, K_2CO_3, acetone, rt, 48 h) afforded the *N*-TFA protected amathaspiramide F (**33**) (84%), which was Trauner's synthetic intermediate.[3] The TFA group was removed by $LiBH_4$ to give the (−)-amathaspiramide F (**1**) (53%). The spectroscopic data of the synthetic (−)-**1** were in good agreement with those of the natural product.[30]



Scheme 15. Synthesis of (−)-**1**.

In conclusion, we achieved the stereoselective total synthesis of (−)-amathaspiramide F (**1**) from the α-hydroxy-α-ethynylsilane **2** in 17 steps (1.3% overall yield). The key features of the present synthesis are as follows: (1) stereoselective construction of the contiguous C5 and C9 stereogenic centers by the ester-enolate Claisen rearrangement of the α-acyloxy-α-alkenylsilane **22** having an *N*-Boc-homoallylglycine as the acyloxy group, (2) efficient diastereoselective construction of the aza-spirohemiaminal **28** by the use of the sterically bulky heptamethyldisilazane to avoid the undesired β-elimination, and (3) electrophilic 4′,6′-dibromination of the 3′-substituted phenol **28** with *n*-Bu_4NBrCl_2. During the construction of the consecutive C5 and C9 chiral centers, a high *threo* selectivity was observed in the ester-enolate Claisen rearrangement of both the (*E*)- and the (*Z*)-α-acyloxy-α-alkenylsilanes **5** having *N*-Boc-proline as the acyloxy group. The synthesis of other congeners of amathaspiramide (A–E) as well as the biological evaluation of **1** is currently in progress in our laboratories.

3. Experimental section

3.1. General methods

All reagents and solvents were purchased from either Aldrich Chemical Company, Inc., Merck & Co., Inc., Nacalai Tesque Company, Ltd, Peptide Institute, Tokyo Kasei Kogyo Co. Ltd, or Wako Pure Chemical Industries, Ltd, and used without further purification unless otherwise indicated. Dichloromethane (CH_2Cl_2) was distilled from diphosphorus pentaoxide (P_2O_5). Tetrahydrofuran (THF), diethyl ether (Et_2O), acetonitrile (CH_3CN), and dimethylformamide (DMF) of anhydrous grade were used. Ozone was generated by Japan Ozone ON-3-2. Specific optical rotation ($[\alpha]_D$) was taken on a Perkin Elmer 241 polarimeter or JASCO P-1030 polarimeter with a sodium lamp (D line). FTIR spectra were measured on a Jasco FT-IR 420 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on either JEOL JNM-LA 300 (300 MHz), JEOL JNM-LA 400 (400 MHz) or Bruker AVANCE 600 (600 MHz) spectrometer at ambient temperature. Chemical shifts of ^1H NMR were reported in parts per million (ppm, δ) relative to $CHCl_3$ (δ=7.26) in $CDCl_3$. ^{13}C NMR spectra were recorded on either JOEL JNM-LA 300 (75 MHz), JOEL JNM-LA 400 (100 MHz), or Bruker AVANCE 600 (150 MHz) spectrometer. Chemical shifts of ^{13}C NMR were reported in ppm (δ) relative to $CHCl_3$ (δ=77.0) in $CDCl_3$. Low resolution mass spectral (LRMS) analysis and high resolution mass spectral (HRMS) analysis were measured on either JEOL JMS-D300 or JEOL JMS-AX500 spectrometer by means of electron ionization (EI), chemical ionization (CI), or fast atom bombardment ionization (FAB). All reactions were monitored by thin layer chromatography (TLC), which was performed with glass-support precoated plates (Merck Kieselgel 60 F_{254}, 0.25 mm). TLC visualization was accompanied using UV lamp (254 nm) or a charring solution (ethanolic *p*-anisaldehyde, ethanolic phosphomolybdic acid, aqueous potassium permanganate, and butanolic ninhydrin). All products were purified by flash column chromatography on silica gel (Daisogel IR-60 1002 W, 40/63 μm) eluting with a solvent mixture of hexane and ethyl acetate (AcOEt) unless otherwise indicated. The activation energy for the enolate Claisen rearrangement was estimated by the B3LYP/6-31G* single-point energy calculations, based on the optimized transition state structure from Hartree–Fock 3-21G calculations.

Full experimental details and characterization data of *erythro*-**11**, *erythro*-**12**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, **33**, and (−)-**1** were reported.[4]

*3.1.1. 1-(tert-Butyldimethylsilyl)-3-(3-methoxyphenyl)prop-2-yn-1-ol (**3**).* To a solution of $PdCl_2(PPh_3)_2$ (1.72 g, 2.45 mmol), CuI (467 mg, 2.45 mmol), Et_3N (3.4 mL, 36.77 mmol), and iodoanisole (3.7 mL, 31.86 mmol) in THF (44 mL) was added dropwise **2** (4.17 g, 24.51 mmol) in THF (18 mL) at rt, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was exposed to saturated NH_4Cl and was extracted with ether. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=30:1) to give **3** (4.56 g, 67%) as yellow oil: FTIR (neat) 3446, 2216, 2171, 1604, 1576, 1489, 1481, 1464, 1429, 1391, 1363, 1316, 1289, 1249, 1206, 1175, 1165, 1082, 1048, 1014 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, *J*=8.0 Hz, 1H), 6.99 (d, *J*=8.0 Hz, 1H), 6.93 (m, 1H), 6.85 (dd, *J*=8.0, 2.6 Hz, 1H), 4.44 (s, 1H), 3.80 (s, 3H), 1.51 (br s, 1H), 1.02 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 129.3, 124.4, 123.8, 116.3, 114.3, 90.4, 87.9, 55.2, 55.0, 26.9, 17.0, −7.8, −8.4; HRMS (EI) *m*/*z* calcd $C_{16}H_{24}O_2Si$ for $(M)^+$ 276.1546, found 276.1547.

*3.1.2. (Z)-1-(tert-Butyldimethylsilyl)-3-(3-methoxyphenyl)prop-2-en-1-ol {(Z)-**4**}.* To a solution of $PdCl_2(PPh_3)_2$ (117 mg, 0.167 mmol) and **5** (4.6 g, 16.7 mmol) in THF (30 mL) was added dropwise tributyltin hydride (5.4 mL, 19.9 mmol) in THF (20 mL), and the reaction mixture was stirred at rt for 1 h. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=90:1) to give (*E*)-1-(*tert*-butyldimethylsilyl)-3-(tributylstannyl)-3-(3-methoxyphenyl)prop-2-en-1-ol (9.5 g) with a small amount of impure material. To the resulting (*E*)-1-(*tert*-butyldimethylsilyl)-3-(tributylstannyl)-3-(3-methoxyphenyl)prop-2-en-1-ol were added AcOH (40 mL) and MeOH (80 mL), and the reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was exposed to saturated $NaHCO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=50:1) to give **4** (4.3 g, 93%) as yellow oil: FTIR (neat) 3446, 1597, 1577, 1490, 1464, 1433, 1362, 1255, 1147, 1081, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, *J*=7.6 Hz, 1H), 6.84–6.78 (3H), 6.41 (d, *J*=11.4 Hz, 1H), 5.83 (t, *J*=11.4 Hz, 1H), 4.81 (d, *J*=11.4 Hz, 1H), 3.81 (s, 3H), 1.37 (br s, 1H), 0.96

(s, 9H), 0.09 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 138.4, 133.9, 129.1, 128.0, 121.2, 114.2, 112.5, 62.3, 55.2, 27.0, 17.1, −7.1, −8.7; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{25}O_2Si$ $(M-H)^+$ 277.1624, found 277.1624.

*3.1.3. tert-Butyl (Z)-1-(tert-butyldimethylsilyl)-3-(3-methoxyphenyl)-allyl pyrrolidine-1,2-dicarboxylate {(Z)-**5**}.* To a solution of **4** (404 mg, 1.46 mmol) in CH_2Cl_2 (4.4 mL) were added *N*-Boc-L-proline (631 mg, 2.93 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI, 560 mg, 2.93 mmol), and 4-*N*,*N*-dimethylaminopyridine (DMAP, 18 mg, 0.15 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was exposed to saturated NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=20:1) to give (*Z*)-**5** (673 mg, 97%, a mixture of diastereomers, dr=1:1) as colorless oil: FTIR (neat) 1733, 1699, 1598, 1576, 1489, 1471, 1464, 1393, 1365, 1257, 1160, 1121, 1087, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.20 (1H), 7.11–6.99 (2H), 6.79–6.75 (1H), 6.37–6.33 (1H), 6.03–5.96 (1H), 5.63–5.56 (1H), 4.37 (dd, *J*=8.6, 3.2 Hz, 1/3H), 4.29 (dd, *J*=8.8, 3.7 Hz, 2/3H), 3.82–3.81 (3H), 3.56–3.48 (5/3H), 3.41–3.35 (1/3H), 2.29–2.12 (1H), 2.04–1.97 (1H), 1.93–1.86 (2H), 1.46 (s, 9/3H), 1.42 (s, 18/3H), 0.85 (s, 9/3H), 0.84 (s, 18/3H), −0.00 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.7, 159.59, 159.52, 154.2, 153.8, 138.5, 138.3, 129.4, 129.3, 129.27, 129.25, 128.6, 128.3, 120.97, 120.94, 113.6, 113.3, 113.1, 112.9, 79.9, 79.4, 66.94, 66.88, 59.4, 59.2, 55.2, 46.4, 46.3, 30.8, 29.8, 28.41, 28.37, 26.73, 26.70, 24.3, 23.4, 17.00, 16.97, −7.37, −7.40, −8.02, −8.04; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{41}NO_5Si$ $(M)^+$ 475.2754, found 475.2754. A complex ^{1}H NMR was observed because of a mixture of diastereomers and rotamers.

3.1.4. (R)-1-tert-Butyl 2-methyl 2-{(R*,E)-3-(tert-butyldimethylsilyl)-1-(3-methoxyphenyl)allyl}pyrrolidine-1,2-dicarboxylate (threo-**6**).* To a solution of hexamethyl disilazane (1.0 mL, 4.96 mmol) in degassed THF (7 mL) was added *n*-BuLi in *n*-hexane (4.26 mmol) at −78 °C and the reaction mixture was stirred at −78 °C for 20 min. To the solution was added a solution of (*Z*)-**5** (674 mg, 1.42 mmol) in THF (8 mL). After removing the cooling bath, the reaction mixture was stirred at rt for 1.5 h. The pH of the reaction mixture was adjusted to 1 with 1 N HCl, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue. To a solution of crude residue in diethyl ether was added dropwise a solution of diazomethane in diethyl ether at 0 °C for 1 h. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=20:1) to give *threo*-**6** (612 mg, 88%, dr=16:1) as colorless oil: FTIR (neat) 1748, 1697, 1599, 1454, 1434, 1396, 1248, 1160, 1052, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 1H), 6.83–6.74 (3H), 6.46–6.38 (1H), 5.72 (d, *J*=20.5 Hz, 1/2H), 5.66 (d, *J*=20.5 Hz, 1/2H), 4.76 (d, *J*=6.2 Hz, 1/2H), 4.55 (d, *J*=6.0 Hz, 1/2H), 3.76 (s, 3H), 3.71 (s, 3H), 3.61 (m, 1/2H), 3.43 (m, 1/2H), 2.58–2.35 (2H), 2.18 (m, 1H), 1.86 (m, 1H), 1.53 (m, 1H), 1.46 (9/2H), 1.40 (9/2H), 0.81 (9H), 0.00 (6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 174.3, 159.1, 159.0, 153.8, 153.0, 147.0, 146.8, 142.3, 141.7, 130.1, 130.0, 128.6, 128.3, 122.4, 122.3, 116.2, 116.1, 111.9, 80.4, 79.4, 70.4, 69.9, 55.12, 55.08, 54.1, 52.8, 52.0, 47.91, 47.88, 34.8, 33.1, 28.4, 28.3, 26.42, 26.40, 23.3, 22.7, 16.7, 16.6, −6.0, −6.2, −6.3; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{44}NO_5Si$ $(M+H)^+$ 490.2989, found 490.2977. A complex ^{1}H NMR was observed because of a mixture of rotamers.

According to the procedure described above, (*E*)-**5** (220 mg, 0.46 mmol) was used instead of (*Z*)-**5** to give *threo*-**6** (206 mg, 91%, an inseparable mixture of diastereomers, *threo*/*erythro*=3.5:1) as colorless oil.

*3.1.5. (E)-1-(tert-Butyldimethylsilyl)-3-(3-methoxyphenyl)prop-2-en-1-one (**9**).* To a suspension of NaH (13.2 mg, 0.552 mmol) in THF (1.9 mL) was added the Horner–Emmons reagent **8** (200 mg, 0.752 mmol) at 0 °C under an argon atmosphere. After the reaction mixture was stirred at rt for 5 min, to the mixture was added *m*-anisaldehyde (**7**, 30 μL, 0.251 mmol). The reaction mixture was stirred at rt for 15 h, and then quenched by saturated NH_4Cl. The mixture was extracted with AcOEt, and organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=10:1) to give **9** (72 mg, quant) as pale red oil: FTIR (neat) 1697, 1638, 1624, 1578, 1562, 1488, 1464, 1434, 1392, 1363, 1290, 1274, 1251, 1193, 1159, 1048, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.35–7.29 (2H), 7.15 (d, *J*=7.8 Hz, 1H), 7.07 (m, 1H), 6.99 (d, *J*=16.4 Hz, 1H), 6.94 (dd, *J*=7.8, 2.4 Hz, 1H), 3.83 (s, 3H), 0.97 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 235.3, 159.9, 140.6, 136.3, 131.3, 129.9, 121.0, 116.0, 113.3, 55.3, 26.6, 16.8, −6.1; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{25}O_2Si$ $(M+H)^+$ 277.1624, found 277.1617.

*3.1.6. (E)-1-(tert-Butyldimethylsilyl)-3-(3-methoxyphenyl)prop-2-en-1-ol {(E)-**4**}.* To a solution of **9** (67 mg, 0.243 mmol) and cerium chloride·$7H_2O$ (135 mg, 0.365 mmol) in MeOH (1.2 mL) was added sodium borohydride (11 mg, 0.291 mmol) at 0 °C, and the reaction mixture was stirred for 5 min at 0 °C. The reaction mixture was exposed to saturated NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=30:1) to give (*E*)-**4** (62 mg, 92%) as pale yellow oil: FTIR (neat) 3459, 3001, 2954, 2928, 2884, 2856, 1692, 1640, 1599, 1579, 1489, 1464, 1433, 1391, 1362, 1317, 1287, 1252, 1193, 1156, 1047, 1007 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, *J*=7.9 Hz, 1H), 6.95 (d, *J*=7.9 Hz, 1H), 6.89 (m, 1H), 6.76 (m, 1H), 6.45–6.44 (2H), 4.36 (m, 1H), 3.82 (s, 3H), 1.44 (br s, 1H), 0.99 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 139.1, 133.1, 129.5, 125.2, 118.6, 112.2, 111.6, 67.3, 55.1, 26.9, 17.1, −7.5, −8.9; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{25}O_2Si$ $(M-H)^+$ 277.1624, found 277.1636.

*3.1.7. tert-Butyl (E)-1-(tert-butyldimethylsilyl)-3-(3-methoxyphenyl)-allyl pyrrolidine-1,2-dicarboxylate {(E)-**5**}.* To a solution of (*E*)-**4** (1.09 g, 3.92 mmol) in CH_2Cl_2 (19 mL) were added *N*-Boc-L-proline (1.71 g, 7.84 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 1.51 mg, 7.84 mmol), and 4-*N*,*N*-dimethylaminopyridine (DMAP, 47 mg, 0.39 mmol) and the mixture was stirred at rt for 2.5 h. The reaction mixture was exposed to saturated NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=30:1) to give (*E*)-**5** (1.75 g, 94%, a mixture of diastereomers, dr=1:1) as colorless oil: FTIR (neat) 1745, 1699, 1599, 1579, 1470, 1397, 1365, 1252, 1159, 1087, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.18 (1H), 6.95–6.84 (2H), 6.78–6.73 (1H), 6.47–6.34 (1H), 6.26–6.17 (1H), 5.55–5.46 (1H), 4.45 (m, 38/100H), 4.33 (dd, *J*=8.6, 3.3 Hz, 62/100H), 3.80 (3H), 3.54–3.39 (2H), 2.30–2.14 (1H), 2.10–1.86 (3H), 1.47–1.33 (9H), 0.95 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 172.6, 172.5, 172.3, 159.70, 159.67, 154.22, 154.17, 153.9, 138.9, 138.40, 138.36, 129.8, 129.42, 129.41, 129.32, 129.29, 128.49, 128.45, 127.7, 127.6, 127.4, 127.1, 127.0, 118.8, 118.7, 112.7, 112.54, 112.48, 111.7, 111.62, 111.55, 79.91, 79.86, 79.6, 79.4, 69.6, 69.5, 69.41, 69.37, 69.3, 59.3, 59.2, 59.1, 55.1, 46.5, 46.4, 46.23, 46.20, 30.8, 30.0, 29.9, 29.6, 28.4, 28.3, 28.2, 26.84, 26.81, 24.3, 24.2, 23.5, 23.3, 16.99, 16.96, 16.94, −7.4, −7.85, −7.88, −7.95; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{41}NO_5Si$ $(M)^+$ 475.2754, found 475.2758. A

complex ^{1}H NMR was observed because of a mixture of diastereomers and rotamers.

3.1.8. (R)-Methyl 2-{(R*)-1-(3-methoxyphenyl)allyl}pyrrolidine-2-carboxylate (threo-**10**).* To a solution of *threo*-**6** (50 mg, 0.099 mmol, dr>20:1) in propionitrile (0.2 mL) was added *p*-toluenesulfonic acid monohydrate (170 mg, 0.89 mmol), and the reaction mixture was stirred at 100 °C for 21 h. To the reaction mixture was added saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=10:1) to give *threo*-**10** (24 mg, 88%) as colorless oil: FTIR (neat) 3352, 1732, 1599, 1490, 1455, 1435, 1316, 1260, 1193, 1135, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J*=8.1 Hz, 1H), 6.84–6.82 (2H), 6.73 (m, 1H), 6.30 (dt, *J*=19.3, 9.5 Hz, 1H), 5.19–5.10 (2H), 3.77 (s, 3H), 3.63 (d, *J*=9.5 Hz, 1H), 3.56 (s, 3H), 2.96–2.93 (2H), 2.30 (br s, 1H), 2.14–2.01 (2H), 1.73 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 159.3, 142.8, 137.5, 129.0, 120.6, 117.5, 114.0, 112.0, 72.8, 56.8, 55.0, 51.9, 47.1, 34.3, 25.1; HRMS (CI) *m*/*z* calcd for $C_{16}H_{22}NO_3$ $(M+H)^+$ 276.1599, found 276.1597.

3.1.9. (R)-Methyl 1-(2,2,2-trifluoroacetyl)-2-{(R*)-1-(3-methoxyphenyl)allyl}pyrrolidine-2-carboxylate (threo-**11**).* To a solution of *threo*-**10** (13.2 mg, 0.048 mmol) in CH_2Cl_2 (0.5 mL) were added pyridine (5.8 μL, 0.072 mmol) and trifluoroacetic anhydride (TFAA, 8.1 μL, 0.057 mmol) at 0 °C, and the reaction mixture was stirred at rt for 10 min. The reaction mixture was exposed to saturated $NaHCO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=10:1) to give *threo*-**11** (16.2 mg, 91%) as colorless oil: FTIR (neat) 1750, 1691, 1599, 1584, 1492, 1454, 1351, 1299, 1266, 1226, 1199, 1152, 1118, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J*=7.8 Hz, 1H), 6.80–6.73 (m, 3H), 6.27 (ddd, *J*=17.1, 10.5, 6.6 Hz, 1H), 5.26–5.15 (2H), 4.75 (d, *J*=6.6 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.70 (m, 1H), 2.67–2.51 (2H), 2.22 (m, 1H), 2.06 (m, 1H), 1.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 159.3, 155.3, (q, *J*=36.6 Hz), 140.5, 136.6, 129.0, 121.5, 118.6, 115.8 (q, *J*=283.6 Hz), 115.2, 113.0, 72.5, 55.1, 52.6, 49.6, 48.5 (q, *J*=3.5 Hz), 32.1, 24.2; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{21}NO_4F_3$ $(M+H)^+$ 372.1422, found 372.1426.

3.1.10. (R)-Methyl 1-(2,2,2-trifluoroacetyl)-2-{(R*)-formyl(3-methoxyphenyl)methyl}pyrrolidine-2-carboxylate (threo-**12**).* Ozone was bubbled into a solution of *threo*-**11** (16 mg, 0.043 mmol) in MeOH (3.5 mL) at −78 °C for 1 min (flow rate of O_2: 150 NL/h, which corresponded to 3 g/h of O_3). To the mixture was added dimethyl sulfide (4.8 μL, 0.065 mmol). The mixture was warmed to rt and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=10:1) to give *threo*-**12** (16 mg, quant) as colorless oil: FTIR (neat) 1744, 1690, 1600, 1489, 1455, 1313, 1265, 1233, 1215, 1153, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (d, *J*=1.6 Hz, 1H), 7.26 (t, *J*=8.3 Hz, 1H), 6.89 (dd, *J*=8.3, 1.7 Hz, 1H), 6.73–6.68 (2H), 5.14 (d, *J*=1.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.66 (m, 1H), 2.74–2.54 (2H), 2.47 (ddd, *J*=14.1, 7.5, 3.8 Hz, 1H), 1.98 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 172.0, 160.0, 155.8 (q, *J*=37.2 Hz), 132.0, 129.8, 122.8, 116.0, 115.8 (q, *J*=285.7 Hz), 114.5, 72.0, 56.0, 55.2, 53.2, 48.0 (q, *J*=3.6 Hz), 32.2, 24.4; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{19}O_5NF_3$ $(M+H)^+$ 374.1245, found 374.1196.

3.1.11. (5R,9S*)-9-(3-Methoxyphenyl)-1-(2,2,2-trifluoroacetyl)-1-aza-7-oxa-6-oxospiro[4,4]nonane (threo-**13**).* To a solution of *threo*-**12** (20 mg, 0.054 mmol) in MeOH (0.5 mL) was added sodium borohydride (2.4 mg, 0.064 mmol) at 0 °C, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was exposed to saturated NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=15:1) to give *threo*-**13** (8 mg, 43%) as colorless oil: FTIR (neat) 1787, 1691, 1653, 1494, 1456, 1217, 1148, 1021 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, *J*=8.0 Hz, 1H), 6.90 (dd, *J*=8.0, 2.0 Hz, 1H), 6.72 (d, *J*=8.0 Hz, 1H), 6.64 (d, *J*=2.0 Hz, 1H), 4.71 (t, *J*=8.4 Hz, 1H), 4.62 (dd, *J*=10.9, 8.4 Hz, 1H), 4.50 (dd, *J*=10.9, 8.4 Hz, 1H), 3.80–3.76 (4H), 3.63 (m, 1H), 2.08 (ddd, *J*=12.5, 6.6, 5.1 Hz, 1H), 1.96 (ddd, *J*=12.5, 9.1, 7.0 Hz, 1H), 1.85 (m, 1H), 1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 160.3, 155.9 (q, *J*=37.8 Hz), 135.4, 130.4, 120.3, 116.0 (q, *J*=287.1 Hz), 114.4, 113.5, 70.9, 67.7, 55.2, 48.3 (q, *J*=4.0 Hz), 44.1, 30.2, 23.5; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{17}NO_4F_3$ $(M+H)^+$ 344.1109, found 344.1102.

3.1.12. (S)-Methyl 2-{(R*)-1-(3-methoxyphenyl)allyl}pyrrolidine-2-carboxylate (erythro-**10**).* To a solution of **6** (190 mg, 0.39 mmol, *threo*/*erythro*=3.5:1) in propionitrile (0.5 mL) was added *p*-toluenesulfonic acid monohydrate (664 mg, 3.50 mmol), and the reaction mixture was stirred at 100 °C for 21 h. To the reaction mixture was added saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=30:1) to give *threo*-**10** (73 mg, 68%) and *erythro*-**10** (20 mg, 19%) as colorless oil: FTIR (neat) 3353, 1729, 1636, 1598, 1583, 1490, 1454, 1435, 1314, 1265, 1178, 1122, 1102,1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J*=7.8 Hz, 1H), 6.99 (m, 1H), 6.94 (d, *J*=7.8 Hz, 1H), 6.77 (dd, *J*=7.8, 2.6 Hz, 1H), 6.22 (dt, *J*=15.0, 9.0 Hz, 1H), 5.07 (s, 1H), 5.01 (m, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.63 (d, *J*=9.2 Hz, 1H), 2.91 (dt, *J*=9.7, 7.1 Hz, 1H), 2.78 (dt, *J*=9.7, 6.6 Hz, 1H), 2.25 (br s, 1H), 2.04 (ddd, *J*=13.2, 7.9, 5.7 Hz, 1H), 1.77 (dt, d, *J*=13.2, 7.7 Hz, 1H), 1.55–1.31 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 159.2, 141.9, 138.4, 128.8, 122.0, 116.4, 115.2, 112.2, 73.5, 57.3, 55.2, 52.2, 46.6, 33.8, 24.9; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{22}NO_3$ $(M+H)^+$ 276.1599, found 276.1607.

3.1.13. (5S,9S*)-9-(3-Methoxyphenyl)-1-(2,2,2-trifluoroacetyl)-1-aza-7-oxa-6-oxospiro[4,4]nonane (erythro-**13**).* To a solution of *erythro*-**12** (15.3 mg, 0.041 mmol) in CH_2Cl_2 (0.5 mL) was added sodium borohydride (5.1 mg, 0.135 mmol) at 0 °C, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was exposed to saturated NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=15:1) to give *erythro*-**13** (5.0 mg, 34%) as colorless oil: FTIR (neat) 1778, 1690, 1602, 1493, 1456, 1216, 1146, 1038 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (t, *J*=8.0 Hz, 1H), 6.88 (dd, *J*=8.0, 2.2 Hz, 1H), 6.81 (d, *J*=8.0 Hz, 1H), 6.77 (m, 1H), 4.84 (dd, *J*=10.7, 9.1 Hz, 1H), 4.59 (t, *J*=9.1 Hz, 1H), 3.78 (s, 3H), 3.71–3.66 (2H), 3.04 (m, 1H), 2.61 (m, 1H), 2.22 (dt, *J*=12.2, 5.7 Hz, 1H), 2.10 (m, 1H), 1.92 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 159.9, 156.5 (q, *J*=37.5 Hz), 135.1, 129.9, 121.0, 115.8 (q, *J*=285.0 Hz), 114.2, 114.1, 71.1, 69.1, 55.2, 53.5, 48.2 (q, *J*=4.0 Hz), 39.4, 24.3; HRMS (EI) *m*/*z* calcd for $C_{16}H_{16}O_4NF_3$ $(M)^+$ 343.1031, found 343.1030.

*3.1.14. tert-Butyl 1-(((Z)-3-(3-methoxyphenyl)-1-(tert-butyldimethylsilyl)allyloxy)-carbonyl)pent-4-enylcarbamate (**15**).* To a solution of (*Z*)-**4** (1.01 g, 3.68 mmol) in CH_2Cl_2 (11 mL) were added *N*-Boc-homoallylglycine (racemic, 1.29 g, 5.63 mmol), 1-ethyl-3-(3-

dimethylaminopropyl)-carbodiimide (EDCI, 1.08 g, 5.63 mmol), and 4-*N*,*N*-dimethylaminopyridine (DMAP, 45 mg, 0.37 mmol) and the mixture was stirred at rt for 3 h. The reaction mixture was exposed to saturated NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=20:1) to give **15** (1.75 g, 97%, a mixture of diastereomers, dr=1:1) as colorless oil: FTIR (neat) 3360, 1715, 1641, 1599, 1579, 1492, 1464, 1435, 1392, 1366, 1254, 1165, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, *J*=7.9 Hz, 1H), 7.05 (m, 1H), 6.98 (d, *J*=7.9 Hz, 1H), 6.77 (dd, *J*=7.9, 2.4 Hz, 1H), 6.37 (d, *J*=11.9 Hz, 1H), 6.04 (d, *J*=11.3 Hz, 1/2H), 5.98 (d, *J*=10.8 Hz, 1/2H), 5.79 (m, 1H), 5.60 (dt, *J*=11.3, 8.8 Hz, 1H), 5.08–4.93 (3H), 4.34 (m, 1H), 3.81 (s, 3H), 2.20–2.02 (2H), 1.92 (m, 1H), 1.71 (m, 1H), 1.43 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3/2H), 0.01 (s, 3/2H), −0.05 (s, 3/2H), −0.07 (s, 3/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 172.5, 159.5, 155.1, 138.2, 138.1, 137.0, 136.9, 129.24, 129.23, 129.0, 128.9, 128.7, 128.6, 120.8, 115.5, 115.4, 113.5, 112.9, 112.8, 79.5, 67.5, 67.2, 55.1, 53.3, 53.11, 53.10, 53.0, 32.0, 29.3, 29.2, 28.2, 26.6, 16.87, 16.85, −7.4, −7.5, −8.0, −8.3; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{43}NO_5Si$ $(M)^+$ 489.2911, found 489.2925.

3.1.15. tert-Butyl (E,3R,4S*)-4-(methoxycarbonyl)-3-(3-methoxyphenyl)-1-(tert-butyldimethylsilyl)octa-1,7-dien-4-ylcarbamate (**16**).* To a solution of diisopropyl amine (0.41 mL, 3.0 mmol) in degassed THF (1.5 mL) was added *n*-BuLi in *n*-hexane (1.75 mL, 2.73 mmol) at −78 °C and the reaction mixture was stirred at −78 °C for 20 min. To the solution was added a solution of **15** (487 mg, 1.00 mmol, dr=1:1) in degassed THF (2.5 mL) and $ZnCl_2$ in Et_2O (1.50 mL, 1.50 mmol) at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. After removing a cooling bath, the reaction mixture was stirred at rt for 1.5 h. The pH of the reaction mixture was adjusted to 1 with 1 N HCl, and the mixture was extracted with ether. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue. To a solution of the crude residue in diethyl ether was added dropwise a solution of diazomethane in diethyl ether at 0 °C for 1 h. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=30:1) to give **16** (322 mg, 64% yield, an inseparable mixture of diastereomers, dr=4.2:1) as yellow oil: FTIR (neat) 3426, 1716, 1641, 1600, 1493, 1391, 1365, 1285, 1258, 1167, 1085, 1051, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.15 (1H), 6.77–6.60 (3H), 6.51 (dd, *J*=18.6, 9.5 Hz, 4/5H), 6.39 (dd, *J*=18.3, 9.3 Hz, 1/5H), 5.88 (d, *J*=18.6 Hz, 4/5H), 5.80–5.69 (6/5H), 5.46 (m, 1H), 4.98–4.90 (2H), 4.31 (d, *J*=9.3 Hz, 4/5H), 3.93 (d, *J*=8.8 Hz, 1/5H), 3.78–3.75 (27/5H), 3.66 (s, 3/5H), 2.59 (m, 1H), 2.12–2.04 (2H), 1.73 (m, 1H), 1.45 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 172.6, 159.3, 159.2, 153.9, 153.6, 145.2, 144.8, 141.5, 140.8, 137.9, 137.6, 131.9, 129.0, 128.9, 121.5, 120.6, 115.0, 114.8, 114.64, 114.55, 112.2, 112.1, 79.1, 66.9, 60.3, 59.6, 57.8, 55.1, 55.0, 52.4, 52.1, 33.3, 31.7, 28.8, 28.4, 28.3, 26.5, 26.4, 21.0, 16.6, 16.6, 14.2, −6.0, −6.1, −6.27, −6.33; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{46}NO_5Si$ $(M+H)^+$ 504.3145, found 504.3135.

3.1.16. (S)-1-tert-Butyl 2-methyl 2-{(R*,E)-3-(tert-butyldimethylsilyl)-1-(3-methoxyphenyl)allyl}pyrrolidine-1,2-diarboxylate (erythro-**6**).* To a solution of **16** (160 mg, 0.317 mmol, dr=4.2:1) in 1,4-dioxane/H_2O (3 mL, 3:1) were added OsO_4 in *t*-BuOH (0.015 mL, 0.096 mmol) and 4-methylmorpholine *N*-oxide (NMO, 74.3 mg, 0.634 mmol) at 0 °C, and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture was exposed to aqueous $NaHSO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue. To a solution of the residue in *t*-BuOH/pH 6.86 buffer (3 mL, 3:2) was added $NaIO_4$ (127 mg, 0.612 mmol) at 0 °C, and the reaction mixture was stirred at rt for 3 h. The reaction mixture was exposed to aqueous $NaHSO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue. To a solution of the residue in AcOH (3 mL) was added $NaBH_3CN$ (38 mg, 0.612 mmol) at rt. The reaction mixture was stirred at 70 °C for 45 min, and the solvent was evaporated in vacuo to give a crude residue. The excess hydride was quenched with aqueous $NaHCO_3$ and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt=30:1) to give *erythro*-**6** (103 mg, 69%, an inseparable mixture of diastereomers, dr=4.5:1) as colorless oil: FTIR (neat) 1748, 1701, 1600, 1366, 1255, 1162, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 1H), 6.97–6.94 (3/2H), 6.83–6.73 (3/2H), 6.40–6.30 (1H), 5.75–5.63 (1H), 4.76 (d, *J*=6.2 Hz, 1/10H), 4.62 (d, *J*=8.0 Hz, 4/10H), 4.55 (d, *J*=6.0 Hz, 1/10H), 4.45 (d, *J*=8.0 Hz, 4/10H), 3.78–3.71 (3H), 3.63 (s, 3/2H), 3.61 (s, 3/2H), 3.36–3.21 (1H), 2.58–2.29 (2H), 2.18–1.80 (5/2H), 1.66–1.1.56 (1/2H), 1.46 (9/2H), 1.41 (9/2H), 0.81 (9H), 0.00 (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 174.3, 173.5, 173.3, 158.9, 153.7, 153.1, 152.9, 147.0, 146.8, 146.5, 145.7, 142.7, 142.6, 142.3, 141.7, 130.7, 130.0, 129.6, 128.4, 128.3, 122.7, 122.5, 122.4, 122.3, 116.4, 116.1, 111.9, 111.7, 111.3, 80.3, 80.1, 79.4, 71.2, 70.4, 69.9, 56.1, 55.1, 55.0, 54.1, 52.8, 51.9, 51.7, 48.9, 48.6, 47.9, 35.6, 34.8, 34.6, 33.1, 28.3, 26.4, 23.3, 23.2, 22.8, 22.6, 16.5, −5.9, −6.2, −6.3; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{44}NO_5Si$ $(M)^+$ 489.2911, found 489.2893. A complex ^1H NMR (400 MHz, $CDCl_3$) spectrum was observed because of a mixture of diastereomers and rotamers.

Acknowledgements

This study was financially supported by a Grant-in-Aid (16201045, 19201045, and 16073214) for Scientific Research from the Japan Society of the Promotion of Science (JSPS) and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supplementary data

The characterization data of the new compounds **3**, (*Z*)-**4**, (*Z*)-**5**, *threo*-**6**, **9**, (*E*)-**4**, (*E*)-**5**, *threo*-**10**, *threo*-**11**, *threo*-**12**, *threo*-**13**, *erythro*-**10**, *erythro*-**13**, **15**, **16**, and *erythro*-**6** are available. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.10.051.

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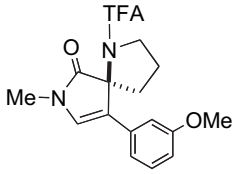
18. The reaction of α-acyloxy-α-vinylsilane having Boc-proline as the acyloxy group (>95% ee, Eq. 2) gave the rearranged product (71% ee) under the conditions in the absence of HMPA, suggesting the contamination of the monoanionic *E*-enolate.[6d] According to the energy calculation results (Scheme 6), the *E*-enolate derived from (*E*)-**5** would undergo the enolate Claisen rearrangement via both the transition states **M** and **N** to give the *threo* and *erythro*-**6**, respectively. Therefore, the moderate *threo* selectivity (dr 3.5:1) would be observed in the reaction of (*E*)-**5** without HMPA.
19. The relative configuration of the hemiaminal moiety in **17** was assigned as shown in Scheme 8 since this compound was identical with the compound derived from the phenol derivative **28** (MeI (1 equiv), K_2CO_3 (1 equiv), acetone, rt, 15 h, 30%).
20. At elevated temperature (NBS (2.2 equiv), DMF, 100 °C), a trace amount of the dehydrated **34** was observed by the ^{1}H NMR analysis of the reaction mixture.



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21. The reaction of **17** with Br_2 (2.2 equiv) in the presence of AcOH or SiO_2 (CH_2Cl_2, rt, 10 min) also gave the monobrominated product **18** in moderate yield (22–30%). The reaction of **17** with NBS (2 equiv) and TsOH (0.22 equiv) in DMF (rt, 18 h) afforded a trace amount of **18**.
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24. The absolute configuration of the minor isomer was not determined.
25. The reaction without $ZnCl_2$ resulted in the decreased yield of **23** (28%).
26. The spirolactone **29** was obtained as a single diastereomer. The relative stereochemistry of **29** was not determined.
27. Lower amounts of methylamine (2 equiv) resulted in the decreased yield of **28** (<20%).
28. For the electrophilic 4,6-dibromination of 3-substituted phenol, see: (a) Osuna, M. R.; Agurrie, G.; Somanathan, R.; Molins, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2261–2266; (b) Hashimoto, A.; Jacobson, A. E.; Rothman, R. B.; Dersch, C. M.; George, C.; F-Anderson, J. L.; Rice, K. C. *Bioorg. Med. Chem.* **2002**, *10*, 3319–3329.
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30. The optical rotation of the synthetic (−)-**1** was $[\alpha]_D^{28}$ −39.0 (*c* 0.30, MeOH), which is in good agreement with that of the synthetic **1** reported by Trauner {$[\alpha]_D^{25}$ −41.0 (*c* 0.50, MeOH)},[3] while the natural sample was recorded as $[\alpha]_D$ −10.0 (*c* 0.0023, MeOH).[1]