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Total Synthesis of (−)-Amathaspiramide F

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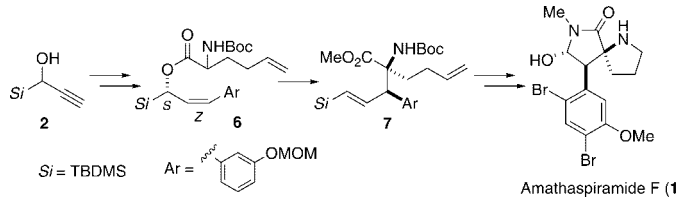
ABSTRACT



The stereoselective total synthesis of the marine alkaloid (−)-amathaspiramide F (1) was achieved from the α-hydoxy-α-ethynylsilane 2. The crucial steps in this synthesis involved not only the enolate Claisen rearrangement of the α-acyloxy-α-alkenylsilane 6 for the construction of the nitrogen-containing quaternary carbon center, but also the chemoselective formation of the azaspirohemiaminal 12 using heptamethyldisilazane as the methylamine equivalent and the regioselective dibromination of the phenol moiety of 12 using *n*-Bu_4NBrCl_2.

Amathaspiramides A−F were isolated from a New Zealand collection of the marine bryozoan *Amathia wilsoni* by Prinsep et al. in 1999 (Figure 1).[1] The structural features common

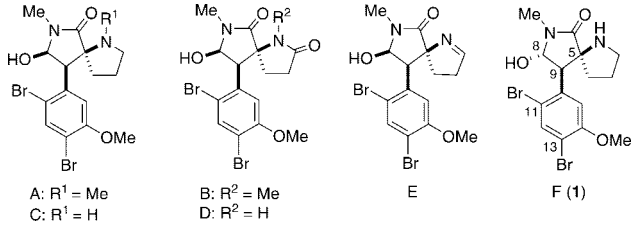


Figure 1. Amathaspiramides.

to these 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. These structures suggest that these alkaloids would have an important biological activity.[2] However, only preliminary biological tests regarding their antimicrobial, antiviral, and cytotoxic activities have been performed for amathaspiramides A−C and E (moderate antimicrobial and cytotoxic activities for A and E and potent antiviral activity against Polio virus type-I for E), while those of the other congeners have not yet been reported probably due to only minute quantities being available from the marine sources. Only one example for the total synthesis of amathaspiramide F (**1**) has been reported by Trauner et al.[3] Their unique structure together with unanswered questions surrounding their biological activity prompted us to synthesize these alkaloids. In this paper, we describe the total synthesis of **1** via the enolate Claisen rearrangement of an α-acyloxy-α-alkenylsilane as a key step.

(1) Morris, B. D.; Prinsep, M. R. *J. Nat. Prod.* **1999**, *62*, 688–693.

(2) For several biologically active natural products containing cyclic spirolactam or hemiaminal structure, see the following examples. Massadine: (a) Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N *Org. Lett.* **2003**, *5*, 2255–2257. Azaspirene: (b) Asami, Y.; Kakeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett.* **2002**, *4*, 2845–2848. Axinellamine: (c) Urban, S.; Leone, P. A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hopper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731–735. Pseurotin A: (d) Komagata, D.; Fujita, S.; Yamashita, N.; Saito, S.; Morino, T. *J. Antibiot.* **1996**, *49*, 958–959. Synerazol: (e) Ando, O.; Satake, H.; Nakajima, M.; Sato, A.; Nakamura, T.; Kinoshita, T.; Furuya, K.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 382–389.

(3) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4556–4559.

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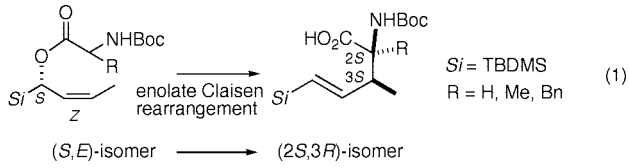
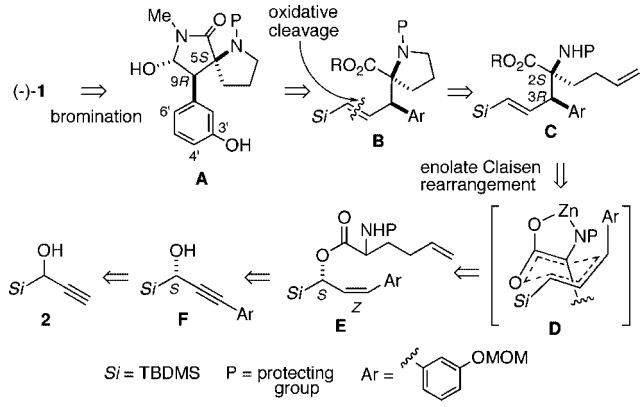
The optically active α-acyloxy-α-alkenylsilane has received significant attention because of its chirality as well as functional group transferring properties from the α- to γ-position through a metal-catalyzed cationic rearrangement[4] or an electrocyclic rearrangement of the enolate derived from its acyloxy group.[5] In particular, the $ZnCl_2$-assisted ester–enolate Claisen rearrangement[6] 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, e.g., the (*S*,*E*)- and (*S*,*Z*)-α-alkenylsilane produced the (2*S*,3*R*)- and (2*S*,3*S*)-vinylsilane, respectively (eq 1).[5a]



(1)

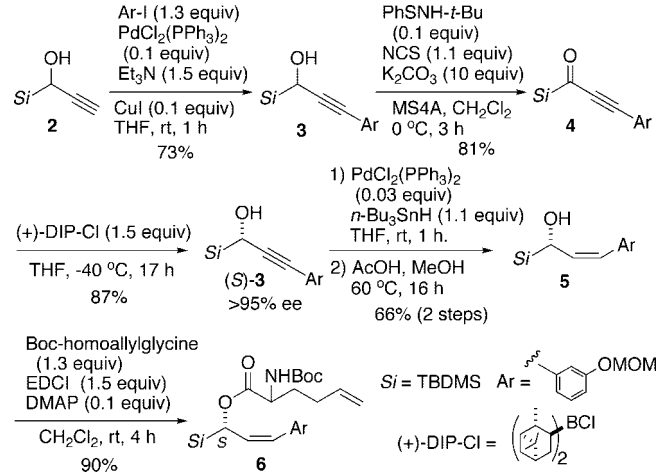
We considered that this method is applicable for the stereoselective construction of the consecutive C5 and C9 chiral centers of **1**. We envisioned that (*S*,*Z*)-α-acyloxysilane **E**, prepared from the α-hydroxy-α-ethynylsilane **2**, would undergo the $ZnCl_2$-assisted enolate Claisen rearrangement to give (2*S*,3*R*)-**C** via a chairlike transition state as shown in Scheme 1. This can be converted into the azaspirohemiaminal **A** by the following sequence of transformations: (1) cleavage of the terminal olefin followed by the construction of the pyrrolidine **B** and (2) cleavage of the vinylsilane group and subsequent formation of a spirohemiaminal unit with methylamine. The dibromination to the aromatic ring of **A** involves a critical problem in the choice of the phenoxy protecting group. Our preliminary studies indicated that the electrophilic brominaton of the methoxy derivative did not provide the desired 4′,6′-dibromo derivative but a 6′-monobromo compound.[7] Further attempts to introduce the 4′-bromo group were not successful at all, suggesting that a highly reactive phenol is needed for the dibromination of **A**. Thus, methoxymethyl group, readily removable under mild acidic conditions, was chosen for the protecting group of the phenol moiety.

Scheme 1



The synthesis began with the preparation of the enolate Claisen precursor, (*S*,*Z*)-α-acyloxysilane **6**, from the readily available racemic α-hydroxy-α-ethynylsilane **2** (Scheme 2).[8] The palladium-catalyzed Sonogashira coupling of **2** with the MOM-protected 3-iodophenol under standard conditions afforded the desired coupling product **3** (73%). The oxidation of **3** using Jones reagent or other chromium reagents was rather troublesome when forming the desired silyl ketone **4** in moderate yields due to the significant loss of the TBDMS group. On the other hand, this group was found to be stable under the Mukaiyama oxidation conditions (NCS and catalytic PhSNH-*t*-Bu) to give **4** in 81% yield without any loss of the TBDMS group.[9] The enantioselective reduction of **4** by (+)-DIP-

Scheme 2

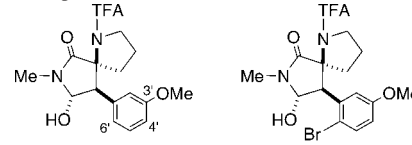


(4) (a) Sakaguchi, K.; Higashino, M.; Ohfune, Y. *Tetrahedron* **2003**, *59*, 6647–6658. (b) Sakaguchi, K.; Yamada, T.; Ohfune, Y. *Tetrahedron Lett.* **2005**, *46*, 5009–5012. (c) Sakaguchi, K.; Okada, T.; Yamada, T.; Ohfune, Y. *Tetrahedron Lett.* **2007**, *48*, 3925–3928.

(5) (a) Sakaguchi, K.; Suzuki, H.; Ohfune, Y. *Chirality* **2001**, *13*, 357–365. (b) Morimoto, Y.; Takanishi, M.; Kinoshita, T.; Sakaguchi, K.; Shibata, K. *Chem. Commun.* **2002**, 42–43. (c) Sakaguchi, K.; Yamamoto, M.; Kawamoto, T.; Yamada, T.; Shinada, T.; Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **2004**, *45*, 5869–5872. (d) Sakaguchi, K.; Yamamoto, M.; Watanabe, Y.; Ohfune, Y. *Tetrahedron Lett.* **2007**, *48*, 4821–4824.

(6) The $ZnCl_2$-assisted dianionic enolate Claisen rearrangement of the N-protected α-amino acid allyl ester was originally developed by Kazmaier: Kazmaier, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 998–999.

(7) In the preliminary studies, it was found that the electrophilic bromination of the 3′-methoxy derivative **18** [NBS (2 equiv), DMF, rt, 18 h] gave only the 6′-monobrominated product **19** in 84% yield (Supporting Information). At elevated temperature, the reaction was sluggish, and no 4′,6′-dibrominated product was obtained.



18 19

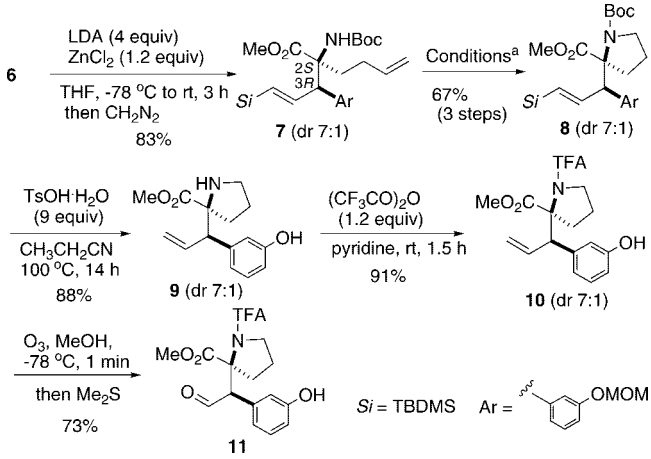
(8) Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M.; Ohfune, Y. *Tetrahedron Lett.* **2000**, *41*, 6589–6592.

(9) Matsuo, J.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739–6750.

Cl[10] gave the optically pure (*S*)-α-hydroxysilane **3** (87%, >95% ee). The (*S*,*Z*)-olefin **5** was prepared by the Pd-catalyzed hydrostanylation of (*S*)-**3** followed by an acidic treatment (66%, two steps).[11,12] The esterification of **5** with racemic Boc-homoallylglycine was effected by using EDCI in the presence of the catalytic DMAP to give the (*S*,*Z*)-α-acyloxysilane **6** in 90% yield.

Next, we examined the enolate Claisen rearrangement of (*S*,*Z*)-**6** for the construction of the C5 and C9 stereocenters. The treatment of (*S*,*Z*)-**6** with LDA (4 equiv) in the presence of $ZnCl_2$ smoothly proceeded to give the desired (2*S*,3*R*)-isomer **7** as an inseparable mixture of its diastereomer[13] (83%, dr 7:1 by ^1H NMR) (Scheme 3).[14] The stereochemistry

Scheme 3

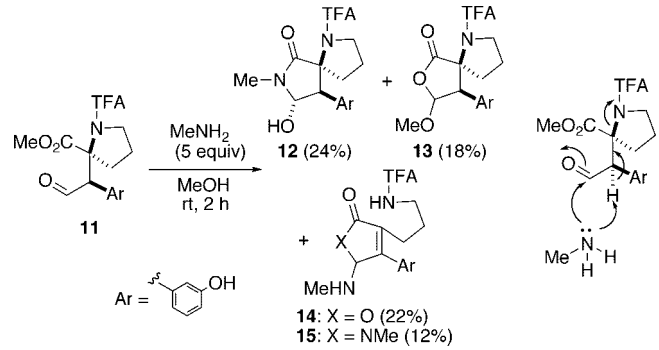


[a] Conditions: (1) OsO_4 (0.05 equiv), NMO (2 equiv), 1,4-dioxane−H_2O, (3:1), rt, 16 h; (2) $NaIO_4$ (1.7 equiv), *t*-BuOH−pH 6.7 buffer (3:2), rt, 3 h; (3) $NaBH_3CN$ (1.7 equiv), AcOH, 70 °C, 1 h.

of the products was determined by converting them into the corresponding spirolactams **12** (vide infra). The fact that (2*S*,3*R*)-**7** was obtained as the major diastereomer suggested that the chairlike transition state **D** (Scheme 1) is the preferential pathway for this transformation. The mixture was converted to the α-substituted proline **8** 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 **7**). The silyl group was removed under acidic conditions to avoid the troublesome oxidative cleavage of the vinylsilane group.[15] This reaction gave the protection-free phenol derivative **9** in 88% yield. Reprotection of the resulting amino group with a trifluoroacetyl (TFA) group gave **10** (91%), which, upon ozonolysis, afforded the aldehyde **11** (dr 7:1). The minor diastereomer was removed at this stage by flash chromatography to give diastereomerically pure (2*S*,3*R*)-**11** (73%).

For completion of the total synthesis of **1**, the unexploited spirohemiaminal formation and dibromination of the aromatic group remained to be solved. The initial attempt for construction of the spirohemiaminal was the treatment of **11** with excess methylamine in MeOH. The reaction gave the desired spirohemiaminal **12** as the exclusive diastereomer in 32% yield but was not reproducible. Control experiments using 5 equiv of methylamine revealed that the reaction gave a mixture of products consisting of the desired **12** (24%), spirolactone **13**[16] (18%), butenolide **14** (22%), and lactam **15** (12%) (Scheme 4).[17] It was assumed that the attack of

Scheme 4



the methylamine on the proton attached to the α-position of the carbonyl group resulted in the formation of the retro-Michael products **14** and **15**, since further treatment of each product under the same reaction conditions remained unchanged. Based on these results, we postulated that the sterically bulky heptamethyldisilazane instead of the methylamine would prevent the undesired β-elimination reaction. In fact, the treatment with excess heptamethyldisilazane gave **12** in 50% yield and was reproducible. Only **15** was the byproduct (12%) isolated from the reaction mixture (Scheme 5). The relative stereochemistry of **12** including the hydroxy group at C8 was assigned as shown in Scheme 5 by the NOE experiments. Prior to examining the dibromination of **12**, we observed that the bromination of the phenol derivative **10** with NBS (DMF, 0 °C) gave the 2′,4′,6′-tribrominated product as the exclusive product indicating that NBS or Br_2 is not a suitable reagent for the 4′,6′-dibromination of **12**.[18] Thus, we chose tetrabutylammonium dichlorobromate (*n*-

(10) (a) Sonderquist, E. J.; Anderson, C. L.; Miranda, E. I.; Rivera, I. *Tetrahedron Lett.* **1990**, *31*, 4677–4680. (b) Dahr, R. K. *Aldrichim. Acta* **1994**, *27*, 43–51.

(11) Liron, F.; Garrev, P. L.; Alami, M. *Synlett* **1999**, 246–234.

(12) Hydrogenation of **3** using the Lindlar catalyst did not give any olefin product even at high pressure (5 atm). The use of Pd/C produced the corresponding alkane.

(13) The absolute configuration of the minor isomer was not determined.

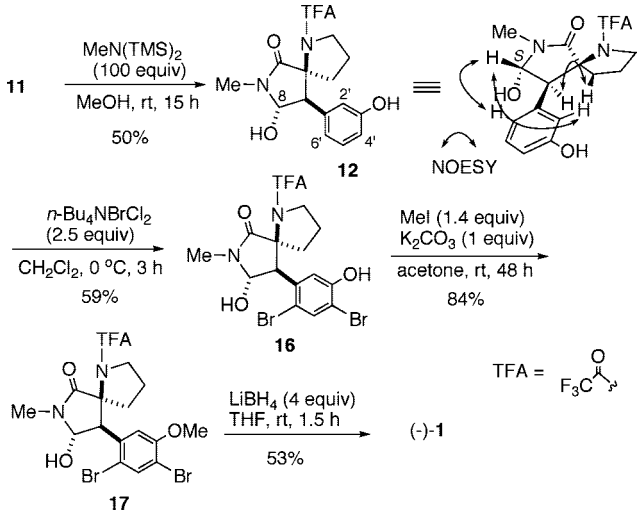
(14) The reaction without $ZnCl_2$ resulted in the decreased yield of **7** (28%).

(15) It is reported that the ozonolysis of the vinylsilane does not give the corresponding aldehyde; see: (a) Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294–295. (b) Murakami, M.; Sakita, K.; Igawa, K.; Tomooka, K. *Org. Lett.* **2006**, *8*, 4023–4046.

(16) The spirolactone **13** was obtained as a single diastereomer. The relative stereochemistry of **13** was not determined.

(17) Lower amounts of methylamine (2 equiv) resulted in the decreased yield of **12** (<20%).

Scheme 5



Bu_4NBrCl_2) that is reported by Negoro et al.[19] to be an effective reagent for the electrophilic *o*,*p*-dibromination of phenols as a mild source of bromonium chloride. The reaction of **12** using *n*-Bu_4NBrCl_2 (2.5 equiv) in CH_2Cl_2 at 0 °C for 3 h smoothly proceeded to give the desired 4′,6′-dibrominated product **16** in 59% yield without forming the undesired tribromide. Finally, etherification of the phenol moiety of **16** afforded the *N*-TFA protected amathaspiramide F (**17**) (84%), which was Trauner's synthetic intermediate.[3] The TFA group was removed by $LiBH_4$ to give the (−)-amathaspiramide F (**1**) (53%).[20] The spectroscopic data of the synthetic (−)-**1** were in good agreement with those of the natural product.

In summary, the stereoselective total synthesis of (−)-amathaspiramide F (**1**) was achieved from the α-hydoxy-α-ethynylsilane **2** in 17 steps (1.3% overall yield). The synthesis is highlighted by the stereoselective construction of the consecutive C5 and C9 stereogenic centers by the ester enolate Claisen rearrangement, novel azaspirohemiaminal formation using the sterically bulky heptamethyldisilazane to avoid the undesired β-elimination, and 4′,6′-dibromination of the 3′-substituted phenol with *n*-Bu_4NBrCl_2. The synthesis of the other congeners (A−E) as well as the biological evaluation of **1** is currently in progress in our laboratories.

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Supporting Information Available: Full experimental details and characterization data of all the synthetic products are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Electrophilic 4,6-dibromination of 3-substituted phenol: (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.

(19) Negoro, T.; Wada, M.; Someya, M. *Bull. Fac. Educ. Wakayama Univ. Natur. Sci.* **1998**, *48*, 1–7.

(20) The optical rotation of the synthetic (−)-**1** showed $[\alpha]^{28}_D$ −39.0 (*c* 0.30, MeOH), which is in good agreement with that of the synthetic **1** reported by Trauner [$[\alpha]^{25}_D$ −41.0 (*c* 0.50, MeOH)],[2] while the natural sample was recorded as $[\alpha]_D$ −10.0 (*c* 0.0023, MeOH).[1]