Natural Product Synthesis

DOI: 10.1002/ange.201109221

Total Syntheses of All the Amathaspiramides**

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In memory of David Y. Gin

In pursuit of the scalable synthesis of highly functionalized natural products with a diverse spectrum of accessible congeners, we considered it conceptually challenging to synthesize amathaspiramides A (**1**)–F (**6**) owing to their diverse substructures within a uniform core skeleton (Figure 1). Prinsep and co-workers isolated these natural

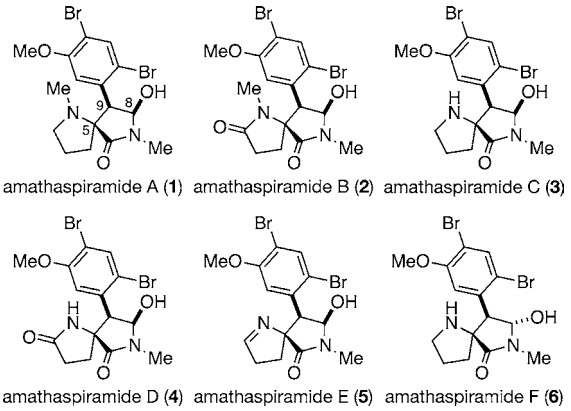
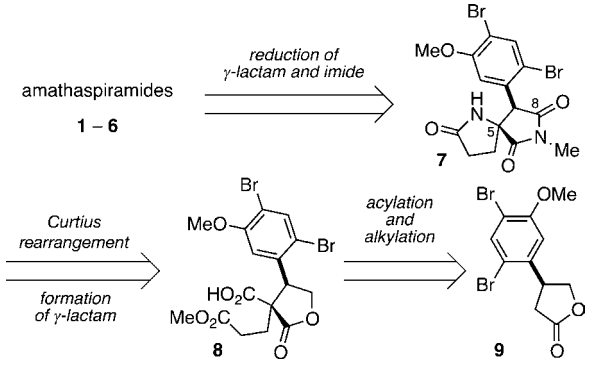


Figure 1. Amathaspiramide alkaloids.

products in 1999 from a New Zealand collection of the marine bryozoan *Amathia wilsoni*.[1] The structural motif of these compounds is characterized by the densely functionalized diazaspiro[3.3]nonane framework equipped with an intriguingly stable *N*-acyl hemiaminal at C-8, a benzylic center at C-9 linked to a dibromomethoxyphenyl group, and a variable pyrrolidine moiety connected through the tetrasubstituted spiro center at C-5. Among these compounds, amathaspiramides A and E exhibit antiviral activity against poliovirus type 1, cytotoxicity to BSC-1 cells, and antimicrobial activity toward *Bacillus subtilis*.[1] Furthermore, a recent report has proved structurally similar compounds to be promising β-turn mimetics.[2] Despite these valuable aspects, the limited availability of natural samples has hampered further investigations on these molecules and their analogues. Of these six compounds, total synthesis has been reported for only amathaspiramide F, an 8*S* member, by the Trauner[3] and Ohfune groups.[4] At the outset of our synthetic study, we envisioned establishing a scalable and versatile synthetic route to all amathaspiramides whose pyrrolidine moieties range over the cyclic imine (**5**), and secondary (**3**, **6**) and tertiary amines (**1**) to unsubstituted (**4**) and *N*-methyl γ-lactam (**2**). Therefore, a systematic access is required for establishing the configuration at C-8 and the variable oxidation states of the spiro pyrrolidine units starting from a common intermediate.

As shown in Scheme 1, our approach is based on the idea that each member of the amathaspiramides can be derived from the common intermediate **7** by sequential reduction. We



Scheme 1. Retrosynthetic analysis.

envisioned that Schwartz's reagent, [$Cp_2Zr(H)Cl$] ($Cp = C_5H_5$), could play a key role in the crucial reduction of the lactam moiety to the cyclic imine,[5] which could then be reduced to the corresponding secondary amine. Additionally, hitherto unexplored stereochemical control of the unusually stable 8*R* *N*-acyl hemiaminal moiety in amathaspiramides A–E could be possible by the regioselective reduction of the C-8 carbonyl group of the cyclic imide in **7** from the sterically less crowded face. Combined with the known method for the generating products with the 8*S* configuration,[3,4] we reasoned that all the amathaspiramides with variable spiro pyrrolidine substructures and C-8 configurations of the *N*-acyl hemiaminal could be synthesized from **7**. The γ-lactam moiety in **7**, which possesses a tetrasubstituted stereogenic center at C-5, could be derived from carboxylic acid **8** by means of a Curtius rearrangement and subsequent lactam cyclization. γ-Lactone **9** was thus envisioned as the starting point for the sequential introduction of the carboxyl group and the three-carbon alkyl chain onto the α-position of the lactone.

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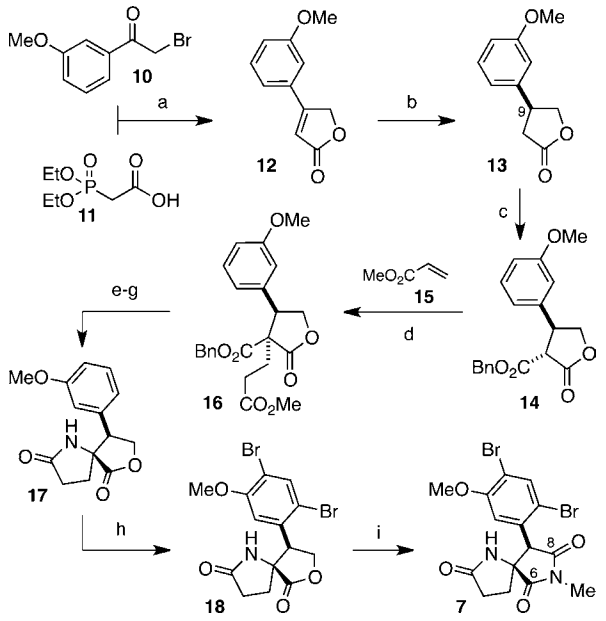
[**] Financial support for this work was provided by Grants-in-Aid (21790009 and 20002004) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201109221.

Our synthesis commenced with the one-step preparation of butenolide **12** from commercially available 3′-methoxyphenacyl bromide (**10**) by means of S_N2 substitution with **11** followed by an intramolecular Horner–Wadsworth–Emmons reaction (Scheme 2).[6] The copper-catalyzed asymmetric



Scheme 2. Construction of the spiro bicyclic structure. Reagents and conditions: a) K_2CO_3, THF, 50 °C, 62 %; b) CuCl (10 mol %), (*S*)-DTBM-SEGPHOS (1.0 mol %), NaO*t*Bu, PMHS, *t*BuOH, THF, RT, 72 % 98 % *ee*; c) LHMDS, THF, −78 °C; CbzCl, 90 %; d) methyl acrylate (**15**), K_2CO_3, DMF, 70 °C, 90 %; e) H_2 (1 atm), Pd/C, MeOH, RT; f) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C to RT; evaporation; NaN_3, acetone–H_2O; g) 1,4-dioxane, 100 °C; HCl aq., reflux, 77 % (3 steps); h) Br_2 (3.0 equiv), $ZnCl_2$ (4.0 equiv), HCO_2H (10 equiv), CH_2Cl_2, 84 %; i) $MeNH_2$, MeOH, THF, reflux; evaporation; PDC, Celite, CH_2Cl_2, RT, 44 %. DTBM-SEGPHOS = (*S*)-(+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, PMHS = polymethylhydrosiloxane, LHMDS = lithium hexamethyldisilazide, CbzCl = benzyl chloroformate, PDC = pyridinium dichromate.

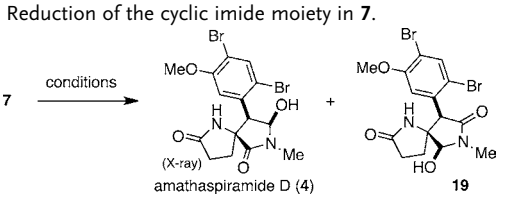
reduction of the unsaturated lactone was performed according to Lipshutz's method.[7] The desired chiral lactone **13** with 98 % *ee* was obtained on a 20 g scale in 72 % yield, thereby establishing the latent C-9 configuration at the benzylic position. To introduce the quaternary center to the α-position of the carbonyl group, the lithium enolate of **13** was reacted with CbzCl to afford cyclic malonate **14**. This was subsequently subjected to a Michael addition with methyl acrylate (**15**) in the presence of a catalytic amount of K_2CO_3 to selectively afford **16**. The crucial tetrasubstituted spiro center at C-5 was subsequently constructed by a Curtius rearrangement. Thus, benzyl ester **16** was subjected to hydrogenolysis and the resultant acid was converted to the acyl azide in two steps. Subsequent Curtius rearrangement was performed in 1,4-dioxane at 100 °C to give the intermediate isocyanate, which was successfully hydrolyzed in an aqueous medium to afford γ-lactam **17** without appreciable formation of a urea byproduct.

We next focused on the introduction of two bromine atoms on the aromatic ring. As Ohfune et al. reported, dibromination is problematic after the construction of the core structure of amathaspiramides.[4] In fact, introduction of the second bromine atom at the position *ortho* to the methoxy group was difficult by treatment with bromine even in combination with ordinary acid sources. After extensive experimentation, we could successfully and selectively introduce two bromine atoms at the *ortho* and *para* positions using bromine in the presence of both zinc chloride and formic acid.[8] It should be noted that the second bromide could not be introduced using either zinc chloride or formic acid alone, indicating the formation of the more powerful hypobromous formate.[9]

We next aimed at constructing the 8*R* *N*-acyl hemiaminal moiety. According to the reports by the Trauner[3] and Ohfune groups,[4] cyclization of the *N*-methyl amide to the aldehyde selectively gave the *S* hemiaminal, indicating the *S* isomer to be thermodynamically more stable at the *N*-acyl hemiaminal. We envisioned that reduction of the cyclic imide from the less hindered face is likely to establish the 8*R* stereochemistry, assuming that the C-8 stereocenter would be sufficiently stable for further manipulations. Cyclic imide **7** was synthesized in one pot from **18** in 44 % yield by aminolysis of the lactone with methylamine in methanol followed by oxidation with PDC.

With cyclic imide **7** in hand, we proceeded to form the *N*-acyl hemiaminal moiety by a regio- and stereoselective partial reduction of the imide moiety (Table 1). Although initial attempts using $NaBH_4$ reduced the imide, reduction occurred only at the C-6 carbonyl group to give **19** (Table 1, entry 1). Almost the same result was obtained by employing the Luche conditions (Table 1, entry 2), L-Selectride (entry 3), or $LiAlH_4$ at lower temperature (entry 4). After extensive examination of various reductive conditions, DIBAL was found to facilitate the desired regio- and stereoselective transformation (Table 1, entry 5). Accordingly, the desired 8*R* hemiaminal was successfully obtained in 52 % yield without formation of the *S* isomer. The change in the regioselectivity

Table 1: Reduction of the cyclic imide moiety in **7**.

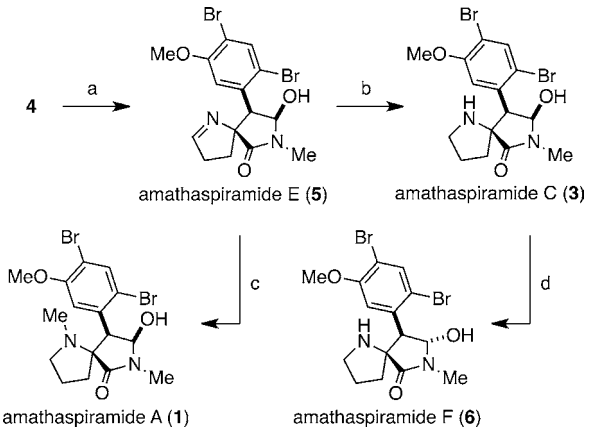


Entry	Reagent	*T* [°C]	Solvent	**4** [%][f]	**19** [%][f]
1[a]	$NaBH_4$	0	MeOH	0	98
2[b]	$NaBH_4$, $CeCl_3 \cdot 7H_2O$	0	MeOH	0	86
3[c]	L-Selectride	−78	THF	0	67
4[d]	$LiAlH_4$	−78	THF	0	80
5[e]	DIBAL	−78	CH_2Cl_2	52	0

[a] Conditions: $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 10 min. [b] Conditions: $NaBH_4$ (4.0 equiv), $CeCl_3 \cdot 7H_2O$ (4.0 equiv), MeOH, 0 °C, 50 min. [c] Conditions: L-Selectride (4.0 equiv), THF, −78 °C, 50 min. [d] Conditions: $LiAlH_4$ (2.0 equiv), THF, −78 °C, 50 min. [e] Conditions: DIBAL (2.3 equiv), CH_2Cl_2, −78 °C, 20 min. [f] Yield of the isolated product.

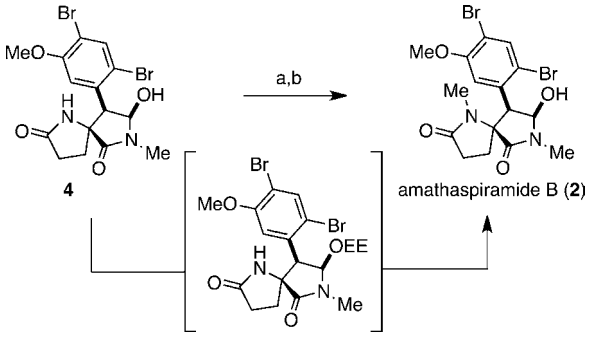
could be explained in terms of the reduction of the inductive effect and increase of the steric bulk of the γ-lactam as a result of the formation of the nitrogen–aluminum bond caused by DIBAL. The subtle change in the environment of the C-6 carbonyl enhanced the relative reactivity of the C-8 carbonyl, resulting in its reduction from the less hindered side to give the 8*R* hemiaminal **4**. The 8*R* hemiaminal showed surprising stability, which allowed conventional handling and even purification on silica gel. Amathaspiramide D (**4**) was thus synthesized from **7** in 52% yield on a 5 g scale. An X-ray crystallographic analysis of synthetic **4** confirmed, for the first time, the unambiguous structure of the amathaspiramide alkaloids bearing a 8*R* *N*-acyl hemiaminal moiety.[10]

We envisioned that amathaspiramide D (**4**) could serve as a versatile precursor for the synthesis of all the other amathaspiramides. Toward this end, it was necessary to reduce the γ-lactam moiety without affecting the other functional groups in the molecule. Consequently, we focused on the use of Schwartz's reagent, $[Cp_2Zr(H)Cl]$, which is known to effect the transformation of a lactam to the corresponding cyclic imine.[5,11] To our delight, upon treatment with $[Cp_2Zr(H)Cl]$, amathaspiramide D (**4**) was directly reduced to the imine without affecting the tertiary amide at C-6 and *N*-acyl hemiaminal at C-8, affording amathaspiramide E (**5**) in 67% yield (Scheme 3). Fortunately, the imine moiety in **5** could be selectively reduced to the secondary amine by treatment with $NaBH_3CN$ and AcOH in methanol to afford amathaspiramide C (**3**) in 65% yield. Similarly, reductive methylation of **5** with formaldehyde under similar conditions furnished amathaspiramide A (**1**) in 78% yield. Since amathaspiramide F (**6**) differs from amathaspiramide C (**3**) only in the configuration of the *N*-acyl hemiaminal at C-8, epimerization of the C-8 center was attempted. Under the conventional acidic conditions, however, no epimerization was observed, and elimination of the hydroxy group occurred under harsher conditions. Gratifyingly, epimerization took place under basic conditions with a catalytic amount of Cs_2CO_3 in MeCN, resulting in the formation of the thermodynamic mixture of the products (**6**/**3** = 13:1). From this mixture, the 8*S* isomer amathaspiramide F (**6**) was isolated in 82% yield.



Scheme 3. Total syntheses of amathaspiramides A, C, E, F. Reagents and conditions: a) $[Cp_2Zr(H)Cl]$ (2.0 equiv), THF, −30 °C to RT, 67%; b) $NaBH_3CN$, AcOH, MeOH, RT, 65%; c) HCHO aq., $NaBH_3CN$, AcOH, MeOH, RT, 78%; d) Cs_2CO_3 (10 mol%), MeCN, RT, 82%.

Since the C-8 *N*-acyl hemiaminal moiety in **4** is stable under weakly acidic conditions and labile to isomerization under basic conditions, it should be protected for the introduction of the *N*-methyl group of amathaspiramide B (**2**; Scheme 4). Among the various protecting groups examined, an ethoxyethyl (EE) group was chosen because of the ease of deprotection under mildly acidic conditions. After protection of the hydroxy group of **4**, methylation was performed by treatment with MeI and Cs_2CO_3 to give, after workup with aqueous HCl, amathaspiramide B (**2**) in 75% yield.



Scheme 4. Total synthesis of amathaspiramide B (**2**). Reagents and conditions: a) CSA (1.0 mol%), ethyl vinyl ether, CH_2Cl_2, RT; b) MeI, Cs_2CO_3, MeCN, RT; HCl aq., THF, RT, 75% (2 steps). CSA = camphorsulfonic acid.

In conclusion, we have achieved the concise and efficient total syntheses of all the known amathaspiramide alkaloids **1**–**6** on 0.1 to 5 g scales. Our synthesis underscores the importance of the mild conditions for reduction of the amide with Schwartz's reagent in the synthesis of complex molecular frameworks; this allowed the streamlined preparation of the amide, imine, secondary amine, and tertiary amine from a common intermediate. Regio- and stereoselective reduction of cyclic imide **7** using DIBAL as the only effective reagent gave rise to the hitherto unavailable 8*R* stereochemistry. In addition, C-8 *N*-acyl hemiaminal moiety was successfully epimerized to the thermodynamically more stable 8*S* isomer only under basic reaction conditions. Our first total syntheses of amathaspiramides A (**1**), B (**2**), C (**3**), D (**4**), E (**5**) with 8*R* stereochemistry combined with an X-ray crystallographic analysis of **4** unequivocally confirmed the stereochemistry of these molecules. Further syntheses of analogues of the amathaspiramides and biological studies are underway.

Received: December 28, 2011
Published online: January 27, 2012

Keywords: alkaloids · amathaspiramide · reduction · spiro compounds · total synthesis

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