Natural Product Synthesis

DOI: 10.1002/ange.200904603

Total Synthesis of Piperazimycin A: A Cytotoxic Cyclic Hexadepsipeptide**

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Piperazimycin A (**1**, Figure 1) is a cyclic hexadepsipeptide which was isolated from the fermentation broth of a *Streptomyces* sp., cultivated from marine sediments near the island of Guam by Fenical and co-workers in 2007.[1] When

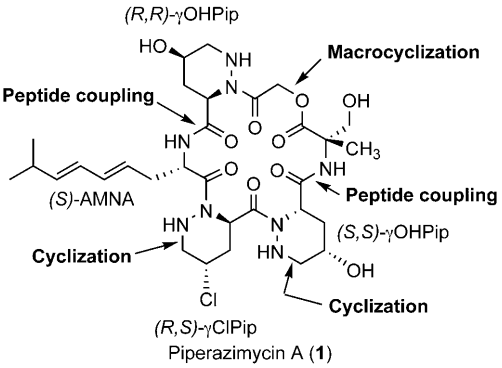

Figure 1. Structure of piperazimycin A and its bond disconnection analysis.

screened using the National Cancer Institute's panel of 60 cancer cell lines, piperazimycin A exhibited in vitro cytotoxicity toward multiple tumor cell lines with a mean GI_{50} value of 100 nM.[1] Additional analysis revealed that this compound had a nearly three-fold more potent activity against solid tumors than against the leukemia cell lines tested. This selectivity is not enough to support the development piperazimycin A for the treatment of cancer because of the general cytotoxicity. Structure-activity relationship (SAR) studies of this natural product would not only be able to overcome this drawback, but also open a new avenue for exploring the possible mode of action of this compound. However, before comprehensive SAR studies can become a reality, an efficient total synthesis of piperazimycin A is required. Herein, we disclose the first total synthesis of this natural product.

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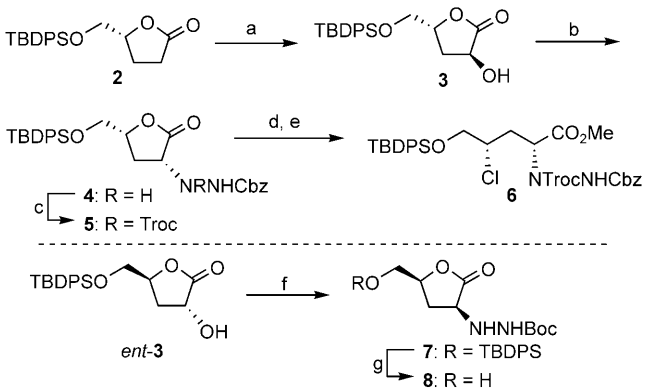
[**] We are grateful to the Chinese Academy of Sciences, the National Natural Science Foundation of China (grant no. 20632050 and 20621062), and the Ministry of Science and Technology of China (grant no. 2010CB833200) for their financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200904603.

Structurally, piperazimycin A is an 18-membered macrocycle which is composed of a hydroxyacetic acid and five rare amino acids. These amino acid residues include an (*S*)-α-methylserine, a novel (*S*)-2-amino-8-methyl-4,6-nonadienoic acid (*S*-AMNA), two γ-hydroxypiperazic acids ((*S*,*S*)-γOHPip and (*R*,*R*)-γOHPip), and one γ-chloropiperazic acid ((*R*,*S*)-γClPip). The γ-substituted piperazic acid residues have also been found in other antitumor cyclodepsipeptides such as polyoxypeptins,[2] and antibiotic cyclodepsipeptides such as monamycins,[3] himastatin,[4] lydiamycins,[5] and dentigerumycin.[6] The total synthesis of piperazic acid containing natural products has received much attention during the past decades.[7–9] Although some cyclodepsipeptides with the γ-substituted piperazic acid residues have been synthesized successfully,[9c,d,g] none of them contain a dipeptide unit having two piperazic acid residues (such as (*R*,*S*)-γClPip-(*S*,*S*)-γOHPip in piperazimycin A). This difficult-to-install dipeptide presents a new synthetic challenge. Indeed, we have prepared both the protected (*R*,*S*)-γClPip and (*S*,*S*)-γOHPip units, but failed in installing them under various conditions, especially using acid chlorides as coupling reagents.[10] Accordingly, we planned to assemble this section of the molecule by forming two piperazine rings only after the connection of their precursors,[11] as indicated in Figure 1. Since the ester part of this molecule is the only less sterically hindered site, we decided to carry out the macrocyclization through an ester bond formation.

The synthetic routes to requisite fragments **6** and **8** are illustrated in Scheme 1. Treatment of the known lactone **2**[12,13] with LiHMDS and subsequent trapping of the resulting anion with MoOPH[14] gave the desired *trans*-alcohol **3** in 73% yield (79% brsm) with a 6:1 diastereoselectivity. The *trans*-alcohol **3** was reacted with triflic anhydride, and then exposed to benzyl carbazate to afford hydrazide **4** in 81% yield.[15] Protection of **4** with TrocCl led to formation of **5**, which upon saponification and subsequent methylation provided a methyl ester, which was chlorinated using Ph_3P and CCl_4 to deliver **6**.

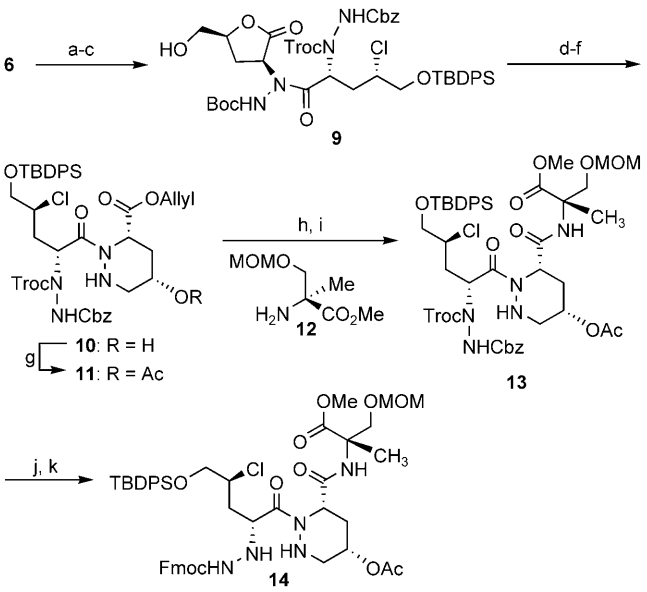
In a parallel procedure, the enantiomer of *trans*-alcohol **3** (*ent*-**3**) was reacted with Tf_2O and then treated with *tert*-butyl carbazate to give hydrazide **7** in 88% yield. Removal of the TBDPS ether in **7** by reaction with TBAF and AcOH provided alcohol **8** in quantitative yield. These fragments could then used to assemble the required (*R*,*S*)-γClPip/(*S*,*S*)-γOHPip fragments (see below). Notably, **6** and **8** could be easily converted into protected γ-hydroxypiperazic acid and γ-chloropiperazic acid, respectively. Although several groups have reported their efforts for assembling these γ-substituted piperazic acids,[9] our method apparently represents one of the simplest procedures.



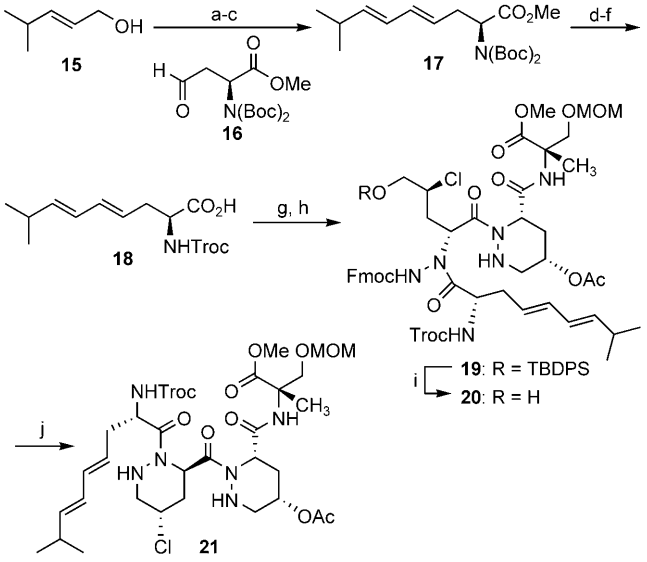
Scheme 1. Reagents and conditions: a) LiHMDS, THF, −78 °C; then MoOPH, −78→−30 °C, 73 %, 79 % brsm; b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C; then benzyl carbazate, 2,6-lutidine, reflux, 81 %; c) TrocCl, aq $NaHCO_3$, $CHCl_3$, 0 °C→RT, 95 %; d) aq LiOH, THF, 0 °C; then MeI, DMF, 69 %; e) PPh_3, CCl_4, reflux, 86 %; f) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C; then *tert*-butyl carbazate, 2,6-lutidine, reflux, 88 %; g) TBAF, HOAc, THF, quant. TBDPS = *tert*-butyldiphenylsilyl; Cbz = benzyloxycarbonyl; Troc = 2,2,2-trichloroethoxycarbonyl; Boc = *tert*-butyloxycarbonyl; HMDS = hexamethyldisilazane; MoOPH = Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide); brsm = based on recovered starting material; Tf = trifluromethanesulfonyl; Troc = 2,2,2-trichloroethoxycarbonyl; TBAF = tetra-*n*-butylammonium fluoride.

Methyl ester **6** was saponified and the resulting acid was treated with oxalyl chloride to afford the acyl chloride, which was then coupled with **8** under the assistance of K_2CO_3 in methylene chloride to give the N-acylation product **9** in 74 % yield (Scheme 2). The reaction conditions indicated here are crucial for chemoselectivity because only the O-acylation product was isolated when Et_3N was used as a base. Sulfonylation of the hydroxy group of **9** with Tf_2O, removal of the Boc protecting group with CF_3CO_2H, and then intramolecular N-alkylation of the resulting amine gave the piperazide, which was saponified and treated with allyl bromide to provide allyl ester **10** in 67 % overall yield. The hydroxy group of **10** was protected with Ac_2O to afford **11**. After cleavage of the allyl ester in **11** using $[Pd(PPh_3)_4]$/*N*-methylaniline, the free acid was coupled with the (*S*)-α-methylserine derivative **12** (prepared from (*Z*)-α-MeSer-OMe,[16] see the Supporting Information) under HATU/HOAt/*i*Pr_2NEt reaction conditions to give linear peptide **13**. Removal of the Troc group by reduction with activated zinc, and exchange of the Cbz group for a Fmoc protecting group in one step using $Pd(OH)_2/H_2$/FmocOSu/$NaHCO_3$ afforded amide **14**, which was ready for condensation with the (*S*)-AMNA fragment.

As depicted in Scheme 3, our construction of the (*S*)-AMNA fragment started with bromination of the allyl alcohol **15**.[17] The allyl bromide was reacted with *n*Bu_3P, and then treated with NaHMDS to provide an ylide, which was reacted with aldehyde **16**[18] to afford *trans,trans*-diene **17** in 70 % yield as a single isomer. Using the double Boc-protected aldehyde **16** in the Wittig reaction was found to be essential for the exclusive production of **17**, because low yield and stereoselectivity were observed when a mono-Boc-protected



Scheme 2. Reagents and conditions: a) aq LiOH, THF, 0 °C; b) oxalyl chloride, DMF, CH_2Cl_2; c) **8**, K_2CO_3, CH_2Cl_2, 0 °C, 74 %; d) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C; then CF_3CO_2H; e) aq LiOH, THF, 0 °C; f) allylic bromide, $KHCO_3$, DMF, 67 % yield for three steps; g) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C→RT, 97 %; h) $[Pd(PPh_3)_4]$, *N*-methylaniline, THF; i) **12**, HATU, HOAt, *i*Pr_2NEt, CH_2Cl_2, 90 % yield for two steps; j) Zn, 1 M KH_2PO_4, THF, 97 %; k) $Pd(OH)_2$, H_2, FmocOSu, $NaHCO_3$, MeOH, 74 %. DMF = *N*,*N*-dimethylformamide; DMAP = 4-dimethylaminopyridine; MOM = methoxymethyl; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluoro-phosphate; HOAt = 1-hydroxyazobenzotriazole; Fmoc = 9-fluorenylmethyloxycarbonyl; Su = succinimide.



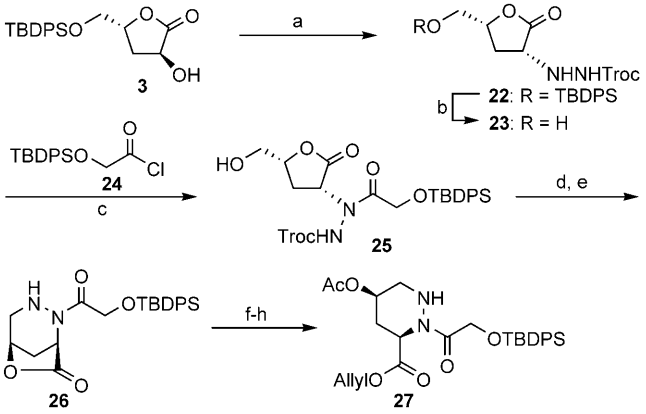
Scheme 3. Reagents and conditions: a) PBr_3, Et_2O, −30 °C to RT; b) *n*Bu_3P, Et_2O, 84 % yield for two steps; c) NaHMDS, THF, −78 °C, then **16**, −78 °C, 70 %; d) CF_3CO_2H, CH_2Cl_2; e) TrocCl, aq Na_2CO_3, $CHCl_3$, 0 °C→RT; f) aq LiOH, THF, 0 °C, quant. for three steps; g) oxalyl chloride, DMF, CH_2Cl_2; h) **14**, K_2CO_3, CH_2Cl_2, 0 °C, 75 %; i) TBAF, HOAc, THF, 65 %, 98 % brsm; j) PPh_3, DEAD, THF, reflux, 98 %. DEAD = diethylazodicarboxylate.

aldehyde was employed. The additional Boc group might increase the steric bulk of the substrate and prevent isomerization of the intermediate oxaphosphetane, thereby giving better stereoselectivity. After removal of the Boc group with CF_3CO_2H, the liberated amine was reacted with TrocCl to afford the Troc-protected amino ester, which was then hydrolyzed with aqueous LiOH to provide amino acid **18**. Treatment of **18** with oxalyl chloride and subsequent coupling of the acyl chloride with the hydrazide **14** gave amide **19** in 75% yield. Notably, **14**, having two free NH groups at the piperazic unit and the terminally monoprotected α-hydrazino amide unit, was able to couple with the acyl chloride. The exclusive formation of **19** clearly indicates that the free piperazic NH group is much less reactive than free hydrazide NH group. The subtle difference in the both electronic and steric effects could account for this phenomenon.

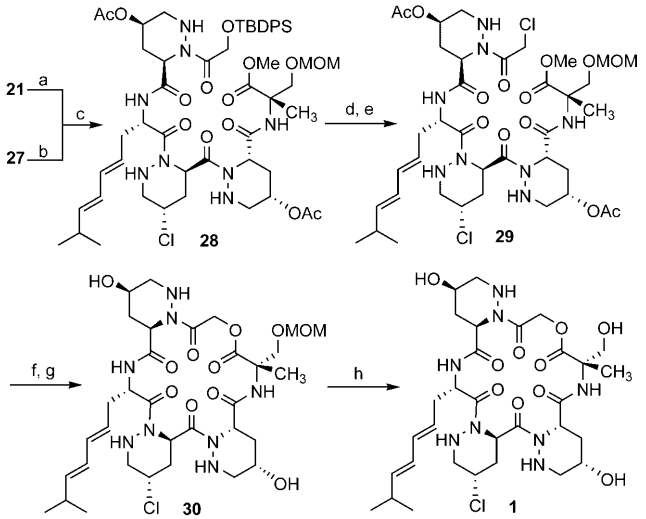
To obtain the second piperazine ring, the TBDPS protecting group in **19** needed to be removed first, but this was challenging because both the base sensitive Fmoc and acid sensitive MOM were present. After performing experiments, we were pleased to find that this deprotection could be accomplished by treatment of **19** with TBAF (2 equiv) and AcOH (8 equiv) in THF. In this case the desired alcohol **20** was isolated in 65% yield (98% brsm). For the closure of the piperazine ring, we initially attempted to use a sequence of hydroxy-group activation and subsequent intramolecular *N*-alkylation, but unfortunately we encountered problems when screening reagents to remove the Fmoc group. To our delight, when we executed Mitsunobu conditions,[19] alcohol **20** was converted into the desired tetrapeptide **21** in almost quantitative yield. This transformation contains two steps: an intramolecular substitution and the removal of the Fmoc group, which has not yet been reported. Obviously, this method could also be used to assemble related piperazic acid derivatives.

With the tetrapeptide **21** in hand, the construction of the dipeptide fragment **27** became our next task. Treatment of *trans*-alcohol **3** with triflic anhydride, and then exposure of the resulting triflate to 2,2,2-trichloroethyl carbazate[20] provided hydrazide **22** in 75% yield (Scheme 4). Removal of the TBDPS ether afforded alcohol **23**, which was coupled with acid chloride **24**[21] to give the N-acylation product **25** in 80% yield. Sulfonylation of the hydroxy group of **25** with Tf_2O, subsequent removal of the Troc protecting group to deliver the amine, and then intramolecular N-alkylation of the amine gave piperazide **26** in 85% overall yield. After saponification of **26**, the liberated acid was treated with allyl bromide and acetic anhydride to give allyl ester **27** in 90% overall yield.

The connection of the tetrapeptide **21** with the dipeptide **27** and the completion of the synthesis are depicted in Scheme 5. Treatment of **21** with activated zinc afforded an amine, which was then coupled with the acid released from allyl ester **27** to give linear peptide **28** in 80% yield. The stage was now set for the crucial macrocyclization, and we planned to use a substitutive macrolactonization strategy which was initially reported by Kellogg and co-workers to close the macrocycle.[22] Accordingly, removal of the TBDPS ether in **28** afforded an alcohol, which was exposed to triphenylphosphine and hexachloroacetone (PPh_3/HCA)[23] to provide



Scheme 4. Reagents and conditions: a) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C; then 2,2,2-trichloroethyl carbazate, 2,6-lutidine, reflux, 75%; b) TBAF, HOAc, THF, 98%; c) **24**, K_2CO_3, CH_2Cl_2, 0°C, 80%; d) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C; e) Zn, 1 M KH_2PO_4, THF, 85% for two steps; f) aq LiOH, THF, 0°C; g) allylic bromide, $KHCO_3$, DMF; h) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0°C to RT, 90% for three steps.



Scheme 5. Reagents and conditions: a) Zn, 1 M KH_2PO_4, THF; b) [Pd(PPh_3)$_4$], *N*-methylaniline, THF, quant.; c) HATU, HOAt, *i*Pr_2NEt, CH_2Cl_2, 80% yield from **21**; d) TBAF, HOAc, THF, quant.; e) PPh_3, HCA, THF, 0°C→RT, 89%; f) aq LiOH, THF, 0°C, 95%; g) NaI, K_2CO_3, DMF, 40°C, 79%; h) TMSCl, TBAB, BuSH, CH_2Cl_2, 0°C→RT, 78%. HCA = hexachloroacetone; TMS = trimethylsilyl; TBAB = tetra-*n*-butylammonium bromide.

chloride **29** in 89% yield. The methyl ester and acetyl protecting groups in **29** were carefully removed by saponification. When treatment of the resulting acid under reported reaction conditions (Cs_2CO_3, DMF, 80°C),[22] the desired macrocycle could not be detected, and only decomposition of the acid was observed. Fortunately, when we treated this intermediate with NaI and K_2CO_3 in DMF at 40°C, we isolated the desired cyclization product **30** in 79% yield. To the best of our knowledge, this is the first report using the substitutive macrolactonization strategy to synthesize natural cyclic depsipeptides, eventhough it was reported 19 years ago. Indeed, this success was essential for the completion of the

total synthesis of piperazimycin A because condensative macrolactonization at this site using Yamaguchi,[24] Shiina,[25] Mukaiyama,[26] Corey–Nicolaou,[27] and Mitsunobu conditions[19] failed to give any desired product. This problem might result from the low nucleophilicity of the hydroxy group and the steric hindrance of the α-methylserine section. Finally, the MOM ether of **30** was removed with TMSCl and TBAB in the presence of *n*BuSH,[28] which acted as a cation scavenger, producing piperazimycin A **1** in 78% yield. All analytical data of the synthetic material were identical to those of natural piperazimycin A.[1]

In conclusion, we have accomplished the first total synthesis of piperazimycin A (3.4% overall yield for 26 linear steps), which features a concise elaboration of its difficult-to-install (*R*,*S*)-γClPip/(*S*,*S*)-γOHPip dipeptide fragment and a macrocyclization through an S_N2 reaction of an *N*-2-chloroacetyl moiety with a carboxylate anion. The former will be of benefit for synthesizing related natural products like dentigerumycin and monamycins, while the latter will prompt the application of the substitutive macrolactonization strategy in cyclodepsipeptide synthesis (specially for macrolactonization with the sterically hindered acids). Our synthetic route could also be used for assembly of piperazimycin A analogues, thereby exploring its structure-activity relationship. Investigations in this direction are actively being pursued in our laboratory and the results will be disclosed in due course.[29]

Received: August 18, 2009
Published online: October 16, 2009

Keywords: antitumor activity · depsipeptides · macrocyclization · natural products · total synthesis

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