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Synthesis and preliminary biological evaluation of truncated zoanthenol analogues

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Abstract—Zoanthamines are a family of marine alkaloids that have complex heptacyclic structures and are reported to be interleukin-6 modulators. While the structure of zoanthamines, especially the ABC-ring portion, is similar to that of steroids, the CDEFG-ring portion, composed of aminoacetal and lactone core, is a unique structural element. In this report, we designed and synthesized ABC-ring **6** and CDEFG-ring **7**, which are truncated analogues of the northern and southern hemispheres of zoanthenol **5**, respectively, and which incorporate all of the functionality of each hemisphere. A preliminary SAR study suggested that the hydrochloride of the CEFG-ring portion is an active pharmacophore for suppressing the growth of interleukin-6-dependent MH60 cells.

1. Introduction

Zoanthamines (**1**, **2**, **5**) are a family of marine alkaloids isolated from the zoanthid *Zoanthus* sp. and possess a unique array of skeletal and stereochemical complexities.[1] Zoanthamines have several pharmacological properties,[1,2] and their activity as a possible osteoporosis drug is of particular interest. Uemura and co-workers reported that norzoanthamine hydrochloride **4** suppressed the loss of bone weight and strength in ovariectomized mice.[3] Unlike estrogens, serious side effects, such as an increase in uterine weight, are not observed. Therefore, the mode of action of **4** on osteoporosis appears to be different from that of estrogen.[3c,4] In addition, norzoanthamine and its hydrochloride are reported to suppress interleukin-6 (IL-6) production.[3] Because IL-6 is known as a mediator of bone resorption in osteoporosis,[5] it is likely that the activity as an IL-6 modulator might be associated with its effects on osteoporosis[6,7] (Fig. 1).

The structure of zoanthamines, especially the ABC-ring portion, is similar to that of steroids. On the other hand, the CDEFG-ring portion, composed of an aminoacetal and a lactone, is a unique structural element. We thus hypothesized that the CDEFG-ring portion and its hydrochloride might be a pharmacophore of the zoanthamines. To date, neither the total synthesis of zoanthamines[8,9] nor the structure–activity relationship (SAR) study using synthetic analogues has been reported, although SAR study using natural product derivatives has been described.[1e]

In this report, we designed the ABC-ring **6** and the CDEFG-ring **7**, which are truncated analogues of the northern and southern hemispheres of zoanthenol **5**, respectively, and which incorporate all of the functionality of each hemisphere. We report herein the synthesis and the preliminary biological evaluation of these truncated analogues.

2. Synthesis

As outlined in Scheme 1, we planned the synthesis of the truncated analogues (**6**, **7**) to allow the total synthesis of zoanthenol **5**. A fully functionalized ABC-ring moiety **10** was designed as a key intermediate that could be

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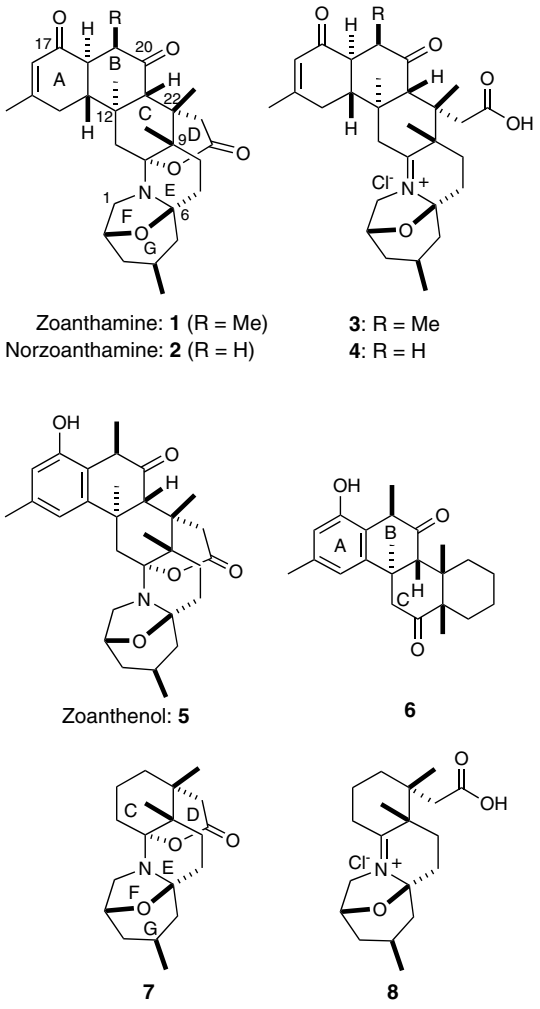
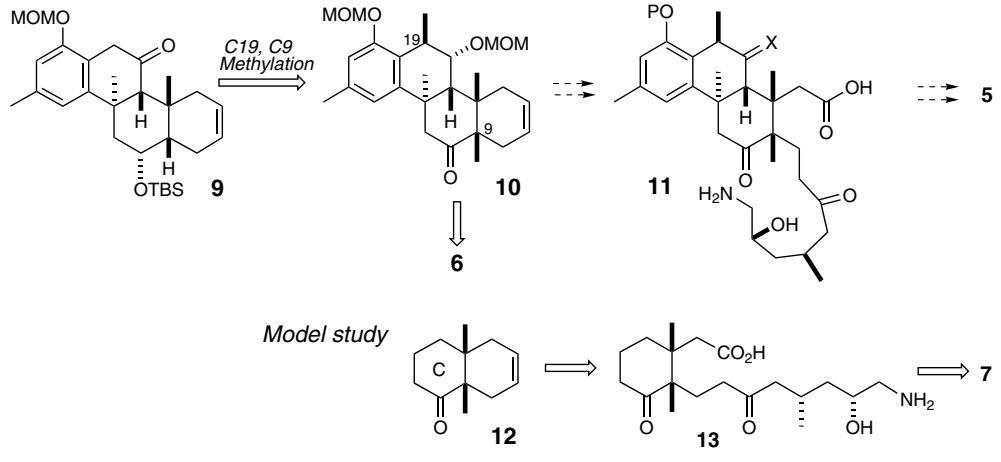


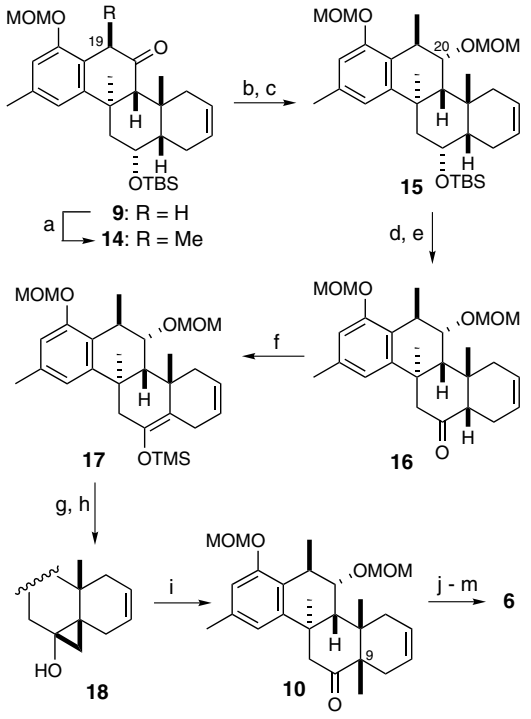
Figure 1. Structures of zoanthamines (**1**, **2**, and **5**), designed analogues (**6**, **7**), and its hydrochlorides (**3**, **4**, and **8**).

converted to the analogue **6** and that would also install the aminoacetal–lactone core (DEFG-ring portion) after the oxidative cleavage of double bond followed by cyclization of **11** leading to **5**. Compound **10** would be synthesized from the previously reported compound **9**[8c] by incorporation of C19 and C9 methyl groups.[10] For the synthesis of the analogue **7**, we performed a model study to establish a synthetic route to **5** starting from **10**. In this model study, we used the C-ring moiety **12**, which possesses the double bond and ketone functionalities found in **10**.

To synthesize **10** and **6**, the C19 methyl group was first incorporated into the ketone **9**[8c] via regio- and stereocontrolled alkylation (Scheme 2). Deprotonation of **9** with lithium diisopropylamide (LDA) followed by addition of methyl iodide generated **14** in 91% yield. Reduction of ketone **14** with lithium aluminumhydride and subsequent protection as a methoxymethyl (MOM) ether gave a 3:1 diastereomeric mixture of **15** and its C20 epimer (77%, two steps).[11] Treatment of **15** with tetrabutylammonium fluoride (TBAF) in *N*,*N*′-dimethylpropyleneurea (DMPU) at 95 °C cleanly removed the silyl group, producing the corresponding alcohol,[12] which was oxidized by Dess–Martin periodinane to furnish ketone **16** in quantitative yield (two steps). We then conducted the critical C9 methylation installing consecutive quaternary centers on the C-ring. Conditions developed for the methylation in the previously reported model study[8a] were applied to the more elaborated substrate **16**. First, exposure of **16** with trimethylsilyl iodide (TMSI) and $HN(TMS)_2$ produced silyl enol ether **17** regioselectively, which was then treated with methyl lithium to generate the corresponding lithium enolate. Treatment of the lithium enolate with samarium iodide (SmI_2) and chloroiodomethane produced the desired cyclopropanol **18**, which was then exposed with *p*-toluenesulfonic acid (TsOH) to produce the key intermediate **10** in 42% yield (three steps). As expected, the SmI_2-mediated Simmons–Smith reaction proceeded exclusively at the less hindered β-face of the enolate. We therefore accomplished the synthesis of the fully elaborated ABC-ring system of **5** in a highly stereocontrolled manner. The analogue **6** was then synthesized via a four step procedure: (i) removal of the MOM groups, (ii) protection of the phenol as a benzyl



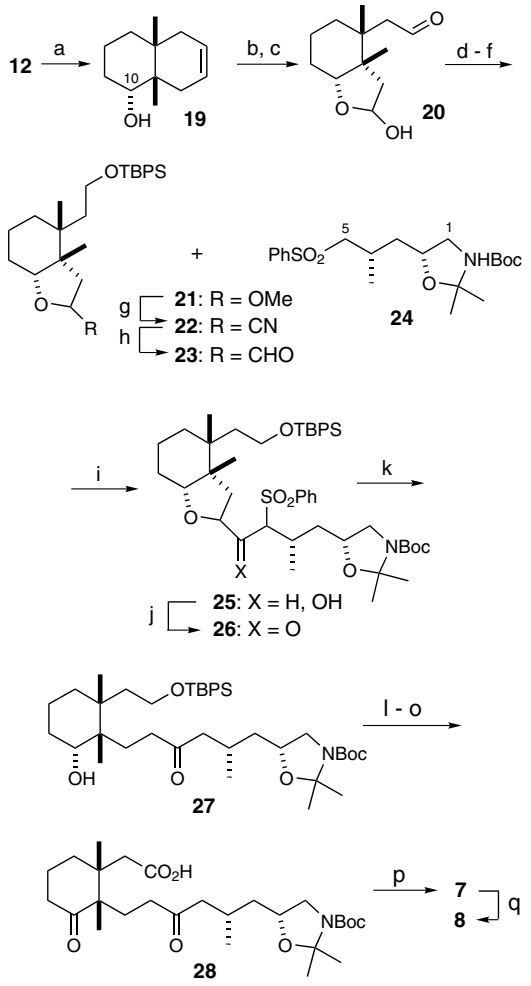
Scheme 1. Synthesis plan of zoanthenol (**5**) and designed analogues (**6**, **7**).



Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, then MeI, HMPA, −78 °C → rt, 91%; (b) $LiAlH_4$, Et_2O, 0 °C; (c) MOMCl, $(i\text{-}Pr)_2NEt$, $(CH_2Cl)_2$, 50 °C, 77% (**15**/C20*epi*-**15** = 3:1, two steps); (d) TBAF, DMPU, 95 °C; (e) Dess–Martin periodinane, CH_2Cl_2, 99% (two steps); (f) TMSI, $HN(TMS)_2$, hexane, −20 °C to rt, 75%; **16** 25% (recovery); (g) MeLi, DME, HMPA, 0 °C; (h) SmI_2, $ClCH_2I$, THF, −78 °C → rt; (i) *p*-TsOH, CH_2Cl_2, 0 °C, 42% (three steps), **16** 25% (recovery); (j) TMSBr, CH_2Cl_2, −40 → −20 °C; (k) BnBr, Cs_2CO_3, DMF, 76% (two steps); (l) Dess–Martin periodinane, CH_2Cl_2; (m) H_2, Pd/C, AcOEt, 40% (two steps).

ether, (iii) Dess–Martin oxidation, and (iv) treatment with Pd/C under a H_2 atmosphere.

We next turned our attention to the synthesis of the analogue **7** starting from **12**[13] (Scheme 3). Stereoselective reduction of ketone **12** by treatment with lithium in NH_3–EtOH–Et_2O yielded a 3:1 mixture of **19** and C10*epi*-**19** (87% yield). After separation, OsO_4-catalyzed dihydroxylation of **19** and subsequent oxidative cleavage of the resulting diol produced **20** in 89% yield (two steps). Reduction of the aldehyde **20** followed by conversion of the hemiacetal into the corresponding methyl ketal and protection of alcohol as silyl ether furnished **21** (60% yield, three steps). Treatment of the methyl ketal **21** with TMSCN and TMSOTf produced the nitrile **22** in 91% yield,[14] which was reduced with DIBAL-H to give aldehyde **23**.[15] To connect the C1–C5 unit **24**[16] with **23**, we next conducted a Julia coupling reaction. Deprotonation of the sulfone **24** with *n*-BuLi and subsequent treatment with **23** produced the corresponding adduct **25**, which was oxidized to generate ketone **26**. Upon treatment of **26** with SmI_2 in the presence of methanol as a proton source, successive desulfonation and cleavage of the furan ring furnished **27** in 79% yield, which was then converted to **28** by standard synthetic procedures. Finally, we constructed



Scheme 3. Reagents and conditions: (a) Li, NH_3, Et_2O/EtOH, −60 °C, 87% (**19**/C10*epi*-**19** = 3:1); (b) OsO_4, NMO, *t*-BuOH–H_2O, 90%; (c) $NaIO_4$, THF–H_2O, 99%; (d) DIBAL-H, CH_2Cl_2, −78 °C; (e) TsOH·H_2O, MeOH; (f) TBPSCl, imidazole, DMF, 60% (three steps); (g) TMSCN, TMSOTf, CH_2Cl_2, 0 °C, 91%; (h) DIBAL-H, CH_2Cl_2–hexane, −90 °C; (i) **24**, *n*-BuLi, THF, −78 °C; (j) Dess–Martin periodinane, pyridine, CH_2Cl_2, 37% (three steps); (k) SmI_2 (20 equiv), MeOH (5 equiv), THF, −78 °C → rt, 79%; (l) Dess–Martin periodinane, pyridine, CH_2Cl_2, 99%; (m) TBAF, THF, 99%; (n) Dess–Martin periodinane, pyridine, CH_2Cl_2, 99%; (o) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O; (p) AcOH/H_2O (96:4), 100 °C, 10 h, then Na_2SO_4, rt, 1 h, 61% (three steps); (q) HCl, Et_2O.

the aminoacetal and lactone core according to the protocol reported by Kobayashi and co-workers.[9c] Treatment of **28** in AcOH/H_2O (96:4) at 100 °C followed by the addition of anhydrous sodium sulfate produced the pentacyclic analogue **7** in 61% yield (three steps). The hydrochloride salt **8** was also synthesized by exposure with HCl in Et_2O.[1e]

3. Biological evaluation

With the synthetic analogues in hand, we performed a preliminary SAR study to investigate the ability to inhibit the growth of IL-6-dependent MH60 cells

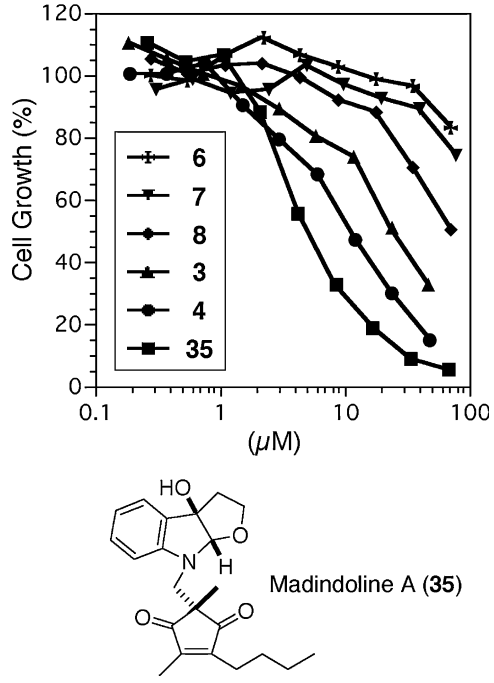


Figure 2. Effects of hydrochlorides of zoanthamines (**3**, **4**), synthetic analogues (**6**, **7**), and **8** on the growth of IL-6-dependent MH60 cells. Madindoline A (**35**) was used as a positive control.

(Fig. 2).[17] Madindoline A (**35**) was used as a positive control for inhibition of IL-6 effects [$IC_{50} = 8\,\mu M$].[6,18] We first confirmed that the hydrochlorides of zoanthamines **3** and **4** suppressed IL-6-induced cell growth of the MH60 cells in a dose-dependent manner [IC_{50} for **3** and **4** was 26 and 13 μM, respectively].[19] We also found that the hydrochloride of the CEFG-ring analogue **8** dose-dependently suppressed cell growth, although the potency [$IC_{50} = \approx 70\,\mu M$] was lower than for **3** and **4**. In contrast, the analogues, ABC-ring **6** and CDEFG-ring **7**, showed very weak inhibitory activities. Thus, the hydrochloride of CEFG-ring portion may be an active pharmacophore for zoanthamine inhibition of IL-6 activity.

In summary, we have synthesized truncated analogues (**6**, **7**) of zoanthenol **5** in a stereocontrolled manner. A preliminary SAR study suggested that the hydrochloride of CEFG-ring part is required for suppression of growth of IL-6-dependent MH60 cells. This study not only provides synthetic strategies for the total synthesis of zoanthamines but also gives insight into the active pharmacophore. Further investigations are currently underway in our laboratories.

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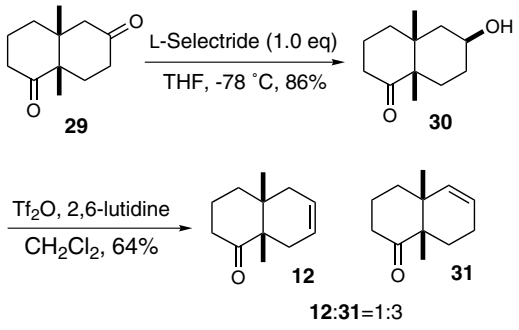
10. Carbon numbering corresponds to that for zoanthenol **5**, see Ref. 1h.
11. The 3:1 diasteromeric mixture was subjected to the synthesis of **6** without separation.
12. No reaction was observed when **15** was treated with TBAF in refluxing THF.
13. The C-ring moiety **12** was synthesized as follows. The ketone **29** was readily available from *S*-(+)-Wieland-Miescher ketone, see: Vellekoop, A. S.; Smith, R. A. J. *Tetrahedron* **1998**, *54*, 11971,



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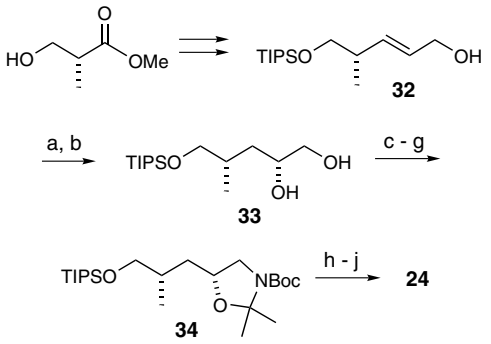
15. DIBAL-H reduction of nitrile **22** always yielded **23** and a primary amine in a 1:1 ratio.



Scheme 4. Reagents and conditions: (a) *t*-BuOOH, Ti(O*i*-Pr)$_4$, diethyl-L-(+)-tartrate, MS4A, −20 °C, CH_2Cl_2, 90%; (b) DIBAL-H, toluene, 0 °C, 96%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2; (d) NaN_3, DMF, 73% (two steps); (e) Pd/C, THF; (f) $(Boc)_2O$, NaOH, 84% (two steps); (g) 2,2-dimethoxypropane, *p*-TsOH, benzene, 96%; (h) TBAF, THF, 95%; (i) PhSSPh, *n*-Bu_3P, pyridine, 91%; (j) *m*CPBA, $NaHCO_3$, 0 °C, CH_2Cl_2, 93%.

16. The C1–C5 unit **24** was synthesized as shown in Scheme 4. Allyl alcohol **32** was synthesized from methyl 2*S*-3-hydroxy-2-methylpropionate according to reported protocols, see: Ishiwata, A.; Sakamoto, S.; Noda, T.; Hirama, M. *Synlett* **1999**, 692.
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