Tetrahedron Letters xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Total synthesis and biological evaluation of marinopyrrole A and analogs

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ARTICLE INFO

Article history:
Received 8 September 2010
Accepted 15 September 2010
Available online xxxx

Dedicated to Harry Wasserman on the occasion of his 90th birthday

Keywords:
Marine natural products
Total synthesis
Atropisomers
Clauson-Kaas reaction

ABSTRACT

A five-step total synthesis of the antibiotic marinopyrrole A (**1**) is described. The developed synthetic technology enabled the synthesis of several marinopyrrole A analogs whose antibacterial properties against methicillin-resistant *Staphylococcus aureus* TCH1516 were evaluated.

Marinopyrroles A and B (**1** and **2**, Fig. 1) are two recently reported alkaloids endowed with promising antibiotic activities against methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Isolated from an obligate marine *Streptomyces* (strain CNQ-418, collected from the sea floor near La Jolla, CA), these structurally unusual molecules exist as enantiopure *M*-(−)-atropisomers at ambient temperature. The absolute structure of (−)-**2** was established through X-ray crystallographic analysis and (−)-**1** through spectroscopic comparisons. Due to their novel molecular structures and promising biological properties, the marinopyrroles have attracted considerable attention. The preparation of several semisynthetic analogs,[2] a study of the mode of action,[3] and a total synthesis[4] of marinopyrrole A [(±)-**1**] have been reported. A recent evaluation of the pharmacological properties of marinopyrrole A revealed potent anti-MRSA activity and favorable in vitro kinetics.[5] We set out to develop a total synthesis that could deliver large amounts of material and would be flexible enough to allow the construction of a wide range of analogs for probing structure–activity relationships (SARs). We report herein a short and efficient total synthesis of marinopyrrole A (**1**) and a series of analogs, as well as their biological evaluation.

Although a direct, late-stage dimerization of two fully elaborated pyrrole units could be imagined, such a route might be limiting in terms of substrate scope and coupling efficiency. An alternative approach involving early construction of the bis-pyrrole system followed by site-specific introduction of the benzenoid rings and chlorine residues would allow easy access to a variety of designed analogs. Scheme 1 summarizes the developed five-step route to marinopyrrole (−)-**1** (natural) and (+)-**1** (unnatural) from the readily available building blocks aminopyrrole **3**[6] and 2,5-dimethoxytetrahydrofuran (**4**; commercially available). Thus, a PPTS-promoted Clauson-Kaas reaction[7] between **3** and **4** in refluxing 1,4-dioxane furnished bis-pyrrole **5** in 43% yield, establishing the crucial C–N bond. The latter compound underwent smooth mono-addition of lithiated anisole **6**, in THF at −78 °C, to afford tricycle **7** in 80% yield. Friedel–Crafts arylation of **7** with acid chloride **8**, mediated by $AlCl_3$ in CH_2Cl_2 at 0–25 °C, led to the marinopyrrole core structure **9** in 64% yield. Despite multiple potential chlorination sites, compound **9** underwent selective pyrrole *tetra*-chlorination with 4.1 equiv of sulfuryl chloride[8] (SO_2Cl_2) in CH_2Cl_2 at 0 °C to

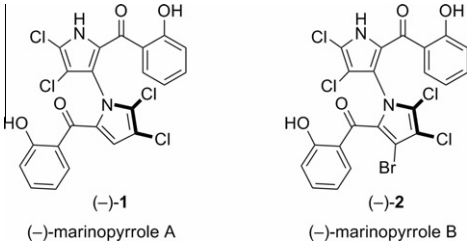

Figure 1. Marinopyrroles A (**1**) and B (**2**).

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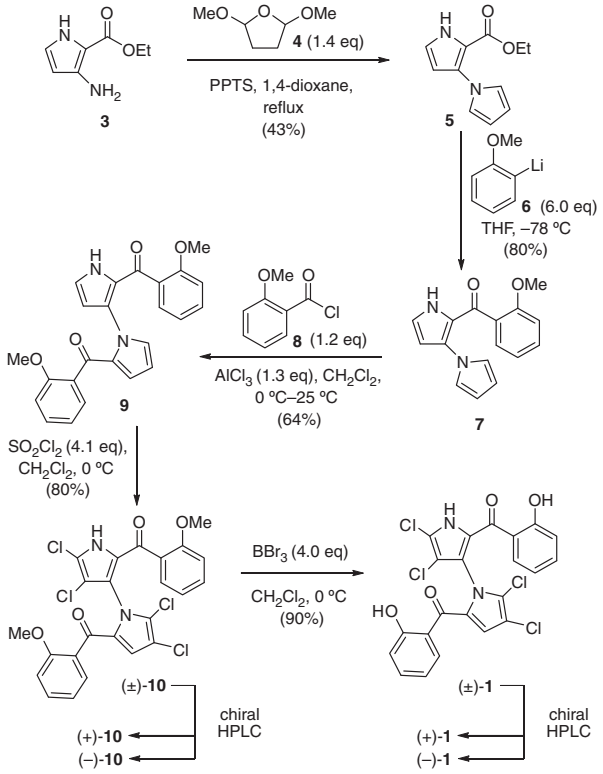
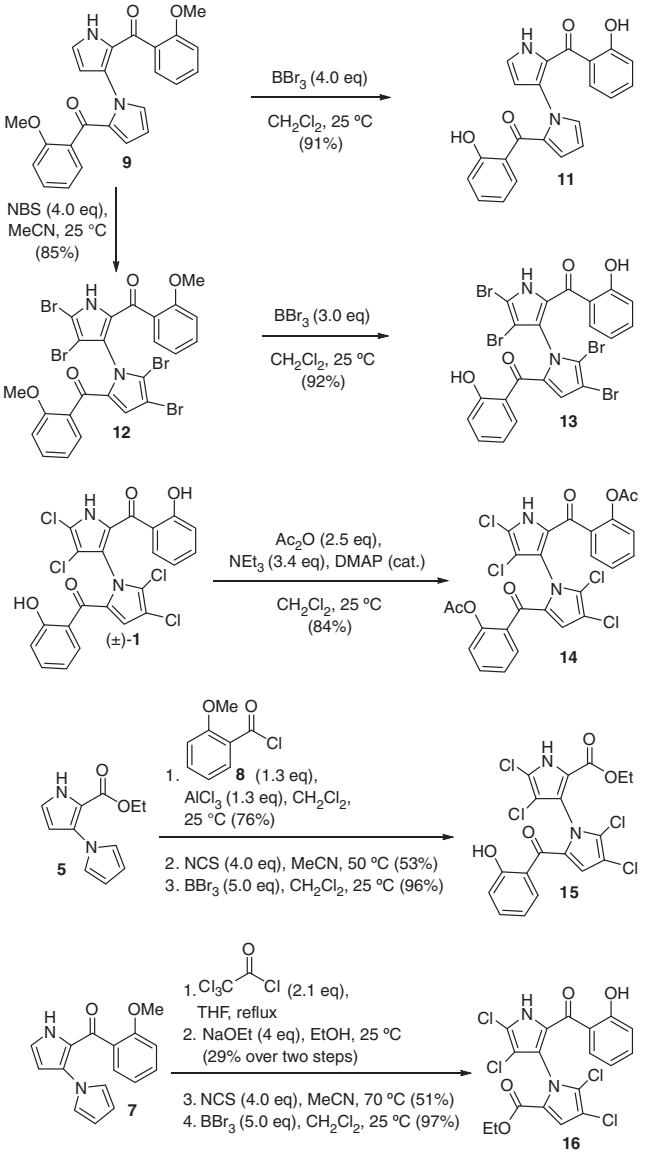
0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.09.059



Scheme 1. Synthesis of marinopyrrole A [(+)-**1** and (−)-**1**].



Scheme 2. Synthesis of marinopyrrole A analogs **11**–**16**.

generate a dimethyl marinopyrrole A derivative (±)-**10** in 80% yield.[4] Exposure of tetrachloride (±)-**10** to additional SO_2Cl_2 or other chlorination reagents [e.g., *N*-chlorosuccinimide (NCS)] led to *para*-chlorination of the aryl moieties. Similarly, attempts to brominate the remaining pyrrole position to prepare methyl-protected (±)-**2** led only to *para*-bromination of the aryl rings. That compound **10** exists as two stable atropisomers was confirmed by chiral HPLC separation (4:1 hexanes:*i*-PrOH, Chiralcel® OD-H) of the two enantiomers [(+)-**10** and (−)-**10**]. These enantiomers demonstrated remarkable thermal stability, showing no detectable racemization in DMF at 120 °C after 24 h. In contrast, marinopyrrole A (**1**) racemizes completely at that temperature.[2] Finally, cleavage of the methyl ethers of (±)-**10** (BBr_3, CH_2Cl_2, 0 °C, 90% yield) delivered racemic marinopyrrole A [(±)-**1**] in five steps and 16% overall yield from aminopyrrole **3**. The two enantiomers of (±)-**1** were separated by chiral HPLC under the published conditions (19:1 hexanes:*i*-PrOH, Chiralcel® OD-H)[1] to afford (+)-**1** and (−)-**1**.

The developed technology for the total synthesis of marinopyrrole A was employed for the synthesis of designed analogs **11**–**16** as summarized in Scheme 2. Thus, demethylation of compound **9** (BBr_3, CH_2Cl_2, 91% yield) gave dehalogenated marinopyrrole A **11**.[4] Treatment of bis-pyrrole **9** with 4.0 equiv of *N*-bromosuccinimide (NBS) led to selective *tetra*-bromination on the pyrrole rings to afford **12** in 85% yield. As observed with tetrachloride **10**, exposure of **12** to further amounts of NBS led to *para*-bromination of the aryl moieties. Compound **12** was then demethylated (BBr_3, CH_2Cl_2, 92% yield) to provide tetrabromomarinopyrrole **13**. Acetylation of the phenolic oxygens of (±)-**1** proceeded readily with acetic anhydride and NEt_3 in the presence of catalytic amounts of DMAP, furnishing diacetylmarinopyrrole A **14** in 84% yield.[2,3] Mono-arylated marinopyrrole **15** was prepared from bis-pyrrole **5** through a three-step sequence involving a Friedel–Crafts *C*-arylation with acid chloride **8**, *tetra*-chlorination with NCS in MeCN at 50 °C, and demethylation with BBr_3 in CH_2Cl_2 to afford **15** in 39% overall yield. Similarly, **16** was prepared from **7** in 14% overall yield though a four-step sequence involving *C*-acylation with trichloroacetylchloride in refluxing THF, trichloromethyl displacement with NaOEt in EtOH, *tetra*-chlorination (NCS, MeCN, 70 °C), and cleavage

Table 1
Antibacterial activities of synthetic marinopyrroles

Entry	Compound	MIC_{50}[a] (μg/mL)
1	(±)-**1**	0.375–0.750
2	(+)-**1**	0.189
3	(−)-**1**	0.189
4	**9**	>96
5	(±)-**10**	>96
6	**11**	48
7	**12**	>96
8	**13**	0.75
9	**14**	0.375
10	**15**	3
11	**16**	1.5

[a] Tested against MRSA TCH1516 (ATCC BAA-1717).

of the methyl ethers (BBr_3, CH_2Cl_2). Although compounds **12**–**16** likely exist as enantiomeric atropisomers stable at room temperature, no chiral HPLC separation was undertaken prior to their testing due to the potency equivalence of the two marinopyrrole A enantiomers (see Table 1, entries 2 and 3).[1]

The synthesized compounds [(±)-**1**, (+)-**1**, (−)-**1**, (±)-**10**, and **11**–**16**] were evaluated for their antibacterial activities against TCH1516, a strain representative of the current epidemic clone of community-acquired MRSA.[5] The results are shown in Table 1. Thus, synthetic racemic [(±)-**1**] and enantiopure [(+)-**1** and (−)-**1**] marinopyrroles (entries 1–3) exhibited antibacterial potencies comparable to those of their naturally-derived counterparts.[1] Interestingly, the tetrabrominated congener of marinopyrrole A **13** (entry 8) exhibited comparable potency to marinopyrrole A, while the dehalogenated analog **11** (entry 6) was significantly less active, indicating the importance of the halogen atoms for biological activity. It was also clear that the free phenolic groups were necessary for activity since dimethylated marinopyrrole derivatives [**9**, (±)-**10**, and **12**] showed no activity (entries 4, 5, and 7, respectively). Bis-acetylated marinopyrrole **14** (entry 9) showed similar antibacterial potency to marinopyrrole [(±)-**1**] itself, possibly due to in situ ester hydrolysis within the cell. Excision of one of the two phenolic rings from the marinopyrrole structure led to active, but less potent analogs, as demonstrated by compounds **15** and **16** (entries 10 and 11, respectively). When these compounds were tested in the same assay, but in the presence of 20% normal pooled human serum, they were found to lose antibacterial activity, presumably due to protein adsorption.

In summary, a concise total synthesis of marinopyrrole A (**1**) that allows for large scale preparation of this novel natural product and its analogs is reported. The synthesized compounds were evaluated for activity against the clinically-important USA 300 clone of MRSA, with several showing strong antibacterial potencies. However, all suffered complete loss of antibacterial activity in the presence of human serum, suggesting utility in topical but not systemic formulations. Further structural modifications, including the design of prodrug-like compounds, may be necessary in order to improve the pharmacological profile of the marinopyrroles.

Acknowledgments

Financial support for this work was provided by The Skaggs Institute for Chemical Biology, a National Institutes of Health (U.S.A.) grant and Ruth L. Kirschstein National Research Service Award (NRSA) (to N.M.H.), and a National Science Foundation graduate fellowship (to N.L.S.).

Supplementary data

Supplementary data associated (further experimental details for the synthesis and biological evaluation of compounds as well as selected physical properties of compounds) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.059.

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