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Total Synthesis of Seongsanamide B

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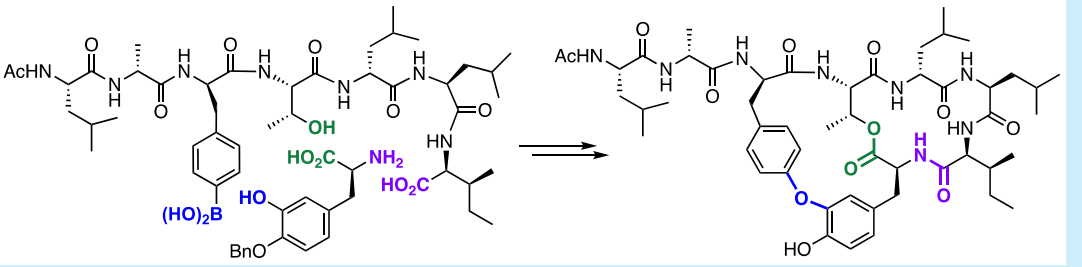

ABSTRACT: The first total synthesis of the bicyclic depsipeptide natural product seongsanamide B is described. The successful approach employed solid-phase peptide synthesis of a core heptapeptide, incorporating on-resin esterification, followed by solution-phase macrolactamization and a late stage intramolecular Evans–Chan–Lam coupling to generate the biaryl ether of the isodityrosine unit.

The seongsanamides A–F (Figure 1) were isolated by Choi and co-workers in 2018 from a *Bacillus safensis* strain and were shown to exhibit antiallergenic properties on bone-marrow-derived mast cells (BMMCs).[1] The increasing prevalence of allergic diseases, such as asthma, in recent decades has led to increased interest in the discovery of novel antiallergy agents.[2,3] Seongsanamides A–D exhibited dose-dependent inhibition of β-hexosaminidase release and were noncytotoxic at 20 μM. Further, seongsanamide A was orally active in a mouse model with antiallergenic activity comparable to known H_1 blocker fexofenadine.

Seongsanamides A–D are bicyclic peptides biosynthesized by nonribosomal peptide synthetases (NRPSs). Monocyclic seongsanamide E is the putative precursor to seongsanamide B, lacking the biaryl ether linkage—generated by CYP-catalyzed oxidative coupling—that forms the isodityrosine unit and second ring. In addition to the biaryl ether linkage between Tyr-3 and Tyr-8, seongsanamides A–D also contain an ester linkage between the hydroxyl group of Thr-4 and the C-terminal carboxylate of Tyr-8, designating these compounds as bicyclic depsipeptides. The biosynthesis of seongsanamide F **6** is presumed to proceed through a truncation during the NRPS pathway. The presence of three epimerase domains in the NRPSs correspond to the presence of D-residues at positions Ala-2, Tyr-3, and Leu-5.

To date, none of the seongsanamides has succumbed to total synthesis. The intriguing biological activity of the seongsanamides, together with their unusual structures and our long-standing interest in the synthesis of tyrosine cross-linked cyclic peptide natural products,[4–7] prompted our investigations into the synthesis of seongsanamide B.

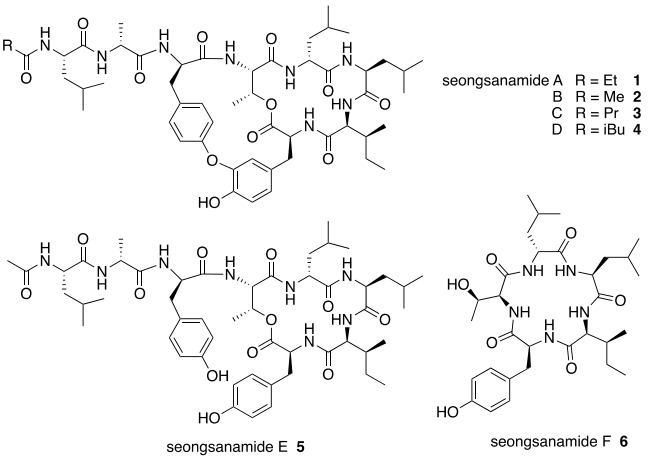

Figure 1. Structures of seongsanamides A–F.

The main challenges in the total synthesis of seongsanamide B include the formation of the biaryl ether linkage that forms the isodityrosine unit, together with construction of the macrolactone, in addition to the issues that frequently plague peptide macrocyclizations.[8–12] A number of approaches to the synthesis of isodityrosines have been reported, including

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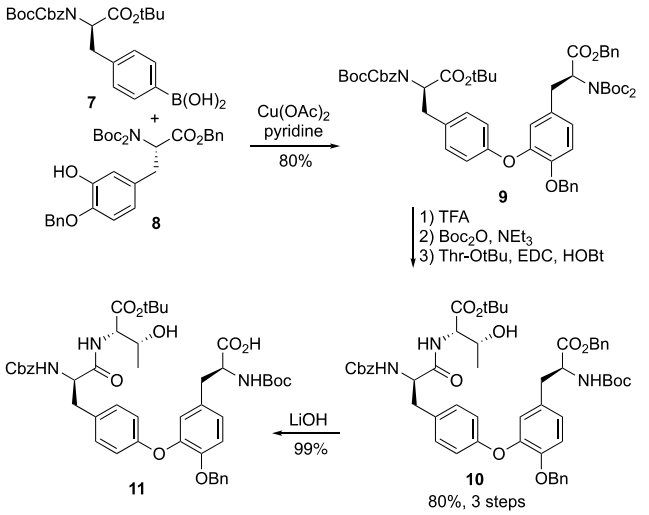
Scheme 1. Early-Stage Macrolactonization Approach



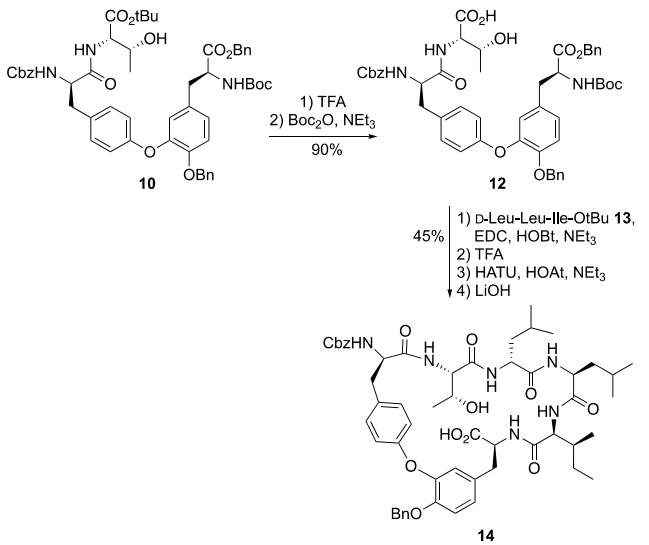
Ullman[13−19] and Evans−Chan−Lam[20−25] coupling reactions,[26] Dötz benzannulation,[27] and nucleophilic aromatic substitution (S_NAr) reactions.[28−34]

We first attempted an early biaryl ether construction, envisaging late-stage macrolactamization to generate the bicycle (Scheme 1). An Evans−Chan−Lam coupling of phenylalalanine boronic acid and DOPA derivatives **7** and **8** was chosen to generate protected isodityrosine **9**. Cleavage of the three Boc groups and *tert*-butyl ester was followed by reprotection of the DOPA amine. Subsequent coupling of Thr-O*t*Bu to the tyrosine carboxylate generated peptide **10**, with hydrolysis of the benzyl ester then providing acid **11**. Attempted macrolactonization of **11** under a variety of coupling conditions was unsuccessful. Related macrolactamizations to generate isodityrosine-containing cyclic peptides have proven difficult,[5,6] as have macrolactonizations to generate cyclic depsipeptides.[35−38]

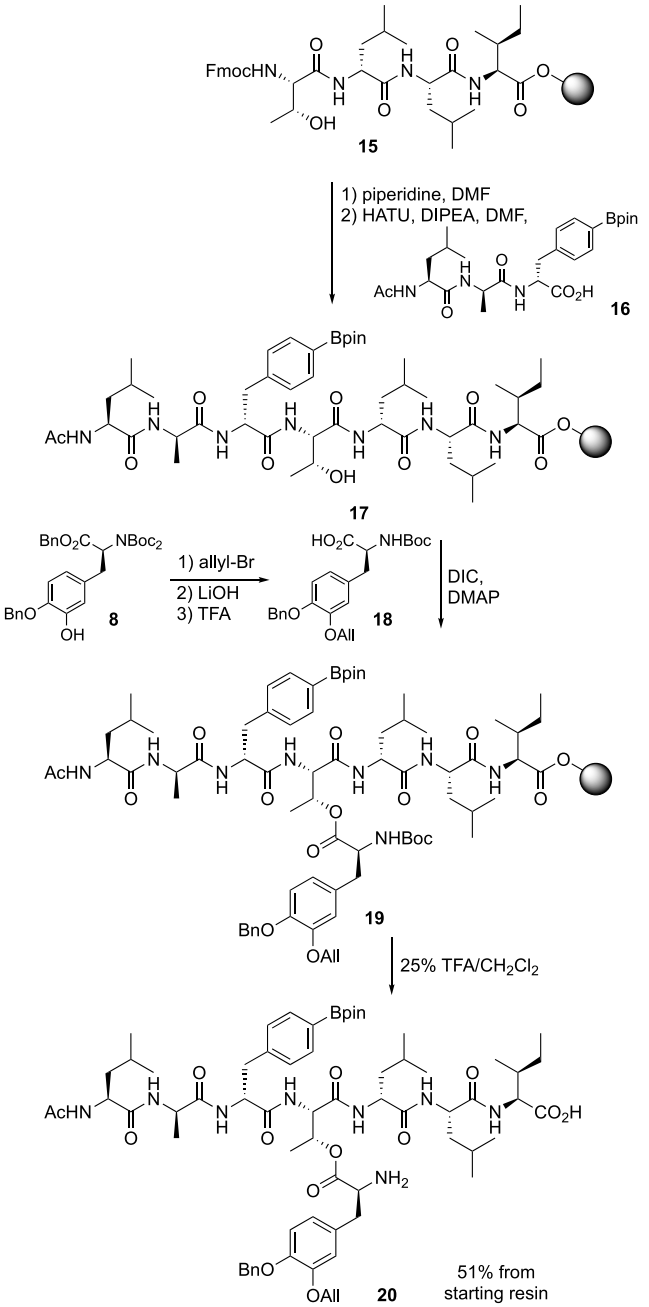
Next, we envisaged that cyclization to generate the lactone may be facilitated if the alcohol and acid groups were already constrained in a macrolactam, and thus, a late-stage macrolactonization strategy was pursued. Accordingly, the *tert*-butyl ester of **10** was removed to give acid **12**, which was then coupled to Leu-Leu-Ile-O*t*Bu **13** to afford the corresponding isodityrosine-containing pentapeptide. Deprotection of the N- and C-termini with TFA, followed by macrolactamization at the Ile-7-Dopa-8 junction, gave the corresponding cyclic peptide, which was treated with LiOH to effect hydrolysis of the benzyl ester to afford **14** (Scheme 2). Transannular lactonization of **14** was investigated; however, all attempts toward generation of the ester bridge were again unsuccessful.[39,40]

With both early and late macrolactonization strategies toward seongsanamide B unsuccessful, we elected to investigate a more traditional approach toward the depsipeptide component, incorporating an early-stage ester formation with a late-stage construction of the biaryl ether. Accordingly,

Scheme 2. Late-Stage Macrolactonization Approach



Scheme 3. SPPS of Linear Peptide Containing Ester Link



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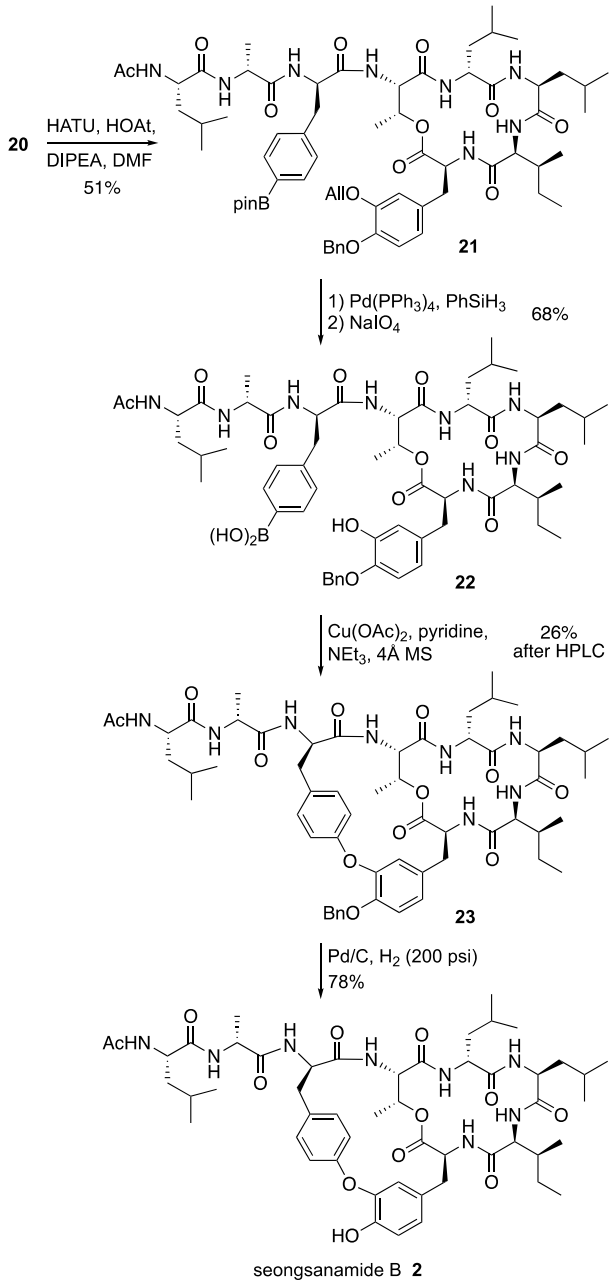
resin-bound tetrapeptide **15** was prepared through standard Fmoc-SPPS and then a fragment coupling with tripeptide **16** generated resin-bound heptapeptide **17** incorporating a phenylalanine-boronic acid residue. The protected DOPA **18** was prepared from **8** and then coupled to the Thr-4 side chain hydroxyl group to generate the ester-linked adduct **19**, which was cleaved from the resin to furnish **20** (Scheme 3). Attempts to purify **20** by HPLC resulted in partial protodeborylation of the Phe-Bpin residue, so the crude peptide was carried into the next step.

At this stage, the two key cyclizations were the final steps to be completed. Macrolactamization was effected by treatment of **20** with HATU, HOAt and DIPEA in a dilute (0.8 mM) solution of DMF/CH_2Cl_2 (1:1), which provided the cyclized protected depsipeptide **21** after 12 h (Scheme 4). Removal of the allyl group with $(Ph_3P)_4Pd$ and subsequent oxidative cleavage of the pinacolboronate ester afforded peptide **22** possessing phenolic and arylboronic acid groups. Intramolecular Evans–Cham–Lam coupling was successful, generating the bicyclic depsipeptide **23**. Not surprisingly, it is noted that the successful route to the bicyclic structure matches the proposed biosynthetic pathway.

Scheme 4. Synthesis of Seongsanamide B 2



Benzyl ether deprotection of **23** was performed to afford seongsanamide B (**2**). The overall yield of seongsanamide B was 3.6% over 16 steps (from chlorotrityl resin) with only two HPLC purifications required. The NMR spectra (^1H, ^{13}C, COSY, NOESY and ROESY) of the synthetic material were all in agreement with those reported for the natural product (note; several misassigned peaks were corrected upon correlation with seongsanamides A, C and D, and the synthetic material, see the SI), indicating successful synthesis and confirmation of the structure of seongsanamide B. Interestingly, the resonance for the Thr-4 γ-methyl group in the ^1H NMR spectra of seongsanamides A–D occurs remarkably upfield (δ ~0.38 ppm) compared with the typical position of such resonances. For example, in seongsanamide E the equivalent resonance occurs at δ 1.12,[1] a typical shift observed in numerous depsipeptides.[41−43] Presumably, the additional conformational constraints in the bicyclic seongsanamides imposed by the biaryl ether linkage position the Thr-4 methyl group in close proximity to the Tyr-3 aromatic ring, such that anisotropic effects result in a significant upfield shift. The potential for atropisomers in the seongsanamides, a feature not unusual in biaryl ether cross-linked peptides,[44] was also briefly examined. No mention of atropisomers was noted in the original report of the isolation of these natural products. Heating of seongsanamide B to 130 °C for 2 h resulted in no change in the NMR spectrum, indicating either a low barrier to rotation about the biaryl bond such that discrete atropisomers do not exist or a high barrier such that interconversion does not occur.

In conclusion, we have completed the first synthesis of seongsanamide B employing a combination of solid-phase and solution-phase synthetic strategies and a key late-stage Evans–Chan–Lam coupling. The work described here lays the foundation for generating analogues of the seongsanamides with a view to development of candidates with improved antiallergic activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01642.

Experimental procedures and NMR and MS data (PDF)

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Notes

The authors declare no competing financial interest.

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