

Total Synthesis of (–)-Hennoxazole A

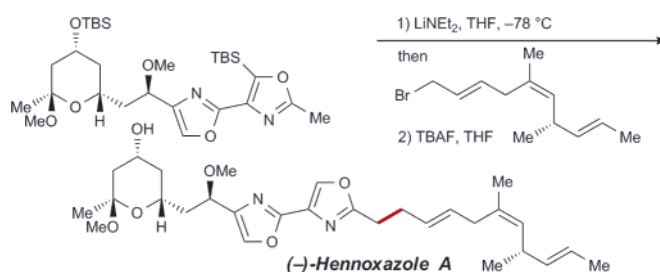
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ABSTRACT



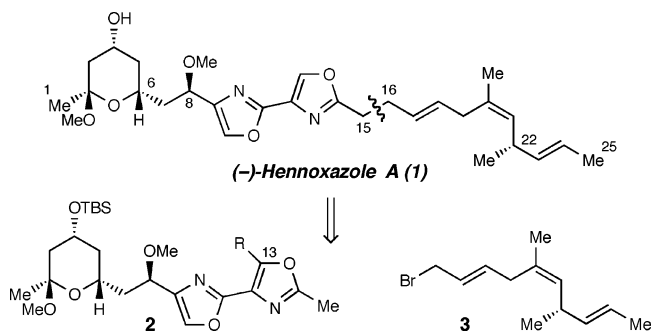
An enantioselective, convergent, total synthesis of the antiviral marine natural product (–)-hennoxazole A has been completed in 17 steps, longest linear sequence, from serine methyl ester and in 9 steps from an achiral bisoxazole intermediate. Elaboration of a thiazolidinethione allowed for rapid assembly of the pyran-based ring system. Key late-stage coupling was effected by deprotonation of the bisoxazole methyl group, followed by alkylation with an allylic bromide side chain segment.

Marine natural products have become increasingly important as lead compounds for the development of new drugs as a consequence of their intriguing structural diversity and biological activity.¹ Hennoxazole A (**1**), first isolated by Scheuer from the marine sponge *Polyfibrospongia*, displays antiviral activity against herpes simplex type 1, as well as peripheral analgesic behavior.² The two contiguous 2,4-disubstituted oxazole rings are a structural feature common only to the hennoxazole, diazonamide, and muscoride families of marine metabolites.³ Additionally, the nonconjugated triene side chain bearing a remote stereogenic center and a trisubstituted Z-double bond is limited in its conformational freedom by virtue of A^{1,3} strain and adopts an unusual helical secondary structure that may contribute to the biological activity of hennoxazole A.^{4b} Interest in this natural product has spurred total syntheses by the Wipf,⁴

Williams,⁵ and Shioiri⁶ laboratories.⁷ In this communication, we report the shortest asymmetric total synthesis of hennoxazole A to date.

The development of relatively mild conditions for the preparation of oxazoles has made the late-stage assembly of these ring systems a common, albeit not always efficient, strategy in the synthesis of oxazole-containing targets.⁸ Approaches involving end game functionalization of *intact* oxazole rings, however, provide the opportunity to use relatively simple oxazoles as starting materials and then carry

Scheme 1. Synthetic Strategy toward Hennoxazole A

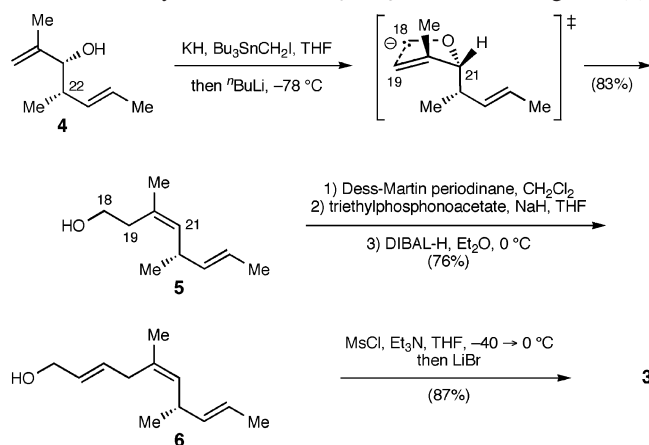


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Scheme 2. Synthesis of the C₁₆–C₂₅ Side Chain Fragment (3)



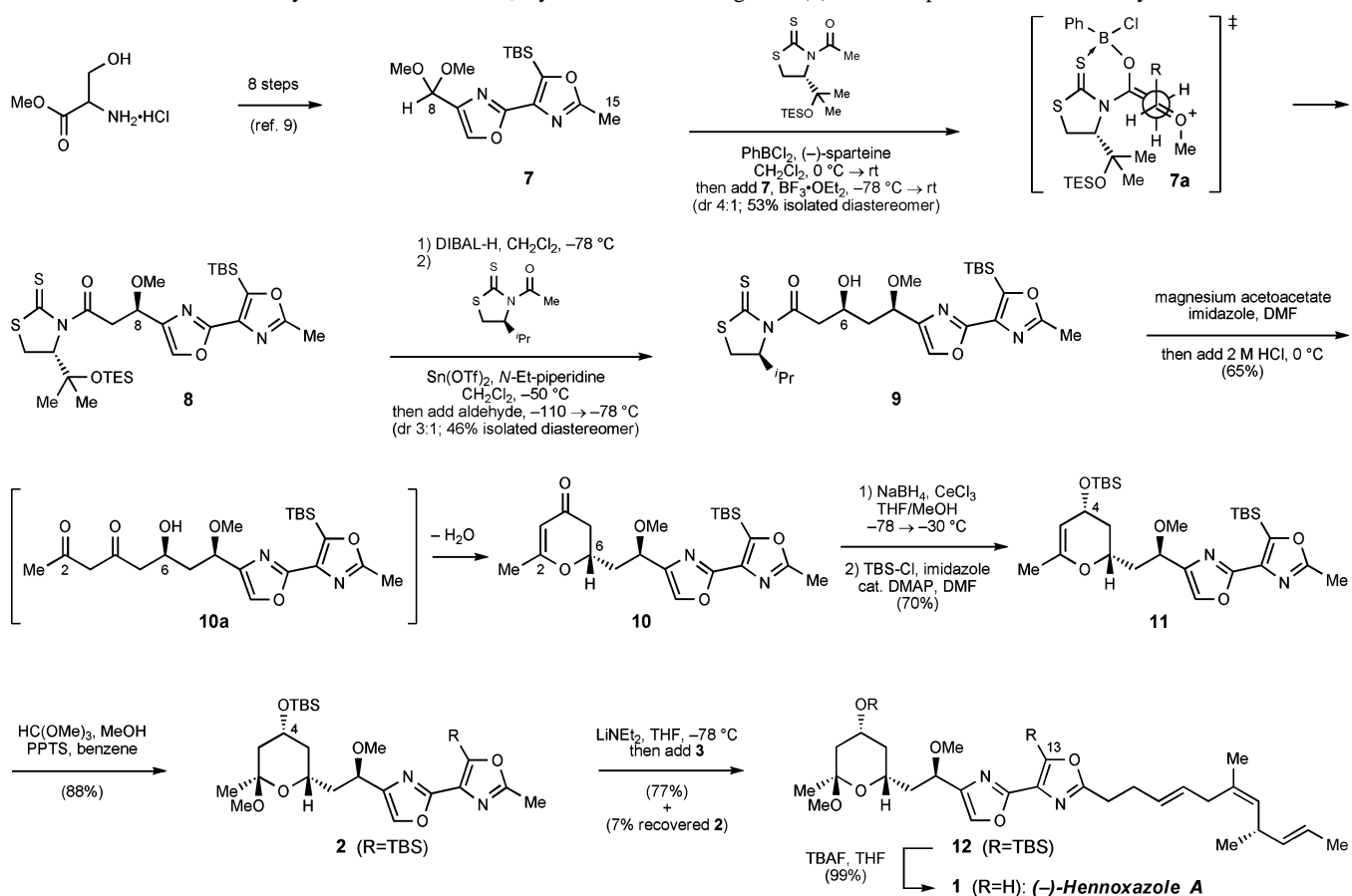
these, practically inert, heterocycles through a variety of synthetic transformations unscathed. In consideration of these issues, our synthesis plan for hennoxazole A (Scheme 1) diverges from precedent and involves late-stage construction of the C₁₅–C₁₆ bond by deprotonation of an elaborate bisoxazole fragment (**2**) at the C₁₅-methyl group, followed by alkylation with an allylic bromide C₁₆–C₂₅ side chain fragment (**3**). Our early work on model systems demonstrated

the viability of this convergent approach, but also indicated that protection at C₁₃ would be required since ring deprotonation (when R = H) proved to be favored over lateral deprotonation both kinetically and thermodynamically.⁹

The synthesis of skipped triene side chain fragment **3** (Scheme 2) began with allylic alcohol **4**, which can be prepared in four steps from commercially available (*S*)-3-butyn-2-ol.⁵ The trisubstituted C₂₀–C₂₁ Z-double bond was expeditiously installed via a [2,3]-Wittig–Still rearrangement; avoidance of A^{1,2} strain in the early transition state presents one diastereoface of the C₁₉–C₂₀ double bond to the intermediate C₁₈-anion, leading to homoallylic alcohol **5** as a single isomer.¹⁰ Dess–Martin oxidation,¹¹ followed by *E*-selective Horner–Wadsworth–Emmons olefination and reduction of the resulting ester, gave allylic alcohol **6**. Treatment with mesyl chloride and lithium bromide completed the synthesis of electrophilic coupling fragment **3**.

Preparation of nucleophilic coupling partner **2** (Scheme 3) commenced with a Lewis acid promoted aldol-like reaction¹² between bisoxazole dimethyl acetal **7** (prepared in eight steps from commercially available serine methyl ester hydrochloride)⁹ and the boron enolate of the *N*-acetyl thiazolidinethione recently developed by Sammakia.¹³ The diastereoselectivity of this transformation can be rationalized by open transition state **7a**. This direct installation of the

Scheme 3. Synthesis of the C₁–C₁₅ Pyran/Bisoxazole Fragment (2) and Completion of the Total Synthesis



C₈-methyl ether in **8** also circumvents elimination difficulties encountered when a more conventional aldol/etherification sequence was attempted. Reductive cleavage¹⁴ of the thione auxiliary to the β-methoxy aldehyde was followed by an auxiliary-directed acetate aldol reaction,¹⁵ required to override the 1,3-*anti* selectivity bias intrinsic to such systems.¹⁶ Encouraged by our previous success with the kavalactones in efficiently refunctionalizing *N*-acyl thiazolidinethiones,¹⁷ we postulated that this similar aldol product (**9**) might be directly converted into methyl ketone **10a**. Gratifyingly, treatment with magnesium acetoacetate¹⁸ and imidazole not only led to the desired transacylation reaction—presumably through the intermediacy of an acyl imidazolide—but also,

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upon quenching with aqueous acid, provided cyclodehydrated pyrone **10**. Notably, this transformation is accomplished in a single step without the need for protecting groups. Luche reduction,¹⁹ hydroxyl-group protection, and mixed methyl acetal formation, in accordance with Wipf's pioneering work,⁴ finalized the synthesis of C₁–C₁₅ pyran/bisoxazole coupling fragment **2**.

With both coupling partners in hand, we endeavored to unite them in the pivotal transformation of the synthesis. Using the same conditions that had been successful for model fragment couplings,⁹ treatment of bisoxazole **2** with LiNEt₂ and allylic bromide **3** led to the anticipated union in 77% yield, thus securing the entire carbon framework of the natural product. Double TBS deprotection of **12** provided (–)-hennoxazole A, having spectra identical in all respects to those published previously.^{4–6}

In conclusion, we have developed a convergent asymmetric route to hennoxazole A that proceeds in a longest linear sequence of 17 steps from commercially available starting materials and in only 9 steps from an achiral bisoxazole intermediate. Significant to the efficiency of the synthesis are the direct stereocontrolled installation of the C₈-methyl ether, the rapid functionalization of thiazolidinethione derivatives, and the final convergent fragment coupling featuring the alkylation of an intact bisoxazole core.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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