Total Synthesis of (−)-Hennoxazole A

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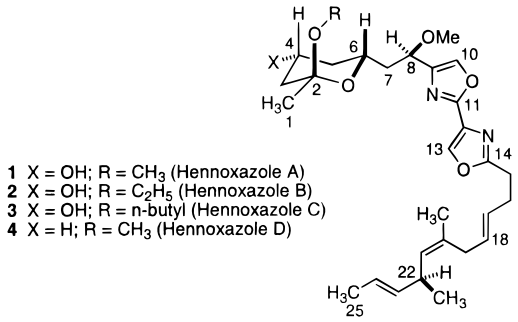
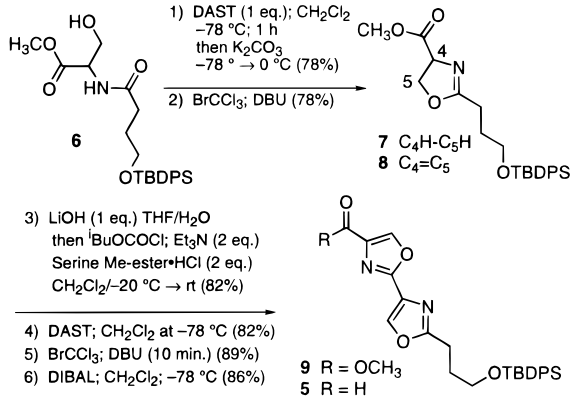
Since 1986, there has been a dramatic increase in the number of examples and structural complexity of bioactive natural products containing the oxazole ring. Marine organisms are rich sources of these novel metabolites.[1] Bisoxazoles, in which the two rings are directly linked via a single bond, are exemplified by the hennoxazoles (**1**−**4**), first isolated from the sponge *Polyfibrospongia* in 1991.[2] Hennoxazole A (**1**) displays potency against herpes simplex virus type 1 and peripheral analgesic activity comparable to that of indomethacin. The absolute configuration of **1** and the issue of relative stereochemistry at C_8 and C_{22} have been resolved following synthesis of the (+)-enantiomer of **1** by Wipf and Lim.[3] Herein we report an efficient strategy providing for an enantiocontrolled convergent total synthesis of (−)-hennoxazole A.



Our plans sought the direct incorporation of a fully functionalized tetrahydropyran segment (C_1−C_7) with C-linkage to the heterocyclic core and creation of C_8 chirality. Concerns for stability of the nonconjugated triene, including the remote stereochemistry of the C_{22} bis-allylic methine, suggested attachment of the C_{18}−C_{25} portion in the final stages.

The 2,4-disubstituted bisoxazole **5** was assembled as summarized in Scheme 1. Using a mixed anhydride procedure, the coupling of 4-(*tert*-butyldiphenylsiloxy)butanoic acid[4] and (±)-serine methyl ester hydrochloride afforded **6**. Cyclization to oxazoline **7** occurred in a single step with diethylaminosulfur trifluoride (DAST)[5] at −78 °C. Oxidation with bromotrichloromethane and DBU cleanly effected dehydrogenation to oxazole **8**.[6] Reiteration of this protocol illustrates a general and highly effective synthesis of these heterocycles. Studies of the addition of reactive nucleophiles to aldehyde **5** led to competing ring deprotonation.[7] However, the application of a mild asymmetric allylation strategy was developed to yield functionalized homoallylic alcohols[8] based upon the pioneering efforts of E. J. Corey.[9] Adaptation of this concept has expeditiously led to construction of the C_1−C_{17} portion of hennoxazole A as shown in Scheme 2.

Scheme 1



Formation of the (*R*)-homoallylic C_8 alcohol **14** was achieved by transmetalation of optically pure stannane **12** with (*R,R*)-bromoborane **13**[9] via allylic transposition to yield an intermediate borane for facile condensation with aldehyde **5**. Stereocontrol is induced from the 1,2-diphenylethane sulfonamide auxiliary (10.5:1 dr), and is predicted from a chairlike transition state with minimized steric repulsions.[10] Stannane **12** was conveniently prepared via copper-catalyzed Grignard addition starting from 2-bromo-3-trimethylsilylpropene[11] and nonracemic epoxide **10**.[12] The superior reactivity characteristics of allylstannane **12** were required as the silane **11** failed to undergo transmetalation with **13**, and direct attempts for Lewis acid mediated condensations of **11** with aldehyde **5** were unproductive.[13]

Mild transketalization of **14** with bis-(trifluoroacetoxy)iodobenzene[14] gave **15**, which was converted to ketone **16** via oxidative cleavage.[15] Although ketone **16** was susceptible to β-elimination of methanol, Terashima reduction[16] using (+)-*N*-methylephedrine resulted in a remarkably efficient reagent-based hydride addition with high diastereofacial selectivity (8:1 ratio of C_6 alcohols). This new application[17] of the Terashima protocol

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(5) No evidence for the formation of an intermediate fluoride was observed, and fluoride-induced desilylation was not encountered. Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947.

(6) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.

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(9) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

(10) Preexisting C_4 asymmetry does not play a significant role in the diastereofacial addition. Model studies of the allylation reaction with achiral Lewis-acids ($TiCl_4$; CH_2CH_2; −78 °C) produced a mixture of alcohols (40:60 ratio) favoring the corresponding C8 (*S*)-isomer.

(11) Nishiyama, H.; Yokoyama, H.; Harimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267.

(12) Synthesis of epoxide **10** proceeds via alkylation of 2-lithio-2-methyl-1,3-dithiane with (*S*)-epichlorohydrin (97% ee; Aldrich) affording net inversion at C_4 (for Mosher ester analysis of **11**; see Supporting Information). Seebach, D. *Synthesis* **1969**, *17*. Braun, M.; Seeback, D. *Chem. Ber.* **1976**, *109*, 669.

(13) Common protecting units, such as esters, thioketals, silyl ethers, and simple ethers are stable to our reaction conditions utilizing bromoborane **13**, whereas acetals and ketals do not survive. Quantitative conversion of **11** to its corresponding bromide required the use of recrystallized *N*-bromosuccinimide with a low temperature, aqueous $NaHSO_3$ quench to prevent hydrolysis of the 1,3-dithiane.

(14) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989,** *30*, 287.

(15) (a) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

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(17) The use of achiral hydride sources ($LiBH_4$, $NaBH_4$, super hydride) or (−)-*N*-methylephedrine provided selectivity slightly favoring the undesired (*S*)-isomer. Interestingly, our Terashima reduction ((+)-*N*-methylephedrine) of the corresponding (*S*)-methyl ether (C8) of ketone **16** gave predominantly the all-syn arrangement (ratio > 20:1).

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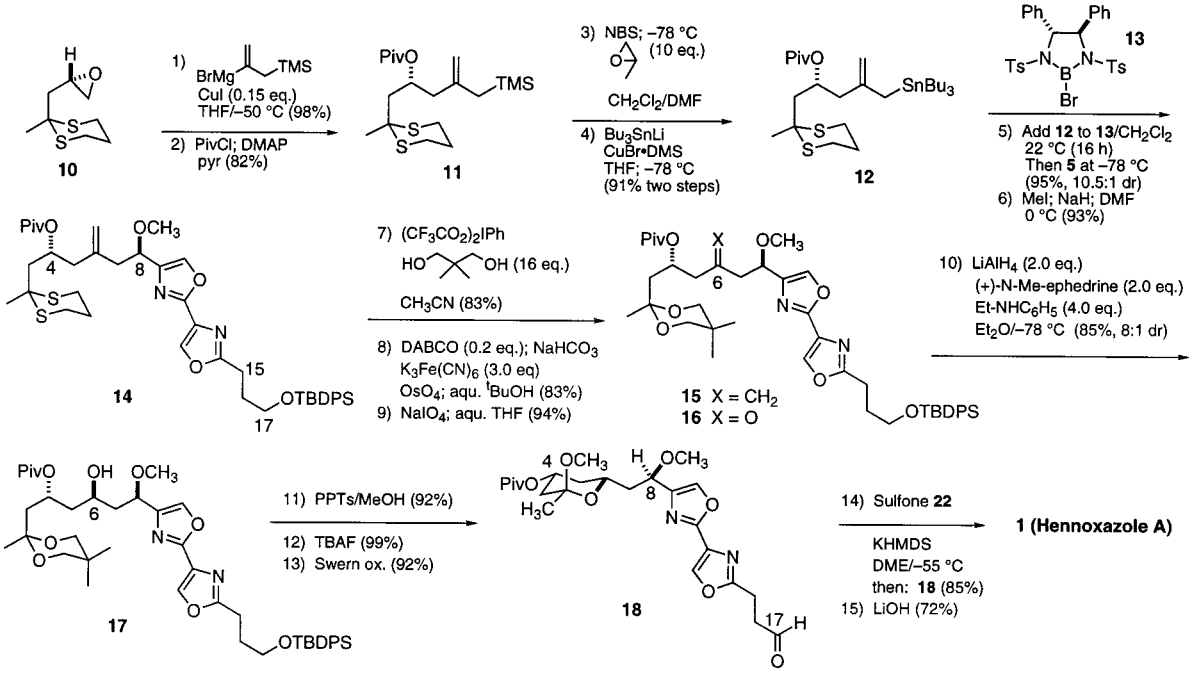
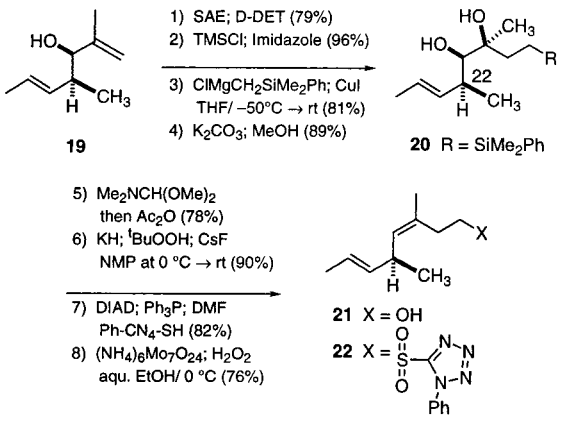
Scheme 2



Scheme 3



presents opportunities for matched and mismatched reductions of chiral, acyclic β-alkoxyketones. Our studies have important implications for stereocontrolled synthesis of 1,3,5-polyols originating from acetoacetate biogenesis.[18] Finally, the formation of **18** was secured upon mild acidic treatment of **17**, producing a single tetrahydropyran isomer.

The remote C_{22} asymmetry of the nonconjugated triene segment was obtained through chirality transfer in a 2,3-Wittig rearrangement yielding **19** (Scheme 3).[19,20]

Following a Sharpless asymmetric epoxidation of **19** and protection of the secondary alcohol, nucleophilic oxirane opening with the Grignard reagent derived from (chloromethyl)dimethylphenylsilane led to 1,2-diol **20**. Syn-elimination to the trisubstituted *Z*-olefin was efficiently carried out via ketalization with *N*,*N*-dimethylformamide dimethylacetal with subsequent addition of acetic anhydride.[21] Tamao oxidation of the phenylsilane as described by Woerpel[22] provided **21** in 90% yield. Replacement of the primary alcohol with 1-phenyl-1*H*-tetrazole-5-thiol occurred under Mitsunobu conditions. Careful oxidation of the resulting sulfide produced a separable mixture of sulfone **22** (76%) and the corresponding sulfoxides (24%), which were resubmitted to the oxidation conditions to provide additional sulfone (92% overall). Prolonged reaction times resulted in products of olefin epoxidations.

The total synthesis of **1** (Scheme 2) was completed by generation of the α-sulfonyl carbanion of **22** with KHMDS in DME at -55 °C followed by addition of aldehyde **18**. Spontaneous elimination of the intermediate β-hydroxysulfone upon warming to ambient temperature facilitates a one-pot generation of $C_{17}-C_{18}$ alkene with excellent *E*-selectivity (*E*:*Z* ratio 91:9) in 85% yield. The Kocienski modification[23] of the Julia–Lythgoe olefination is particularly noteworthy because it provides high trans-stereoselectivity in the absence of factors such as α-chain branching or conjugation. Hydrolysis of the C_4 pivaloate ester (LiOH in aqueous THF/MeOH (72%)) provided synthetic hennoxazole A (**1**) as a clear, colorless oil; $[\alpha]^{22}_D$ $-46.2°$ (*c* 1.0, $CHCl_3$), $[\alpha]^{22}_D$ lit. $-47°$ (*c* 3.1, $CHCl_3$),[2] identical in all respects with spectra provided for the natural product.[3]

In conclusion, our convergent route to **1** has offered important advances for asymmetric allylations, efficient oxazole preparations, and a promising new application of the Terashima reduction.

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Supporting Information Available: Procedures and spectral data for all compounds of the synthesis pathway, and proton NMR spectra for **1**, and compounds **6**–**22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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