Total Synthesis of the Enantiomer of the Antiviral Marine Natural Product Hennoxazole A

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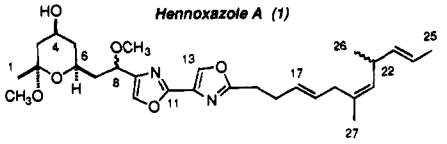
A large number of extracts from marine organisms show moderate to high activity in antiviral screening essays and might therefore prove useful as a source of unconventional lead structures in the development of effective drugs against viral diseases.[1] Hennoxazole A (**1**) was isolated by Ichiba et al.[2] from a marine sponge, a *Polyfibrospongia* sp. (phylum Porifera), and was shown to be highly active against herpes simplex virus (HSV-1, IC_{50} = 0.6 μg/mL). This structurally diverse natural

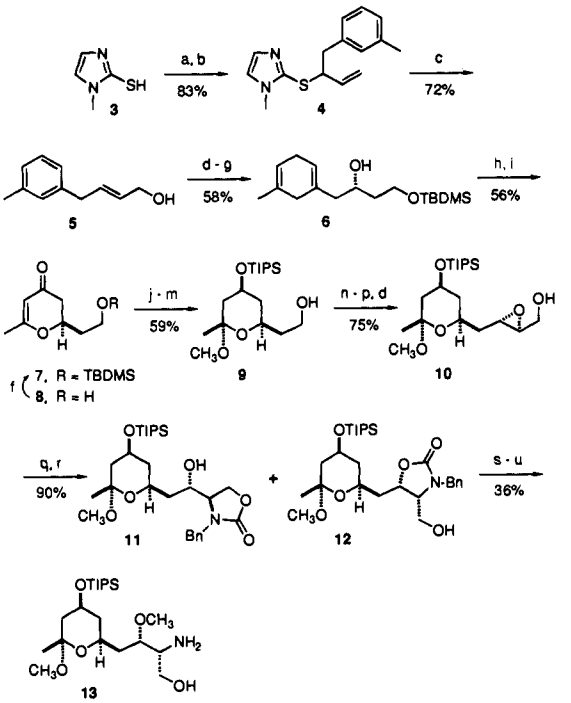


product incorporates a bisoxazole, a pyranoid glycoside, and a skipped triene unit. The relative configuration at C(2), C(4), and C(6) was determined by NMR experiments;[2] the absolute configuration as well as the stereochemistry at C(8) and C(22) remain unresolved.

As a part of our program for the synthesis and study of marine natural products,[3] we have recently embarked on the total synthesis and structure elucidation of hennoxazole A. In this communication, we report the preparation of the (2*S*,4*S*,6*S*,8*S*,-22*R*)-isomer **2**. Key features of our synthesis are (1) a highly convergent strategy that combines pyran and triene segments via a novel bisoxazole synthesis; (2) the use of a *m*-xylene as a pyran synthon; (3) a vinyl cuprate S_N2 displacement of a sterically hindered allylic ester at C(22).[4]

For the synthesis of the left side (C(1)−C(10)) segment of hennoxazole A, an Evans−Mislow rearrangement[5] of the *S*-oxide of thioether **4** provided the (*E*)-allylic alcohol **5**[6] in >96% diastereomeric purity (Scheme 1). Sharpless asymmetric epoxidation[7] followed by oxirane reduction with Red-Al[8] introduced the secondary alcohol function at C(6) that was used as a linchpin for the construction of the pyran stereocenters at C(2) and C(4). Selective silylation of the primary alcohol and dissolving metal reduction yielded the diene **6** in seven steps and 35% overall yield from commercially available mercaptoimidazole (**3**). Ozonolysis followed by reductive workup completed the unraveling of the β-diketone functionality from the meta-substituted xylene.[9] After treatment of the complex mixture of keto-enol as well as cyclic isomers of the intermediate 6-hydroxy-8-silyloxy-2,4-octanedione with *p*-TsOH in THF,

Scheme 1[a]



[a] (a) Allyl bromide, 6 M NaOH, CH_2Cl_2, $BnNEt_3Cl$, 35 °C. (b) *n*-BuLi, α-bromo-*m*-xylene, THF, −78 °C to 20 °C. (c) MCPBA, MeOH, −30 °C to 20 °C; then Et_2NH, 20 °C. (d) *tert*-Butyl hydroperoxide, L-(+)-diisopropyl tartrate, $Ti(O\text{-}i\text{-}Pr)_4$, 4 Å MS, −20 °C. (e) Red-Al, THF, −15 °C. (f) TBDMSCl, Im, CH_2Cl_2. (g) Li, NH_3, *tert*-amyl alcohol, THF, −40 °C. (h) O_3, EtOAc, −78 °C; then H_2, $Pd(OH)_2$, 20 °C. (i) TsOH, THF, 20 °C. (j) $NaBH_4$, $CeCl_3$, THF/MeOH, −20 °C. (k) TIPSCl, Im, DMAP, DMF. (l) $HC(OMe)_3$, MeOH, PPTs, benzene, 20 °C. (m) LiOH, dioxane/EtOH/H_2O, 90 °C. (n) TPAP, NMO, 4 Å MS, CH_2Cl_2, 20 °C. (o) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C. (p) DIBALH, THF, 0 °C. (q) BnNCO, Et_3N, CH_2Cl_2, 20 °C. (r) NaH, THF, 0 °C to 20 °C. (s) NaH, MeI, Ag_2O, THF, 0 °C to 20 °C. (t) LiOH, dioxane/EtOH/H_2O, 80 °C. (u) H_2, $Pd(OH)_2$, MeOH, 20 °C.

56% of a 1:2 mixture of pyranones **7** and **8** was isolated. Reprotection of the primary alcohol function with TBDMS-Cl converted **8** back to the desired silyl ether **7**. 1,2-Reduction of the enone with $NaBH_4$ in the presence of $CeCl_3$[10] occurred exclusively via axial attack, and the resulting secondary allylic alcohol was silylated with TIPS-Cl and the glycal function solvolyzed in MeOH in the presence of PPTs and methyl orthoformate to give the desired axial anomer in 71% overall yield from **7**. Selective cleavage of the primary TBDMS ether vs the secondary TIPS ether was best accomplished under strongly basic conditions with LiOH in a ternary mixture of dioxane/ethanol/water (1:1:2).

Side-chain extension of **9** to give alcohol **10** proceeded in 75% yield via oxidation with catalytic perruthenate,[11] Wadsworth−Emmons reaction, DIBALH reduction, and Sharpless asymmetric epoxidation. The protocol of Kishi[12] and Roush[13] was chosen for the introduction of the amino function at C(9). Treatment of epoxy alcohol **10** with benzyl isocyanate, followed by cyclization of the intermediate urethane, resulted in a 87:13 mixture of isomeric oxazolidinones **11** and **12**. The desired major product **11** was purified by chromatography on SiO_2, *O*-methylated, hydrolyzed, and hydrogenated to give the amino

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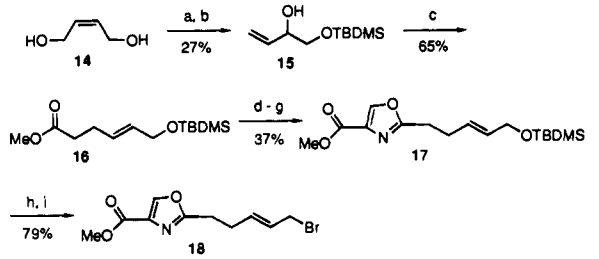
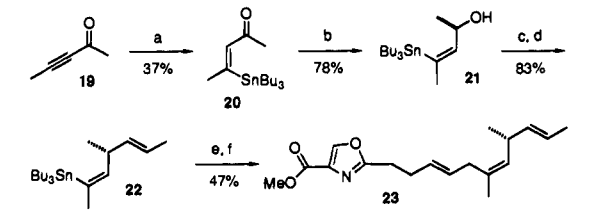
Scheme 2[a]



[a] (a) $HgSO_4$, H_2SO_4, H_2O, 100 °C. (b) TBDMSCl, Im, CH_2Cl_2. (c) $MeC(OMe)_3$, $C_2H_5CO_2H$, 140 °C. (d) LiOH, MeOH/H_2O, 20 °C. (e) Serine-OMe, *i*-BuOC(O)Cl, NEt_3, CH_2Cl_2, −15 °C to 0 °C. (f) Burgess reagent, THF, 70 °C. (g) $CuBr_2$, DBU, HMTA, CH_2Cl_2, 20 °C. (h) TBAF, THF, 20 °C. (i) NBS, Ph_3P, CH_2Cl_2, −30 °C to 0 °C.

Scheme 3[a]



[a] (a) [(PhS)Bu_3SnCu]Li, THF, −50 °C. (b) (*S*)-Oxazaborolidine, catecholborane, toluene, −30 °C to −20 °C. (c) 2,4,6-Trimethylbenzoyl chloride, 2,6-lutidine, CH_2Cl_2, 20 °C. (d) [(*E*)-MeC=C)]$_2$CuLi, THF, −20 °C. (e) I_2, CH_2Cl_2, 20 °C. (f) (i) *t*-BuLi, THF, −78 °C; (ii) $ZnCl_2$, −78 °C to 20 °C; (iii) **18**, $Pd_2(dba)_3$·$CHCl_3$, $AsPh_3$, THF, 20 °C.

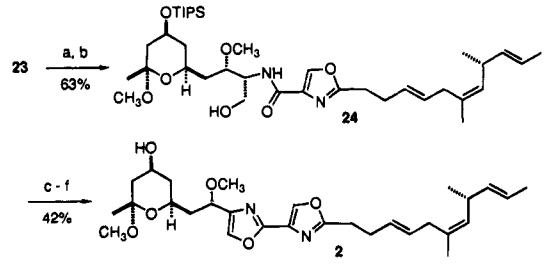
alcohol **13**. Overall, the left-side segment was thus prepared in 21 steps and in 3% yield.

A Pd-catalyzed coupling between allylic bromide **18** and the zinc reagent derived from vinyl stannane **22** established an efficient access to the right-side (C(11)−C(25)) segment of hennoxazole A. Acid-catalyzed rearrangement[14] of (*Z*)-butenediol (**14**) and silylation of the primary alcohol function provided allylic alcohol **15** in multigram quantities (Scheme 2).

The functionalized ester **16** was readily obtained by Claisen rearrangement[15] in the presence of trimethyl orthoacetate and acid. Saponification and coupling with serine methyl ester was followed by cyclodehydration with the Burgess reagent[16] to give an intermediate oxazoline that was oxidized to the oxazole with cupric bromide[17] in the presence of DBU and hexamethylenetetramine. *O*-Desilylation and bromination[18] of the allylic alcohol led to the π-allyl palladium precursor **18**.

Conjugate addition of the cuprate[19] derived from copper(I) thiophenoxide and Bu_3SnLi to ynone **19** provided vinyl stannane **20** in 37% yield as a single geometric isomer (Scheme 3). Asymmetric reduction of **20** with 20% tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2*c*][1,3,2]oxazaboroleborane[20] in the presence of stoichiometric quantities of catecholborane[21] gave (*R*)-allylic alcohol **21** in 85% ee and 78% chemical yield. After considerable experimentation, we found that conversion of **21** to the 2,4,6-trimethylbenzoate allowed a subsequent very clean S_N2 inversion with propenyl cuprate to provide the skipped diene **22** in 83% yield. Direct palladium-catalyzed coupling of the vinyl stannane with allylic bromide **18** failed due to the considerable $A^{1,3}$-strain in stannane **22**, which was recovered unchanged from the reaction mixture. However, coupling of the corresponding vinylzinc[22] reagent, which was obtained from **22** via tin iodine exchange, metal halogen exchange, and Li → Zn transmetalation, was successful and provided the skipped triene as a single isomer. The right-side segment **23** was therefore prepared in a total of 15 steps and in 3% yield as calculated for the longest linear sequence.

Scheme 4[a]



[a] (a) NaOH, MeOH/H_2O, 20 °C. (b) **13**, PyBroP, EtN(*i*-Pr)$_2$, CH_2Cl_2, 20 °C. (c) Dess−Martin, CH_2Cl_2, 20 °C. (d) $BrCl_2CCCl_2Br$, PPh_3, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C to 20 °C. (e) DBU, CH_3CN, 20 °C. (f) TBAF, THF, 20 °C.

The final segment condensation involved the challenging preparation of the bisoxazole moiety (Scheme 4). Coupling of the acid derived from **23** with amino alcohol **13** with the PyBroP reagent[23] provided amide **24** in 63% yield. Oxazole synthesis via oxidation/cyclodehydration[24] was best performed in the presence of the hindered base 2,6-di-*tert*-butyl-4-methylpyridine and stopped at the intermediate 10-bromooxazoline. In the presence of Et_3N,[24] only traces of the desired bisoxazole could be isolated. Decreased amounts of amine led to extensive cleavage of the acid-sensitive pyran portion of the molecule. The bromooxazoline was subsequently dehydrohalogenated with DBU in acetonitrile, and final desilylation with TBAF provided (2*S*,4*S*,6*S*,8*S*,22*R*)-hennoxazole **2** in an overall yield of 26% from the right-side segment **23**.

Synthetic **2** and natural[25] hennoxazole A have identical high-field ^1H NMR and ^{13}C NMR data. The $[\alpha]^{21}_D$ −47° (*c* 3.1, $CHCl_3$) for natural material is opposite to our (2*S*,4*S*,6*S*,8*S*,-22*R*)-hennoxazole **2** ($[\alpha]^{21}_D$ +50° (*c* 0.2, $CHCl_3$). In addition, CD spectra for **1** and **2** are inverted, and both compounds co-elute on RP-HPLC. On the basis of these results, we propose the (2*R*,4*R*,6*R*,8*R*,22*S*)-stereochemistry, e.g., the enantiomer of **2**, for natural hennoxazole A. Further clarification of the relative and absolute configuration of **1** will be gained by the total syntheses of additional stereoisomers, which are currently underway in our laboratories.

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Supplementary Material Available: ^1H NMR, ^{13}C NMR, and HRMS spectra of **2** and ^{1} H NMR spectra of synthetic intermediates; ^1H NMR spectrum of natural hennoxazole A; CD spectra and HPLC traces of **2** and natural hennoxazole A (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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