JOC Article

Total Synthesis of (−)-Hennoxazole A

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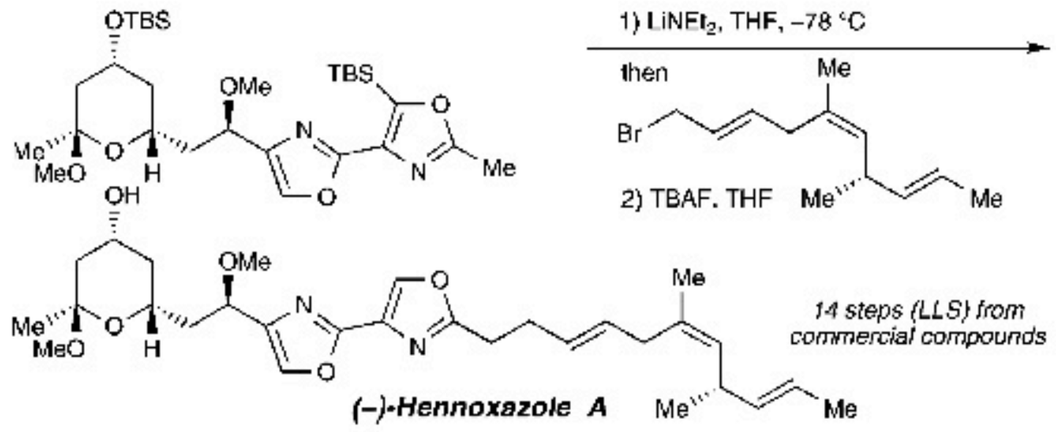

An enantioselective, convergent total synthesis of the antiviral marine natural product (−)-hennoxazole A is completed in 14 steps (longest linear sequence) from commercially available 4-methyloxazole-2-carboxylic acid. Synthesis of the C_1-C_{15} pyran/bisoxazole fragment takes advantage of an aldol-like coupling between a dimethyl acetal and an *N*-acetylthiazolidinethione for the direct, stereoselective installation of the C_8-methoxy-bearing stereocenter. A one-pot acetoacetate acylation/decarboxylation/cyclodehydration of another elaborate thiazolidinethione allows for rapid assembly of the pyran-based ring system. Synthesis of the $C_{15}-C_{25}$ skipped triene side chain fragment makes use of a [2,3]-Wittig−Still rearrangement for efficient installation of the trisubstituted *Z*-double bond. Key late-stage coupling of the two fragments is effected by deprotonation of the methyl group on the bisoxazole system using lithium diethylamide, followed by alkylation with an allylic bromide side chain segment to form the $C_{15}-C_{16}$ bond.

Introduction

In 1991, a research team led by Paul Scheuer at the University of Hawaii reported the isolation and structural elucidation of hennoxazoles A−D (Figure 1) from a species of *Polyfibrospongia* sponge off the coast of Miyako island in Okinawa, Japan.[1] Further investigation by Higa[2] disclosed four additional members of this natural product family, hennoxazoles E−G and hennoxazole A acetate. The most abundant member of the group, hennoxazole A, is also the most active, displaying antiviral activity against herpes simplex 1 ($IC_{50} = 0.6\ \mu g/mL$) and peripheral analgesic activity comparable to that of indomethacin.

Structurally, the hennoxazoles contain a bisoxazole ring system at their molecular core. The muscorides[3] and diazonamides[4] are the only other natural products known to include two contiguous 2,4-disubstituted oxazoles in their frameworks.[5] Other structurally distinctive features of the hennoxazoles include the functionalized pyranyl ring and the nonconjugated triene side chain containing a trisubstituted *Z*-double bond and a remote stereogenic center. The original structure determination work established the correct atomic connectivity but left many of the stereochemical details ambiguous; although the assignment of relative stereochemistry about the C_2-C_6 pyran ring

(1) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173−3174.

(2) Higa, T.; Tanaka, J.-i.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227−2230.

(3) For a lead reference on the muscorides see: Coqueron, P.-Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411−1414.

(4) For a lead reference on the diazonamides see: Poriel, C.; Lachia, M.; Wilson, C.; Davies, J. R.; Moody, C. J. *J. Org. Chem.* **2007**, *72*, 2978−2987.

(5) Several other natural products containing more than two contiguous oxazoles are also known, including the mycalolides, ulapualides, and kabiramides—which have three directly linked oxazole rings—and telomestatin, which has seven. For a review of the syntheses of oxazole-containing natural products, see: (a) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995−12042. (b) Palmer, D., Ed. *Heterocyclic Compounds*; J. Wiley and Sons: New York, 2003; Vol. 60, Part A. (c) Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907−1922. For a lead reference on telomestatin, see: (d) Doi, T.; Yoshida, M.; Shin-ya, K.; Takahashi, T. *Org. Lett.* **2006**, *8*, 4165−4167.

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