ORGANIC LETTERS

1999
Vol. 1, No. 7
1137−1139

# A Convergent Stereoselective Total Synthesis of Racemic Phthoxazolin A

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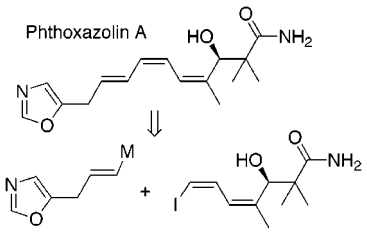
**Received August 20, 1999**

## ABSTRACT

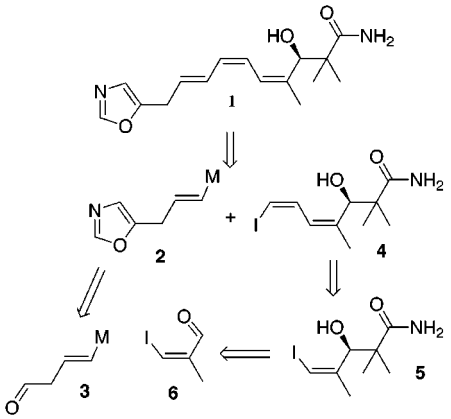



**The first total synthesis of phthoxazolin A is reported which involves a convergent series of palladium-catalyzed cross-coupling reactions to stereoselectively construct the *Z*,*Z*,*E*-trienyl unit of phthoxazolin A. The most important steps of the synthesis involve using vinylboronate pinacol ester as a vinyl dianion equivalent, by employing a Heck coupling of a vinyl iodide with the vinylboronate, followed by a deboronation–iodination sequence with inversion of alkene stereochemistry and Stille coupling of the resulting vinyl iodide.**

Compounds containing polyenes are present in nature in many forms, e.g., in insect pheromones, members of the retinoid family, and complex antibiotics.[1] Their activities frequently depend on the geometry of the unsaturated bonds, and it is therefore important to synthesize these polyenes in a stereocontrolled manner. As part of a program aimed at developing new methodologies for the stereocontolled synthesis of polyene-containing systems, we became interested in phthoxazolin A **1**, a metabolite of *Streptomyces* sp.[2] Phthoxazolin A **1** represents an unsynthesized example of a group of biologically active phthoxazolins and has potent herbicidal activity vs radish seedlings and velvet leaf in pre- and post-emergence treatments. Because phthoxazolin A **1** represents a useful new class of herbicide which contains a potentially challenging *Z*,*Z*,*E*-trienyl moiety, we decided to develop a synthesis of this compound in order to test the applicability in synthesis of a new vinylboronate dianion methodology previously developed in our group.[3] In this Letter, we report the first total synthesis of phthoxazolin A **1**, in racemic form.

The synthesis of **1** was formulated to take advantage of a series of highly stereoselective palladium-mediated coupling reactions, as outlined by the retrosynthetic plan shown in Scheme 1. Phthoxazolin A **1** can be broken into fragments

**Scheme 1.** Retrosynthetic Analysis for Phthoxazolin A



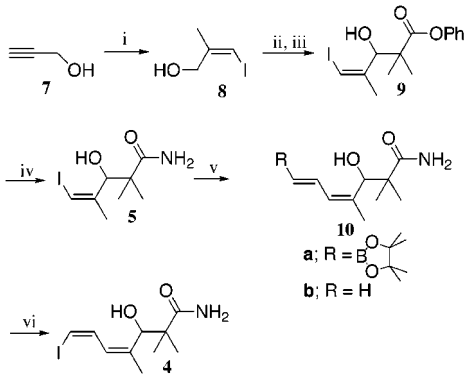

(1) Rychnovosky, S. D. *Chem. Rev.* **1995**, *95*, 2021.
(2) (a) Omura, S. *J. Antibiot.* **1990**, *43*, 1034. (b) Tanaka, Y.; Kanaya, I.; Takahashi, Y.; Shinose, M.; Omura, S. *J. Antibiot.* **1993**, *46*, 1208. (c) Tanaka, Y.; Kanaya, I.; Shiomi, K.; Omura, S. *J. Antibiot.* **1993**, *46*, 1214. (d) Shiomi, K.; Arai, N.; Shinose, M.; Takahashi, Y.; Yoshida, H.; Inabuchi, J.; Tanaka, Y.; Omura, S. *J. Antibiot.* **1995**, *48*, 714.

10.1021/ol990967b CCC: $18.00 
**Published on Web 09/14/1999**

**2** and **4** via retro-Stille or Suzuki couplings. In turn, this leads to a but-3-enal metal equivalent **3**, with the aldehyde function acting as the precursor moiety of the oxazole unit. Fragment **4** can be disconnected, after a stereoselective haloalkenyl chain extension via fragment **5**, using a retro-aldol reaction. Thus, aldol product **5** would be available from (*Z*)-3-iodo-2-methylpropenal **6**. It was our expectation that using palladium-catalyzed coupling reactions for the coupling of fragments **2** and **4**, and for the conversion of fragment **5** to **4**, would be sufficiently mild that isomerization of the alkene functions would not occur, providing a highly stereoselective route to phthoxazolin A.

Propenal **6** was prepared from propargyl alcohol **7**, using a stereoeselective copper(I)-catalyzed methyl Grignard addition reaction[4] and in situ iodinolysis sequence to give **8**. This was followed by Swern oxidation to provide aldehyde **6**, which was subjected to immediate aldol condensation due to the instability of **6**, to produce racemic phenol ester **9**. Many attempts were made to generate aldol fragment **5** in an enantioselective fashion, using both chiral auxiliary[5] and catalytic asymmetric[6] methods, but without success. The synthesis was therefore progressed in the racemic series. Thus ester **9** was converted into the stable primary amide fragment **5** by treatment with aqueous ammonia (Scheme 2).

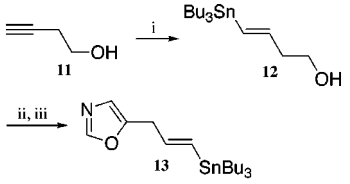
**Scheme 2.** Synthesis of Intermediate **4**




*Reagents*: i) a) MeMgBr, CuI, $Et_2O$, -5 °C, 2 h; b) ICl, $Et_2O$, -5 °C to r.t., 16 h; 65%; ii) a) $COCl_2$, DMSO, -78 °C, 15 min, then **3**, -78 °C, 30 min; b) $Et_3N$; 61%, crude; iii) $(CH_3)_2CHCOOPh$, $TiCl_4$, $Et_3N$, DCM, -78 °C, 2 h, then **6** from step ii, 2 h; 64%; iv) $NH_3$aq, MeCN, 2 d; 96%; v) vinylboronate pinacol ester, $Et_3N$, $Pd(Ph_3)_4$, MeCN, Δ, 4 days; 43 %; vi) a) ICl, DCM, -78 °C, 2 h; b) MeONa, MeOH, -78 °C, 30 min; 69%.

We then turned to the first of the important cross-coupling reactions. Vinyl iodide **5** underwent a Heck coupling reaction with vinylboronate pinacol ester[7] to stereoselectively access dienylboronate **10a** in 43% yield using methods similar to those reported previously, with the exception that for this reaction it was found that the addition silver(I) or thallium-(I) salts had a deleterious effect on the coupling.[3,8] This Heck product was also accompanied by 35% of the corresponding Suzuki product **10b**.[3] The next step required a boronate−iodine exchange on dienyl boronate **10a**, with clean inversion of the alkene stereochemistry. This was smoothly accomplished to provide dienyl iodide **4**, using a previously established method involving iodine monochloride addition and methoxide-mediated elimination.[3d] Thus, dienyl iodide **4** was ready for coupling with a fragment of type **2**. Iodide **4** had to be used directly without purification due to its instability.

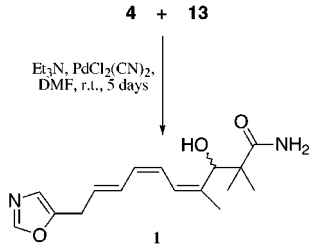
**Scheme 3.** Synthesis of Intermediate **2** Equivalent




Reagents: i) n-$Bu_3SnH$, AIBN, Δ, 2 h; 84%; ii) a) $COCl_2$, DMSO, -78 °C, 10 min then **9**, -78 °C, 30 min; b) $Et_3N$; 60%, crude; iii) TosMIC, aldehyde **3** from step ii, $K_2CO_3$, MeOH, Δ, 6 h; 15%.

Initial attempts to generate an equivalent of the vinyl metal system **2** revolved around using a boronate function for the metal moiety M. Unfortunately, a vinylboronate-derived system related to **3** turned out to be far too reactive for the subsequent formation of an oxazole ring system. This problem was circumvented by employing the highly unstable synthon **13**, which was synthesized as an equivalent of **2** in a straightforward manner from stannane alcohol **12**. In turn, this was derived from butenyne **11** (Scheme 3). Thus, tri-*n*-butyltin hydride addition to **11**, followed by Swern oxidation (via yet another highly unstable intermediate, i.e., aldehyde **3**, M = n-$Bu_3Sn$) and direct oxazole formation with tosylmethyl isocyanide[9] gave the fragment **13**, which was used immediately upon preparation.

**Scheme 4.** Final Stille Coupling To Produce Phthoxazolin A




(3) (a) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599. (b) Stewart, S. K.; Whiting, A. *J. Organomet. Chem.* **1994**, *482*, 293. (c) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3925. (d) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3929.

(4) The procedure is similar to that reported (Kotora, M.; Negishi, E. I. *Synthesis* **1997**, 121) with the exception of using methylmagnesium bromide and quenching the reaction with ICl.

(5) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (c) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (d) Cage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.

The final step thus involved a mild Stille cross-coupling[10] reaction between dienyl iodide **4** and vinylstannane **13**, which provided racemic phthoxazolin A[11] in 22% yield (Scheme 4). Further studies to apply vinylboronates for the synthesis of more complex polyene-containing natural products are underway.

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(7) Hoffman, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 2013.

(8) Exhaustive deoxygenation of the reaction mixture was required prior to addition of the catalyst. Under these conditions, absolutely pure (tetrakis-triphenylphosphinyl)palladium(0) catalyst was required, without co-addition of any other metal salts, and this combination produced the highest Heck: Suzuki ratio and the highest yield.

(9) van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153.

(10) Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J. L. *Synlett* **1999**, *1*, 141.

(11) All spectroscopic and analytical properties were identical to those reported in the literature (See ref 2).