A Convergent Stereoselective Total Synthesis of Racemic Phthoxazolin A

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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 preand 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



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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 reaction⁴ 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 auxiliary⁵ and catalytic asymmetric⁶ 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).

We then turned to the first of the important cross-coupling reactions. Vinyl iodide **5** underwent a Heck coupling reaction

MeOH. -78 °C. 30 min: 69%

with vinylboronate pinacol ester⁷ 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.



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-Bu₃Sn) and direct oxazole formation with tosylmethyl isocyanide⁹ gave the fragment **13**, which was used immediately upon preparation.



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⁽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.

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The final step thus involved a mild Stille cross-coupling¹⁰ reaction between dienyl iodide **4** and vinylstannane **13**, which

provided racemic phthoxazolin A¹¹ 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 (tetrakistriphenylphosphinyl)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.

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⁽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).