Synthesis of Pyragonicin

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ABSTRACT



A stereocontrolled convergent synthesis of the annonaceous acetogenin pyragonicin (1) is presented. The key intermediates were accessed using asymmetric Horner–Wadsworth–Emmons (HWE) methodology. A reagent controlled zinc-mediated stereoselective coupling, joining the two highly functionalized intermediates 3 and 4, then provided the core structure.

The annonaceous acetogonins class of natural products constitutes a growing number of about 400 isolated members that has attracted much attention from both chemists and biologists in recent years.¹ This interest emanates from the structural diversity and potent biological effects exhibited by these structures, including antimicrobial, pesticidal, and more importantly cytotoxic properties. Pyragonicin was isolated in 1998 by McLaughlin et al. and was proposed to have the structure **1**.² Structurally it belongs to the nonclassical subgroup of acetogenins together with, e.g., pyranicin (**2**),² mucocin,³ and muconin.⁴ As part of our continuing studies of the acetogenins, we wished to develop a synthetic route to pyragonicin to provide material for structural comparison purposes and for further investigation of activity.



In our retrosynthetic analysis of pyragonicin (Scheme 1), we identified a key disconnection at C12/C13 resulting in two fragments: the butenolide fragment **4**, which is identical to that used in our recent synthesis of pyranicin (**2**),^{5a} and a tetrahydropyran (THP) fragment **3**, similar to an intermediate in the pyranicin synthesis but differing in the length of the aliphatic chain. As illustrated in Scheme 1, we planned to obtain THP **3** from the simpler THP derivative **5**, which in turn is accessed from *meso*-dialdehyde **8**⁶ via an asymmetric Horner–Wadsworth–Emmons (HWE) desymmetrization (5 steps, 62% overall). Butenolide **4** is constructed from *rac*-**6** by a parallel kinetic HWE resolution and a subsequent reaction sequence involving a stereoconvergent Pd-catalyzed substitution. We envisioned the coupling of fragments **3** and **4**, with a concomitant installation of the C13 stereocenter, using the reagent-controlled, zinc-mediated addition of alkynes to aldehydes developed by Carreira and co-workers.⁷

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This reaction has previously been shown to proceed in the presence of unprotected propargylic alcohols.⁸

In the synthetic direction, ester 5^{5a} was subjected to a one-pot DIBAL reduction/Wittig reaction, providing the olefinated product 9 in good yield with moderate E:Zselectivity (\sim 1:10) (Scheme 2). Selective deprotection of the



primary silvl ether 9 by treatment with activated alumina⁹ followed by a Dess-Martin oxidation gave the desired pyragonicin THP-fragment 3 in good yield.

A key step in the synthesis is the stereoselective joining of THP-fragment 3 and butenolide fragment 4 (Scheme 3).

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The butenolide moiety of annonaceous acetogenins is known to be prone to base-induced epimerization.¹⁰ However, in aprotic solvents at ambient temperature, Et₃N has been shown not to cause epimerization of the butenolide stereocenter.¹¹

With this precedent at hand, we used the Carreira conditions for the coupling. Pleasingly, the reaction proceeded cleanly, albeit to 40% conversion based on 4,¹² using an excess of reagents,¹³ 1.5 equiv of aldehyde 3, and 1.0 equiv of acetylene 4. It should be noted that both unreacted 3 and 4 could potentially be recovered from the reaction mixture, but 4 is difficult to separate from the desired product 11, which makes the recycling of 4 less practical than 3. Instead, the separation was effected at a later point (see below). An exact quantification of the stereoselectivity could not be achieved because of the \sim 1:10 mixture of alkene isomers and the presence of 4, but at no point in the remaining steps of the synthesis could we detect any minor stereoisomer attributed to C13, indicating a selectivity of 13R: $13S \ge 95:5.^{14}$

The final steps then proceeded as expected (Scheme 3). Diimide reduction of a mixture of 11 and 4 gave an inseparable mixture of the corresponding reduced products. Global deprotection using aqueous HF afforded pyragonicin (1) in 34% yield over three steps, along with readily separated

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⁽¹²⁾ As determinded by ¹H NMR analysis after filtration through a short plug of silica.

⁽¹³⁾ Because of the small scale, an excess of reagents were used: $Zn(OTf)_2$, 2.0 equiv; (-)-NME, 3.0 equiv; and Et_3N , 5.0 equiv.

⁽¹⁴⁾ The C13 stereocenter was assigned by analogy with a similar transformation^{5a} and similar syntheses of 1,4-dihydroxy-2-alkynes using the Carreira methodology.8

butenolide 12 (51%), thus accounting for 85% of the total amount of the butenolide fragment 4 used in the coupling with 3.

The spectroscopic data of **1** (IR, ¹H and ¹³C NMR) were, within the normal error limits for such data, identical to those reported by McLaughlin. However, there was a strong discrepancy in the optical rotation;¹⁵ this discrepancy is similar to what has been found for pyranicin (**2**).^{5a,b} An authentic sample of pyragonicin was not available to us for purposes of direct comparison. To ensure that the C34 stereocenter was not epimerized in the coupling step, we employed Figadère's method^{10a} to confirm that, within limits of detection, no epimerization had occurred.¹⁶

In conclusion, we have developed a stereoselective synthesis of the proposed structure of pyragonicin with the longest linear sequence comprising 16 isolated intermediates from cyclohexadiene (overall yield 6.4%) and 16 isolated intermediates from *rac*-acrolein dimer (6) (overall yield 5.5%). A key feature of the synthesis is a mild, stereoselective coupling reaction using Carreira's asymmetric acetylide addition with a substrate bearing an adjacent unprotected hydroxyl group and a base-sensitive butenolide moiety. The Carreira addition should be of general use for late stage fragment coupling in syntheses of annonaceaous acetogenins containing a 1,4-diol subunit.

Full details of this study, as well as studies directed toward the synthesis of related acetogenins, will be reported in due course.

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Supporting Information Available: Characterization data and experimental procedures for all new materials (1, **3**, **9**, **10**, and **12**). This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁵⁾ Our synthetic material: $[\alpha]_{2^{5}D}^{2^{5}} + 10.5$ (*c* 0.125, CHCl₃); natural **1** $[\alpha]_{D}^{2^{5}} - 25.6$ (*c* 0.008, CHCl₃).² In this context, it should be noted that a large variation has been noted for the optical rotation of natural jimenizin, a structurally related annonaceous acetogenin.

⁽¹⁶⁾ See Supporting Information for further details.