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Stereoselective Syntheses of the Bioactive Polypropionates Aureothin, *N*-Acetylaureothamine, and Aureonitrile

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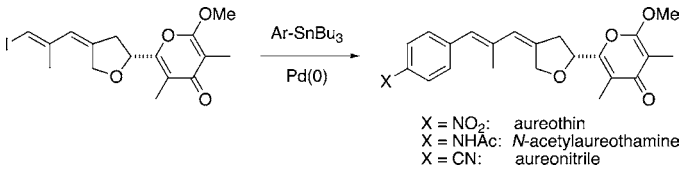
ABSTRACT



Concise total syntheses of the bioactive polypropionates aureothin, *N*-acetylaureothamine, and aureonitrile are described.

Several strains of *Streptomyces* synthesize highly unsaturated polypropionates with interesting biological profiles. Structurally, these natural products are characterized by an aryl polyene moiety consisting of (formally) conjugated trisubstituted double bonds, and an alkylidene tetrahydrofuran ring substituted with an α-methoxy-γ-pyrone (Figure 1). Aureothin (**1**), isolated from *S.* thioluteus,[1] exhibits significant antifungal and antitumor activities.[2] The homologous nitrophenyl tetraene spectinabilin (**4**), found in fermentation broths of *S. spectabilis*,[3] showed inhibitory activity against Rauscher leukemia virus reverse transcriptase and also appears to have antimalarial and immunosuppressant properties.[4] The related acetamide *N*-acetylaureothamine (**2**), isolated from *S. netropsis*, has been shown to be highly effective against *Helicobacter pylori*.[5] It therefore represents an important lead compound for the development of new therapeutic agents against gastric ulcer.

Despite their interesting biological profiles and unusual structures, relatively little attention has been given to these compounds by the synthetic community. This situation is likely to change, however, with the renewed general interest in highly unsaturated polypropionates of this class[6] and the recent report of Hertweck et al. that aureonitrile (**3**), an analogue of **1** obtained by mutasynthesis, exhibits significantly enhanced cytostatic effects against HeLa and K-562 tumor cells.[7] In 1995, Nishiyama and Namamura reported a semisynthesis of enantioenriched (+)-**1** and established its absolute configuration as **(*R*)**.[8] Very recently Baldwin et al. disclosed total syntheses of (±)-**1** and (±)-**2** based on olefin cross-metathesis and Suzuki cross-coupling reactions.[6a]

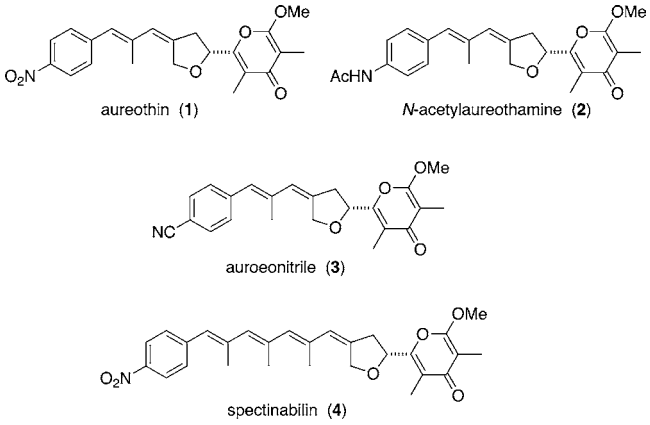


Figure 1.

(1) (a) Maeda, K. *J. Antibiot.* **1953**, *6*, 137. (b) Hirata, Y.; Nakata, H.; Yamada, K.; Okuhara, K.; Naito, T. *Tetrahedron* **1961**, *14*, 252.
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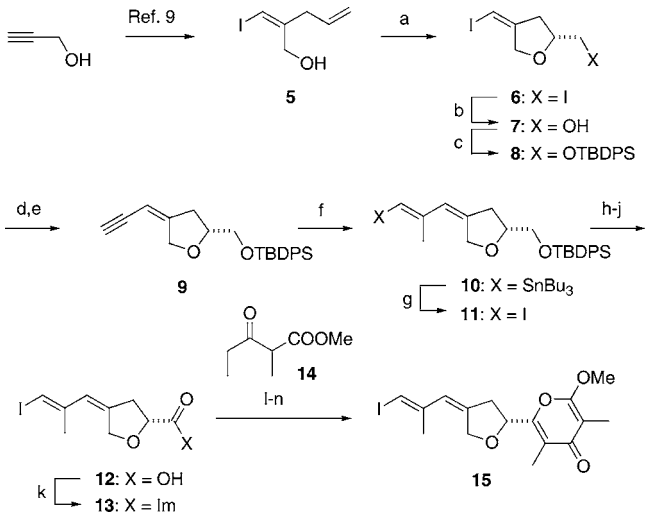
Scheme 1[a]



[a] Reagents and conditions: (a) I_2, $NaHCO_3$, 3 Å m.s., MeCN, 0 °C, 97%; (b) CsO_2CCF_3, DMF, 3 Å m.s., 90 °C, then basic workup, 83%; (c) TBDPSCl, imidazole, DMF, 95%; (d) 3 equiv of TMSA, 10 mol % $Pd(Ph_3P)_2Cl_2$, 5 mol % CuI, THF, Et_3N, 70 °C, 96%; (e) K_2CO_3, DCM, MeOH, 99%; (f) 4.5 equiv of *n*-$Bu_3SnMgMe$, 1 equiv of CuCN, THF, 0 °C, then 20 equiv of MeI, 0 °C to room temperature, 78%; (g) I_2, DCM, 95%; (h) TBAF, THF, 0 °C to room temperature, 85%; (i) $(COCl)_2$, DMSO, Et_3N, DCM; (j) 6 equiv of $AgNO_3$, 9 equiv of NaOH, H_2O, EtOH, 86% (two steps); (k) CDI, THF, 95%; (l) NaH, *n*-BuLi, −78 °C to −20 °C; (m) DBU, PhH, 45% (two steps); (n) $MeOSO_2F$, DCM, 65%.

We now wish to give an account of our own work on aureothin and related molecules. While our efforts have so far only yielded racemic **1**, **2**, and **3**, our convergent strategy is highly stereoselective and gives rapid access to a range of natural products and, potentially, numerous biologically active analogues.

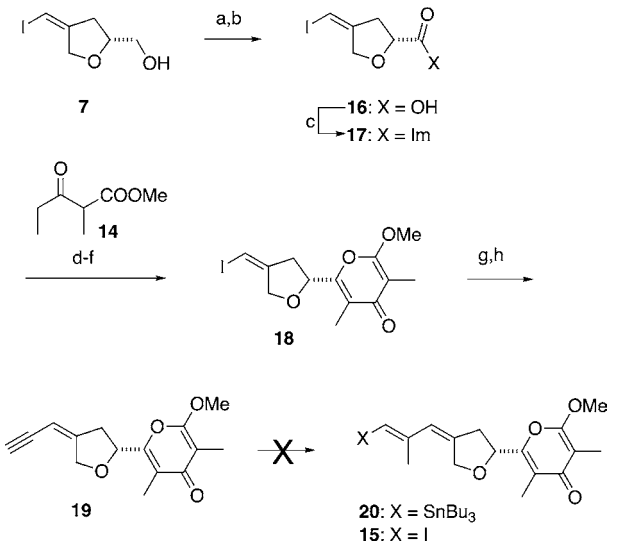
Our synthesis starts with the known copper-catalyzed addition of allylmagnesium bromide to propargylic alcohol, followed by iodination, to afford (*Z*)-iodoallylic alcohol **5** as a single stereoisomer.[9] Iodoetherification then gave racemic iodide **6**, which was converted into iodomethylene tetrahydrofuran **8** via S_N2 displacement followed by hydrolysis and silylation of the resulting primary alcohol **7**.

Sonogashira coupling to trimethylsilyl acetylene (TMSA) followed by desilylation gave enyne **9**. In a key step of our synthesis, this material was then converted into (*E*,*Z*)-iododiene **11** using Nozaki's and Uenishi's method.[10] Treatment of **9** with tributylstannyl methylmagnesium in the presence of catalytic amounts of cuprous cyanide, followed by alkylation of the resulting 1,2-dimetallic intermediate with methyl iodide, gave vinyl stannane **10** as a single diastereomer in good yield.[11] Subsequent tin−iodine exchange then afforded vinyl iodide **11**.

Desilylation followed by a carefully optimized two-step oxidation gave carboxylic acid **12**.[12] The installment of the α-methoxy-γ-pyrone moiety was achieved by conversion of **12** into the acyl imidazole **13**, followed by Claisen-type condensation with the dianion of β-ketoester **14**.[6j] Subsequent base-catalyzed cyclization and regioselective methylation gave the key building block **15** in good overall yield.

In attempt to render our strategy more convergent, we introduced the α-methoxy-γ-pyrone moiety early in the synthesis (Scheme 2). To this end, primary alcohol **7** was oxidized to give carboxylic acid **16**, which was activated as the acyl imidazole **17**. Installment of the pyrone moiety, as before, afforded building block **18**. Sonogashira coupling,

Scheme 2[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, DCM; (b) 6 equiv of $AgNO_3$, 9 equiv of NaOH, H_2O, EtOH, 95% (two steps); (c) CDI, THF, 95%; (d) NaH, *n*-BuLi, −78 °C to −20 °C; (e) DBU, PhH, 43% (two steps); (f) $MeOSO_2F$, DCM, 70%; (g) 3 equiv of TMSA, 10 mol % $Pd(Ph_3P)_2Cl_2$, 5 mol % CuI, THF, Et_3N, 85%; (h) TBAF, THF, 0 °C to room temperature, 83%.

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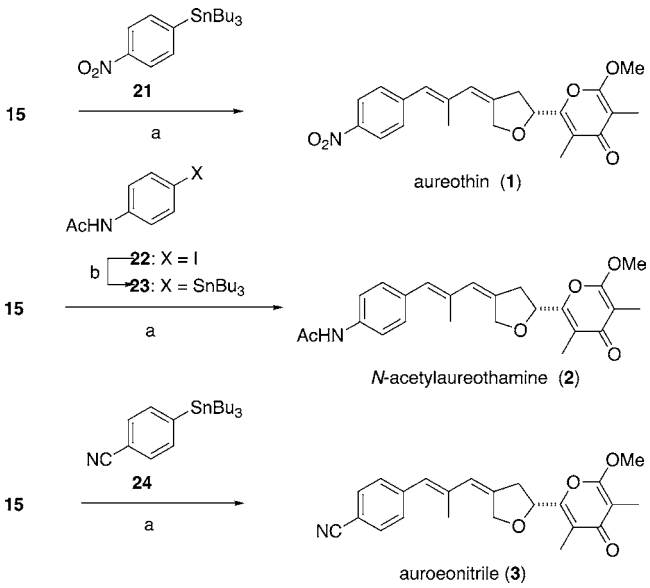
followed by desilylation, proceeded uneventfully to afford enyne **19**. Unfortunately, the Nozaki−Uenishi method broke down when the α-methoxy-γ-pyrone was already in place. Despite many attempts, we were unable to convert enyne **19** into vinyl stannane **20** or vinyl iodide **15**.

With key building block **15** in hand, we proceeded to couple it with a variety of stannanes. Stille-coupling[13] of **15** and the known aryl stannane **21**[14] gave aureothin (**1**) (Scheme 3). The combination of **15** and stannane **23**, which was

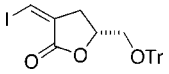
Scheme 3[a]



[a] Reagents and conditions: (a) 5 mol % $Pd(PPh_3)_4$, 10 mol % CuI, 2 equiv of CsF, DMF, 45 °C, 65−75%. (b) 10 mol % $Pd(MeCN)_2Cl_2$, $(n\text{-}Bu_3Sn)_2$, HMPA, 55%.

prepared from commercially available aryl iodide **22** via palladium-catalyzed iodine−tin exchange, afforded *N*-acetylaureothamine (**2**). Aureonitrile (**3**) was synthesized via Stille-coupling of **15** and the known stannane **24**.[15] All synthetic compounds were obtained in good yields and showed spectra identical to those of the natural products.

In summary, we have described a short, modular synthesis of aureothin, *N*-acetylaureothamine, and aureonitrile, which could open access to numerous analogues of these biologically active molecules. Efforts toward the asymmetric synthesis involving asymmetric cyclo-etherifications or enantiomerically pure Sato's lactone **25**[16] are currently underway.



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The use of building blocks **15** and **18** in a synthesis of spectinabilin (**4**) and its isomers SNF4435 C and D is also under active investigation. Note that vinyl iodides **15** and **18** could serve as useful building blocks for a range of potentially biologically active analogues of aureonitrile that are not easily available through mutasynthesis.

Acknowledgment. This work was supported by National Institutes of Health Grant R01 GM067636. D.T. thanks Eli Lilly, Glaxo Smith Kline, Amgen, and AstraZeneca Young Investigator Awards.

Supporting Information Available: Spectroscopic and analytical data for compounds **1**−**3**, **6**−**13**, and **15**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In an improvement of the original procedure, vinyl stannane **10** could be isolated and fully purified by chromatography on triethylamine deactivated silica gel (see Supporting Information).

(12) High yields were achieved by oxidizing the extremely sensitive intermediate aldehyde immediately with silver(I) reagent (see Supporting Information).

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