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A Short Total Synthesis of Aureothin and *N*-Acetylaureothamine

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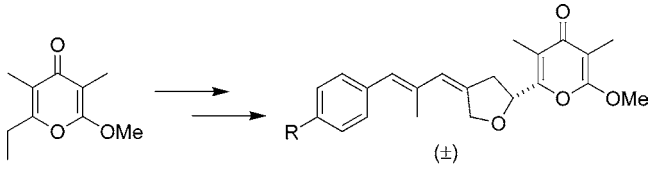
ABSTRACT



The total synthesis of the nitrophenyl pyrones, (±)-aureothin and (±)-*N*-acetylaureothamine, starting from known 2-ethyl-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one are described. The key steps involved in the synthesis are the construction of the tetrahydrofuran motif using a palladium-catalyzed cycloaddition and the ruthenium-catalyzed cross-metathesis reaction of an alkenyl boronic ester.

Aureothin **1** and *N*-acetylaureothamine **2** are two unusual natural products, both featuring a rare nitroaryl group and a highly substituted conjugate diene system. *N*-Acetylaureothamine **2**, isolated from *Streptomyces netropsis*, has been shown to be a highly selective and potent agent against *Helicobacter pylori*, a common cause of chronic gastritis.[1] Aureothin **1** has been found in the mycelia of several actinomycetes, and possesses antitumor, antifungal, and pesticidal activities.[2] Recently, studies on the biosynthesis of **1** have revealed that an unprecedented type of *N*-oxygenase, AurF, is responsible for the oxidation of *p*-aminobenzoate to the corresponding nitro compound, which serves as a starter unit for the polyketide synthase resulting in the formation of **1**.[3] Furthermore, a multifunctional cytochrome P450 monooxygenase, AurH, catalyzes the formation of the exomethylene tetrahydrofuran ring of **1**.[4] Both compounds are members of a small family of nitrophenyl pyrones featuring a tetrahydrofuran-derived motif (Figure 1).[5]

Our continued interest in polypropionate metabolites, and in particular their biomimetic synthesis, has driven us to search for new and efficient methods for polyene-pyrone synthesis.[6] Herein we report short total syntheses of (±)-aureothin **1** and (±)-*N*-acetylaureothamine **2**.[7,8]

Our retrosynthetic analysis of **1** and **2** is outlined in Scheme 1. We envisaged that the congested diene system could be constructed via a sequence of *trans*-selective Suzuki

(1) Taniguchi, M.; Watanabe, M.; Nagai, K.; Suzumura, K.-I.; Suzuki, K.-I.; Tanaka, A. *J. Antibiot.* **2000**, *53*, 844.

(2) (a) Hirata, Y.; Nakata, H.; Yamada, K.; Okuhara, K.; Naito, T. *Tetrahedron* **1961**, *14*, 252−274. (b) Oishi, H.; Hosogawa, T.; Okutomi, T.; Suzuki, K.; Ando, K. *Agric. Biol. Chem.* **1969**, *33*, 1790. (c) Schwartz, J. L.; Tishler, M.; Arison, B. H.; Shafer, H. M.; Omura, S. *J. Antibiot.* **1976**, *29*, 236. (d) Maeda, K. *J. Antibiot.* **1953**, *6*, 137.

(3) He, J.; Hertweck, C. *J. Am. Chem. Soc.* **2004**, *126*, 3694.

(4) He, J.; Müller, M.; Hertweck, C. *J. Am. Chem. Soc.* **2004**, *126*, 16742.

(5) Isoaureothin: Ishibashi, Y.; Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1992**, *33*, 521 and references therein. **3**: Kakinuma, K.; Hanson, C. A.; Rinehart, K. L. *Tetrahedron* **1976**, *32*, 217. Luteothin: Washizo, F.; Umezawa, H.; Sugiyama, N. *J. Antibiot.* **1954**, *7*, 60. **4** and **5**: (a) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541. (b) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548. (c) Kurosawa, K.; Takahashi, K.; Fujise, N.; Yamashita, Y.; Washida, N.; Tsuda, E. *J. Antibiot.* **2002**, *55*, 71. (d) Lim, Y.-H.; Parker, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 15968.

(6) (a) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett.* **2002**, *21*, 3731. (b) Moses, J. E.; Baldwin, J. E.; Brückner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670. (c) Moses, J. E.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 6447.

(7) Although **1** and **2** exist as single enantiomers in Nature, it has been reported that **1** is very prone to racemization. Thus, racemization of **1** occurs within 24 h in $CDCl_3$ at room temperature, see: Nair, M. G.; Chandra, A.; Thorogod, D. L. *Pestic. Sci.* **1995**, *43*, 361.

(8) A previous total synthesis provided (−)-**1** with low ee in only 0.01% yield from **9** in 13 steps, see: Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3643.

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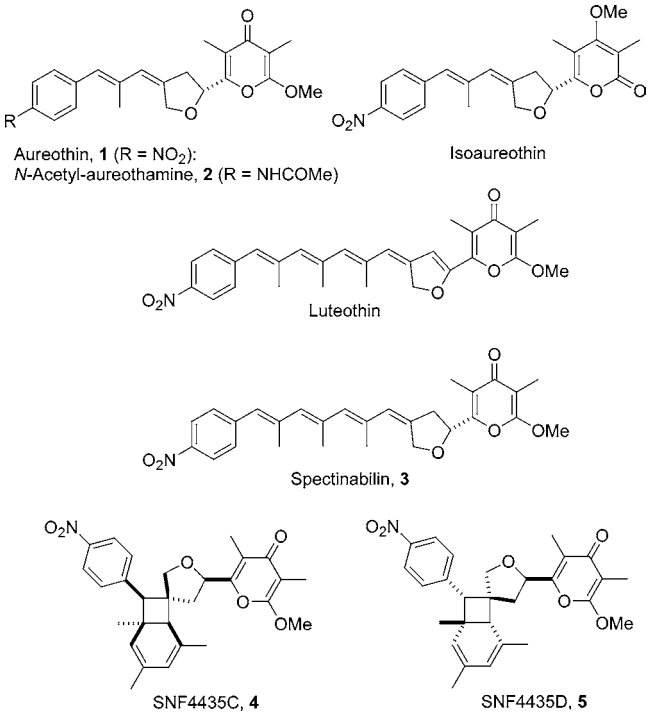
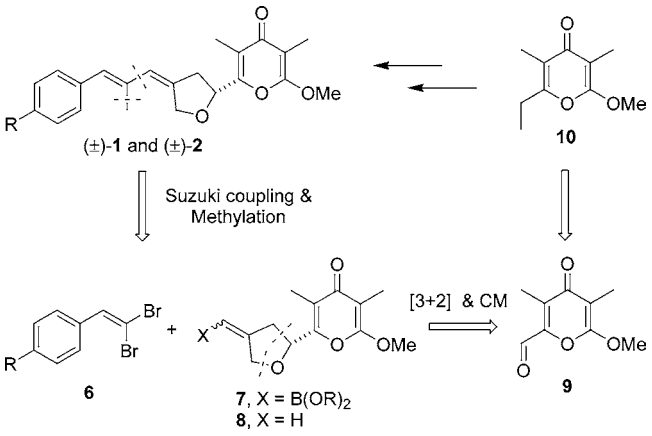


Figure 1. Family of nitroaryl-substituted γ-pyrone metabolites.

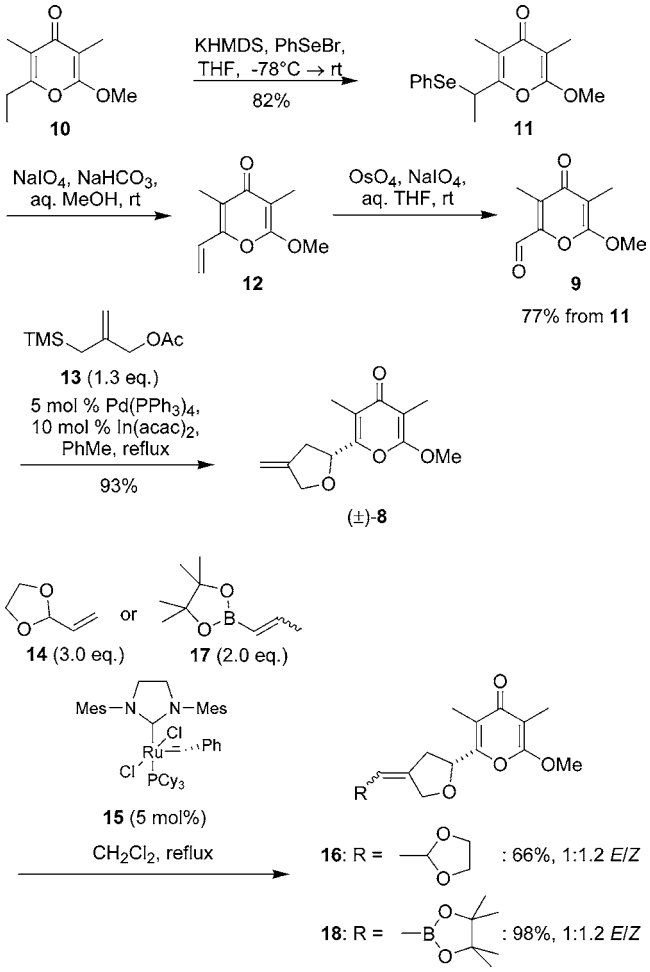
Scheme 1. Retrosynthesis of (±)-**1** and (±)-**2**



coupling of dibromide **6** with boronic ester **7** and subsequent stereospecific methylation. We believed that cross metathesis (CM) could be used for the construction of boronic ester **7** from alkene **8**, while the tetrahydrofuran ring in **8** could conceivably be obtained by subjecting **9** to [3+2] cycloaddition with a palladium trimethylenemethane complex. This led back to the known aldehyde **9**, which we prepared from readily accessible ethyl pyrone **10**.[9]

Preparation of aldehyde **9** from **10** began by converting **10** to the corresponding phenylselenyl compound **11** via its potassium enolate. Subsequent oxidation of **11** using $NaIO_4$ yielded the rather unstable olefin **12**.[10] Further oxidation of **12** furnished aldehyde **9** in excellent overall yield using the Lemieux−Johnson protocol.[11] This short route to **9** constitutes a considerable improvement compared to the previously published route,[12] thus allowing easy access to this important building block.[13]

Scheme 2. Synthesis of Tetrahydrofuran Fragment **18**[a]



Next, we turned our attention to the construction of the tetrahydrofuran framework of **1** and **2**. We found to our delight that the palladium-bound TMM complex generated from **13** and $Pd(PPh_3)_4$ underwent a facile reaction with **9** in the presence of $In(acac)_2$ as cocatalyst affording an excellent yield (93%) of **8**.[14,15] The recent reports of the cross metathesis of alkenyl boronic esters with 1,1-disubstituted

(9) Hatakeyama, S.; Ochi, N.; Takano, S. *Chem. Pharm. Bull.* **1993**, *41*, 1358.

(10) Oxidation with $H_2O_2/NaHCO_3$ instead afforded a lower yield (55%) of **12**.

(11) Rappo, R.; Allen, D. S., Jr.; Lemieux, U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

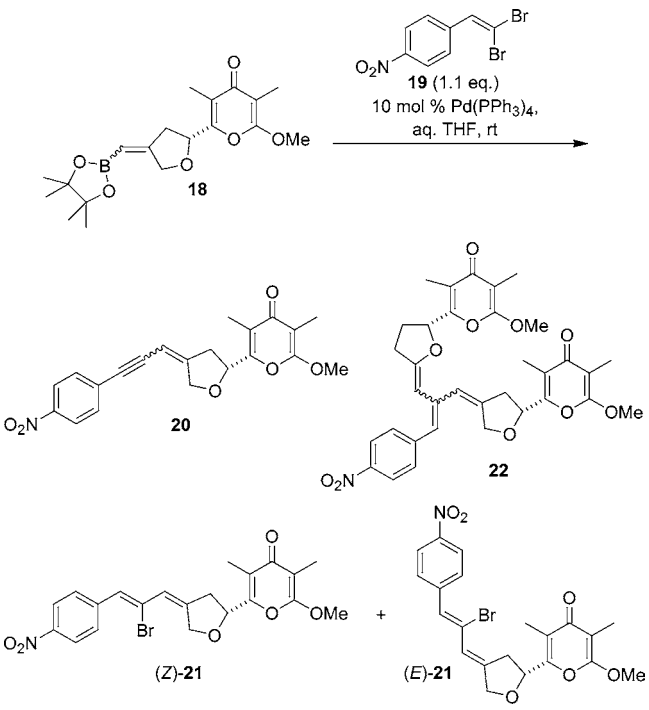
(12) (a) Suzuki, E.; Sekizaki, H.; Inoue, S. *J. Chem. Res.* **1977**, *200*, 2273. (b) Suzuki, E.; Hamajima, R.; Inoue, S. *Synth. Commun.* **1975**, 192.

(13) Moses, J. E. D. Phil Thesis, University of Oxford, Oxford, UK, 2004.

(14) (a) Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7903. (b) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778.

(15) The use of the 2-[(tributylstannyl)methyl]-2-propen-1-yl acetate/$Pd(OAc)_2$ + PPh_3 system instead provided a comparable yield (88%) of **8**.

Scheme 3. Influence of Base on the Suzuki-Coupling of Boronic Ester **18** with Dibromide **19**[a−c]



Yield/%	21 :	20 :	22
NaOH	0	70	0
Tl_2CO_3	20	20	20
TlOEt	72	0	0

[a] The ratio of **20**, **21**, and **22** was determined by ^{1}H NMR of the crude product. [b]**20** and **21** were obtained as 1:1.2 *E*/*Z* mixtures of isomers. [c]**22** was obtained as a mixture of isomers.

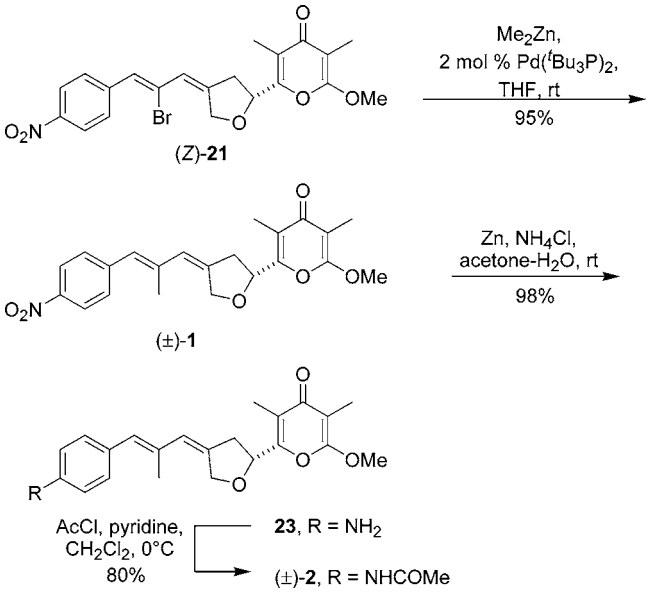
olefins seemed an attractive approach to the otherwise not easily accessible boronic ester **18**.[16]

Initially, the CM reaction of **8** with commercially available 2-vinyl-1,3-dioxolane **14** and catalyst **15** was attempted, which gave a good yield of the CM product **16**. Having established the viability of **8** in CM reactions, we exposed **8** to the reaction with **15** and alkenyl pinacol boronate **17**[16] to furnish **18** in almost quantitative yield, albeit with low *E*/*Z*-selectivity.

With the key cross-coupling partner **18** at hand, we set out to examine the Suzuki coupling with the known dibromide **19**[17] that was prepared in high yield (87%) from *p*-nitrobenzaldehyde (Scheme 3). Suzuki couplings of alkenyl dibromides are known to occur with high *trans*-selectivity;[18] however, the choice of base is sometimes crucial in order to obtain only the monoalkylated product.[19] We found that the use of NaOH as base was plagued by the formation of the unexpected alkyne **20**, due to dehydrobromination of **19** and/or **21**. The use of Tl_2CO_3 was not successful either, as it gave further rise to the formation of the dialkylated product **22** in addition to **20** and **21**. Gratifyingly, the use of TlOEt afforded exclusively the desired intermediate **21** in a satisfying 72% yield (42% isolated yield of (*Z*)-**21**).[20,21] The configuration of the *Z*-isomer was confirmed by an NOESY experiment.

The palladium-catalyzed methylation of alkenyl halides with Grignard or zinc reagents can be problematic due to configurational instability of the intermediate palladium species leading to products of stereoinversion.[22,23] To accomplish the stereospecific conversion of (*Z*)-**21** to (±)-**1**, we first attempted the recently reported palladium-catalyzed Suzuki−Miyaura coupling of trimethylboroxine ($Me_3B_3O_3$, Cs_2CO_3, $Pd(PPh_3)_4$, aq DMF, 80 °C).[24] Disappointingly, this led to extensive decomposition of the starting material. Instead, we were pleased to find that the exposure of (*Z*)-**21** to the Negishi-type coupling with Me_2Zn and catalytic amounts of $Pd(^tBu_3P)_2$ gave the light-sensitive (±)-aureothin **1** with complete retention of the required *E*-stereochemistry and in excellent yield (Scheme 4).[23] The (±)-aureothin **1**

Scheme 4. Stereospecific Methylation of (*Z*)-**21** and Conversion to (±)-**1** and (±)-**2**



obtained had identical spectral data (^{1}H NMR, ^{13}C NMR, and IR) to those previously reported for (+)-aureothin.[8]

A suitable reduction/acetylation sequence of **1** was all that remained for the synthesis of **2**. We found that neither a

(16) (a) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

(17) Shastin, A. V.; Korotchenko, V. N.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2001**, *14*, 2081.

(18) (a) Rousch, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710. (b) Rousch, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708.

(19) Starr, J. T.; Evans, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 1351.

(20) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.

(21) The *E*- and *Z*-isomers of **21** were easily separated by column chromatography.

(22) Zeng, X.; Hu, Q.; Qian, M.; Negishi, E.-I. *J. Am. Chem. Soc.* **2003**, *125*, 13636.

(23) Shi, J.-C.; Zeng, X.; Negishi, E.-I. *Org. Lett.* **2003**, *11*, 1825.

(24) Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 6237.

$SnCl_2$-mediated reduction nor the ultrasound-assisted reduction of (±)-**1** with Sm/NH_4Cl[25] was compatible with our substrate. On the other hand, by employing Zn/NH_4Cl instead, a very clean transformation followed yielding **23** in a 98% yield. Acetylation with AcCl afforded pure (±)-*N*-acetylaureothamine **2**, identical by spectral analysis (^{1}H NMR, ^{13}C NMR, and IR) with that previously reported for (+)-**2**.[1]

In conclusion, we have developed short total syntheses of (±)-aureothin **1** and (±)-*N*-acetylaureothamine **2** affording the natural products in 23% and 18% overall yield from known **10**, respectively. Further efforts in our laboratories are now being directed toward the implementation of our developed synthetic methodology for the synthesis of spectinabilin **3**, and its subsequent biomimetic conversion to **4** and **5**.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, **2**, **8**−**9**, **11**−**12**, **18**−**19**, **21**, and **23** and ^{1}H NMR and ^{13}C NMR spectra of (±)-**1** and (±)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047594L

(25) Basu, M. K.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2000**, *41*, 5603.