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The Total Synthesis of (−)-Aurafuron A

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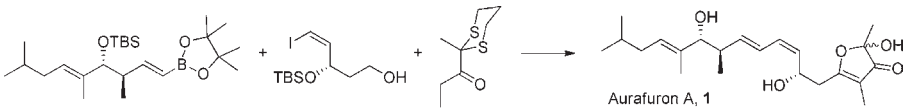
ABSTRACT



The first total synthesis of (−)-aurafuron A is presented. It features a Suzuki cross-coupling reaction and a high yielding anionic aldol addition as central carbon skeleton building reactions. The synthesis confirms the proposed structure including its configuration and allows for detailed SAR studies.

Myxobacteria are a rich source of biologically active natural products exhibiting a variety of variations in their backbone.[1] In particular the spirangiens[2] and aurafurons (**1** and **2**, Figure 1) are of special interest since they address novel yet unidentified cellular targets.

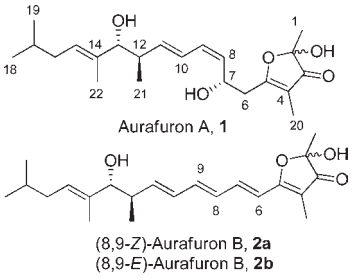


Figure 1. Structures of the aurafurons. Aurafuron B exists as 8,9-*E* and 8,9-*Z* isomers.

The aurafurones were isolated by Höfle and co-workers from the myxobacterium *Stigmatella aurantiaca* DW4/3-1, and their structure was elucidated by a combination of mass spectrometry and NMR spectroscopy.[3] They were shown to have moderate antifungal and antibiotic (MIC for **1**: 6.3 μg mL^{-1}, *mucor hiemalis* DSM 6566), as well as cytotoxic properties (IC_{50} for **1**: 4 μg mL^{-1}, mouse fibroblast cell line L929). Aurafuron A (**1**) contains three defined stereocenters, one racemic hemiacetalic carbon incorporated in the unusual furanone core and two *E*- and one *Z*-configured double bonds. The characteristic 3(2*H*)-furanone[4] core as 2-hemiacetal can be found in other natural products such as AS-183[5] from the fungus *Scedosporium*, polypropionates[6,7] from the marine mollusc *Siphonaria* or the actinofuranones[8] isolated from actinomycetes MAR4, none of which have been made by total synthesis so far. While AS-183 was shown to inhibit the acyl-CoA cholesterol acyltransferase (ACAT) of rabbit liver microsomes, the aurafurons' mode of action still remains unknown.

The biosynthesis consists of several unusual features such as an iterative use of one PKS module and a *post*-PKS Baeyer–Villiger-type oxidation to build up the furanone core.[9] Additionally, it remains undetermined whether aurafuron B is a self-contained natural product or an artifact derived through elimination of aurafuron A

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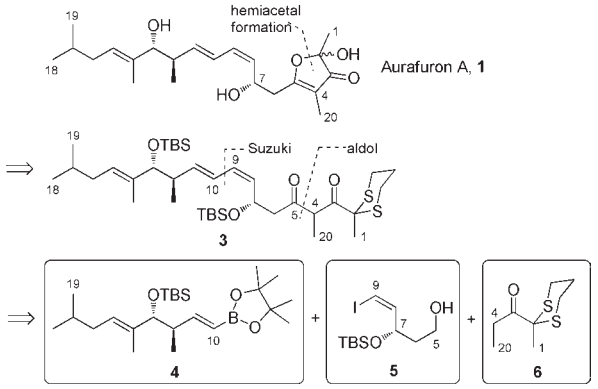
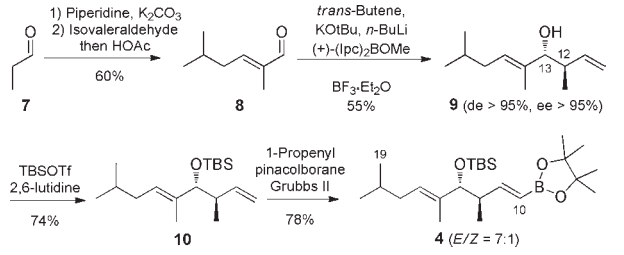
during the isolation procedure. With this state of knowledge in mind, we were aware that incorporation of the furanone through an aldol process would require special attention in order to avoid elimination to the corresponding tetraene.

Scheme 1. Retrosynthetic Analysis



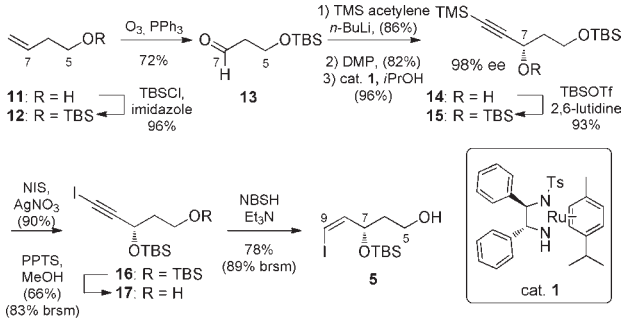
The retrosynthetic analysis of aurafuron A (**1**) sets in from linear intermediate **3** (Scheme 1). Herein the C4–C5 bond was envisioned to be built up *via* an aldol reaction between ethyl ketone **6** and an aldehyde generated at C5. The C9–C10 connection on the other hand can be established using a palladium catalyzed Suzuki reaction between vinyl iodide **5** and pinacol boronate **4**.

Scheme 2. Synthesis of Western Fragment **4**



Western fragment **4** is accessible in five steps from commercially available propionaldehyde (**7**) (Scheme 2). Aldol condensation *via* its piperidino enamine with isovaleraldehyde yields the *E*-configured α,β-unsaturated aldehyde **8** in 60% yield. In this case the undesired *Z*-isomer (7%) is easily separated by column chromatography. The key step in this route is the enantioselective Brown crotyl boration[10] to generate alcohol **9** in 55% yield and higher than 95% *dr* and >95% *ee*, respectively (determined by ^{1}H NMR and Mosher ester method). Silylether protection furnishes the terminal alkene **10** which was subsequently used in Heck reactions with vinyl iodide **5** (*vide infra*). As coupling yields were poor, **10** was further functionalized in a stereoselective (7:1 *E*/*Z*) cross metathesis[11] using Grubbs' second generation catalyst to complete the synthesis of pinacol boronate **4**.

Scheme 3. Synthesis of the C5–C9 Fragment **5**



The synthesis of the central C5–C9 fragment **5** starts from commercially available 3-butene-1-ol (**11**) which is silyl protected and ozonolyzed to give aldehyde **13** (Scheme 3). Attempts to enantioselectively add TMS acetylene using the method developed by Carreira[12] resulted in poor yields of about 15%, albeit in an enantiomeric excess of 92% (chiral GC). Alternatively, a sequence of lithium TMS acetylide addition, Dess-Martin oxidation (Dess-Martin periodinane, DMP),[13] and Noyori reduction[14] was chosen to obtain the *S*-configured alcohol **14** in 68% yield (three steps) and 98% *ee*. Several other methods for enantioselective reduction appeared applicable but were proven somewhat inferior with respect to conversion and enantioselectivities. So, for example, Noyori's BINAl-H reduction[15] shows no conversion, whereas Alpine borane reduction[16] yields 50% of the desired product with 84% ee. Silyl ether protection and iododesilylation, followed by selective primary TBS deprotection, furnishes iodoacetylene **17** in good yields.

The desired *Z*-configured vinyl iodide **5** is built up in a diimide reduction utilizing *ortho*-nitrobenzene sulfonyl hydrazide (NBSH)[17] under basic conditions. As attempted Heck reactions between terminal alkene **10** and vinyl iodide **5** using Jeffery type conditions[18] and variations developed during our synthesis of ratjadon[19] never exceeded yields of 31%, we changed the strategy to a Suzuki reaction between pinacol boronate **4** and vinyl iodide **5**.

(10) Brown, H. J.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.
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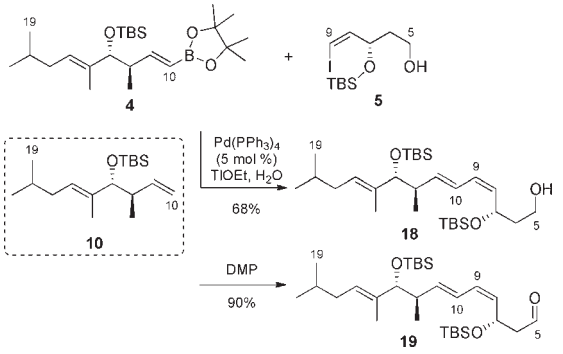
Unfortunately, first attempts utilizing $Pd(PPh_3)_4$ (5 mol %) and diisopropylamine showed very low conversion and isolated yields of only 17%. Motivated by reports from Roush and co-workers during their synthesis of superstolide A[20] and our synthesis of chlorotonil,[11] we found that also in this case the use of thallium salts was essential to provide good yields of 68%. Subsequent Dess-Martin oxidation sets the stage for further manipulations (Scheme 4).

Scheme 4. C9−C10 Bond Formation *via* Suzuki Coupling



With aldehyde **19** in hand, several endgame strategies failed (Figure 2). First, attempts to utilize the C4 enolate of ethyl ketone **20** in all cases led to C6−C7 elimination and formation of a fully conjugated ketone.

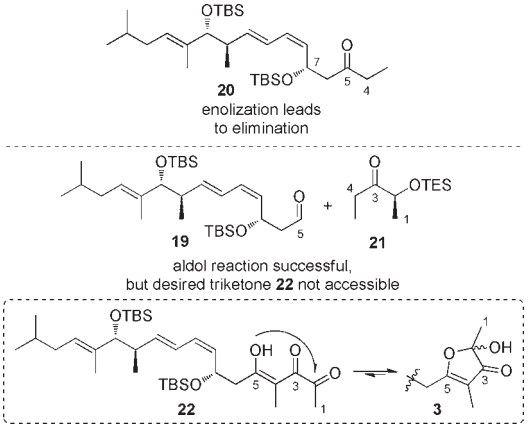
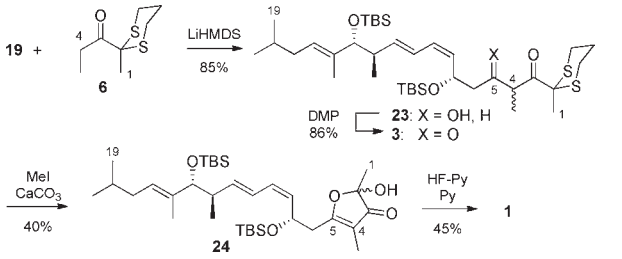


Figure 2. Endgame strategy.

In a second approach we joined aldehyde **19** and lactate derived ethyl ketone **21**[21] in an aldol addition. We envisioned oxidizing the C2 and C5 alcohol functionalities at a late stage to gain the desired triketone **22**. Unfortunately, those subsequent TES deprotection and oxidation attempts proved to be fruitless in all orders due to stable hemiacetal formation[22] and elimination issues.

As we were not able to circumvent these problems using this particular route we changed the C2 protecting group to one in the correct oxidation state and therefore chose to introduce dithiane **6**.[23] Intensive optimization of the aldol addition showed that already a slight surplus of base leads to a considerable drop of conversion. Apparently, in those cases the aldehyde is deprotonated by the excess of base *before* it is able to react with the preformed lithium enolate of ethyl ketone **6**. Running the reaction accordingly and employing a ratio of 2:2:1 (ketone/base/aldehyde), high yields of **23** (85%) could be achieved (Scheme 5). Subsequent Dess-Martin oxidation proceeds slowly, but without detectable formation of the corresponding sulfoxide.

Scheme 5. Completion of the Synthesis



The dithiane hydrolysis of **3** proved to be troublesome and needed intensive elaboration. Several of the following methods were tested and either led to decomposition (buffered or unbuffered Stork's reagent,[24] NBS,[25] visible light/rose bengal[26]) or no conversion ($Hg(ClO_4)_2$,[27] $HgCl_2$,[28] DMP,[29] IBX,[30] benzene selenic anhydride[31]). An attempted Pummerer type hydrolysis[32] which employed *m*CPBA, followed by Ac_2O and Et_3N, gave a complex mixture. Finally, we were able to obtain the corresponding furanone (**24**) under methylation conditions using large

(20) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 9657.

(21) For highly stereoselective aldol reactions with similar lactate derived ethyl ketones, see: (a) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639. (b) Denmark, S. E.; Pham, S. M. *Org. Lett.* **2001**, *3*, 2201.

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(23) Dithiane **6** is available in two steps from commercially available 2-methyl 1,3-dithiane and propionic aldehyde. For details, see Supporting Information.

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(33) We could also obtain a corresponding furanone in a simplified system which was generated by aldol reaction between dithiane **6** and isovaleric aldehyde and subsequent DMP oxidation.

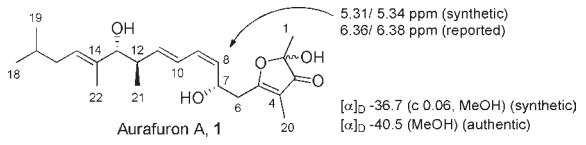

Figure 3. Comparison of spectroscopic data.

excesses of methyl iodide[33,34] in refluxing aqueous acetonitrile in 40% yield accompanied by some decomposition.

The open form of the lactol (**22**) was never observed. A second mild method especially for the hydrolysis of double bond containing dithianes such as **3** was found to be the combination of silver nitrate and *N*-chlorosuccinimide (NCS).[35] **24** could be isolated in a diminished yield of 35% on an 8 mg scale. As the yields dropped further upon upscaling we decided to rely on the above-mentioned methylation conditions. Global deprotection of **3** was accomplished with a HF−pyridine complex in THF with extra pyridrine to furnish aurafuron A (**1**).

The spectroscopic data of synthetic aurafuron A match those of the authentic material.[36] Additionally, the optical rotation of the synthetic material is in good agreement with the authentic material (synthetic $[\alpha]^{20}_{D}$ −36.7, *c* 0.06, MeOH; authentic $[\alpha]^{20}_{D}$ −40.5, MeOH) and thus confirms the structure as well as the proposed configurations of this natural product (Figure 3).

Synthetic access to aurafuron A was established in a longest linear sequence of 15 steps starting from commercially available substances with a total yield of 2.3%. Biological results will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) In our case COSY experiments revealed the C8 proton to have chemical shifts of 5.31/5.34 ppm, whereas the reported values are 6.36/6.38 ppm and by that differ about 1 ppm. As an authentic ^{1}H NMR spectrum is in accordance with the spectrum of the synthetic material, the typo was confirmed by G. Höfle (personal correspondence).

The authors declare no competing financial interest.