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Total Synthesis of Muricadienin, the Putative Key Precursor in the Solamin Biosynthesis

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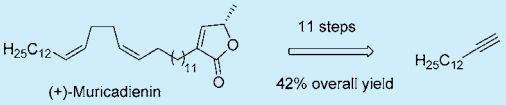
Supporting Information

ABSTRACT: The first total synthesis of muricadienin, the unsaturated putative precursor in the biosynthesis of *trans*- and *cis*-solamin is described. Key steps in the synthesis are a chemoselective hydroboration, a *Z*-selective Wittig reaction, and a Fries rearrangement for introducing the terminal α-substituted butenolide. Thus, muricadienin can be synthesized in 11 steps from commercially available starting materials in 42% overall yield.



The annonaceous acetogenins are a large group of natural products isolated from plants of the genus *annona*.[1,2] They are typically found in leaves, roots, seeds, or plant bark. Structurally they consist of a long unbranched fatty acid chain (C_{32} or C_{34}) which, at one end, is terminated with a butenolide. Characteristic to almost all members is a central saturated oxygen heterocycle (THF or less common THP) which is usually bordered by hydroxy groups (Figure 1). The heterocycle motif may be repeated up to three times.[1]

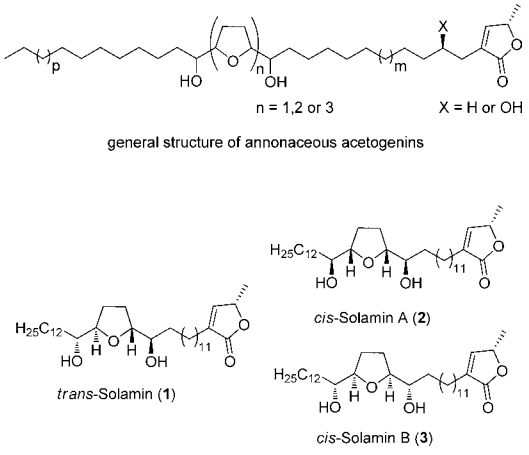


Figure 1. General structure of annonaceous acetogenins and structures of *trans*-solamin and *cis*-solamin A/B.

Although the first acetogenin[3] representatives were isolated and characterized more than 30 years ago, key questions about their biosynthesis are still unclear, in particular the timing and stereoselectivity of the formation of the THF (or THP) core. Similar and in relation to the biosynthesis of polyether antibiotics,[4] one can imagine a reaction sequence that starts from a diene or polyene which is oxidized to a polyepoxide and, in turn, converted to the heterocycle(s) in a cascade-like process.[5] Support for this hypothesis comes from the isolation of putative epoxy intermediates. For instance, the solamins[6,7] (Figure 1), the prototype for all mono-THF-acetogenins, are believed to be derived from muricadienin[8] (**4**) (Scheme 1). Epoxidation of the 1,5-diene subunit could first yield up to four regio- and stereoisomeric monoepoxides, including known epoxymurin A and B[9] (also referred to as epomuricenin) and, subsequently, four stereoisomeric diepoxides (diepomuricanins A1 and A2).[10] Addition of water to *syn*-diepomuricanin A1 could initiate an epoxide-opening−cyclization cascade that delivers *trans*-solamin (**1**). The stereoisomeric *cis*-solamins A (**2**) and B (**3**) could result from the pseudo-C_2-symmetric *anti*-diepomuricanin A2 (Scheme 1).[11]

In addition to these natural metabolites, Figadère et al. have investigated the *in vitro* conversion of natural diepomuricanin A to solamins to shed light on THF formation during acetogenin biosynthesis.[12] Using ^{18}O-labeled water as a nucleophile, they found that diepomuricanin A does not exist as a single isomer, but rather as a mixture of two diastereoisomers: *syn*-diepomuricanin A1 and *anti*-diepomuricanin A2 (Scheme 1), with unknown absolute configuration. Moreover, they were able to show that acidic epoxide opening was not regioselective and a novel iterative mechanism for THF formation through epoxy-diol intermediates was suggested.[12]

In order to study the whole process of THF-biogenesis from the diene precursor to the THF natural product, access to muricadienin (**4**) is required. To our surprise this natural product has so far never been synthesized. In addition, it is worth noting that muricadienin (**4**) has actually never been isolated in analytically pure form. It only proved possible to characterize it from a mixture of related dienes isolated from the seeds and roots of *annona muricata*.[8] As part of our ongoing interest in the development of synthetic methodology to THF-[13] and THP-heterocycles,[14] biomimetic polyepoxide-cyclization cascades and investigations into the biosynthesis of such natural products,[15] we decided to explore a synthesis of muricadienin (**4**).

Retrosynthetically, we considered it strategic to establish the *Z*,*Z*-1,5-diene unit at a late stage in the synthesis from an enyne

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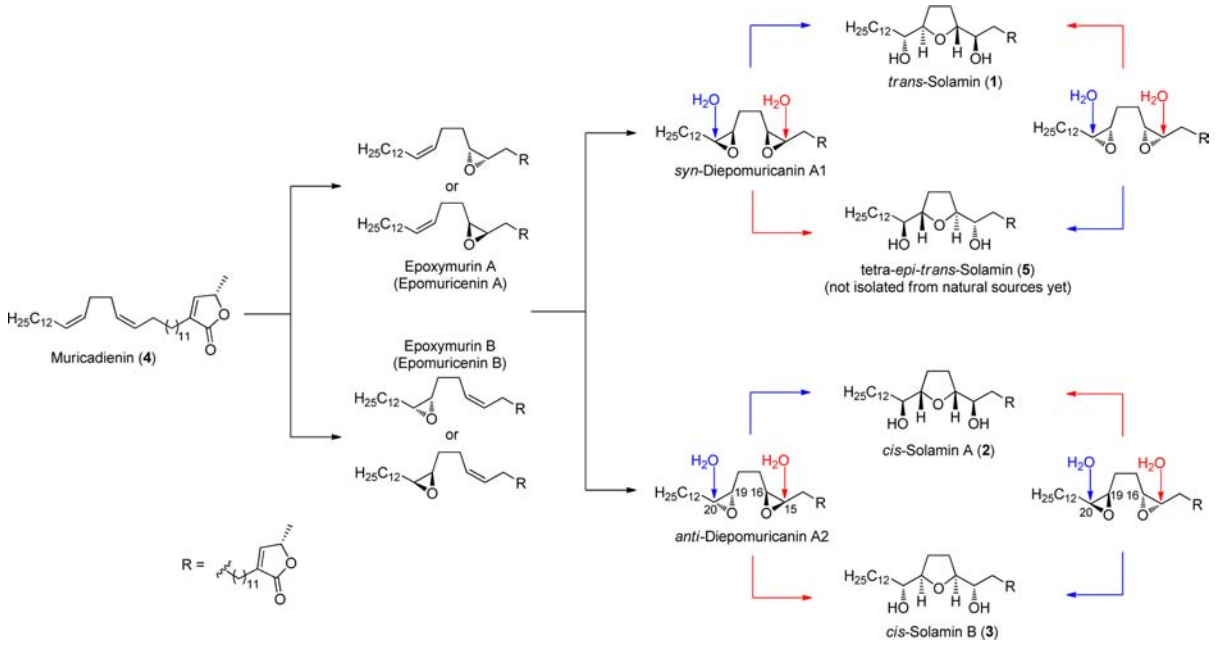
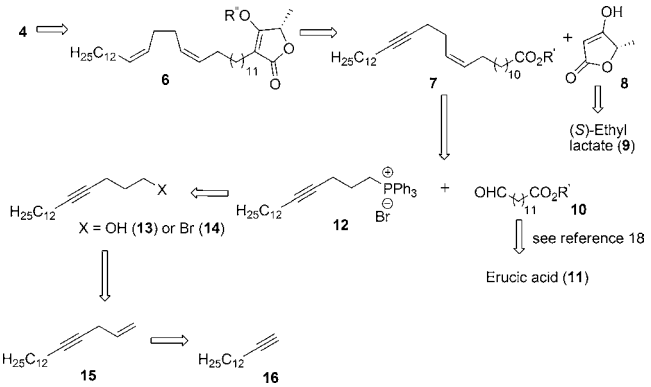
Scheme 1. Proposed Biosynthetic Pathway for *trans*-Solamin and *cis*-Solamin A/B



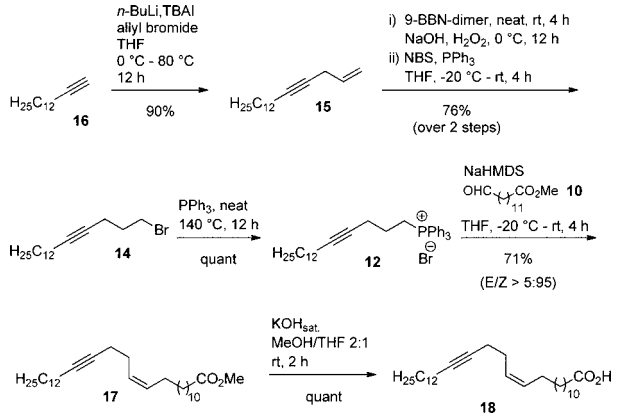
precursor via Lindlar reduction (Scheme 2). The butenolide would be introduced using a recently reported Fries rearrangement[16] which would, in turn, require a late stage deoxygenation. For assembly of the unsaturated long chain fatty acid **7**,[17] a *Z*-selective Wittig reaction or a related olefination reaction was chosen. The aldehyde component **10**, for this coupling, would be available from erucic acid (**11**) using a procedure of Ducho et al.[18] The required phosphonium salt **12** was considered accessible from the corresponding bromide **14**. This halide can easily be traced back to alcohol **13** which should be accessible from the corresponding alkene **15**. The skipped 1,4-enyne **15** was expected to be available from commercial 1-tetradecyne (**16**).

Scheme 2. Retrosynthetic Analysis of Muricadienin



In accord with the retrosynthetic strategy outlined in Scheme 2, our synthesis started from commercially available 1-tetradecyne (**16**). Its terminal deprotonation and capture by allyl bromide gave deconjugated enyne **15** in 90% yield (Scheme 3). Subsequent chemoselective hydroboration[19] of the terminal alkene using 9-BBN followed by bromination[20] of the resulting alcohol using NBS and PPh_3 gave bromide **14** in 76% yield over two steps. Hydroboration under standard conditions (stock solution in THF, 0.5 M) gave high yields on a small scale (up to 5 mmol) but was not scalable. It turned out that the use of freshly prepared 9-BBN-dimer[21] in the absence of any solvent proved necessary to achieve reproducible results and high yields on a preparative scale. The same was true for the ensuing formation of the phosphonium salt **12**. Thus, treatment of the bromide **14** with PPh_3 under neat conditions provided the desired product in quantitative yield. *Z*-selective Wittig olefination under lithium-free reaction conditions[22] using NaHMDS delivered the corresponding 1,5-enyne **17**[17] in 71% yield with a *Z*/*E* ratio of >95:5, determined by NMR.

Scheme 3. Muricadienin Synthesis: Chemoselective Hydroboration and *Z*-Selective Wittig Reaction



Coupling partner aldehyde **10** was synthesized in four steps in a sequence including epoxidation, epoxide hydrolysis, esterification, and periodate mediated glycol cleavage starting from commercially available erucic acid (**11**).[18] The synthesis of muricadienin continued with the saponification of methyl ester **17** using potassium hydroxide in MeOH/THF (2:1) to give the unsaturated long chain fatty acid **18** in quantitative yield.

Introduction of the butenolide was realized following a recently reported DMAP-mediated Fries rearrangement[16]

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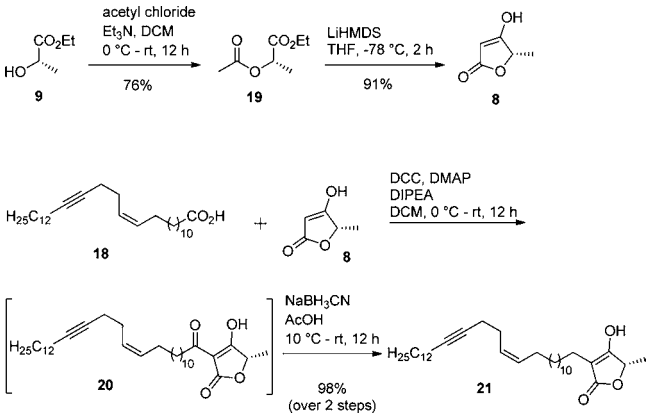
(Scheme 4). The required cyclic β-keto ester **8** was prepared in a straightforward two-step procedure similar to known

Scheme 4. Fries Rearrangement: Introduction of the Terminal α-Substituted Butenolide

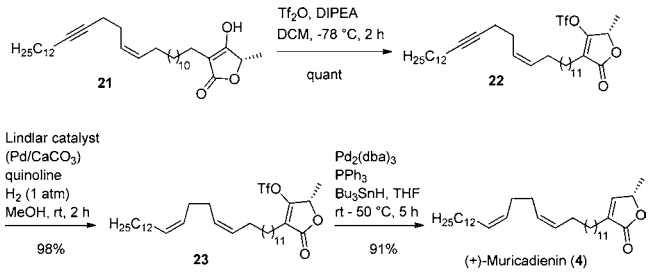


protocols.[23] Thus, acetylation of commercially available (*S*)-ethyl lactate (**9**) followed by Dieckmann condensation provided butenolide **8** in good overall yield (Scheme 4).[23]

Subsequent *O*-acylation with fatty acid **18** was followed by the *in situ* Fries rearrangement triggered by DMAP. The resulting tricarbonyl intermediate **20** was then directly reduced with $NaBH_3CN$ in acetic acid to afford α-alkylated butenolide **21** in an excellent yield of 98% over three chemical transformations.[16]

The final steps of the synthesis were deoxygenation at C3 of the butenolide and partial reduction of the alkyne (cf. Scheme 2). Activation of the enol with triflic anhydride delivered the butenolide triflate **22** in quantitative yield (Scheme 5). Best

Scheme 5. Muricadienin Synthesis: Completion of the Total Synthesis



results for the last two steps of the synthesis were obtained when the subsequent reduction of the vinyl sulfonate was carried out after the partial hydrogenation of the triple bond. Thus, formation of the *Z*,*Z*-1,5-diene unit was accomplished via a stereoselective Lindlar reduction; the product was isolated in almost quantitative yield. Pd-catalyzed reduction[24] of the enol triflate **23** with Bu_3SnH in THF at 50 °C concluded the total synthesis and furnished (+)-muricadienin (**4**) in 91% yield.

In summary, we have presented the first total synthesis of (+)-muricadienin (**4**), the putative key intermediate in the biosynthesis of *cis*- and *trans*-solamin. Starting from commercially available 1-tetradecyne (**16**) the natural product was prepared in 11 steps and an overall yield of 42%. Key steps in our synthesis were a chemoselective hydroboration, a *Z*-selective Wittig reaction, and a DMAP-mediated Fries rearrangement. Thus, sufficient material for investigations into the crucial stages of annonaceous acetogenin biosynthesis can be provided. In addition, it is worth noting that our synthetic strategy is designed such that any other double bond stereoisomer and any combinations thereof will be accessible.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures, spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) The use of poly(methylhydrosiloxane) (PMHS) as a reducing agent with $Pd(OAc)_2$/dppp in DMF at 60 °C allowed the isolation of **4** in merely 33% yield with incomplete conversion. In addition, we were not able to isolate the desired product in pure form (PMHS residuals in the isolated product). Treatment with formic acid under transfer hydrogenation conditions ($Pd(OAc)_2$, PPh_3, Bu_3N) showed no effective product formation (only traces of **4** detectable by TLC).