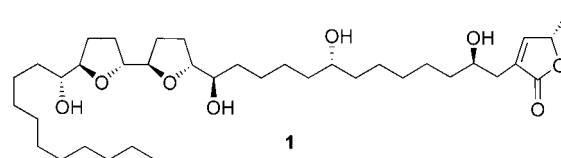


The Total Synthesis of the Annonaceous Acetogenin 10-Hydroxyasimicin**

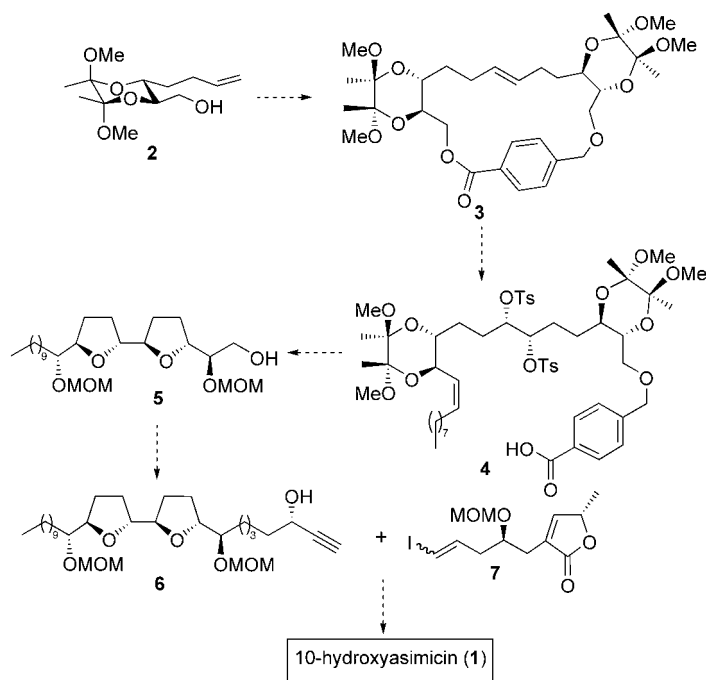
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The annonaceous acetogenins comprise a class of almost 400 natural products that exhibit a remarkably broad spectrum of biological activity. They function as insecticides, fungicides, herbicides, and, perhaps most importantly, in vivo antitumor agents and have been shown to overcome resistance in multidrug-resistant tumors.^[1] Structurally, the acetogenins are characterized by a long lipophilic tail, a central polyoxygenated core, and a terminal α,β -unsaturated γ -lactone. The structural diversity in this family arises principally from variations in the stereochemistry and connectivity of the polyoxygenated central core, which can consist of one or more tetrahydrofuran (THF) rings or, occasionally, a tetrahydropyran (THP) ring with various patterns of hydroxylation. These variations and the stereochemical consequences give rise to an impressive molecular diversity within the family. Owing to their biological activity and limited availability from natural sources, these compounds have attracted worldwide attention and have become the targets for total synthesis for a number of research groups,^[2–9] including our own.^[10] The majority of publications to date have focused on the synthesis of individual members of the family that suit a particular reaction type or stereochemical outcome. Motivated by the bioactivity of the annonaceous acetogenins, we embarked on a project to develop a more general route that utilizes an orthogonal and modular templating approach to provide access to many members in the series. Herein we describe the first successful synthesis of 10-hydroxyasimicin (**1**),^[11] which contains a bis-THF motif in the central core.

The crucial component in the synthesis of any of these natural products is the stereoselective preparation of the polyoxygenated central fragment. 10-Hydroxyasimicin bears adjacent bis-THF rings flanked by two hydroxy groups with a *threo,trans,threo,trans,threo* stereochemistry. Our synthetic strategy to this oxygenated arrangements (Scheme 1) hinged upon the design of a



tether that could temporarily link two BDA-protected alkenol building blocks **2** (BDA = 2,3-butanediol acetal) of, in principle, any desired stereochemical arrangement.^[12] The tether could then induce stereocontrol during the critical ring-closing metathesis (RCM) to give compound **3**.^[13] Subsequent Sharpless asymmetric dihydroxylation and chemoselective cleavage of the tether would afford **4**.^[14] Intramolecular displacement by the unmasked hydroxy groups of the desymmetrized bistosylate **4** would yield the bis-THF unit **5**. Late-stage Sonogashira coupling of the terminal alkyne **6** and the butenolide **7** (constructed through a hetero-Diels–Alder (HDA) reaction to install the 1,5-stereochemical relationship and mask the butenolide double bond simultaneously, as reported in our synthesis of muricatetrocin C)^[10] would



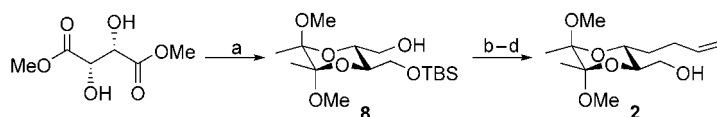
Scheme 1. Proposed synthetic route to 10-hydroxyasimicin (**1**). Ts = *p*-toluenesulfonyl, MOM = methoxymethyl.

complete the carbon skeleton. Finally, selective hydrogenation and global deprotection would furnish the natural product **1** (Scheme 1).

Synthesis of fragment **2** began from (*S,S*)-dimethyl-D-tartrate, which was readily converted into the monoprotected diol **8** in three steps according to a previously established procedure (Scheme 2).^[12] Subsequent tosylation of **8** and treatment of the corresponding tosyl derivative with allylmagnesium bromide in the presence of CuBr afforded **2** in multigram quantities after deprotection with TBAF.

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Scheme 2. Synthesis of alkenol **2**. a) Reference [12]; b) NEt_3 , TsCl , DMAP, CH_2Cl_2 , 1.5 h, room temperature, 99%; c) allylMgBr , CuBr , Et_2O , 8 h, 0°C , 84%; d) TBAF, THF, 5 h, 0°C , 100%. DMAP = 4-(dimethylamino)pyridine, TBAF = tetrabutylammonium fluoride.

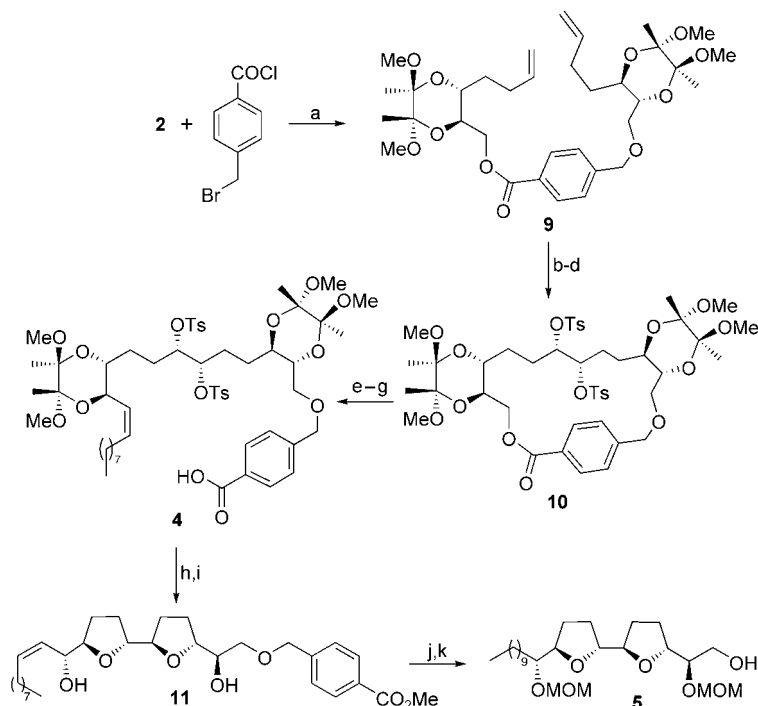
The next step in the synthesis involved the development of a suitable template to link the two alkenol molecules together in order to proceed with an intramolecular metathesis reaction. As mentioned earlier, we required a tethering unit that could adjust the conformation of the macrocycle to control the stereoselectivity during the RCM reaction.^[13] The chosen tethering template should behave as a “molecular workbench” and help orientate the olefin so that one face is preferentially available for attack during a *syn*-stereoselective dihydroxylation reaction.^[14] Furthermore, the tether would play the role of a protecting group upon cleavage of the macrocycle to enable desymmetrization of the core. Hence the unit had to be dissymmetric to allow orthogonal cleavage upon completion of the dihydroxylation. On top of this, a dissymmetric tethering unit would enable us to attach different BDA-protected alkenol units sequentially to produce acetogenins with alternative stereochemistries at the core.^[15] To put these concepts into effect, a differentiated arene with orthogonal substituents was chosen, as we could fine-tune the macrocycle ring size simply by varying the substitution pattern of the aryl system. 4-Bromomethylbenzoyl chloride was found to give the best results and was used in all subsequent investigations.^[16]

Coupling of alkenol **2** with 4-bromomethylbenzoyl chloride in the presence of KHMDS gave the doubly loaded *para*-linked diene **9** in 69% yield. Subsequent treatment of **9** with a second-generation Grubbs catalyst^[17] in dichloromethane at reflux delivered the intramolecular metathesis product in excellent yield, exclusively as the *E* adduct. Sharpless asymmetric dihydroxylation of the olefin with AD-mix- α afforded the diol in a diastereomeric ratio of 16:1 favoring the desired *S,S* product (Scheme 3).^[18] Treatment of the diol with TsCl in pyridine afforded the ditosylated compound **10** in 90% yield.

The macrocycle was opened by treatment of **10** with sodium methoxide in methanol at room temperature to afford the primary alcohol.^[19] Swern oxidation and a subsequent Wittig reaction installed the nine-membered carbon side-chain terminus as the *Z* olefin **4**. Removal of the BDA groups followed by an intramolecular Williamson cyclization with potassium carbonate as the base led to the formation of the bis-THF core **11** in 80% yield over the two steps. Finally, protection of the free secondary alcohols with MOMCl, followed by parallel reduction of the double bond and debenzoylation under transfer-hydrogenation conditions completed the synthesis of fragment **5** (Scheme 3).

Fragment **5** was further elaborated by Dess–Martin oxidation, followed by Horner–Wadsworth–Emmons olefina-

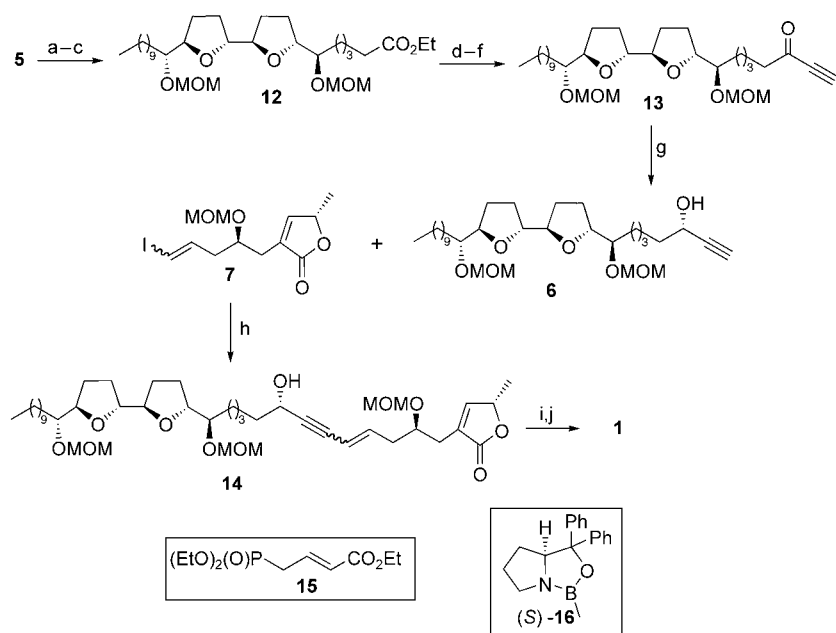
tion with phosphonate **15**, which afforded an *E,E* diene exclusively.^[20] Exhaustive reduction of the *E,E* diene with the Pearlman catalyst then afforded saturated ester **12** in 94% yield (Scheme 4). To generate the last stereocenter, further chain extension to propargylic ketone **13** was required. To this end ketone **13** was obtained by conversion of the saturated ester into the Weinreb amide,^[21] which was then



Scheme 3. Synthesis of bis-THF framework **5**. a) KHMDS, THF, 5 h, $-78 \rightarrow 0^\circ\text{C}$, 69%; b) second-generation Grubbs catalyst, CH_2Cl_2 , 1 h, reflux, 99%; c) AD-mix- α , MeSO_2NH_2 , NaHCO_3 , $t\text{BuOH}/\text{H}_2\text{O}$ (1/1), 96 h, $0^\circ\text{C} \rightarrow \text{RT}$, 96% (*S,S/R,R* 16:1); d) TsCl , pyridine, 20 h, $0^\circ\text{C} \rightarrow \text{RT}$, 90%; e) NaOMe , MeOH , 44 h, room temperature, 93%; f) DMSO , $(\text{COCl})_2$, CH_2Cl_2 , -78°C ; NEt_3 , $-78^\circ\text{C} \rightarrow \text{RT}$, 98%; g) $\text{CH}_3(\text{CH}_2)_8\text{PPh}_3\text{Br}$, $n\text{BuLi}$, THF, 7 h, $-78 \rightarrow 0^\circ\text{C}$, 69%; h) TFA/ H_2O (2:1), 5 min (repeat twice), room temperature; i) K_2CO_3 , MeOH , 3.5 h, reflux, 80% over two steps; j) MOMCl, Hünig base, DMAP, CH_2Cl_2 , 18 h, $0^\circ\text{C} \rightarrow \text{RT}$, 78%; k) Pd/C , $\text{HCO}_2^-\text{NH}_4^+$, MeOH , 2 h, reflux, 79%. HMDS = hexamethyldisilazide, DMSO = dimethyl sulfoxide, TFA = trifluoroacetic acid.

treated with the lithium derivative of trimethylsilylacetylene followed by desilylation with TBAF to give **13** in 60% yield over the two steps.^[22] Diastereoselective oxazaborolidine-catalyzed (CBS)^[23] reduction gave **6** in 78% yield, with an excellent ratio favoring the desired isomer (44:1).

With the synthesis of fragment **6** completed, we now turned our attention to the synthesis of butenolide **7** in preparation for the final coupling reaction. Diene **17** was synthesized in seven steps from 1,4-butanediol according to a previously established procedure (Scheme 5).^[10] As in our synthesis of muricatetrocin **C**, the 1,5-stereochemical relationship in the butenolide moiety was installed through the HDA reaction with nitrosobenzene at 0°C which afforded an inseparable 7:3 mixture of regioisomers favoring the desired adduct **18**.^[24] The N–O bond was cleaved by using freshly



Scheme 4. Synthesis of 10-hydroxyasimicin (**1**). a) DMP, NaHCO₃, CH₂Cl₂, 1 h, 0°C→RT, 95%; b) **15**, NaHMDS, THF, 18 h, −78°C→RT, 81%; c) Pd(OH)₂/C, H₂, THF, 1 h, room temperature, 94%; d) Me(MeO)NH·HCl, iPrMgCl, THF, 1.5 h, −10°C, 82%; e) trimethylsilylacetylene, *n*BuLi, THF, 1 h, −78→0°C; f) TBAF, THF, 20 min, −20°C, 60% over two steps; g) (*S*)-**16**, BH₃·Me₂S, THF, 1 h, −35°C, 78% (*S*/*R* 44:1); h) [Pd(PPh₃)₂Cl₂], CuI, NEt₃, 45 min, room temperature, 86%; i) [Rh(PPh₃)₃Cl], H₂, benzene/EtOH (1:1), 23 h, room temperature, 74%; j) BF₃·OEt₂, Me₂S, 20 min, room temperature, 68%. DMP = Dess–Martin periodinane.

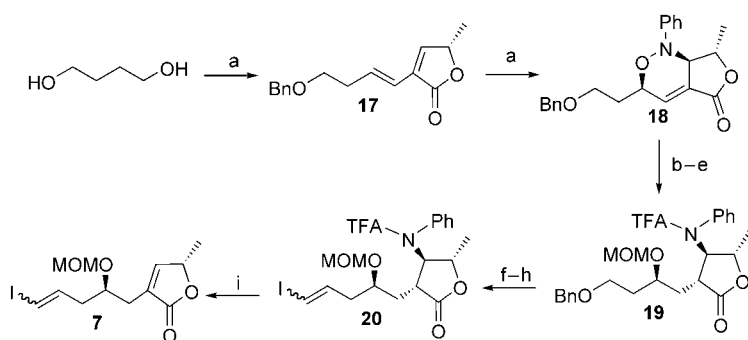
prepared [Mo(CO)₃(MeCN)₃] in the presence of water at room temperature.^[25] Protection of the resultant secondary hydroxy group as a MOM ether enabled the separation of the regio- and stereoisomers through flash-column chromatography, thus avoiding the need for the laborious preparative HPLC separation required in the previous synthesis of muricatetrocin C. Subsequent hydrogenation over catalytic palladium and protection of the amine as the trifluoroacetamide afforded compound **19**. Debenzylation with the Pearl-

man catalyst afforded the free alcohol. Oxidation of the released primary alcohol with TPAP,^[26] followed by one-carbon homologation, according to the Takai procedure,^[27] provided the vinyl iodide **20** as a mixture of isomers (3.7:1 ratio favoring the *E* geometry) in 59% yield over two steps. Subsequent elimination of the trifluoroacetamide group in the presence of DBU in acetonitrile at 0°C afforded fragment **7** without epimerization of the butenolide methyl substituent (Scheme 5).

Sonogashira cross-coupling of vinyl iodide **7** with the propargylic alcohol **6** proceeded smoothly to produce the skeleton **14** in 86% yield (Scheme 4).^[28] The enyne functional group was reduced selectively over the butenolide double bond by using the Wilkinson catalyst to afford the protected acetogenin in 74% yield. Final global deprotection with BF₃·Et₂O in methyl sulfide afforded **1** as a colorless wax in 68% yield. The spectroscopic data for synthetic **1** (¹H NMR, ¹³C NMR, IR, MS, and specific rotation)^[29] were in excellent agreement with those reported for naturally occurring 10-hydroxyasimicin (**1**).^[11]

In conclusion, the successful synthesis of 10-hydroxyasimicin (**1**) demonstrates the potential of the template approach to the oxygenated core of the acetogenins in an efficient and easily adapted manner. This route provides an efficient method for the construction of the bis-THF moiety incorporat-

ing a tether that enhances the stereochemical outcome of the RCM step and enables desymmetrization of the central fragment for further chain extension. The TBS-protected diol building block **8**, arising from (*R,R,S,S*)-2,3-BDA-protected (*S,S*)-dimethyl-D-tartrate, and the highly diastereoselective HDA approach to the butenolide unit are usefully employed in this new synthesis of an acetogenin natural product. Further applications of these general approaches will be employed in the preparation of other members of the acetogenin series in due course.



Scheme 5. Synthesis of butenolide **7**. a) Reference [10]; b) [Mo(CO)₆], MeCN, 4 h, reflux; then **18**, H₂O, 15 min, room temperature; c) MOMCl, Hünig base, DMAP, CH₂Cl₂, 16 h, 0°C→RT, 20% over three steps, including HDA; d) Pd/C, H₂, THF, 2 h, room temperature, 100%; e) TFAA, Hünig base, CH₂Cl₂, 30 min, 0°C, 74%; f) Pd(OH)₂/C, H₂, MeOH, 30 min, room temperature, 99%; g) TPAP, NMO, NEt₃, CH₂Cl₂, 2 h, room temperature, 84%; h) CrCl₂, CHCl₃, THF, 17 h, 0°C→RT, 70% (*E*/*Z* 3.7:1); i) DBU, CH₃CN, 6 h, −15→−5°C (60%). TFAA = trifluoroacetic anhydride, TPAP = tetrapropylammonium perruthenate, DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene.

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- [29] Spectroscopic data for synthetic **1**, a colorless wax: $[\alpha]_{\text{D}}^{25} = +16$ ($c = 0.25$ in CHCl_3 , lit. [11] $[\alpha]_{\text{D}}^{22} = +17.3$ in CHCl_3); ^1H NMR (400 MHz; CDCl_3): $\delta = 7.18$ (d, $J = 1.3$ Hz, 1 H; 35-H), 5.05 (qd, $J = 6.8, 1.4$ Hz, 1 H; 36-H), 3.86 (m, 5 H; 16-H, 19-H, 20-H, 23-H), 3.60 (m, 1 H; 10-H), 3.41–3.38 (m, 2 H; 15-H, 24-H), 2.53 (dddd, $J = 15.2, 3.2, 1.5, 1.5$ Hz, 1 H; 3a-H), 2.40 (dddd, $J = 15.1, 8.3, 1.2, 1.2$ Hz, 1 H; H-3b), 1.97 (m, 8 H; 17-H, 18-H, 21-H, 22-H), 1.70–1.26 (m, 36 H; 5–9-H, 1–14-H, 25–33-H), 1.43 (d, $J = 6.7$ Hz, 3 H; 37-H), 0.88 ppm (t, $J = 6.7$ Hz, 3 H; 34-H); ^{13}C NMR (125 MHz; CDCl_3): $\delta = 174.6$ (C1), 151.8 (C35), 131.2 (C2), 83.2, 83.1 (C16, C23), 81.81, 81.75 (C19, C20), 78.0 (C36), 74.1, 74.0 (C15, C24), 71.7 (C10), 69.9 (C4), 37.34 (C5), 37.3 (C11), 37.2 (C9), 33.41, 33.36, 33.32 (C3, C14, C25), 31.9 (C32), 29.71, 29.61, 29.60, 29.59, 29.47, 29.32 (C6–C8, C12, C13, C26–C31), 29.0 (C21, C18), 28.3 (C17, C22), 25.64, 25.62, 25.5 (C6–C8, C12, C13, C26–C31), 22.7 (C33), 19.1 (C37), 14.1 ppm (C34); IR (thin film): $\tilde{\nu}_{\text{max}} = 3404$ br (OH), 2924, 2853 (CH), 1753 (C=O) cm^{-1} ; HRMS: calcd for $\text{C}_{37}\text{H}_{66}\text{O}_8\text{Na}$ $[M+\text{Na}]^+$: 661.4650; found: 661.4651.