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# Modular Approach to Annonaceous Acetogenins. Total Synthesis of Asimicin and Bullatacin.

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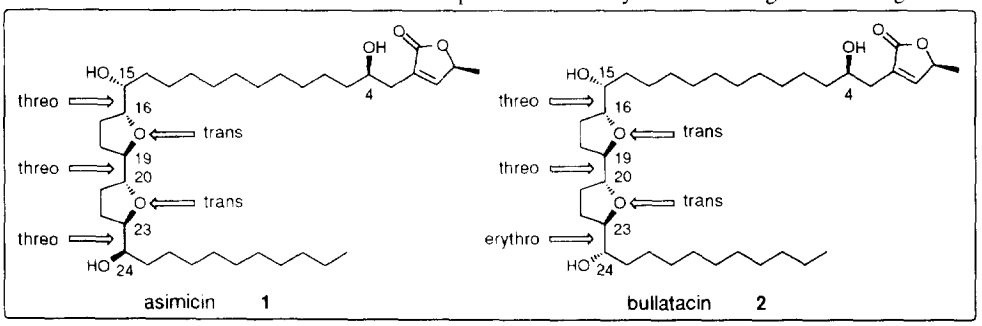
**Abstract**: Starting with a variety of non-functionalized carbon skeletons and employing various combinations of five key transformations provides an easy access to most of the naturally occurring Annonaceous acetogenins. A particular emphasis is given to the dominant structural feature that appears in more than 40% of the known acetogenins. This is a linear, ten-carbon skeleton comprising two adjacent tetrahydrofurane rings flanked with two hydroxyl groups. Efficient, flexible syntheses of asimicin and bullatacin demonstrate this approach.

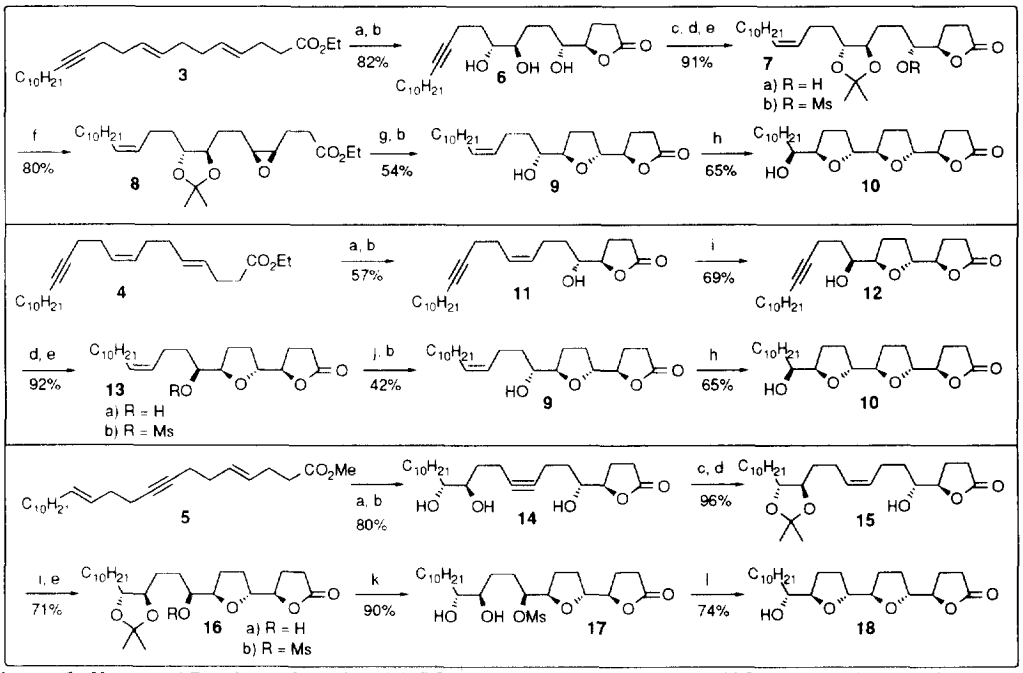
Many members of the rapidly growing family of the Annonaceous acetogenins have shown cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal and antifeedant activities.[1] While most of these fatty acid derivatives exhibit remarkable structural diversity, they share very similar carbon skeletons, with the main variations being the relative and absolute configuration of the various stereogenic oxygen functions. Interestingly, the approximately 130 acetogenins discovered over the past 13 years were isolated from less than 20 plants out of an estimated number of 2300 Annonaceae species. Considering these numbers along with the fact that the absolute configuration of most of the reported compounds is still unknown, one may conclude that it will take a while before the entire naturally occurring repertoire of these biologically important compounds will be discovered and fully characterized. Therefore, there is an urgent need for a massive synthetic effort that will produce combinatorial chemical libraries of such compounds to allow systematic biological screenings.




In this work we show a way to meet this challenge by designing a modular synthetic approach, focusing on the most common structural feature that appears in more than 40% of the known acetogenins, and in the most potent antitumor ones in particular. This is a linear, ten-carbon skeleton comprising two adjacent tetrahydrofurane

rings flanked with two hydroxyl groups as shown in the structures of asimicin, **1**[2] and bullatacin, **2**.[3] With six stereogenic carbinol centers, this unit alone can have as many as 64 different stereoisomers, several of which have already been identified in naturally occurring acetogenins.[1]

Our general synthetic strategy to the bis-THF Annonaceous acetogenins is based on selective placement of the oxygen functions onto a naked, unsaturated carbon skeleton.[4,5,6] Thus, for the synthesis of the above mentioned ten-carbon unit (Scheme 1) we start with a variety of non-functionalized skeletons, **3-5**,[7] and apply various combinations of five key transformations; A) the Sharpless asymmetric dihydroxylation (AD) reaction,[8] B) the Kennedy oxidative cyclization with rhenium oxide,[9] C) alcohol epimerization,[10] D) nucleophilic ring closure onto an activated oxygen function (e.g. mesylate or epoxide), and E) partial hydrogenation of alkynes to cis-alkenes. The diversity of this approach stems from the flexible choice of the appropriate starting skeleton and the variable outline of reaction sequences. Since the AD reaction represents the only origin of asymmetry in the synthesis we usually employ it as the first transformation. The relative stereochemistry of all stereogenic centers is determined by the relative timing of the other four reactions.

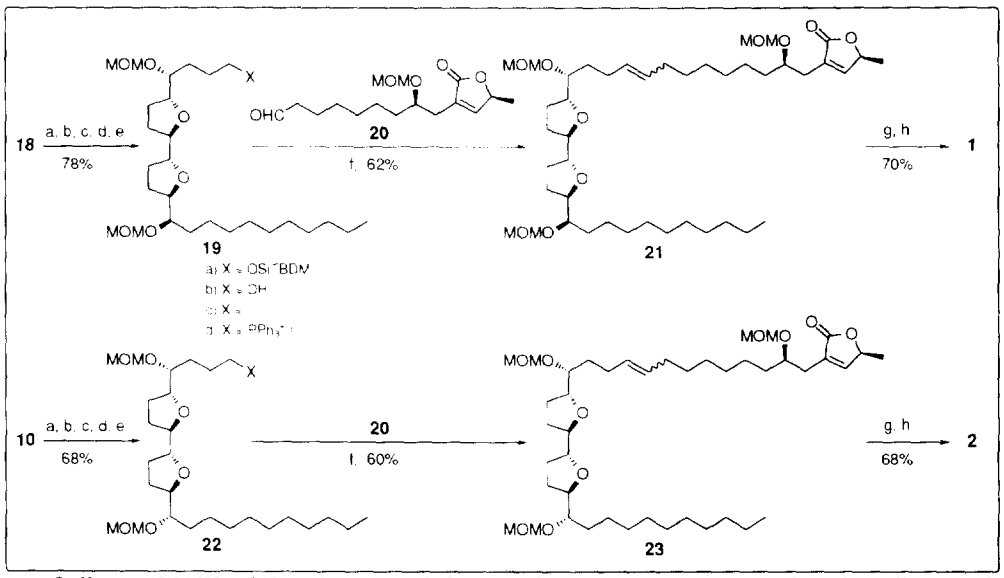


**Scheme 1**. Key: a) AD-mix-β (2 equiv), $MeSO_2NH_2$, butanol:water (1:1), 0°C, 16 h. b) i. aq. KOH then 3N HCl; ii. TsOH (5%), $CH_2Cl_2$, 0.5 h. c) Dimethoxypropane, acetone, TsOH (cat.), 0°C to 25°C, 0.5 h. d) 5% Pd/$CaCO_3$/lead (10%, w/w), hexane/cyclohexene/$Et_3N$ (2:2:1) -10°C, 12 h. e) MsCl (1.5 equiv), $Et_3N$ (2 equiv), $CH_2Cl_2$, 0°C, 1h. f) $K_2CO_3$ (2 equiv), MeOH, 25°C, 0.5h. g) $BF_3.Et_2O$ (1 equiv), $CH_2Cl_2$, -78°C. h) $Re_2O_7$ (3 equiv), $H_5IO_6$, $CH_2Cl_2$, 1h. i) $Re_2O_7$ (3 equiv), lutidine (4 equiv), $CH_2Cl_2$, 2h. j) Cesium propionate (5 equiv), DMF, 100°C, 18 h. k) TsOH (20% w/w), MeOH/$H_2O$ (4:1), 60°C, 16h. l) pyridine, 100°C, 2h.

This modular approach is exemplified here by a fast and variable synthesis of **1** and **2**.[11,12] Thus, starting with carbon skeleton **3** and applying the reaction sequence: A-E-D-B (Scheme 1) produces **10**, a key intermediate

in the synthesis of **1**. Alternatively, intermediate **10** is obtained from skeleton **4** using a different sequence: A-B-E-C-B. The epimeric building block **18** is obtained from skeleton **5** using another sequence of the same basic transformations: A-E-B-D. This approach represents a third synthesis of **10** because **18** can be converted to **10** by the Mitsunobu reaction.

Several elements in the design and execution of the synthetic sequences are noteworthy. 1) The significantly higher reactivity of AD reagents toward E alkenes relative to Z alkenes enables selective dihydroxylation of the former in the presence of the latter.[6,7] 2) Because of the relatively low reactivity of alkynes under conditions of olefin oxidation with either osmium or rhenium, the C-C triple bond may be considered as a protected Z-olefin that can be easily "deprotected" via partial hydrogenation over Lindlar catalyst. 3) Positioning of an ester function at the vicinity of a double bond undergoing AD reaction allows regioselective differentiation of the two resultant hydroxyl groups via formation of a stable lactone.[5,6,13] 4) Ring closure with overall inversion of the configuration at carbon can be done simply via activation of a hydroxyl group, e.g. by mesylation, followed by intramolecular substitution by oxygen, as exemplified by the sequence going from alcohol **16** to mesylate **17** and THF derivative **18**. Alternatively, with the help of an adjacent hydroxyl group, the same ring closure can be performed with overall retention of the configuration at carbon.[5] This is done, for example, by converting mesylate **7** to epoxide **8** followed by ring closure to give the THF derivative **9**. 5) Inversion of a carbinol configuration provides a pair of epimeric intermediates. This represents a useful branching point in synthetic schemes that start with few starting skeletons and lead to diverse chemical libraries.




**Scheme 2**. Key: a) $LiAlH_4$ (2.5 equiv), ether, 0°C then reflux 2 h. b) TBDMSCl (1.2 equiv), diisopropylethyl amine (1.5 equiv), DMAP (0.05 equiv), $CH_2Cl_2$, 0°C - rt, 12 h, then chloromethyl methyl ether (1.5 equiv) and diisopropylethyl amine (2 equiv), 0°C - rt, 12 h. c) TBAF (1 equiv), THF, 0°C - rt, 1 h. d) $I_2$ (1.1 equiv), $PPh_3$ (1.3 equiv), imidazole (1.2 equiv), $CH_2Cl_2$, rt, 0.5 h. e) $PPh_3$ (2 equiv), $NaHCO_3$ (2 equiv), $CH_3CN$, reflux, 16 h. f) *n*-BuLi (1 equiv), THF, -20°C, then aldehyde **20** (1 equiv), 0.5 h. g) $Rh(PPh_3)_3Cl$ (10%, w/w) benzene, EtOH, $H_2$, rt, 2 h. h) $BF_3$-$Et_2O$ (5 equiv), $Me_2S$ (5 equiv), $CH_2Cl_2$, 0°C - rt, 0.5 h.

With the structurally dominant part of **1** and **2** in hand we completed the synthesis of these two acetogenins by attachment of the appropriate butenolide fragment to either **10** or **18** (Scheme 2). Thus, $LiAlH_4$ reduction of **18** produced the corresponding triol in which the primary alcohol and the two secondary alcohols were protected as *t*-butyldimethylsilyl ether and methoxymethyl ethers, respectively, affording **19a**. The primary alcohol was then deprotected with tetrabutylammonium fluoride, converted to iodide **19c** and then to the corresponding Wittig reagent. The latter was reacted with aldehyde **20**[7] to produce alkene **21**. Finally, homogeneous hydrogenation over Wilkinson's catalyst followed by acidic cleavage of the MOM ethers produced asimicin, **1**. Starting with **10** and following the same sequence afforded bullatacin, **2**.

In conclusion, the modular synthetic approach presented here provides an easy access to most of the naturally occurring Annonaceous acetogenins as well as to many of the non-natural ones. To date, only few stereoisomers of the key, ten-carbon fragment have been identified in the naturally occurring compounds.[1,3c] This includes cases where the absolute configuration is known, e.g. asimicin, bullatacin, bullatacinone, uvaricin, trilobacin, rolliniastatin I, and several others where only the relative stereochemistry has been reported, e.g. molvizarin, membranacin, etc. We are currently focusing on the synthesis of a complete library containing all 64 stereoisomers of **1** and **2** to allow their systematic screening for antitumor, antimalarial, immunosuppressive and pesticidal activity.

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