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Total Synthesis of the Potent Antitumor, bis-Tetrahydrofuranyl Annonaceous Acetogenins (+)-Asimicin and (+)-Bullatacin

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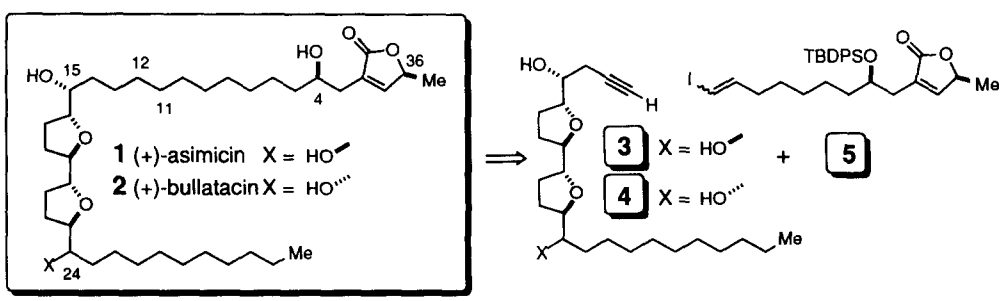
Abstract: *Convergent syntheses of the title compounds involve: a bis-THF-subunit preparation via Sharpless' double asymmetric dihydroxylation and subsequent asymmetric epoxidation; preparation of the C(4)-hydroxybutenolide-containing subunit using a Stille butenolide synthesis; Pd°-mediated coupling of these vinyl iodide and alkyne subunits; and selective Wilkinson reduction of the resulting enyne.*

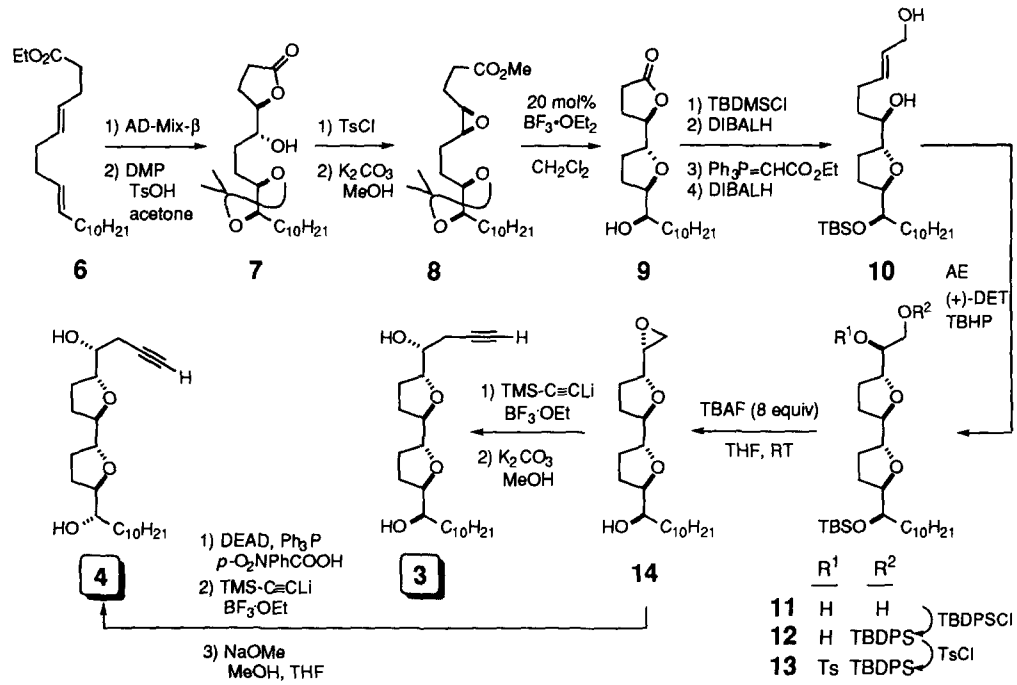
(+)-Asimicin (**1**) and (+)-bullatacin (**2**)—bis-tetrahydrofuranyl, 4-hydroxylated, Annonaceous acetogenins—represent two of the structurally most complex and biologically potent members of this abundant family of antitumor and pesticidal natural products.[2] (+)-Bullatacin possesses remarkable levels both of cytotoxicity against many human tumor cell lines, a feature shared by a number of the 4-hydroxylated acetogenins,[2b,e] and of promising *in vivo* antitumor activity.[3a] (+)-Bullatacin[3a-c] and (+)-asimicin[3d] interfere with mitochondrial electron transport processes by interaction with complex I.

The relative configurations within the bis-THF portions of asimicin[4] and bullatacin[5] were deduced[6] by application of the ^{1}H NMR chemical shift correlation method developed for uvaricin,[6b] the first Annonaceous acetogenin. Details of the entire relative and absolute stereostructure of (+)-asimicin (**1**) and (+)-bullatacin (**2**) were unraveled only recently following extensive analysis of Mosher esters of the natural products.[7] While three syntheses of bis-THF Annonaceous acetogenins or their stereoisomers have been described,[8] the majority of efforts to date have focused on the simpler mono-THF acetogenin targets.[9] Only two of the previously synthesized molecules have contained the C(4)-hydroxyl group[8b,c]—a structural feature that considerably increases the difficulty of the task. The syntheses described here of the subunits **3** (or **4**) and **5** are considerably more efficient than those previously reported.



Preparation of the bis-THF-containing building blocks **3** and **4** is outlined in Scheme 1. In the early stage it follows the elegant strategy of Keinan[9d] who constructed the two carbon longer homolog of lactone **9**. Thus, double asymmetric dihydroxylation[9d,10] of the *E*, *E*-diene **6** (made by the doubly iterative Claisen/Johnson rearrangement of undecanal) provided a crystalline triol lactone that was protected as the acetonide **7** (72%). Tosylation and methanolysis gave epoxide **8** (91%), which underwent Lewis acid catalyzed cyclization to lactone **9** (63%) following hydrolytic workup. Protection of the hydroxyl group as its *t*-butyldimethylsilyl (TBS) ether and standard processing of the lactone gave the chain-extended allylic alcohol **10** (66%). This diol was a suitable substrate for Sharpless asymmetric epoxidation provided that a relatively large amount (50 mol%) of Ti(IV) catalyst was used. The intermediate epoxide spontaneously cyclized to the bis-THF diol **11** (87%, based upon recovered starting material at ~50% conversion). Selective silylation of the primary alcohol as its *t*-butyldiphenylsilyl (TBDPS) ether and tosylation of the lone hydroxyl group in **12** (86%) gave **13** (98%). Desilylation of **13** with excess TBAF (the TBDPS was removed faster than the TBS ether!) cleanly gave the cyclized epoxy alcohol **14** (88%).

Scheme 1

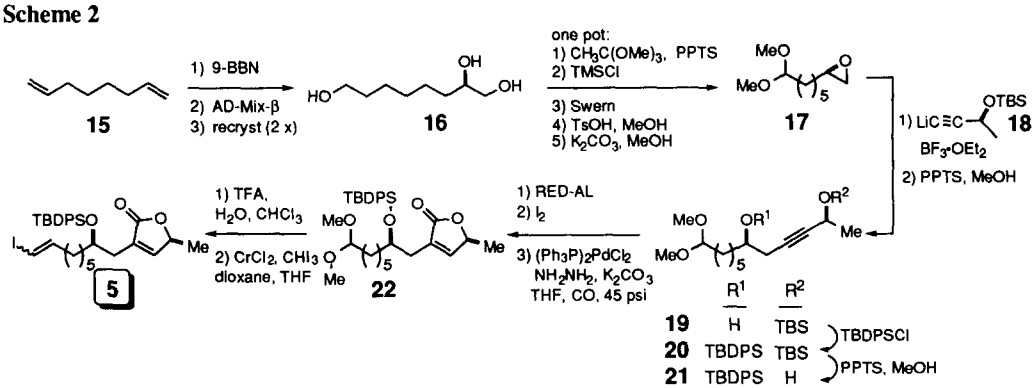


Intermediate **14** contains the same configuration at all stereogenic centers as (+)-asimicin (**1**); the configuration at [C(24)] is opposite to that required for (+)-bullatacin (**2**); **14** represents the point of divergence for preparation of subunits **3** and **4**. The epoxide in **14** was smoothly opened with TMS-C≡C-Li (2.8 equiv) in the presence of BF_3•OEt_2[11] followed by TMS removal to provide the terminal alkyne **3** (70 %). Mitsunobu inversion of the carbinol center in **14** required the use of *p*-nitrobenzoic acid.[12] Acetylide opening of the inverted *p*-nitrobenzoate ester derivative of **14** (2.0 equiv of TMS-C≡C-Li) and methanolysis to remove both the TMS and PNB groups provided the C(24)-epimeric key intermediate **4** (34 %).

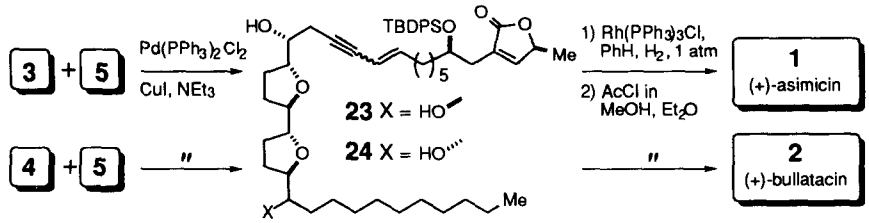
Preparation of the enantiomerically pure butenolide **5** is outlined in Scheme 2.[13] Crystalline triol **16**

was produced in ~80%ee (tris-MTPA ^{1}H NMR analysis) from 1,7-octadiene (**15**) by selective hydroboration of one olefin and asymmetric dihydroxylation[10] of the remaining alkene. Recrystallization gave material of high optical purity (tris-MTPA analysis) in 64% overall yield. In an efficient one-pot procedure[14] the triol **16** was processed into the optically pure epoxyacetal **17** (86%). Opening of this epoxide with the lithium acetylide **18**, derived from optically pure 3-butyn-2-ol,[13] followed by reprotection of a portion of liberated aldehyde gave the homopropargylic alcohol **19** (88%). Silylation of the eventual C(4) hydroxyl group and selective removal of the TBS ether in **20** produced the propargylic alcohol **21** (80%). REDAL reduction and iodine treatment gave a *Z*-vinyl iodide that was readily carbonylated under Stille conditions[15] to produce the butenolide **22** (83%). Hydrolysis of the acetal and generation of the terminal vinyl iodide[16] (~4:1 *E*:*Z* ratio) completed the preparation of subunit **5** (72%).

Scheme 2



Pd°-Catalyzed coupling of alkyne **3** (or **4**) with vinyl iodide **5** gave the enyne **23** (or **24**) in 79% (or 82%) yield. Preliminary model studies and recent precedent[17,9e] established the viability of selective reduction of a conjugated enyne in the presence of the more hindered butenolide alkene. Enyne **23** was hydrogenated with Wilkinson's catalyst in carefully deoxygenated benzene and desilylated to give (+)-asimicin (**1**, mp 68-68.5 °C, 75%). Similar treatment of **24** provided (+)-bullatacin (**2**, mp 68.5-69 °C, 74%). Each of the synthetic samples gave ^{1}H and ^{13}C NMR and HRMS spectra consistent with those from the natural material; the specific rotations for **1** and **2** were $[\alpha]_D^{RT}$ = +14.7 ° (c = 0.31, $CHCl_3$) and $[\alpha]_D^{RT}$ = +12.8 ° [c = 0.26, $CHCl_3$, lit.[5] $[\alpha]_{578}^{25}$ = +13.0 ° (c = 0.004, $CHCl_3$)], respectively. This synthesis represents the most efficient to date of the structurally complex, bis-tetrahydrofuranyl acetogenins.



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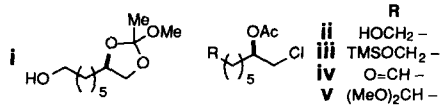
14. a) Dioxolane **i** was opened *in situ* with trimethylsilyl chloride[14b] to the chloroacetate **ii** (or the corresponding TMS ether **iii**). The volatile methanol/TMSOMe/HCl/CH_2Cl_2 mixture was replaced with pure CH_2Cl_2 and Swern oxidation provided **iv**. Volatiles were again removed and replaced with methanolic TsOH (cat.) to generate the dimethylacetal **v**, which gave epoxide **17** simply by addition of excess potassium carbonate. b) Kolb, H.; Sharpless, B. *Tetrahedron* **1992**, *48*, 10515.



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