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Synthesis of (-)-Bullatacin: The Enantiomer of a Potent, Antitumor, 4-Hydroxylated, Annonaceous Acetogenin

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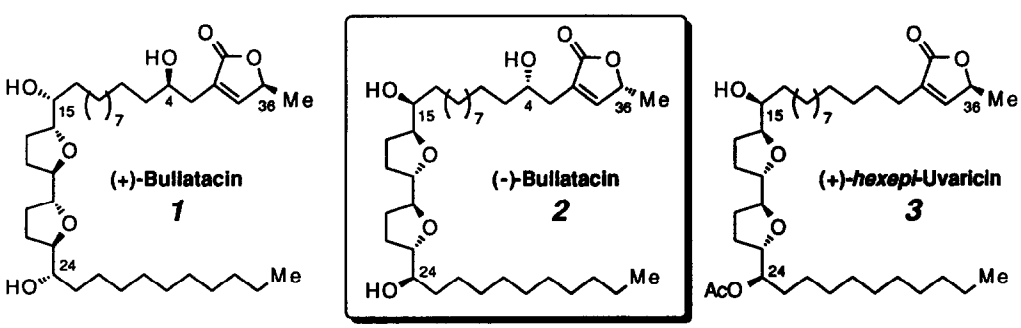
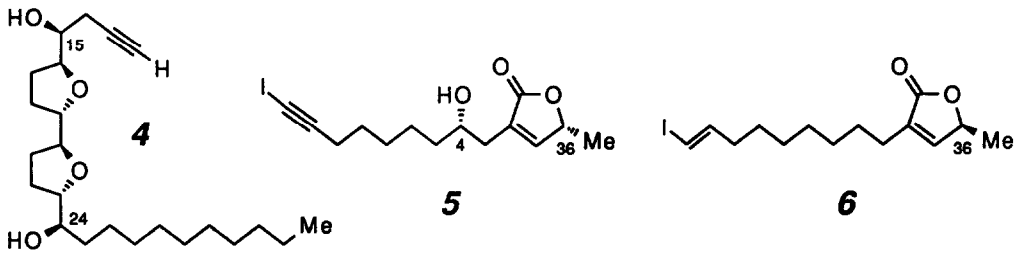
Abstract: Synthesis of the title compound represents the first construction of any of these potent, antitumor Annonaceous acetogenins with the entire relative stereochemistry in place. Palladium(0)-mediated crossed diyne coupling and the use of three, natural, α-hydroxy acids as the origin of all absolute stereochemistry highlight this flexible approach that sets the stage for access to structural analogs for further study.

(+)-Bullatacin (**1**) belongs to one of the structurally more complex subsets of Annonaceous acetogenins and is one of the most potent of these antitumor and pesticidal natural products.[2] Although the isolation and constitution were first reported in 1989,[3] details of the entire relative and absolute stereostructure of (+)-bullatacin (**1**) have been unraveled only recently.[4] (+)-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] as well as of promising *in vivo* antitumor activity.[5a] (+)-Bullatacin,[5a] (+)-annonacin,[5b] and (+)-asimicin[5c] interfere with mitochondrial electron transport processes by interaction with complex I, which is the multi-protein enzyme, NADH-ubiquinone reductase.[6] Described here is the first synthesis

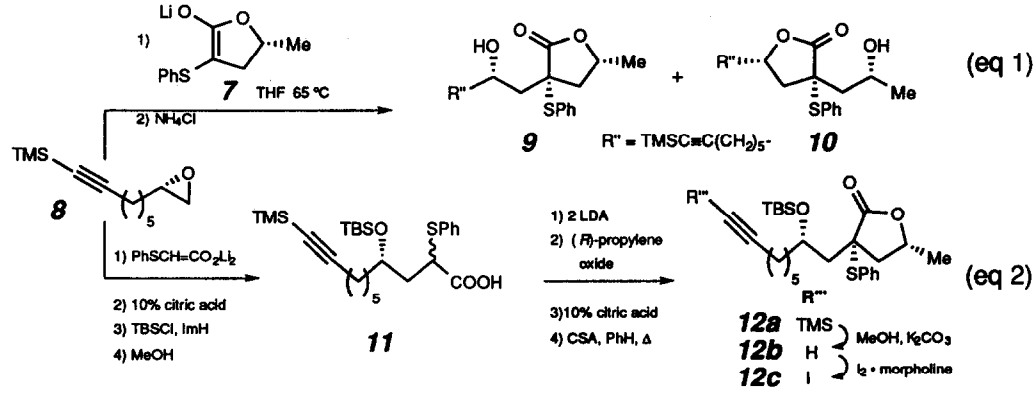


of a molecule bearing the entire relative stereochemistry of a tetrahydrofuranyl Annonaceous acetogenin.[7] (-)-Bullatacin (**2**), the enantiomer of **1**, targeted in part because of our interest in probing its bioactivity *vis-a-vis* the natural antipode,[8] was prepared by a route that provides general access to a variety of 4-hydroxylated congeners. All stereogenic centers derive from natural α-hydroxylated acids--lactic, malic, and tartaric.

By analogy with the strategy developed in our recent synthesis of (+)-15,16,19,20,23,24-*hexepi*-uvaricin (**3**),[9] we envisioned, as the cornerstone of a bullatacin synthesis, the cross-coupling of terminal alkyne **4** with an iodide like **5**. In that previous work, the bis-tetrahydrofuran alkyne **4** was prepared by the "two-tartrate" and "inside-out epoxide cascade" approach and coupled with the vinyliodide **6**.[9]

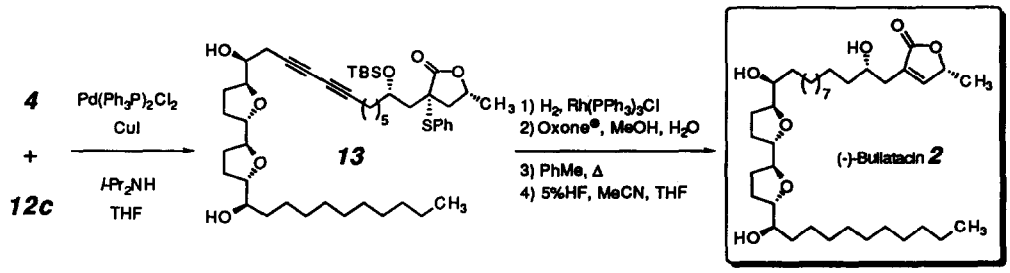


An equivalent of coupling partner **5** (eventually the 1-iodoalkyne **12c**, vide infra) was required in optically pure form. Attempts to alkylate the non-racemic enolate **7** with epoxides like **8** were complicated by translactonization which produced an ~1:2 mixture of regioisomers **9** and **10** (eq 1). Circumvention of this problem required sequential opening of the epoxides **8** and (*R*)-propylene oxide by dilithiated α-phenylthioacetic acid derivatives (eq 2). Thus, reaction



of **8**[10] with $PhSCH=CO_2Li_2$ followed by silylation of the newly created hydroxyl group produced **11** (52% from **8**). Dilithiation and treatment with (*R*)-propylene oxide followed by acid-catalyzed lactonization gave **12a**.[11] Selective removal of the TMS group liberated the terminal alkyne **12b**, which was then iodinated[12] to give **12c** (16% from **11**).

Palladium(0)-mediated coupling[13] of the alkyne **4** with iodoalkyne **12c** provided the diyne **13** in 30-45% yield. Diyne hydrogenation with Wilkinson's catalyst (75%), sulfide oxidation and elimination (70%), and TBS removal (79%) provided (-)-bullatacin (**2**). This synthetic material is identical to natural bullatacin except for its specific rotation {$[\alpha]_D^{RT}$ = -12 ° (c = 0.13, $CHCl_3$) for **2** vs. $[\alpha]_D^{RT}$ = +13.0 ° (c = 0.004, $CHCl_3$) for **1**[3a]} and the fact that the ^1H NMR spectrum of the tris-(*R*)-Mosher derivative of **2** is identical to the analogous tris-(*S*)-derivative of **1**.[4] These differences verify the recently determined absolute configuration of (+)-bullatacin (**1**).[4] Access to additional 4-hydroxylated acetogenins and their analogs now exists; attendant opportunities in synthesis and biology[14] are being pursued.



Acknowledgments

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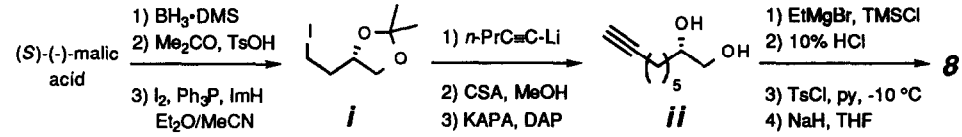
10. a) Epoxide **8** was prepared from (*S*)-(-)-malic acid via alkylation of 1-lithio-1-pentyne with the (*S*)-iodide **i**.[10b] Acetonide hydrolysis, "zipper" reaction to the terminal alkyne **ii**,[10c] trimethylsilylation, tosylation, and epoxide formation gave **7** in six steps and 20% yield from **i**. b) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295. c) Midland, M. M.; Halterman, R. L. *Tetrahedron Lett.* **1981**, *22*, 4171.



11. Isolated as an ~6:1 mixture of **12a** and its C(2)-epimer, separated at the stage of **12c**.
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14. The sample of (-)-bullatacin (**2**) is currently under evaluation for tumor cell cytotoxicity.

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