Highly Efficient Synthesis of the Potent Antitumor Annonaceous Acetogenin (+)-Parviflorin

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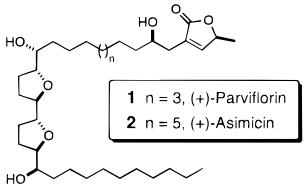
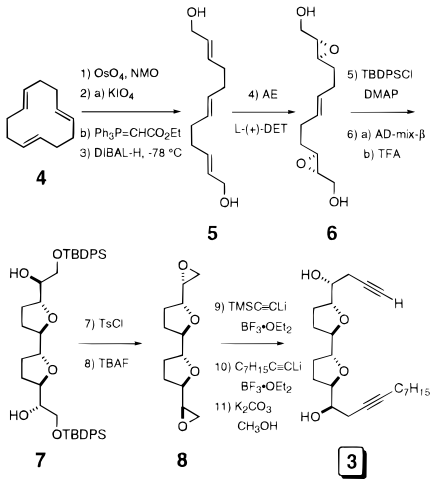
The annonaceous acetogenins are a rapidly growing class of natural products that have received considerable attention.[1] Many members possess a variety of biological effects including potent cytotoxic, antitumor, and pesticidal activities.[2,3] Parviflorin (**1**), a relatively rare C_{35} adjacent bis-THF acetogenin, was isolated by McLaughlin *et al.* both from *Asimina parviflora* Duanl.[4a] and from *Annona bullata* Rich.[4b] Parviflorin showed remarkable selectivity in its cytotoxicity against certain human solid tumor cell lines.[5]

The relative configuration of **1** was elucidated from spectral analysis,[4a] and the absolute configuration was determined using Mosher methodology.[6] Compound **1** showed spectral data very similar to those of asimicin (**2**). They share a *threo/trans/threo/trans/threo* configuration at the THF core and a hydroxyl group at the C(4) position. While five syntheses of bis-THF acetogenins or their stereoisomers have been reported,[7] we now describe a synthetic strategy that significantly improves the overall efficiency for preparation of adjacent bis-THF acetogenins. It culminates in a 14-step synthesis of **1**.



Taking advantage of the C_2 symmetry within the bis-THF subunit, we used a bidirectional chain synthesis strategy for the construction of building block **3** (Scheme 1). Thus, two of the three double bonds in *trans,trans,trans*-1,5,9-cyclododecatriene (**4**) were selectively oxidized with NMO in the presence of a catalytic amount of osmium tetraoxide. Oxidative cleavage of the tetrol with potassium periodate and Wittig extension of the resultant dialdehyde gave a bis-enoate. This was reduced with DIBAL-H to provide the first key intermediate, the bis-allylic alcohol **5**, in 51% overall yield from **4**.

Scheme 1



The stereogenic centers in the bis-THF backbone were installed by sequential double Sharpless asymmetric epoxidation/Sharpless asymmetric dihydroxylation, a strategy used by Taber in the synthesis of (+)-tuberine.[8] Thus, epoxidation of **5** with L-(+)-diethyl tartrate[9] gave the diepoxide **6** [~97% ee after chromatography; >99% ee (Mosher ester analysis) and 87% yield after recrystallization]. The primary alcohols were silylated with TBDPSCl. Asymmetric dihydroxylation[10] then afforded an intermediate diol, which was immediately treated with trifluoroacetic acid to effect an "inside-out" epoxide cascade reaction producing the bis-THF **7** (85% from **6**). Both carbinol centers in **7** were inverted by sequential treatment with TsCl and excess TBAF to produce the second key intermediate, the *threo/trans/threo/trans/threo* diepoxide **8** (87% from **7**). Selective opening of the diepoxide **8** with lithium (trimethylsilyl)acetylide (0.5 molar equiv) in the presence of boron trifluoride etherate[11] provided a mixture of two useful products incorporating one and two (trimethylsilyl)acetylene units (61% and 14%, respectively, based upon recovered starting material). The latter is being used for preparation of C_2 symmetric acetogenin analogs. The former, a desymmetrized bis-THF monoepoxide, was opened with excess 1-lithio-1-nonyne (89%) followed by desilylation to give the terminal alkyne **3** (99%).

Vinyl iodide **9** (Scheme 2) was required for coupling with the terminal alkyne **3**. We recently reported a method to efficiently construct 2-(β-hydroxyalkyl)-4-methylbutenolides.[12] Application to acetogenin targets requires a terminal epoxide with high enantiomeric purity. We now describe an improved general protocol for preparation of enantiomerically pure 1,2-epoxy alkanes that also bear a functional group at their remote terminus. Thus, 1,4-bis(alkenyloxy)benzene **10** (prepared from

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(2) Annonaceous acetogenins interfere with mitochondrial electron transport processes by interaction with complex I, the multiprotein enzyme, NADH-ubiquinone reductase.[3a−c] Selective inhibition of NADH-oxidase in plasma membrane vesicles isolated from HeLa and HL-60 tumor cells compared to the oxidase from rat liver cells has recently been suggested to contribute to the differential cytotoxicities exhibited by bullatacin.[3d]

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(5) E.g., the ED_{50}s for **1** against human A-549 lung carcinoma, MCF-7 breast carcinoma, and HT-29 colon adenocarcinoma are reported to be 1.27 $\times$ 10^{-15}, 1.72, and 0.549 μg/mL, respectively.[4b]

(6) Rieser, M. J.; Hui, Y.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.

(7) (a) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (b) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043. (c) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517. (d) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981. (e) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419.

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(10) Amberg, W.; Bennani, Y.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morkkawa, K.; Wang, Z.-M.; Xu, D.; Shang, X.-L.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 2768.

(11) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. (b) Morris, J.; Wishka, D. G. *Tetrahedron Lett.* **1986**, *27*, 803. (c) Mohr, P.; Tamm, C. *Tetrahedron Lett.* **1987**, *28*, 391.

(12) Hoye, T. R.; Humpal, P. E.; Jiménez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517.

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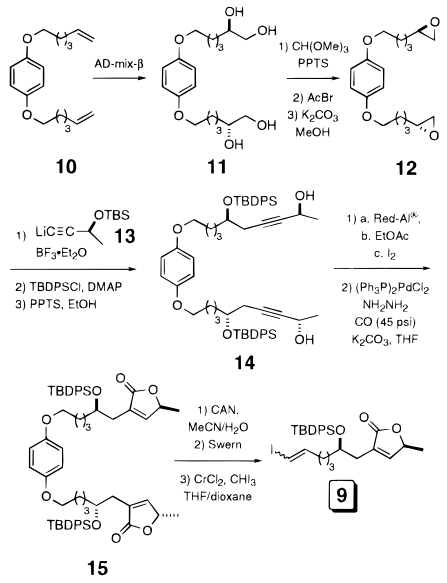
Scheme 2



bis-alkylation of hydroquinone with 6-iodo-1-hexene in 72% yield) was converted to the corresponding tetrol **11** by double asymmetric dihydroxylation with ~9:1 facial selectivity at each alkene using AD-mix-β. Tetrol **11**, which has two ω-functional-1,2-diol units tethered through the hydroquinone linker, was highly crystalline. Recrystallization from ethyl acetate efficiently returned material of very high optical purity [>99% ee (Mosher analysis), 62% yield]. In an efficient one-pot procedure[13] the tetrol **11** was processed into the optically pure bis-epoxide **12** (92%). Opening of **12** with the lithiated optically pure 3-butyn-2-ol derivative **13**, silylation (TBDPSCl) of the eventual C(4) hydroxyl group, and selective removal of the TBS ether produced the propargylic alcohol **14** (68% from **12**). The butenolide **15** was obtained by Red-Al reduction, iodine treatment, and carbonylation under Stille conditions (81% from **14**).[12,14] Oxidative release with CAN then afforded a primary alcohol. Swern oxidation to the corresponding aldehyde and reaction with chromium(II) chloride and iodoform provided the terminal vinyl iodide **9** (68% from **15**, 5:1 mixture of *E*/*Z* isomers).[15]

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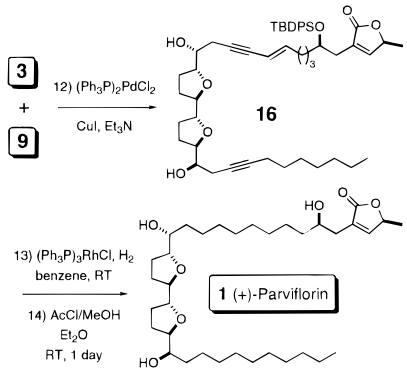
Scheme 3



The final Pd^0-catalyzed coupling of alkyne **3** with vinyl iodide **9**[7a,b,d] gave the enediyne **16** in 82% yield (Scheme 3). Selective hydrogenation with Wilkinson's catalyst (71%) left the butenolide intact. Desilylation gave (+)-parviflorin (**1**, 82%).

In conclusion, the first synthesis of parviflorin (**1**), a 35-carbon-containing annonaceous acetogenin, has been achieved. A highly efficient construction of the adjacent bis-THF backbone and a new general strategy for preparation of 1,2-epoxides of high optical purity have been developed. With these very efficient, convergent strategies it is possible to systematically design and synthesize various acetogenins and their analogs in sufficient quantities for the study of structure−activity relationships, biological testing, and prodrug development.

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Supporting Information Available: Experimental procedures for preparation and characterization data for all new compounds (39 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA953781Q

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