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An Efficient and Versatile Synthesis of the Butenolide Subunit of 4-Hydroxylated Annonaceous Acetogenins

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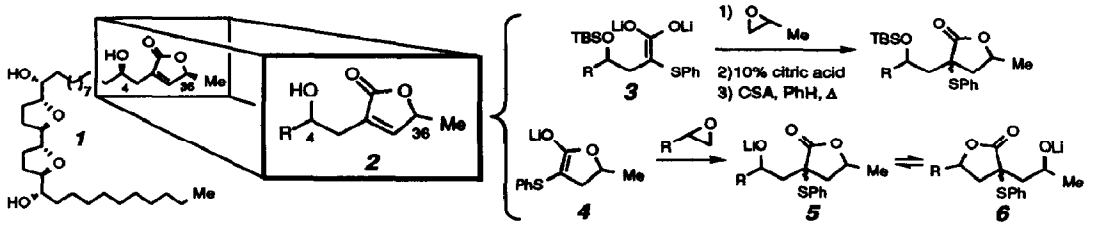
Abstract: *Title butenolides 2 have been synthesized by an efficient and versatile route that provides access to any stereoisomer by use of individual enantiomers of the precursors 3-butyn-2-ol and terminal epoxides.*

The Annonaceous acetogenins are a growing family of natural products that include members with wide ranging biological activities including important antitumor and pesticidal properties.[2] While nearly all of the acetogenins contain a γ-butenolide "head group," the most potent compounds frequently also bear a C(4)-hydroxyl group.[2b] (+)-Bullatacin (1) exemplifies these traits. We have recently:

- developed methods for the determination of relative and absolute configuration at the C(4)- and C(36)-stereogenic centers in 4-hydroxylated acetogenins[3] and
- reported the first synthesis of one of the 4-hydroxyacetogenins--*ent*-bullatacin.[4]

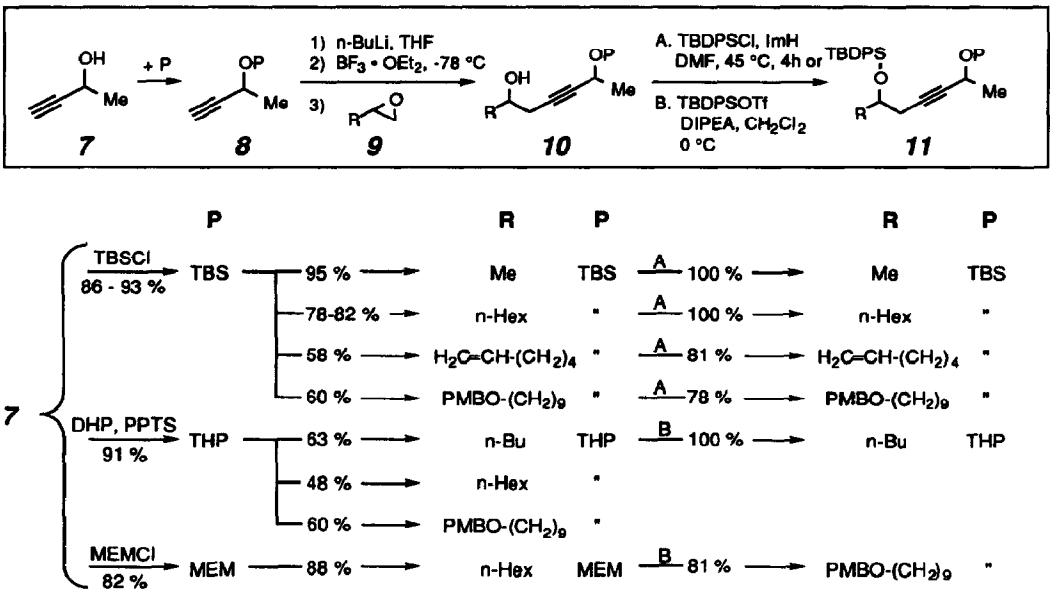
In those earlier efforts we used the serviceable but less than ideal preparation of the crucial β-hydroxyalkyl butenolide subunit 2.[5] Limitations include modest yields in the alkylations of anions 3 and 4 (Scheme 1) by the indicated epoxides and complications introduced by translactonization events (cf. 5 to 6). We now report a significantly improved and versatile strategy for the construction of subunit 2.

Scheme 1



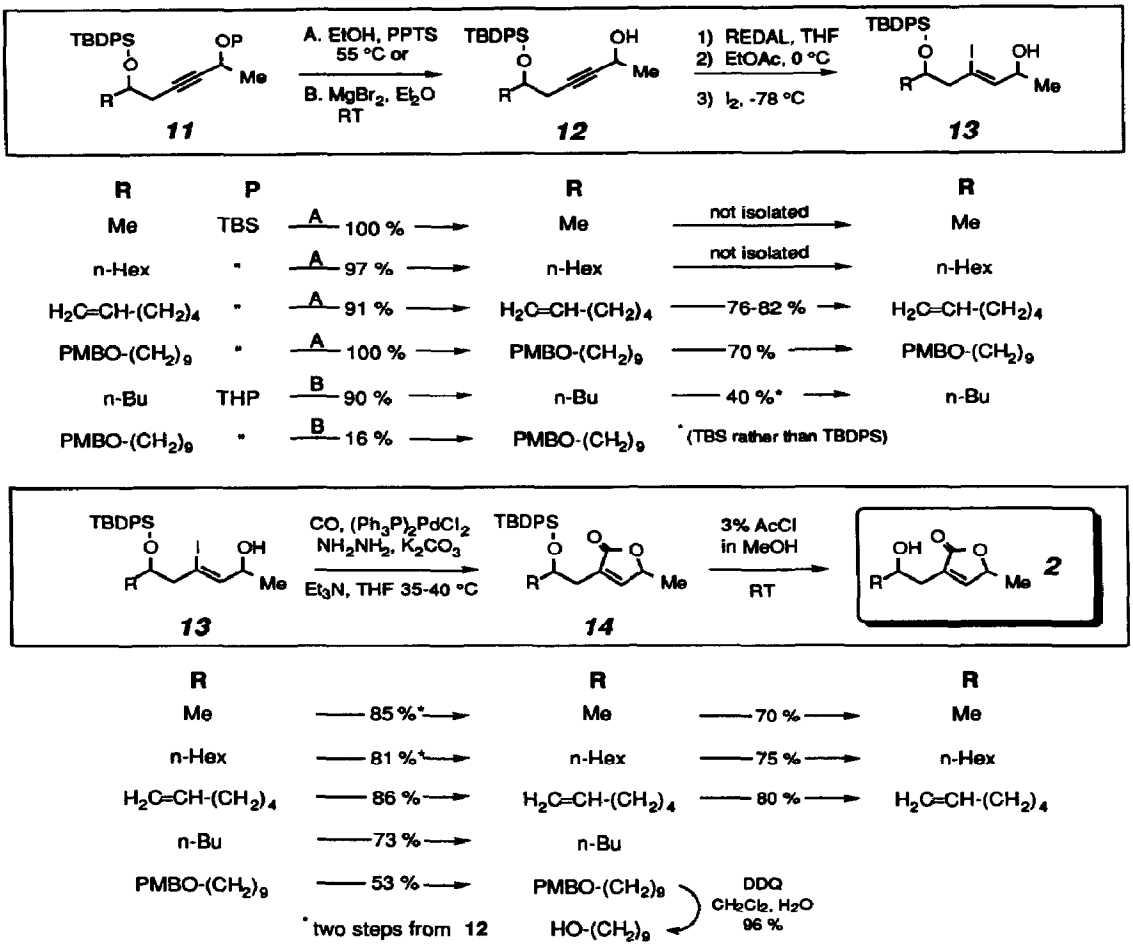
The key carbon-carbon bond forming event capitalized on the efficient $BF_3{\cdot}OEt_2$ mediated reaction of 1-lithio-1-alkynes with epoxides (Scheme 2).[6] Thus, the acetylide derived from 3-butyn-2-ol (**7**), suitably protected as **8**, smoothly opened a variety of terminal epoxides **9** to give the alcohols **10**. The THP protected version of **8** tended to give lower yields in this conversion compared with the MEM or TBS analogs. THP incompatibility with the BF_3 derived Lewis acids in the system during either the reaction or workup were presumed to be responsible. A variety of epoxides proved to be compatible, including ones containing terminal alkene or protected PMB-ether groups. Protection of the newly created alcohol group as the TBDPS ether to provide **11** proceeded smoothly, provided that the reaction was performed with a relatively high concentration (~1.0 M) of substrate **10**. Selective deprotection of the butynol-derived hydroxyl group in the presence of the TBDPS was best achieved by mild acid-catalyzed hydrolysis (EtOH, PPTS, 55 °C) of the OTBS or $MgBr_2$-mediated removal of the OTHP versions of **11**.

Scheme 2



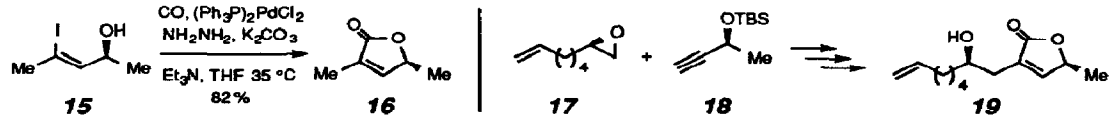
The propargyl alcohols **12** were then converted to the vinyliodides **13** by sequential exposure to REDAL and iodine (Scheme 3).[7] The TBS protected version of **12** was a more marginal substrate for this transformation than the analogous TBDPS ether. The Stille butenolide synthesis[8] was designed as the cornerstone of the overall strategy, and it proved more than worthy. Thus, the vinyliodides **13** were smoothly carbonylated in the presence of *in situ* generated Pd° to produce the lactones **14** in good yield. Use of crude or purified preparations of the vinyliodides worked equally well. Final, HCl-catalyzed hydrolysis of the TBDPS ether in **14** produced the target β-hydroxyalkyl butenolides **2**.

Scheme 3



This route is directly adaptable to the preparation of any stereoisomer of **2**. Successful cyclization of optically pure vinyl iodide **15**[9] to the lactone **16** demonstrated the configurational stability of the butenolide stereocenter [C(36)] under the slightly basic reaction conditions of the Stille cyclization (Scheme 4).[10] Moreover, scalemic samples of epoxide **17**[11] and alkyne **18**[12] were parlayed into the butenolide

Scheme 4



stereoisomer **19**, which had the expected level of configurational purity as judged by careful analysis of the Mosher ester derivative. It is obvious that with proper choice of enantiomeric epoxide and alkyne substrates, any stereoisomer of **19** is accessible by this approach. Finally, the terminally functionalized side-chain in **19** and in **14** [R = HO-$(CH_2)_9$] makes either an attractive potential intermediate for the synthesis of various natural 4-hydroxylated acetogenins as well as their analogs. Such applications are in progress.

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References and Notes

1. Dow Graduate Fellow, 1993-94.
2. Reviews: a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* 1990, *53*, 237. b) Fang, X.; Rieser, M. J.; Gu, Z.; Zhao, G.; McLaughlin, J. L. *Phytochem. Anal.* 1993, *4*, 27.
3. a) Rieser, M. J.; Hui, Y.-H.; 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. b) Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. A.; Ramirez, E. A. manuscript in preparation.
4. Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043.
5. For a recent synthesis of this subunit by a similar strategy and within the context of the synthesis of rolliniastatin 1 see: Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517.
6. 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.
7. e.g., Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236.
8. Stille, J. K.; Cowell, A. *J. Am. Chem. Soc.* **1980**, *102*, 4193.
9. a) Prepared from 3-pentyn-2-ol in 51% overall yield by i) SP-435[9b] catalyzed kinetic resolution and transesterification with isopropenyl acetate[9c,d] and ii) the REDAL/iodination sequence.[7] b) Kindly provided by Novo Nordisk A/S, Novo Alle, 2880 Bagsvaerd, Denmark. c) Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287. d) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129.
10. The %ee of **16** was assessed at ≥ 99% by gas chromatography on a Chiraldex G-TA 30 m x 0.32 mm column: t_R = 17.6 min at 70 °C for 3 min then ramped at 5 °C/min to a final temperature of 150 °C.
11. Prepared by mono-asymmetric dihydroxylation of 1,7-octadiene (AD-mix-β, ~80 %ee by Mosher ester analysis) followed by mono-tosylation (*p*-TsCl, Et_3N, DMAP, CH_2Cl_2) of the diol and epoxide formation (NaH, THF, RT).
12. Prepared by bis-trimethylsilylation of racemic 3-butyn-2-ol [EtMgBr (2.2 equiv), TMSCl, H_3O^+], enzymatic resolution [SP-435 (10 mol%), AcOCH(Me)=CH_2, hexanes, 65 °C, 0.5-2 days; MPLC], TBS ether protection, and selective removal of the akynyl-TMS group (MeOH, K_2CO_3, RT). None of the minor enantiomer could be detected by ^1H NMR analysis of the Mosher ester derivative.

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