Pergamon

Tetrahedron Letters 39 (1998) 1303–1306

TETRAHEDRON LETTERS

# Total Synthesis of the Cytotoxic Annonaceous Acetogenin (30S)-Bullanin

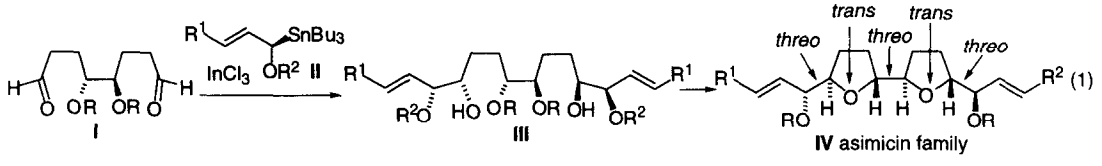
James A. Marshall* and Kevin W. Hinkle

Department of Chemistry, University of Virginia, Charlottesville, VA 22901

Received 30 September 1997; revised 12 November 1997; accepted 16 November 1997

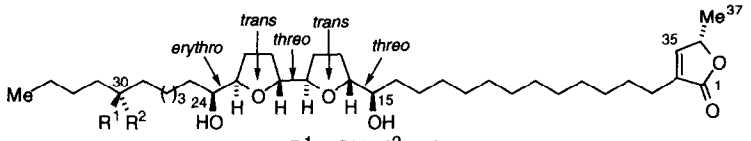
**Abstract:** The total synthesis of (+)-(30S)-bullanin, a highly cytotoxic Annonaceous acetogenin, was effected by a convergent approach in which the key core *bis*-2,2'-tetrahydrofuran stereocenters were introduced through a combination of Sharpless asymmetric dihydroxylation and $S_E2'$ additions of oxygenated nonracemic allylic stannane and indium reagents to γ-oxygenated aldehydes.


We recently disclosed a convergent bidirectional strategy[1] for the synthesis of $C_2$ symmetric 2,2'-*bis*-tetrahydrofurans related to the core units of various Annonaceous acetogenins, a family of plant derived natural products with a remarkable range of biological activities.[2] Our approach employs a nonracemic γ,γ'-dioxygenated dialdehyde, such as **I**, and a nonracemic α- or γ-oxygenated allylic stannane (*cf* **II**) which react under appropriate conditions to form *anti* or *syn* monoprotected 1,2-diol derivatives, such as **III**. These are then cyclized to the *bis*-tetrahydrofuran intermediates (eq. 1). An application of this methodology has recently been employed for the synthesis of asimicin, asiminecin, and asiminocin, three members of the asimicin subclass which feature a *threo, trans, threo, trans, threo* core stereochemistry, as in **IV** (eq. 1).[3,4]

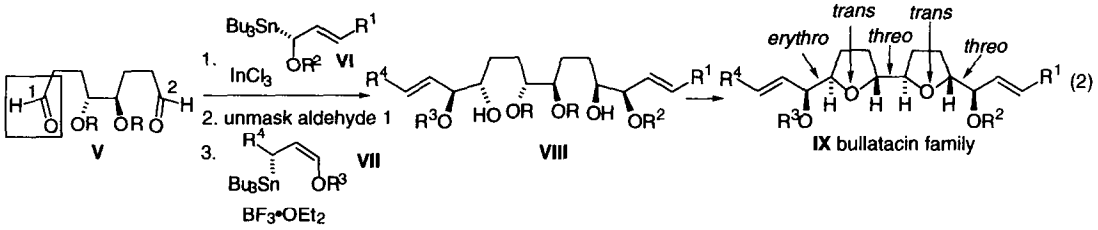



The bidirectional approach, though relatively efficient, is limited to *bis*-tetrahydrofuran acetogenins with a $C_2$ symmetric core unit.[5] Owing to the high biological profile of family members that lack this symmetry element and, in consideration of the minute quantities available from natural sources,[6] we were motivated to extend our methodology to a convergent, but non-bidirectional approach to these *bis*-tetrahydrofuran acetogenins. Our initial efforts were directed at bullanin, a member of the bullatacin subgroup which features an *erythro, trans, threo, trans, threo* core stereochemistry.[7] Bullanin, along with other closely related members of this family, show $ED_{50}$ values on the order of $10^{-12}$-$10^{-14}$ μg/mL against certain human tumor cell lines in cell culture assays.[2]

0040-4039/98/$19.00 
*PII:* S0040-4039(97)10739-0

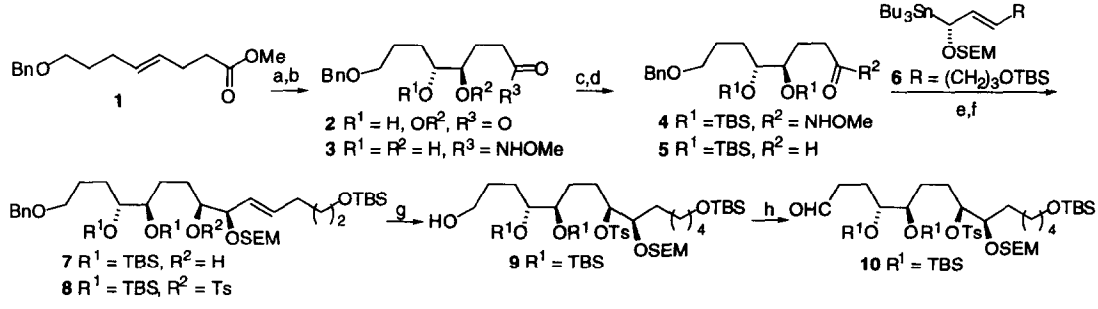



Our general approach is outlined in equation 2. It differs from the previous approach (eq. 1) in that a masked dialdehyde (**V**) serves as the starting material for the core unit and the ensuing core construction entails an *anti* selective ($InCl_3$, α-oxygenated stannane **VI**) and a *syn* selective ($BF_3$•$OEt_2$, γ-oxygenated stannane **VII**) bond construction to install the requisite core unit stereochemistry.



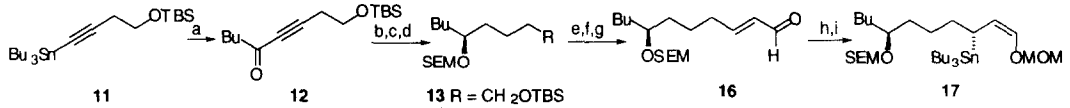

The starting core unit aldehyde **5** was prepared from the Claisen product **1**[8] through Sharpless asymmetric dihydroxylation,[9] leading to the γ-lactone **2**, formation of the Weinreb amide **3**,[10] protection of the resulting diol as the *bis*-TBS ether **4**, and reduction with DIBAL-H. Transmetallation of stannane **6**[4] with $InCl_3$ in the presence of aldehyde **5** afforded the expected *anti* adduct **7** in 86% yield. Following tosylation, hydrogenation over Pd-C proceeded with concomitant hydrogenolysis of the benzyl ether to alcohol **9**, which was oxidized with the Dess-Martin periodinane reagent[11] to aldehyde **10**.

Construction of the C15-C24 appendage began with ynone **12**, prepared by Pd(0)-catalyzed coupling of alkynylstannane **11** with valeryl chloride.[12] Reduction with (*S*)-BINAL-H and protection yielded the SEM ether



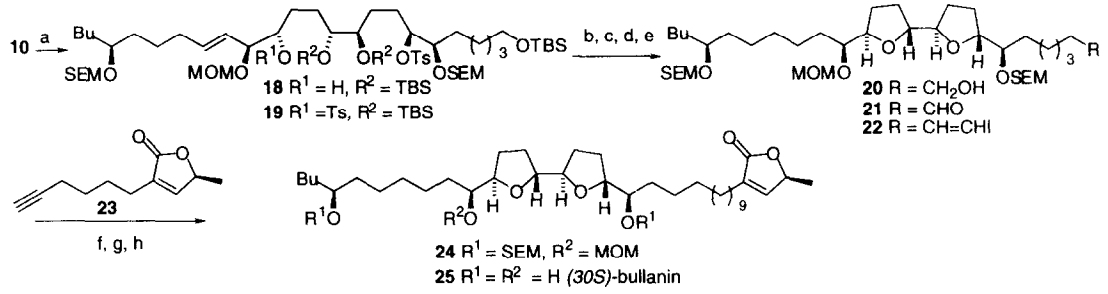

a) AD-Mix-β (100%); b) $AlMe_3$, Me(MeO)NH•HCl (100%); c) TBSCl, Imid. (100 %); d) DIBAL-H (100%); e) $InCl_3$, **6** (86%); f) TsCl, $C_5H_5N$ (72%); g) $H_2$, Pd/C (89%); h) Dess-Martin (90%).

**13** of >95% ee.[13] Hydrogenation, then deprotection-oxidation, led to aldehyde **15** which was homologated to enal **16** through Wittig condensation with (triphenylphosphoranylidene)acetaldehyde.[14] The γ-alkoxystannane **17** of >95% ee was prepared from enal **16** by our published sequence.[13]




a) $(Ph_3P)PdCl_2$, BuCOCl; b) (*S*)-BINAL-H (26% yield for two steps); c) $H_2$, $Rh/Al_2O_3$ (99%); d) SEMCl, $EtN(i\text{-}Pr)_2$ (100%); e) TBAF (80%); f) $(COCl)_2$, DMSO, $Et_3N$ (85%); g) $Ph_3PCHCHO$ (60%); h) $LiSnBu_3$, 1,1'-(azodicarbonyl)dipiperidine, (*S*)-BINAL-H, MOMCl, $i\text{-}Pr_2NEt$ (26%); i) $BF_3{\bullet}Et_2O$ (73%).

Addition of stannane **17** to aldehyde **10** in the presence of $BF_3{\bullet}OEt_2$ proceeded in 92% yield to afford the *syn* adduct **18** as the only detectable stereoisomer.[15] Tosylation of the alcohol followed by exposure to TBAF effected *bis*-tetrahydrofuran cyclization in 52% yield. Introduction of the butenolide moiety and the additional side chain $CH_2$'s was effected through Sonogashiro coupling[16] of vinyl iodide **22**[17] with the alkynyl butenolide **23**.[4] The final steps of the synthesis were achieved through selective reduction of the dienyne multiple bonds with diimide[4] and deprotection of the MOM and SEM ethers with $BF_3{\bullet}OEt_2$ and DMS.[18]




a) $BF_3{\bullet}OEt_2$, **17** (92%); b) TsCl, $C_5H_5N$ (77%); c) TBAF (52%); d) Dess-Martin (81%); e) $CrCl_2$, $CHI_3$ (72%); f) $(Ph_3P)_2PdCl_2$, CuI, **23** (44%); g) $TsNHNH_2$, NaOAc (81%); h) $BF_3{\bullet}OEt_2$, $Me_2S$ (100%)

(+)-Bullanin was isolated from the stem bark of *Asimina triloba* as an inseparable mixture of 30*S* and 30*R* diastereomers.[7] Our synthesis affords the 30*S* isomer. The identity of this material with that of the 30*S* natural isomer was established through $^1H$ NMR comparison of the tri-(*S*)-MTPA (Mosher) ester with that of the (*S*)-Mosher ester of the mixture derived from natural sources. The optical rotation of our synthetic material, $[\alpha]_D$ +24, is in close agreement with the reported value for the mixture, $[\alpha]_D$ +28.

Though not yet optimized, the foregoing synthetic scheme illustrates the feasibility of preparing useful amounts of bullatacin-type acetogenins, and analogues thereof, for biological testing. Our synthesis also confirms the assigned structure and configuration of natural bullanin.

**Acknowledgments.** We are indebted to the National Institutes of Health and the National Science Foundation for research grants (GM39998 and CHE9220166) in support of this work. KWH acknowledges support from an ACS Division of Organic Chemistry Fellowship sponsored by DuPont-Merck. We thank Prof. Jerry McLaughlin for spectra of natural bullanin and the MTPA esters.

**References and Notes.**

1. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247.
2. *Cf.* Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K., McLaughlin, J. L. *Nat. Prod. Reports* **1996**, 275.
3. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989.
4. Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996.
5. For recent reviews of other synthetic approaches, see Figadere, B. *Accts. Chem. Res.* **1995**, 28, 359. Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Israel J. Chem.* **1997**, *37*, 97. See also Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *37*, 7001.
6. These materials occur as nearly inseparable mixtures which are purified following mutiple solvent partitionings, multiple column chromatography, HPLC, and radial chromatography. It is not uncommon to obtain only 5-10 mg of pure material from 15 kg of dried stem bark. *Cf.* Zhao, G.; Chao, J.-F.; Zeng, L.; Rieser, M. J.; McLauglin, J. L. *Bioorg. Med. Chem.* **1996**, *4*, 25.
7. Zhao, G.; Ng, J. H.; Kozlowzki, J. F.; Smith, D. L.; McLaughlin, J. L. *Heterocycles* **1994**, *38*, 1897.
8. Sinka, S. C.; Sinka, A.; Yazbek, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640.
9. Kolb, H. C.; VanNieuwenkze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
10. a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *17*, 4171, b) Nahm, S.; Weinred, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
11. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. Ireland, R. E.; Lin, *J. Org. Chem.* **1993**, *58*, 2899.
12. Stille, J. K.; Tanaka, M. *J. Org. Chem.* **1987**, *109*, 3785.
13. *Cf.* Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.
14. Aldrich Chemical Co., Milwaukee, Wisconsin.
15. Previous work revealed a significant decrease in diastereoselectivity for additions of long-chain oxygenated stannanes compared to the crotyl analogues. This was not observed in the case of the long-chain stannane **17** and aldehyde **10**. Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1994**, *59*, 4122.
16. *Cf.* Sonogashira, in *Comprehensive Organic Synthesis*. Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3. Chapter 2.4.
17. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
18. Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Saski, S. *J. Org. Chem.* **1995**, *60*, 4419.