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

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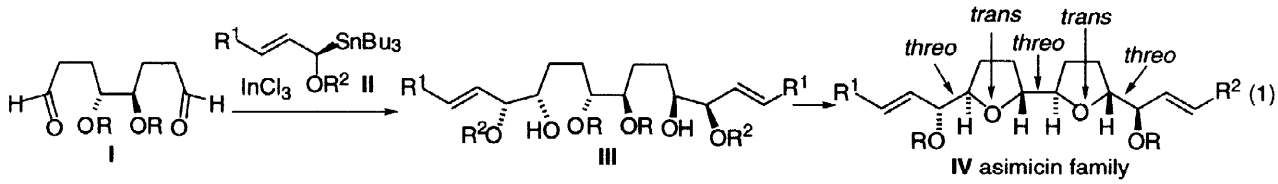
Abstract: The total synthesis of (+)-(30S)-bullanin, a highly cytotoxic Annonaceous acetogenin, was effected by a convergent approach in which the key core *bis*-2,2'-tetrahydrofuran stereocenters were introduced through a combination of Sharpless asymmetric dihydroxylation and S_E2' additions of oxygenated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

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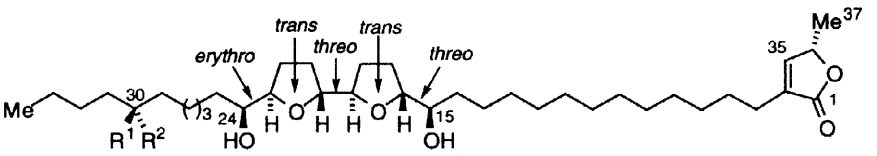
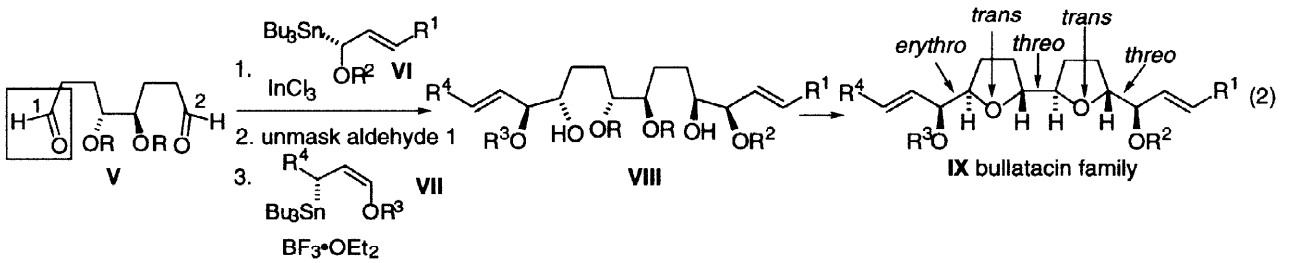


(30S)-Bullanin, R^1 = OH, R^2 = H

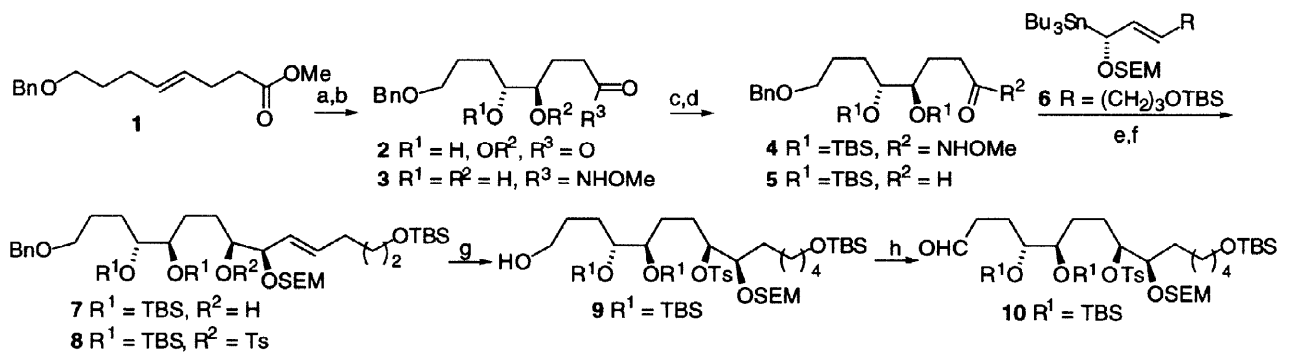
(30R)-Bullanin, R^1 = H, R^2 = OH

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.



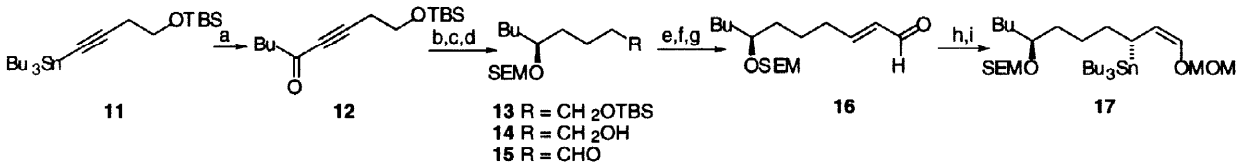
The starting core unit aldehyde **5** was prepared from the Claisen product **1**[8] through Sharpless asymmetric dihydroxylation,[9] leading to the γ-lactone **2**, formation of the Weinreb amide **3**,[10] protection of the resulting diol as the *bis*-TBS ether **4**, and reduction with DIBAL-H. Transmetallation 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%).

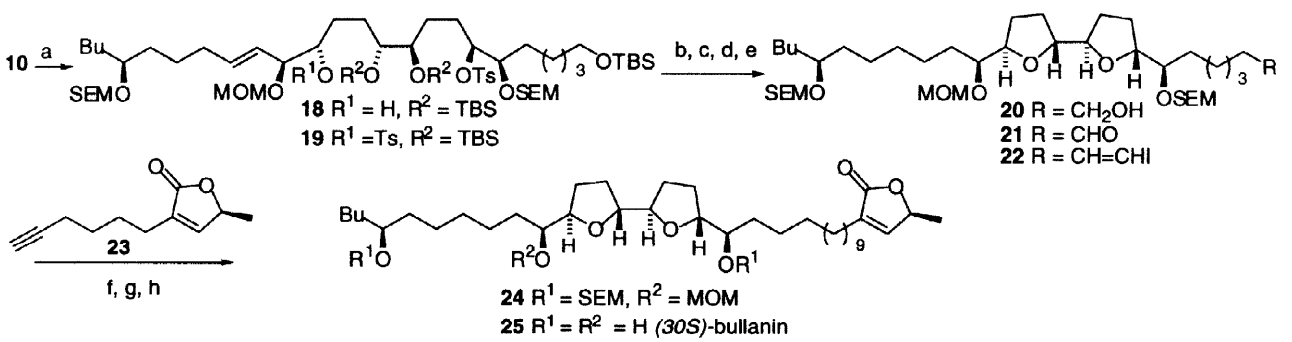
13 of >95% ee.[13] Hydrogenation, then deprotection-oxidation, led to aldehyde **15** which was homologated to enal **16** through Wittig condensation with (triphenylphosphoranylidene)acetaldehyde.[14] The γ-alkoxystannane **17** of >95% ee was prepared from enal **16** by our published sequence.[13]



11 **12** **13** R = CH_2OTBS **14** R = CH_2OH **15** R = CHO **16** **17**

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.

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