Total Synthesis of (−)-Callystatin A

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A total synthesis of the cytotoxic polyketide marine natural product callystatin A is described. The route features chiral allenylmetal additions to construct the polypropionate C15−22 segment and an sp^2−sp^3 Suzuki coupling to join the C1−C11 and C12−C22 subunits.

The cytotoxic polyketide marine natural product callystatin A has been known since 1997, when Kobayashi and co-workers first isolated the substance from the sponge *Callyspongia truncata*.[1] Shortly thereafter, the Kobayashi group reported the first total synthesis of this potent cytotoxic natural product (IC_{50} = 10 pg/mL against KB tumor cells and 20 pg/mL against L1210 cells).[2] Their synthesis and a subsequent effort by Crimmins and King utilized chiral auxiliary aldol methodology to fashion the polypropionate C13−22 segment and an allylic Wittig coupling to join this segment to the C1−C12 subunit.[3] More recently, Smith and Brandt described a novel approach in which a combination of Evans and substrate directed aldol methodology led to the C13−C22 segment, which was joined to C1−C12 by means of a Julia coupling.[4] The synthesis that we now describe differs in several respects from the previous routes.

The overall plan is outlined in Figure 1. In our construction of the C1−C11 segment, we targeted a protected 1,5-diol **I** rather than a protected lactol employed by others as the precursor to the pentenolide moiety.[2−4] The stereochemistry at C5 in **D** derives from the (*S*)-glycidol derivative **A**, as was the case for the previous syntheses. The C10 and C18 stereocenters in **E** and **H** originate with the (*R*)-2-methyl-3-oxygenated propanals **B** and **C**, which are readily available from (*R*)-3-hydroxyisobutyric acid.[5] The remaining four stereocenters at C16, C17, C19, and C20 in **H** result from sequential stereoselective additions of the *(M)*-allenylmetal reagents **F** and **G**, both of which derive from (*S*)-3-butyn-2-ol, to the appropriate aldehydes.[6] It is noteworthy that in the previous synthetic routes an all-syn stereopentad served as a C12−C22 segment precursor. Our choice of an anti,syn,syn,syn array (**H**) seemed inconsequential to the ultimate goal, as the "inverted" C17 stereocenter is ultimately destined to become a carbonyl group. However, this variation proved to have a profound impact on the reactivity of certain advanced synthetic intermediates. Finally, our plan to utilize Suzuki methodology to couple subunits **I** and **J** also differs from previous strategies which employed Wittig or Julia methodology to connect a C1−C12 segment to C13−C22.

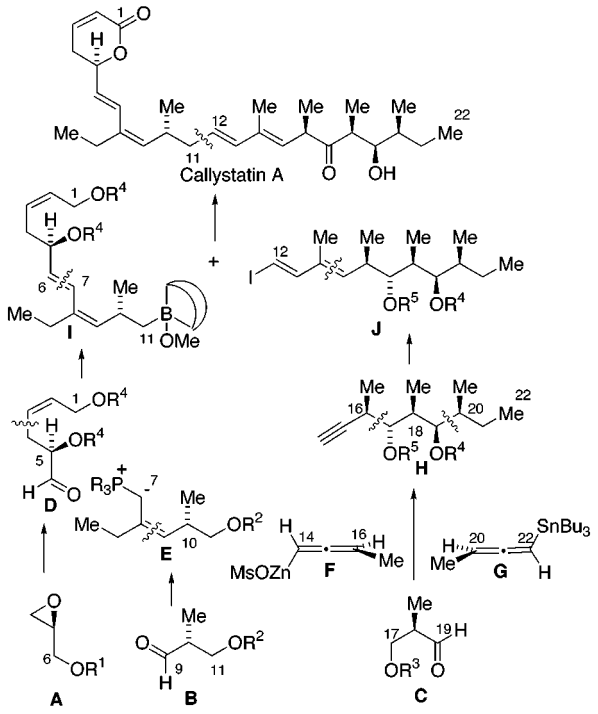
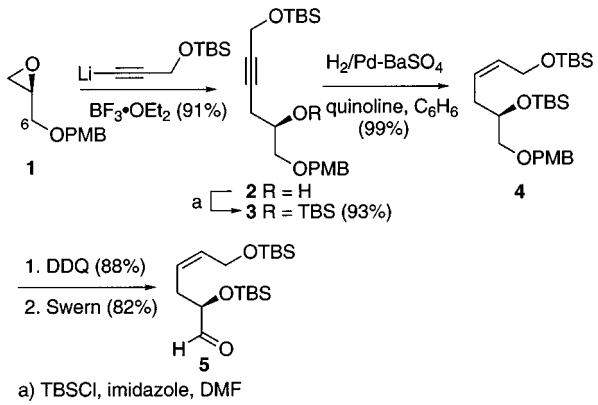


Figure 1. Synthetic plan for callystatin A.

Scheme 1



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(6) Both enantiomers are available from the Aldrich Chemical Co. They can also be prepared from the TBS ethers of (*R*)- or (*S*)-lactic aldehyde. Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, *66*, 1373.

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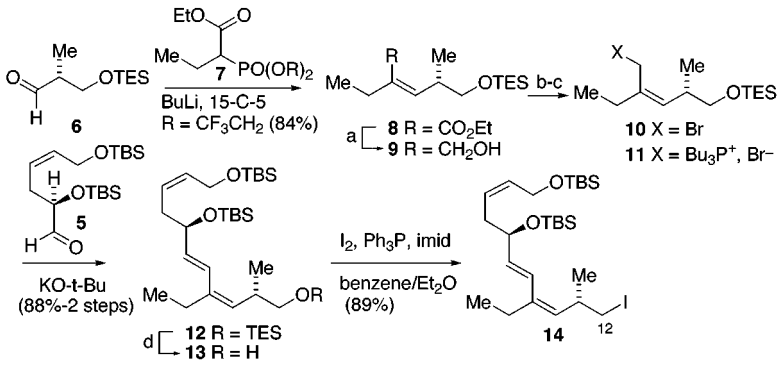
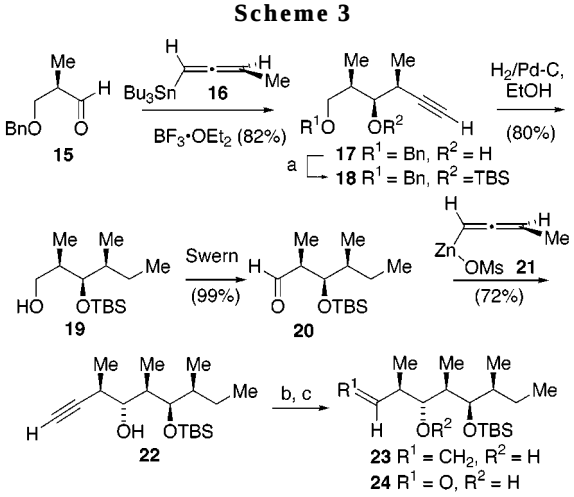
Scheme 2

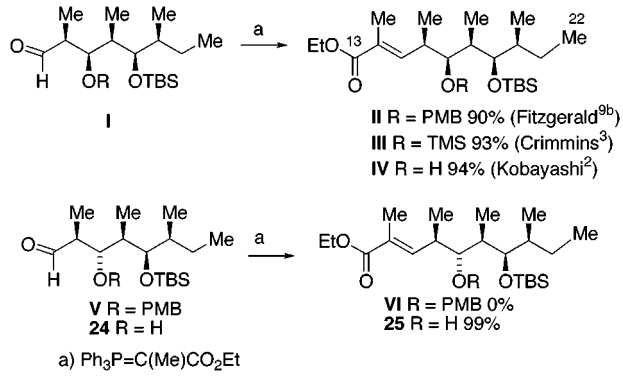


a) DIBAL-H (92%); b) CBr_4, Ph_3P, $EtN(i\text{-}Pr)_2$ (93%); c) Bu_3P, MeCN; d) PPTS, 9:1 MeOH/THF 0 °C (81%)

Scheme 3



a) TBSOTf, 2,6-lutidine (88%); b) H_2/Pd-$BaSO_4$, quinoline, C_6H_6 (99%); c) O_3, CH_2Cl_2; Ph_3P (82%)



a) $Ph_3P{=}C(Me)CO_2Et$

Figure 2. Comparison of Wittig condensations on various aldehyde precursors leading to potential segments of the C13−C22 segment of callystatin A.

Following this plan, we prepared the C1−C6 aldehyde **5** uneventfully as outlined in Scheme 1. As noted above, the route differs somewhat from that used by previous workers.

Further elaboration of aldehyde **5** to the C1−C12 segment **14** of callystatin A commenced with Still−Horner−Emmons condensation of phosphono ester **7** with the (*R*)-aldehyde **6** to afford the (*Z*)-conjugated ester **8** in high yield with 6−8:1 stereoselectivity (Scheme 2).[7] The derived alcohol **9** was converted to bromide **10** with CBr_4 and Ph_3P. The ylide, prepared from bromide **10** by sequential treatment with Bu_3P and then KO-*t*-Bu, condensed with aldehyde **5** in situ to yield diene **12** in 88% yield for the two steps. Cleavage of the TES ether followed by treatment of the free alcohol with I_2 and Ph_3P-imidazole[8] completed the synthesis of this segment.

Construction of the C13−C22 polypropionate subunit of callystatin A began with $BF_3{\cdot}OEt_2$-promoted addition of the (*M*)-allenylstannane **16** to the (*R*)-aldehyde **15** and protection of the resulting syn,syn adduct **17** as the TBS ether **18** (Scheme 3).[9] Hydrogenolysis of benzyl ether **18** with concomitant reduction of the terminal alkynyl group followed by Swern oxidation of alcohol **19** effected conversion to aldehyde **20**.[10] To this was added the (*M*)-allenylzinc reagent **21**, prepared *in situ* from the mesylate of (*S*)-3-butyn-2-ol and Et_2Zn in the presence of 5 mol % $Pd(OAc)_2{\cdot}PPh_3$.[11] The expected anti adduct **22** was thereby produced in 72% yield as a single diastereomer.[12] Partial hydrogenation of alkyne **22** over Pd on $BaSO_4$[13] and ozonolysis of the resulting olefin **23** led to aldehyde **24**. Attempted reduction of the ozonide with dimethyl sulfide resulted in total decomposition of the product. However, the use of Ph_3P proved highly satisfactory.

The TMS ether of aldehyde **24** (R = TMS) proved completely unreactive toward homologation with the α-triphenylphosphonium propionate Wittig reagent, in contrast to previous reactions of this reagent with **I** (R = TMS), the all-syn isomer of aldehyde **24**, which proceeded in near-quantitative yield (Figure 2).[3,9] Furthermore, we have previously converted the PMB ether **I** (R = PMB) of the all-syn aldehyde to the conjugated ester **II** in excellent yield by condensation with the same propionate Wittig reagent.[9b] However, the anti,anti analogue **V** failed to react under identical or even more forcing conditions (refluxing toluene).[14] Borrowing a page from the Kobayashi synthesis,[1] albeit on a conversion

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(11) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.

(12) Experimental details for the preparation of compounds **17**−**20** and **22** will be disclosed in a forthcoming publication (Marshall, J. A.; Schaff, G. M. *J. Org. Chem.*, in press).

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(14) Marshall, J. A.; Chobanian, H. R. Unpublished results.

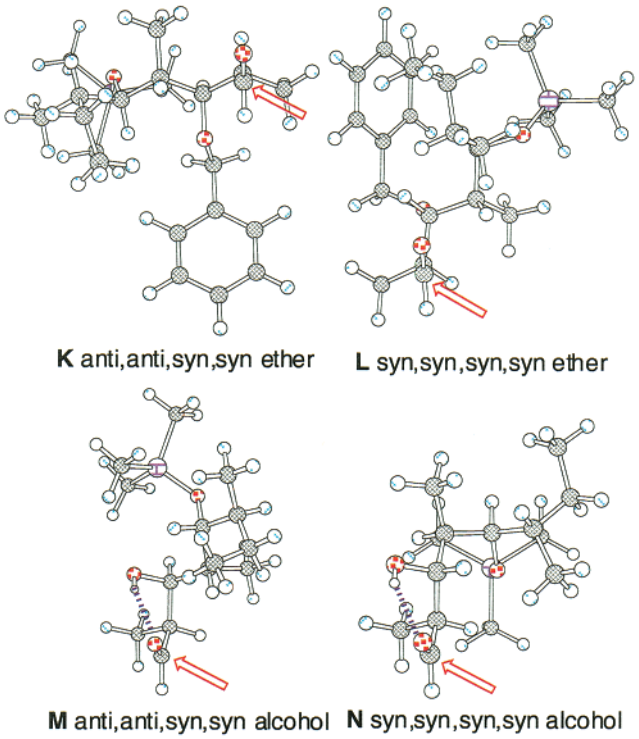


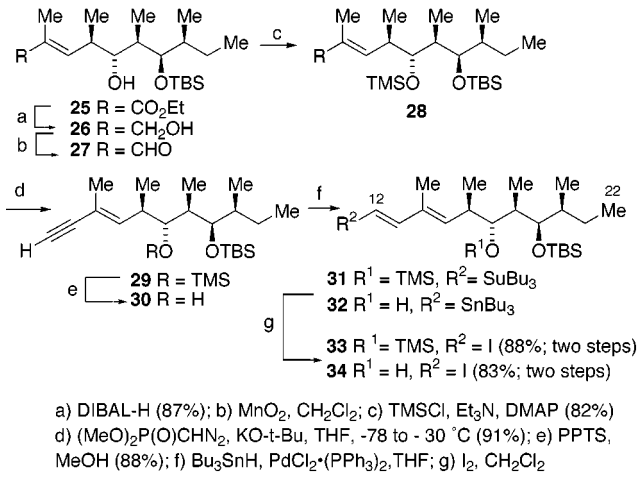
Figure 3. Calculated conformations **K**−**N** of aldehydes **I** (R = PMB or H) and **V** (R = PMB or H) showing the effect of stereochemistry and β-substituents on the facial accessibility of the carbonyl carbon. The β-TBS group was replaced by TMS to simplify the calculations. The red arrows indicate the approach trajectory of an attacking nucleophile, and the dashed blue lines (**M** and **N**) highlight internal hydrogen bonding between the carbonyl oxygen and the β-OH proton.

involving the all-syn isomer of **24** (**I,** R = H), we were finally able to effect the condensation in excellent yield on aldehyde **24** with the C17 alcohol left unprotected.

Molecular mechanics calculations (MacroModel 5.5) provide a possible rationale for these contrasting results (Figure 3). Accordingly, the benzyl ether of the anti,anti,-syn,syn aldehyde adopts conformation **K** in which approaches to both faces of the aldehyde carbon are blocked by nonhydrogen α-substituents. In contrast, the corresponding ether **L** of the all syn aldehyde offers an accessible re face to an attacking nucleophile. Considering the steric bulk of the triphenylphosphonium ylide, this difference could play an important role in the contrasting reactivities of the two diastereomers. The unprotected β-hydroxy anti,anti,syn,syn aldehyde **M** assumes a conformation analogous to **L**, as does the all-syn isomer **N**. Both **M** and **N** possess favorable hydrogen-bonding between the carbonyl oxygen and the β-OH proton.

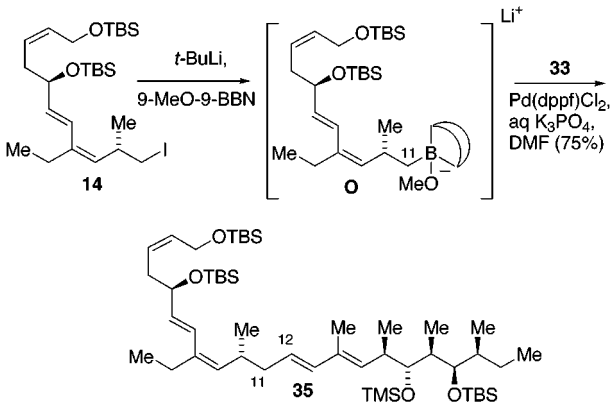
Reduction of ester **25** and oxidation of the resulting allylic alcohol with MnO_2 afforded aldehyde **27** (Scheme 4). Elaboration of this aldehyde to the corresponding vinyl iodide proved somewhat capricious. All attempts to use the Takai protocol (CHI_3 and $CrCl_2$) to generate the vinyl iodide directly met with failure.[15] Envisioning a two-step conversion via the terminal alkyne, we attempted to condense the aldehyde with Ohira's diazophosphonate reagent but without success.[16] The desired enyne **30** was

Scheme 4



a) DIBAL-H (87%); b) MnO_2, CH_2Cl_2; c) TMSCl, Et_3N, DMAP (82%) d) $(MeO)_2P(O)CHN_2$, KO-t-Bu, THF, -78 to - 30 °C (91%); e) PPTS, MeOH (88%); f) Bu_3SnH, $PdCl_2$•$(PPh_3)_2$,THF; g) I_2, CH_2Cl_2

Scheme 5



ultimately prepared in excellent yield by condensation with the Gilbert−Seyferth diazo phosphonic reagent at −30 °C.[17] The necessary vinyl iodide **33** was obtained by an efficient hydrostannation, iodination procedure.

The critical union of subunits **14** and **33** was achieved in 75% yield through Pd-catalyzed coupling of boronate **O** with the iodide **33** (Scheme 5).[18] However, the ensuing selective cleavage of the silyl ethers proved problematic. For example, attempted preferential cleavage of the seemingly more labile C17 OTMS, the C1 OTBS, and the C5 OTBS ethers of **35** over the more hindered C19 OTBS ether with H_2SiF_6 afforded a mono TBS ether, but subsequent oxidation with MnO_2 yielded the enal **36**, rather than the expected γ-lactone **39** (Figure 4). Evidently, cleavage of the *more hindered* C19 OTBS ether took place in preference to that of the seemingly more labile C5 OTBS ether to afford triol **37** rather than **38**. This unexpected outcome may be explained by an internally assisted cleavage of the C19 OTBS ether as illustrated in Figure 4.

We believed that we could skirt this deprotection dilemma by using alcohol **34**, which leaves the C17 alcohol unprotected, in the coupling step. However, use of the previously employed Suzuki coupling conditions ($Pd(dppf)Cl_2$, aqueous K_3PO_4, DMF) led to the coupled

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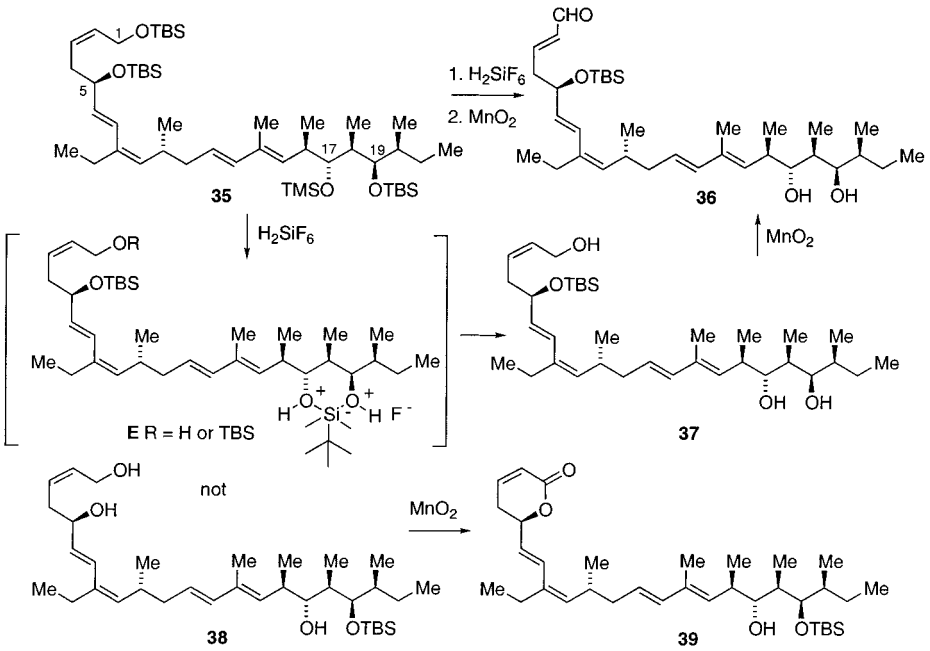
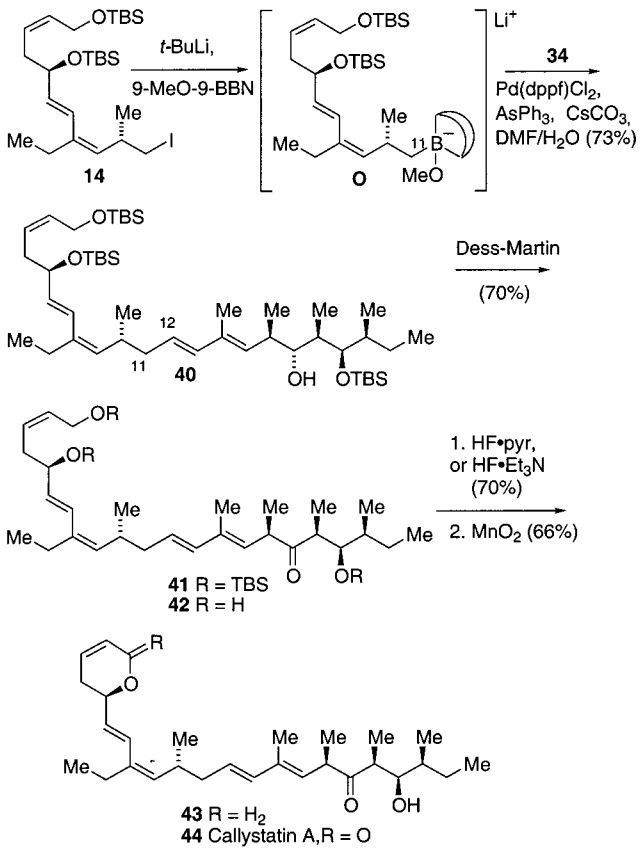


Figure 4. Selective silyl ether cleavage of protected tetrol **35** and subsequent oxidation.

Scheme 6



product in poor yield (40%−55%). We were able to improve this conversion by utilizing a modified version of Johnson's[18c] cross-coupling conditions ($Pd(dppf)Cl_2$, $AsPh_3$, $CsCO_3$, H_2O/DMF), which afforded dienol **40** in 73% yield. Oxidation with the Dess−Martin periodinane reagent yielded ketone **41**.[19] Global deprotection was initially attempted with HF·pyridine in THF. This protocol led to a relatively nonpolar product that was unaffected by prolonged treatment with MnO_2 and is formulated as the cyclic ether **43** arising from acid-catalyzed cyclodehydration. This side reaction was circumvented by using 3HF·Et_3N. Oxidation of the resulting highly polar triol **42** with MnO_2 yielded callystatin A (**44**) $[\alpha]^{20}_D = -118$ ($c = 0.2$, MeOH) [lit.[3] $[\alpha]^{24}_D = -105$ ($c = 0.1$, MeOH), lit.[4] $[\alpha]^{23}_D = -82$ ($c = 0.055$, MeOH)]. The spectral data closely matched that reported for the natural material.

The present synthesis of callystatin A compares quite favorably to previous routes.[1−4,20] Noteworthy features include the high degree of stereocontrol in the allenylmetal additions and the remarkable efficiency of the sp^2−sp^3 Suzuki coupling of the two subunits. The strategy lends itself to the preparation of various stereoisomers and other analogues for possible biological evaluation.

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Supporting Information Available: Experimental procedures and ^1H NMR spectra for all key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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