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Second-Generation Synthesis of the Polypropionate Subunit of Callystatin A Based on Regioselective Internal Alkyne Hydrostannation

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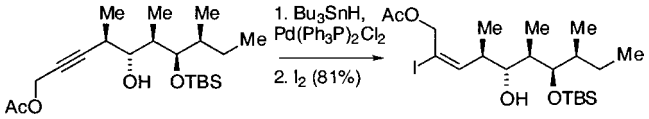
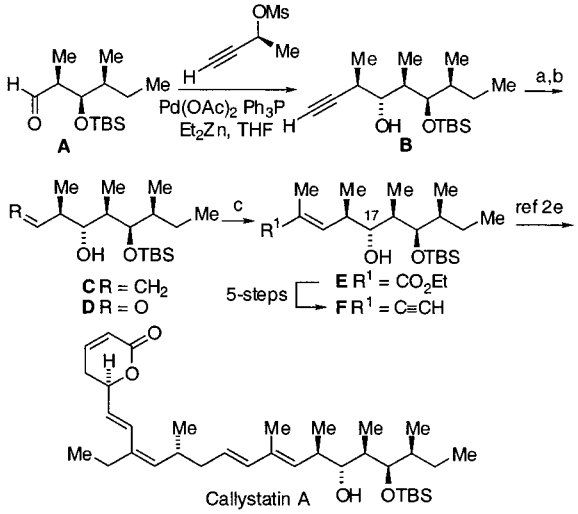
ABSTRACT



An improved route to the polypropionate segment of callystatin A is described in which the efficient directed hydrostannation of an internal alkyne and subsequent iodinolysis provides a key vinylic iodide intermediate.

The marine polyketide callystatin A has generated a great deal of interest since Kobayashi's initial report on its structure and isolation and his ensuing total synthesis.[1] Subsequently, no less than five additional total syntheses were completed.[2] Our own efforts were motivated by the reported levels of cytotoxic activity against several tumor cell lines (IC_{50} = 10 pg/mL against KB cells and 20 pg/mL against L1210 cells).[1] The sequence that we developed was highly convergent and well suited to the production of potentially bioactive analogues.[2e] A key feature of our approach to the C12−C22 polypropionate segment was the use of chiral allenyl tin and zinc reagents to control the relative and absolute stereochemistry (Figure 1).

Recently, we required an additional quantity of callystatin A for studies on differential cytotoxicity. This need provided an opportunity to reexamine a segment of our synthesis that we considered the least satisfactory whereby the homopropargylic alcohol **B** (itself the product of an allenyl zinc addition to aldehyde **A**) was converted to the enyne **F** by way of aldehyde **D** through a somewhat circuitous eight-



a) H_2/Pd-$BaSO_4$ (**B** → **C**); b) O_3, EtOAc; Ph_3P (**C** → **D**); c) Ph_3P=C(Me)CO_2Et (**D** → **E**).

Figure 1. Synthesis of the C12−C21 polyketide subunit of callystatin A.

(1) (a) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859. (b) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *39*, 2349.

(2) (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084. (b) Smith, A. B., III; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685. (c) Kalesse, M.; Quitschalle, M.; Khandavalli, C. P.; Saeed, A. *Org. Lett.* **2001**, *3*, 3107. (d) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751. (e) Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023.

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step sequence. The use of the alkyne moiety of adduct **B** as an aldehyde surrogate for **D**, though workable, was both unaesthetic and inefficient, as was the subsequent appendage of the alkynyl group of **F** via the Wittig ester product **E**. This approach also required that we temporarily protect the C17 alcohol as a TMS ether and then liberate the alcohol after an ensuing homologation step. A more integrated approach would employ the allenylzinc adduct **G** of aldehyde **A** as the precursor to enyne **F** by way of vinyl iodide **H**. This strategy takes direct advantage of the alkyne generated in the allenyl zinc addition to aldehyde **A**, and would allow the C17 alcohol to remain unprotected for the duration of the synthesis (Figure 2).

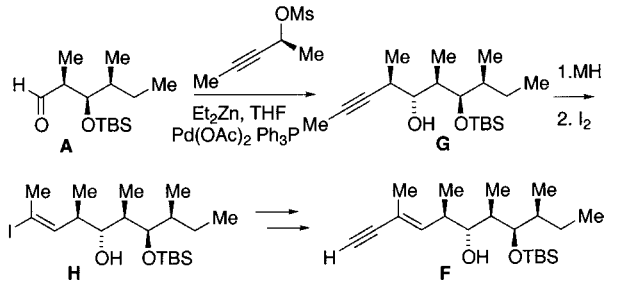
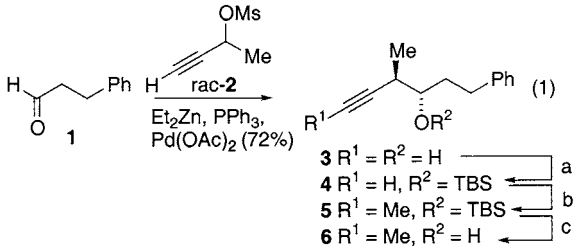


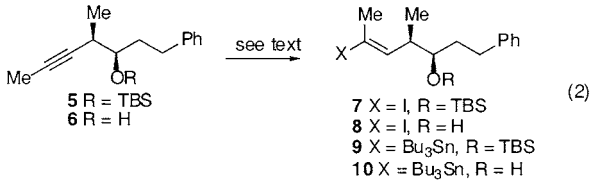
Figure 2. Proposed new route to the C12−C21 subunit of callystatin A.

The conversion of alkyne **G** to vinyl iodide **H** would be most directly achieved by a sequential syn hydrometalation and iodinolysis. However, we were somewhat concerned about both the reactivity of an internal alkyne as well as the regioselectivity of such a hydrometalation. These concerns prompted us to explore this reaction on a less complicated system than **G**. For this study, we prepared the homopropargylic alcohol **6** and silyl ether **5** from hydrocinnamaldehyde (**1**) and the allenylzinc reagent derived from the racemic butynyl mesylate **2**,[3] as outlined in eq 1.



a) TBSCl, Im, DMF (71%); b) BuLi, Me_2SO_4(65%); c) TBAF, THF (92%)

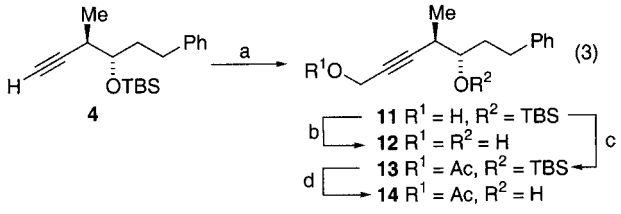
Our initial attention was directed at the hydrozirconation[4] of alkyne **5** and subsequent in situ iodinolysis (eq 2). The results proved to be quite unsatisfactory. The alkynyl TBS ether **5** afforded the vinyl iodide **7** in only 15% yield, and the derived alcohol **6** yielded an intractable mixture of products.



As a possible alternative approach to the vinylic iodide intermediate, we examined the Pd(0)-catalyzed hydrostannation of alkyne **5**. Although most investigators have reported low yields and poor regioselectivities of hydrostannations involving internal alkynes,[5−8] the findings of Benachie et al.[6] on an alkyne closely related to **5** and **G** prompted our consideration of the methodology.

Unfortunately, alkyne **5** proved to be quite unreactive under the reported conditions.[6] Starting material was largely recovered after prolonged reaction times, and none of the desired adduct **9** could be detected (eq 2). The alcohol **6** proved to be slightly more reactive, but the adduct **10** was produced in only 20% yield. Following these unpromising results, we noted a report by Miyake and Yamamoto,[7] who found that Pd(0)-catalyzed hydrostannation of 2-butyn-1-ol afforded a 15:85 mixture of (*E*)-3-(tributylstannyl)-2-buten-1-ol and (*E*)-2-(tributylstannyl)-2-buten-1-ol, suggestive of a directing effect by the propargylic OH.[8]

We postulated that the combination of this presumed directing effect and the presence of a branched alkyl substituent might conspire to enhance the regioselectivity in propargylic alcohols such as **11** (eq 3). Should this be the case, the resulting vinylic hydroxymethyl substituent could serve as a synthetic equivalent of a vinylic methyl group following hydrogenolysis of the allylic alcohol.

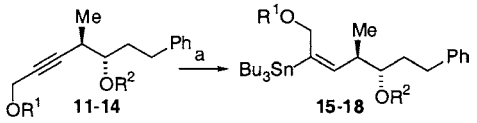


a) BuLi, $(CH_2O)_n$(65%); b) TBAF, THF, (63%); c) Ac_2O, Et_3N, DMAP (89%); d) TBAF, THF (82%)

The validity of this conjecture was tested on the aforementioned alcohol **11**, obtained by formylation of the lithio derivative of alkyne **4** (eq 3). We also prepared diol **12** and acetates **13** and **14** as possible substrates. These latter derivatives were of interest because of a formulated mechanistic pathway for a directed hydrostannation.[8]

(3) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.
(4) (a) Negish, E.-I. In *Organometallics in Synthesis*; Schlosser, M., Ed.; 2nd ed.; Wiley and Sons, Ltd.: Chichester, UK, 2002; p 934. (b) Buchwald, S. L.; LaMaire, S. J.; Nielson, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *34*, 3895. (c) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912.
(5) Cf.: Zhang, H.-X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
(6) Benachie, M.; Skrystrup, T.; Khuong-Huu, F. *Tetrahedron Lett.* **1991**, *32*, 7535.
(7) Miyake, H.; Yamakura, K. *Chem. Lett.* **1989**, 981.
(8) Rice, M. B.; Whitehead, S. L.; Horvath, C. M.; Muchnij, J. A.; Maleczka, R. E. *Synthesis* **2001**, 1495.

Table 1. Hydrostannation of Propargylic Alcohols and Acetates[a]



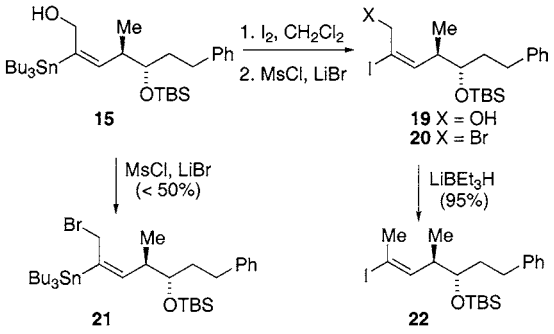
R^1	R^2	yield, %
H	TBS (**11**)	62 (**15**)
H	H (**12**)	65 (**16**)
Ac	TBS (**13**)	83 (**17**)
Ac	H (**14**)	89 (**18**)

[a] Reaction conditions: (a) Bu_3SnH, $Pd(Ph_3P)_2Cl_2$, THF.

In fact, the catalyzed hydrostannation of propargylic alcohol **11** gave vinylstannane **15** as the sole adduct (Table 1). Furthermore, the acetate derivative **13** was equally selective affording adduct **17** in high yield.[9] Similarly, diol **12** and monoacetate **14** provided the vinylstannanes **16** and **18** with excellent regioselectivity. The acetate results were especially encouraging, as we have previously shown that propargylic acetates such as **14** can be formed directly from aldehydes and allenylzinc and indium reagents generated in situ from the mesylate of enantiopure 4-acetoxymethyl-3-butyn-2-ol.[3]

Following this satisfactory solution to the hydrostannation regioselectivity problem, we turned our attention to the issue of hydrogenolysis. As a first step in this direction, we attempted the conversion of stannylated allylic alcohol **15** to bromide **21**. However, the rather unstable allylic bromide could be isolated in no greater than 50% yield (Scheme 1).[10]

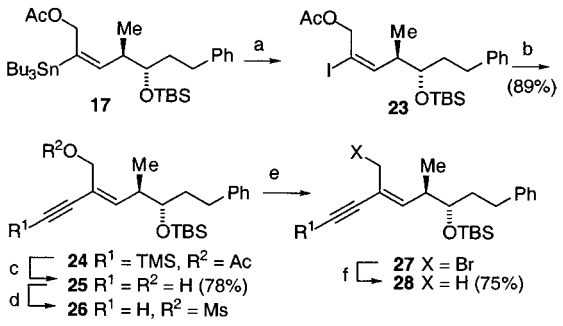
Scheme 1



An alternative route involving iodinolysis of stannane **15** followed by conversion of the derived iodo alcohol **19** to bromide **20** and ensuing treatment with Super Hydride[11] was more successful and afforded the vinylic iodide **22** in excellent yield.[12]

Pursuant to our intended application of the hydrostannation hydrogenolysis sequence, a third option was explored (Scheme 2). Accordingly, the acetoxymethyl stannane **17** was iodinated and the vinylic iodide **23** subjected to Sonogashira coupling[13] with TMS acetylene to afford the enyne **24**. Saponification of the acetate proceeded with concomitant desilylation to yield alcohol **25**, which was converted via mesylate **26** to bromide **27**. Hydrogenolysis with Super Hydride gave rise to enyne **28** in satisfactory overall yield.[14]

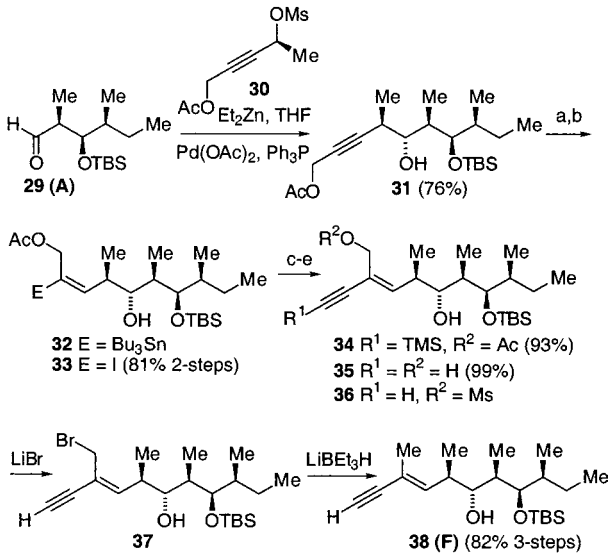
Scheme 2[a]



[a] Reaction conditions: (a) I_2, THF; (b) TMS acetylene, $Pd(PPH_3)_2Cl_2$, CuI, Et_3N; (c) NaOH; (d) MsCl, Et_3N; (e) LiBr; (f) $LiBEt_3H$.

Applying these findings to the callystatin problem, we effected addition of the allenylzinc reagent derived from mesylate **30**, of 95% enantiomeric purity, to aldehyde **29** to produce anti adduct **31** (Scheme 3). Pd-catalyzed hydrostan-

Scheme 3[a]



[a] Reaction conditions: (a) Bu_3SnH, $Pd(Ph_3P)_2Cl_2$; (b) I_2 (81% two-steps); (c) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, TMSC≡CH (93%); (d) NaOH (99%); (e) MsCl, Et_3N.

(9) Maleczka and co-workers have described hydrostannations of acetylenes substituted by $(CH_2)_nOR$ substituents, where R = H, Me, or various silyl groups, and $n = 1-4$.[8] They also examined the corresponding acetates where $n = 2-4$. Methyl propargyl ether exhibited the highest regioselectivity (70:30). Propargyl acetate ($n = 1$) was not examined because of its "reported instability under the reaction conditions." Cf.: Zhang, H. X.; Guibé, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 623.

(10) (a) Collington, E. W.; Myers, A. I. *J. Org. Chem.* **1971**, *36*, 3044. (b) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 7230.

nation of this propargylic acetate followed by iodinolysis gave vinylic iodide **33**, which was coupled with TMS acetylene and subsequently desilylated and saponified to afford the alcohol **35** in high yield. Hydrogenolysis of the hydroxymethyl group of alcohol **35** was effected by the previous two-step procedure to complete the sequence. Enyne **38** (**F** in Figure 1) was thus produced in 82% overall yield. This intermediate was converted to callystatin A along the lines of our previous report.[2d]

The present modified route to enyne **38** from stereotriad **29** proceeds with one less step and considerably higher efficiency (46 vs 30% overall yield) compared to the previous synthesis.[2d] The regioselective hydrostannation methodology should find additional applications in polyketide synthesis, as the propargylic acetate precursors can be prepared in high enantiomeric purity from chiral allenylmetal reagents. Furthermore, enynes such as **34** and **35** could serve as precursors to more highly oxygenated analogues of callystatin A and related biologically important natural products.[15] Studies along these lines will be disclosed in due course.[16]

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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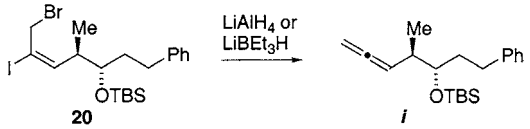
(11) Super Hydride = $LiBEt_3H$. Aldrich Catalog no. 19 972-8.

(12) An initial application of this hydrogenolysis procedure yielded the allene elimination product ***i*** exclusively. This result was subsequently not reproducible.



20 ***i***

(13) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(14) This procedure was developed by Greg Schaff in our laboratory. A detailed report will be forthcoming.

(15) For example, leptomycin and the leptofuranins: Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett.* **1998**, *39*, 8291. Hayakawa, Y.; Sohda, K. Y.; Seto, H. *J. Antibiotics* **1995**, 954.

(16) **(*E*)-*anti*-1-Acetoxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-7-phenyl-2-tributylstannyl-2-heptene (17). General Procedure for the Hydrostannation of Alkynes.** To a solution of propargylic acetate **13** (0.020 g, 0.054 mmol) in 1 mL of THF was added $(PPh_3)_2PdCl_2$ (0.0019 g, 0.0027 mmol). The reaction mixture was stirred for 5 min, and Bu_3SnH (0.021 mL, 0.080 mmol) was added dropwise over 1 min. The solution turned black, and H_2 was evolved toward the end of the addition. The reaction mixture was stirred for 15 min and concentrated under reduced pressure. Flash chromatography on silica gel (100% hexanes) afforded vinylstannane **17** (0.030 g, 83% yield) as a yellow oil: $R_f = 0.30$ (1% EtOAc−hexane); IR (film) 1737, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28−7.24 (m, 5H), 5.69 (dt, $J = 10.0$, 2.0 Hz, 1H), 4.85 (A of ABX, $J = 13.0$, 2.0 Hz, 1H), 4.78 (B of ABX, $J = 13.0$, 2.0 Hz, 1H), 3.62−3.56 (m, 1H), 2.70−2.51 (m, 3H), 2.05 (s, 3H), 1.74−1.69 (m, 2H), 1.52−1.44 (m, 6H), 1.34−1.28 (m, 6H), 0.98 (d, $J = 7.5$ Hz, 3H), 0.91−0.86 (m, 24H), 0.05 (s, 6H), ^{13}CNMR ($CDCl_3$) δ 170.76, 144.35, 142.46, 138.39, 128.32, 128.26, 125.66, 75.21, 66.62, 38.62, 36.96, 32.00, 29.11, 27.32, 25.41, 21.03, 18.11, 17.26, 13.67, 10.03, −4.19, −4.42. Anal. Calcd For $C_{34}H_{62}O_3SiSn$: C, 61.35; H, 9.39. Found: C, 61.49; H, 9.50.