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Total Synthesis of (–)-Callystatin A

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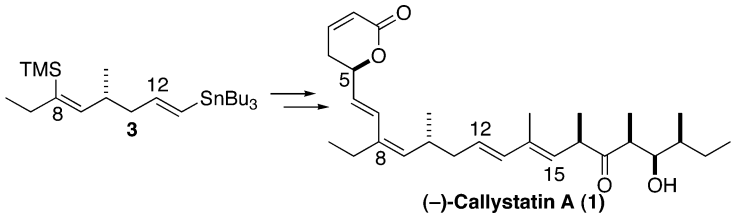
ABSTRACT



A convergent enantioselective synthesis of the natural product (–)-callystatin A (1) is described. Key features of the synthesis include a lipase-mediated kinetic resolution to install the C5 lactone stereochemistry, a hydrozirconation-based approach to the C8–C9 trisubstituted (*Z*)-olefin, and a stereoselective cross-coupling of a vinyl dibromide to install the C14–C15 trisubstituted (*E*)-olefin.

(−)-Callystatin A (**1**) is a polyketide-based natural product isolated in 1997 by Kobayashi and co-workers from the marine sponge *Callyspongia truncata*.[1] Initial biological testing[1,2] revealed remarkable antiproliferative properties (IC_{50} values 10 and 20 pg/mL vs KB and L1210 cell lines, respectively), derived from (−)-callystatin A's ability to interfere with nuclear export signal (NES) dependent protein transport. Structure−activity relationship analysis indicates that the δ-lactone is the principle pharmacophore, although no enhancement of biological activity through analogue synthesis has been reported.[3] (−)-Callystatin A's potent cytotoxicity, along with its challenging structure, has stimulated much attention, culminating in seven total syntheses to date.[4,5]

Our retrosynthetic analysis of (−)-callystatin A (**1**) relies on bond disconnections at the two conjugated dienes, where transition-metal-mediated cross-coupling reactions would enable assembly from three advanced intermediates at a late stage in the synthesis (Scheme 1). Fragment **3** possesses both a vinyl iodide equivalent (vinyl TMS) and a vinylstannane, thereby allowing carbon−carbon bond formation at C13−C14 and C7−C8 in a predetermined sequence. A hydrozirconation−iodination protocol developed in our laboratory facilitates stereoselective installation of the C8-ethyl substituent in **3**, where alkyne **6** serves as the appropriate starting material.[6] Diene RCM provides access to lactol **2**, with C7−C8 bond formation planned through a tandem hydrozirconation−Negishi coupling protocol.[7] Chiral organosilane-mediated bond construction[8] enables stereoselective synthesis

(1) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859−2862.

(2) (a) Murakami, N.; Sugimoto, N.; Tsutsui, Y.; Nakajima, T.; Higuchi, K.; Aoki, S.; Yoshida, M.; Kudo, N.; Kobayashi, M. *Abstracts of Papers, 41st Symposium on the Chemistry of Natural Products*, Nagoya, October 1999, pp 229−234. (b) For a discussion of the biological activity of (−)-callystatin A, leptomycin, and related compounds, see: Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981−1003.

(3) (a) Murakami, N.; Sugimoto, M.; Nakajima, T.; Kawanishi, M.; Tsutsui, Y.; Kobayashi, M. *Bioorg. Med. Chem.* **2000**, *8*, 2651−2661. (b) Murakami, N.; Sugimoto, M.; Kobayashi, M. *Bioorg. Med. Chem.* **2001**, *9*, 57−67.

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(5) For additional studies toward fragment synthesis, see: (a) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett.* **2002**, *43*, 185−187. (b) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett.* **2002**, *43*, 1593. (c) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett.* **2002**, *43*, 8883−8885.

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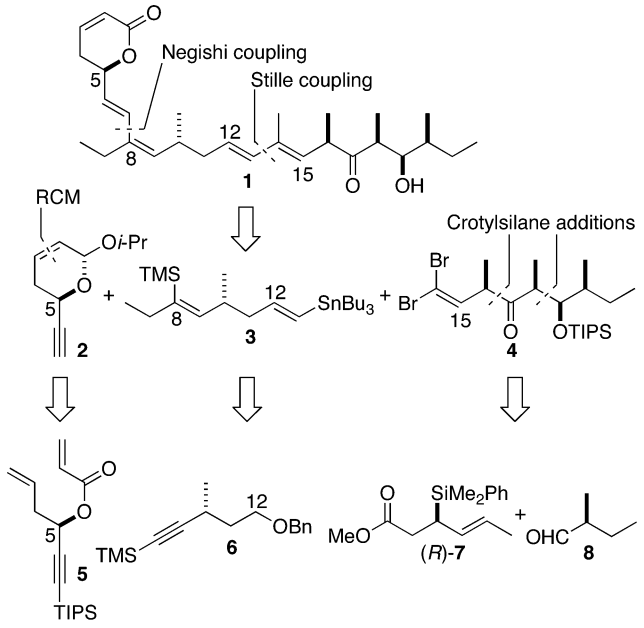
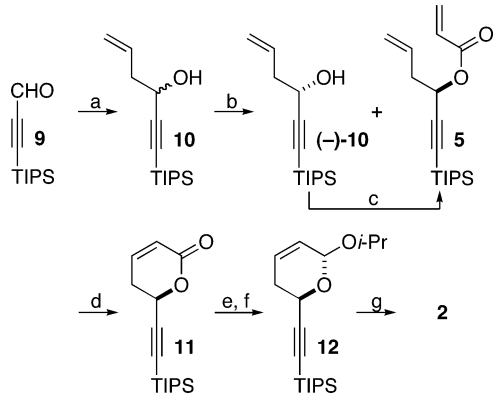
Scheme 1. Retrosynthetic Analysis of (−)-Callystatin A (**1**)



of **4**, with a Stille reaction proposed to form the C13−C14 bond.[9] It is worthy to note that unlike other completed syntheses of (−)-callystatin A, our approach does not include a Still−Gennari reaction for the formation of the trisubstituted C8−C9 (*Z*)-alkene[4a−h] or a phosphorus-based olefination for the trisubstituted C14−C15 (*E*)-alkene.[4a−c,g−h]

Grignard reaction between allylmagnesiumbromide and **9**[10] initiated the synthesis of fragment **2** (Scheme 2), providing racemic propargyl alcohol **10** in excellent yield. Structural similarities between **10** and the known allylic alcohol **13**[11] suggested that this substrate might participate in an enantioselective kinetic resolution with lipase *Pseudomonas* AK,[12]

Scheme 2. Synthesis of Lactol **2**[a]



[a] Reagents, conditions, and yields: (a) allylmagnesium bromide, THF, −20 °C, >99%; (b) vinyl acrylate, lipase AK, hexanes, 7 days, rt, 44% (−)-**10**, 46% **5**; (c) DIAD, acrylic acid, PPh_3, THF, 0 °C to rt, 86%; (d) Grubbs I, CH_2Cl_2, 40 °C, 83%; (e) DIBAL-H, −78 °C, CH_2Cl_2; (f) *i*-PrOH, PPTS, PhH, 80 °C, 82% (two steps); (g) 1.3:1 AcOH/TBAF, THF, rt, 91%.

in the presence of the transesterifying agent vinyl acetate (Figure 1). As anticipated, **10** reacted under these conditions

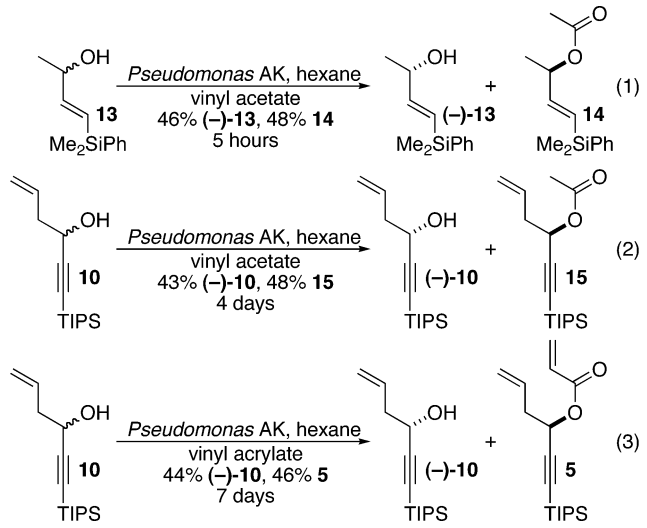


Figure 1. Lipase *Pseudomonas* AK mediated kinetic resolution of **13** (eq 1, ref 11) and **10** in the presence of vinyl acetate (eq 2) and vinyl acrylate (eq 3).

to produce (*R*)-acetate **15** in 48% yield and >95% ee.[13] With this result in hand, we hypothesized that a similar reaction in the presence of vinyl acrylate might resolve **10** with concomitant installation of the requisite acrylate ester on the desired (*R*)-enantiomer. Gratifyingly, this biocatalytic resolution proceeded with excellent stereoselectivity, providing (*R*)-**5** directly in a one-pot process in 46% yield and >95% ee.[13,14] Following chromatographic separation of **5** and (−)-**10**, a Mitsunobu reaction transformed unreacted (−)-**10** to **5** with complete stereochemical inversion. Ruthenium-catalyzed RCM,[15] lactone protection as the isopropoxy acetal, and removal of the silicon protecting group completed the synthesis of **2** in a six-step sequence in 51% overall yield.

The synthesis of fragment **3** from aldehyde **16**[16] commenced with a four-step sequence featuring a hydrozircona-

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(9) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873−8879.

(10) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427−6428.

(11) Sparks, M. A.; Panek, J. S. *Tetrahedron Lett.* **1991**, *32*, 4085−4088.

(12) *Pseudomonas* AK lipase was purchased from Amano International Enzyme Co.

(13) The ee of recovered (*S*)-**10** was >95%. See the Supporting Information for full characterization and the stereochemical assignments of **5** and **15**.

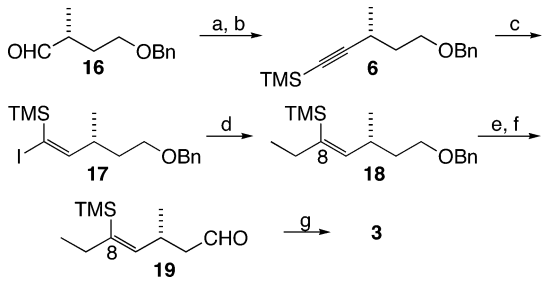
(14) For an example of lipase-mediated acryloyl transfer, see: Bisht, K. S.; Gross, R. A.; Kaplan, D. L. *J. Org. Chem.* **1999**, *64*, 780−789.

(15) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452.

(16) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

tion-iodination method[6] for the installation of the requisite C8-ethyl substituent in the trans configuration (Scheme 3).

Scheme 3. Synthesis of Vinyl Stannane **3**[a]

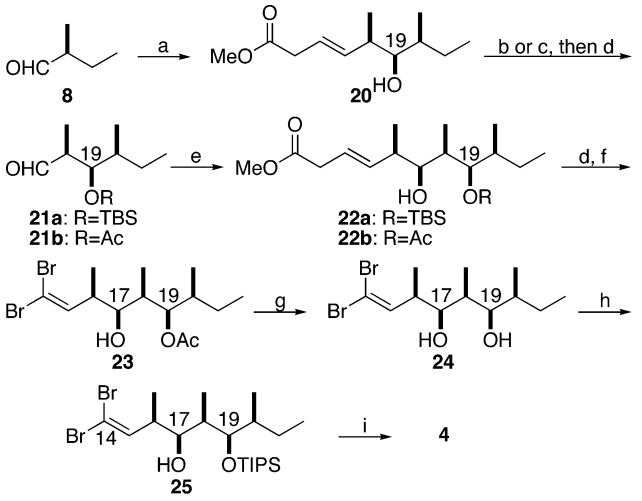


[a] Reagents, conditions, and yields: (a) CBr_4, PPh_3, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 96%; (b) *n*-BuLi, THF, −78 °C, then TMSCl, −78 °C to rt, 98%; (c) Cp_2ZrHCl, THF, 50 °C, 1 h, then I_2, THF, rt, 89%, >20:1 crude dr; (d) EtZnX, $Pd(PPh_3)_4$, THF, rt, 96%; (e) DDQ, CH_2Cl_2/H_2O, rt, 83%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; 92%; (g) $CrCl_2$, Bu_3SnCHI_2, DMF, 0 °C to rt, 68%, *E*/*Z* >20:1.

We have shown that upon exposure to an electrophilic iodine source (I_2, NIS), iododesilylation of **18** occurred with retention of alkene configuration. However, we felt that elaboration of the benzyl ether moiety into the corresponding vinylstannane, prior to iodide formation and cross-coupling, would represent a more convergent approach. Accordingly, treatment of **18** with DDQ followed by Swern oxidation[17] yielded aldehyde **19**, which participated in a chromium(II)-mediated vinylstannation[18] with freshly prepared Bu_3SnCHI_2 to complete the preparation of **3** in seven steps from aldehyde **16**.

Organosilane reagents such as **7** provide rapid access to polypropionate fragments with high levels of selectivity. At first glance, the all-syn C16−C20 stereochemistry in (−)-callystatin A is a readily accessible target, with the (*R*)-configuration of **7** directing the C16 and C18 methyl stereocenters. Accordingly, our synthesis began with treatment of aldehyde **8**[19] with (*R*)-**7** in the presence of $TiCl_4$ to yield homoallylic alcohol **20** as the syn−syn product in 84% yield (Scheme 4). Protection of **20** as a silyl ether and oxidative cleavage afforded aldehyde **21a**, setting the stage for a second crotylation reaction. However, exposure of **21a** to (*R*)-**7** in the presence of $TiCl_4$ produced homoallylic alcohol **20** in >80% yield, with no trace of desired alcohol **22a**. We rationalize that a Lewis acid promoted deprotection−retroaldol−crotylation sequence led to exclusive formation of undesired **20**. Indeed, the analogous reactions with other acid-sensitive ether protecting groups at C19 (OBn, OTES) yielded similar results.[20] To alleviate this difficulty,

Scheme 4. Synthesis of Vinyl Dibromide **4**[a]



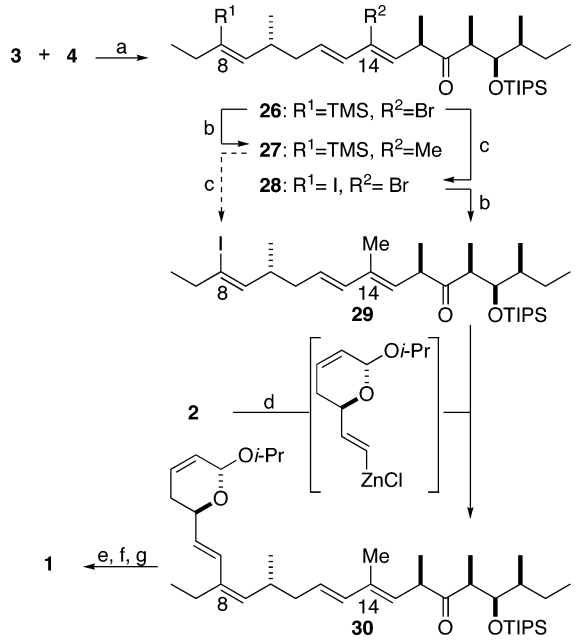
[a] Reagents, conditions, and yields: (a) (*R*)-**7**, $TiCl_4$, CH_2Cl_2, −30 °C, 84%, 10:1 crude dr; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 92%; (c) Ac_2O, pyr, DMAP, CH_2Cl_2, rt, 99%; (d) O_3, pyr, $MeOH/CH_2Cl_2$, −78 °C, then Me_2S; (e) (*R*)-**7**, $TiCl_4$, CH_2Cl_2, −30 °C, **21a** to **22a**: 0%; **21b** to **22b**: 68% (two steps), >20:1 crude dr; (f) CBr_4, PPh_3, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 82% (two steps); (g) K_2CO_3, MeOH, rt, 99%; (h) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 90%; (i) PCC, CH_2Cl_2, rt, 85%.

the acetate analogue **21b** was synthesized and subjected to crotylation conditions. Although **21b** proved remarkably unreactive, prolonged reaction time (−30 °C, 2 d) resulted in formation of the desired homologated alcohol **22b** in good yield. Ozonolytic cleavage and dibromoolefination[21] of the free alcohol[22] directly provided **23**, possessing the fragment's full C14−C22 carbon skeleton. Concerned with removal of the C19 acetate at a late stage, we carried out a two-step protecting group exchange sequence to generate **25**. Interestingly, TIPS protection of diol **24** proceeded with complete regioselectivity at C19, suggesting the different steric environments of the two alcohol functionalities. Oxidation of **25** using PCC completed the advanced fragment **4** in nine steps and 32% overall yield from **8**.

With access to the three advanced fragments, we envisioned the rapid assembly of (−)-callystatin A beginning with C13−C14 carbon−carbon bond formation (Scheme 5). A Pd_2dba_3-mediated cross-coupling[9] between stannane **3** and dibromide **4** yielded vinyl bromide **26**, with the desired (*E*,*Z*)-diene as the only observed product isomer. Installation of the C14-methyl group by the Negishi protocol[23] proceeded smoothly without epimerization or nucleophilic addition to the ketone. Treatment of **27** with the electrophilic iodine source NIS,[24] however, resulted in undesired regioselective iodination of the C14−C15 olefin. Close inspection of the

(17) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.
(18) (a) Hodgson, D. M.; Boulton, L. T.; Maw, G. N. *Tetrahedron* **1995**, *51*, 3713−3724. (b) Hodgson, D. M.; Foley, A. M.; Boulton, L. T.; Lovell, P. J.; Maw, G. N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2911−2922.
(19) White, J. D.; Bolton, D. L.; Dantanarayana, A. P.; Fox, C. M. J.; Hiner, R. N.; Jackson, R. W.; Sakuma, K.; Warrier, U. S. *J. Am. Chem. Soc.* **1995**, *117*, 1908−1939.
(20) Hydroxy aldehyde (**21**, R = H) displayed similar reactivity.
(21) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.
(22) Unusual reactivity of similar intermediates has been reported. See refs 4a,e,f and 5b for details.
(23) For application in related ene−yne systems, see: Shi, J.; Zeng, X.; Negishi, E. *Org. Lett.* **2003**, *5*, 1825−1828.
(24) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647−8650.

Scheme 5. Assembly and Completion of (−)-Callystatin A[a]



[a] Reagents, conditions, and yields: (a) Pd_2dba_3, P(2-fur)$_3$, PhMe, 100 °C, 92%; (b) Me_2Zn, Pd(*t*-$Bu_3P)_2$, THF, 0 °C, **26** to **27**: 96%; **28** to **29**: 93%; (c) NIS, EtCN, **26** to **28**: 84%; (d) (i) Cp_2ZrHCl, THF, rt, (ii) $ZnCl_2$, THF, (iii) **29**, Pd(PPh$_3)_4$, rt, 51%; (e) AcOH, wet THF, rt; (f) PDC, CH_2Cl_2, rt, 74% (two steps); (g) HF/pyr, THF, rt, 88%.

^{1}H NMR spectrum of **27** (Figure 2) shows the electron-rich nature of the C14−C15 alkene relative to the C8−C9 olefin, explained by the strong donor capability of the C14-methyl substituent. Comparison to the ^{1}H NMR spectrum of bromide **26**, however, revealed the possibility of successful iododesilylation on this alternate substrate. Indeed, exposure of **26** to NIS resulted in regioselective addition of I^+ to the C8 carbon, with retention of alkene stereochemistry. Iodo bromide **28** underwent regioselective *bromide* cross-coupling upon treatment with Me_2Zn in the presence of Pd catalyst to form **29**. We postulate that the electron-donating effect of the C8-ethyl group may deactivate the vinyl iodide, providing entry into oxidative addition of the relatively electron-deficient C14-bromide.[25] In summary, this sequence provided fully functionalized iodide **29** in three steps from stannane **3** and vinyl dibromide **4**. Subjection of **2** to Schwartz's reagent followed by in situ treatment with $ZnCl_2$ produced a vinylzinc species that participated in a Pd-catalyzed Negishi coupling with **29** to afford the protected natural product **30** in 51% yield.[26] Completion of the synthesis proceeded through AcOH-promoted lactol deprotection, oxidation, and fluoride-mediated removal of the silyl ether (65% over three steps). Synthetic (−)-callystatin A possesses spectroscopic properties identical to those reported for the natural product.[1,4]

(25) For a discussion of electronic effects in Pd-mediated cross-couplings, see: Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

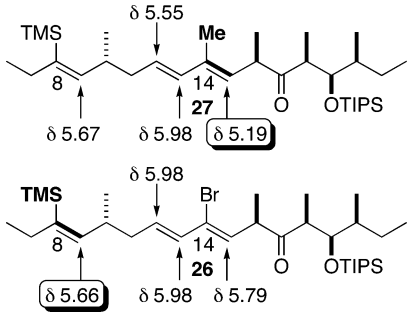


Figure 2. ^{1}H NMR chemical shifts (in ppm) as a measure of relative alkene electronegativity in **27** and **26**. Upon exposure to NIS, highlighted alkenes undergo regioselective electrophilic iodination.

In summary, we have developed an effective synthetic strategy for the total synthesis of (−)-callystatin A, utilizing cross-coupling reactions for the union of three highly functionalized fragments. The approach demonstrates the effectiveness of selective dibromide cross-coupling reactions and features a complimentary hydrozirconation−iodination approach for the stereoselective synthesis of trisubstituted alkenes. These methods should find utility in the synthesis of other related natural and unnatural molecules of biological importance.

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Supporting Information Available: Spectroscopic data and experimental procedures for all new compounds; key spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Reproducibly, iodide **29** was recovered in 20−30% yield from this reaction. Attempts to increase iodide conversion to desired coupling product were unsuccessful.