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Total Synthesis of (−)-Callystatin A

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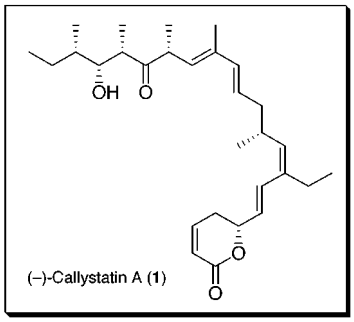
ABSTRACT



An effective total synthesis of (−)-callystatin A (1), member of the leptomycin family of antibiotics, has been achieved. The synthesis features Evans extended aldol methodology to construct the northern polypropionate subunit and two separate Julia olefinations to assemble the conjugated dienes. The total synthesis proceeded in 2.3% overall yield with the longest linear sequence of 15 steps.

In 1997 Kobayashi and co-workers disclosed the isolation and planar structure of (−)-callystatin A (**1**), a remarkably potent cytotoxic agent (e.g., IC_{50} 0.01 ng/mL in vitro against the KB cancer cell line).[1] Subsequently, the Kobayashi group confirmed the relative and absolute stereochemistries of (−)-**1** via partial[2] and total synthesis,[3] and then quite recently reported construction of several structural analogues[4] which provide insight on the structure−activity relationships (SAR). Crimmins and King[5] have also achieved an effective total synthesis of (−)-callystatin A (**1**).[6]

(−)-Callystatin A (**1**) possesses a number of structural features in common with the enzyme inhibitor (−)-ebelactone A,[1,7,8] (**2**) (Figure 1), the immunosuppressant (−)-pironetin[9,10] (**3**), and several other antibiotics.[11] Most similar to (−)-callystatin A (**1**), however, is leptomycin B[12a] (**4**), an antitumor agent shown to exhibit a similar cytotoxic profile.[12b]

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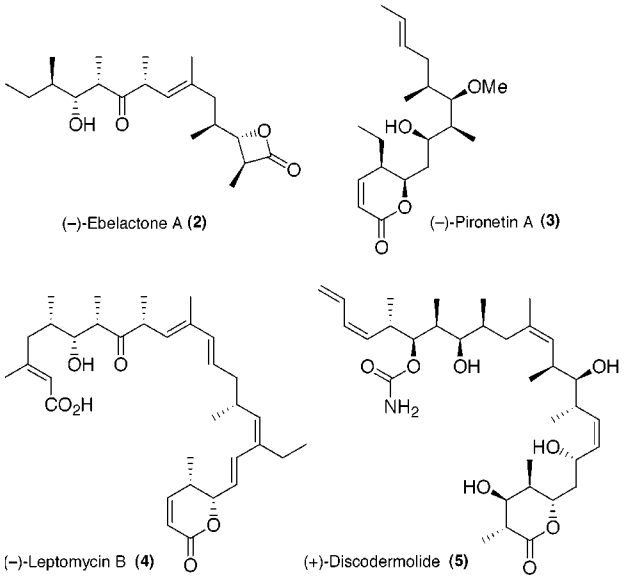


Figure 1. (−)-Callystatin A (**1**), a member of the Leptomycin family of antibiotics, shares certain structural characteristics with (−)-ebelactone B (**2**), (−)-pironetin A (**3**), and (+)-discodermolide (**5**).

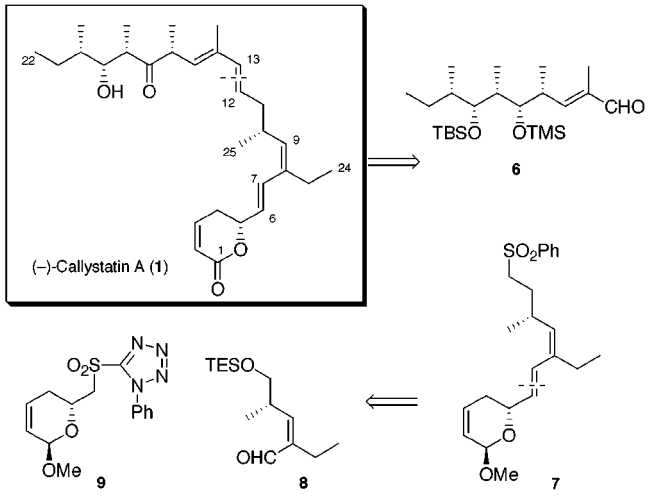
Our interest in (−)-callystatin A (**1**) derived from the structural similarity to (+)-discodermolide (**5**), a tubulin stabilizer.[13] To differentiate these modes of action, we embarked on a total synthesis that would provide sufficient quantities of (−)-callystatin A (**1**) for detailed biological analysis.

Our retrosynthetic plan (Scheme 1) called for late-stage installation of the C(12−13) *E*-olefin via Julia[14] coupling between enal **6** and sulfone **7**. Further analysis of diene **7** suggested a second Julia coupling between enal **8** and Kocienski[15] sulfone **9** to set the C(6−7) *E*-olefin geometry.

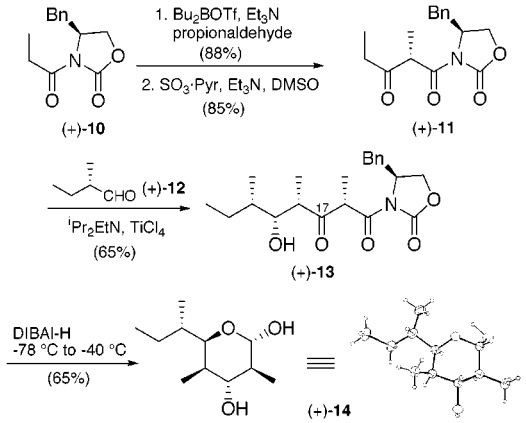
The synthesis of advanced enal **6** (Scheme 2) began with the addition of acyloxazolidinone (+)-**10**[16] to propionaldehyde to furnish the Evans[17] *syn*-aldol in 88% yield with complete diastereoselectivity.[18] Subsequent Parikh−Doering oxidation furnished the *β*-ketoamide (+)-**11**[18] (85%). The titanium enolate derived from (+)-**11** was then treated with aldehyde (+)-**12**, the latter prepared in one step from commercially available (*S*)-(−)-2-methyl-1-butanol, to provide the mismatched aldol (+)-**13**, with a *syn/anti* selectivity of 4:1 (65%).[19] Reduction with diisobutylaluminum hydride (DIBAl-H) next led, in 65% yield, to lactol (+)-**14**, the product resulting from stereoselective reduction of the C(17) carbonyl, removal of the chiral auxiliary, and lactol formation. As an added benefit, lactol (+)-**14** proved to be crystalline; the structure was confirmed by single-crystal X-ray analysis.

Wittig reaction of (carbethoxyethylidene)triphenylphosphorane with lactol (+)-**14** (Scheme 3) next furnished the α,*β*-unsaturated ester (+)-**15** in 96% yield with 10:1 *E*:*Z* selectivity. To remove the minor olefinic isomer, the mixture was subjected to lactonization (catalytic camphorsulfonic acid in $CHCl_3$), thereby permitting ready removal of the *Z* isomer by column chromatography. Selective protection of (+)-**15** was then achieved with 10:1 chemoselectivity via exposure to *tert*-butyldimethylsilyl triflate at −78 °C, to furnish the C(19) mono silyl ether in 45% yield. Higher conversions led to bis-silylation. Although the observed chemoselectivity was fortuitous, the result permitted orthogonal silylation of the remaining C(17) hydroxyl with TMSOTf and 2,6-lutidine to furnish the fully protected ethyl ester (+)-**16**. Recycling expedited material advancement. DIBAl-H reduction and MnO_2 oxidation then secured (+)-**6** for the proposed late-stage Julia coupling (68% yield; two steps).

Scheme 1



Scheme 2



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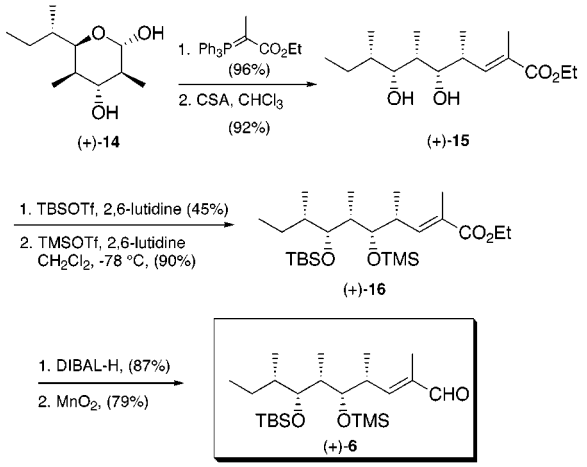
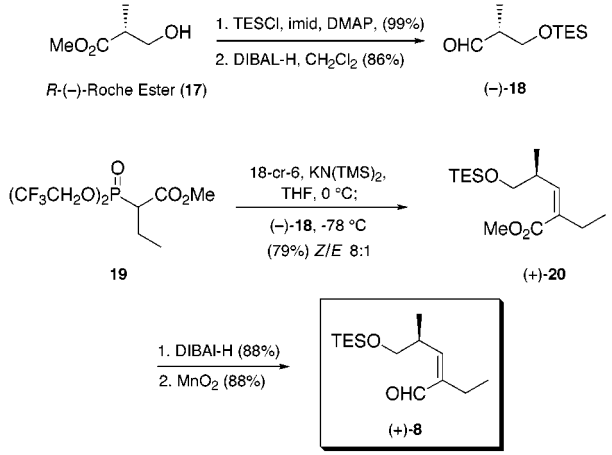
Scheme 3



Turning to advanced sulfone **7** (Scheme 1), we reasoned that **7** should be available via union of enal **8** with Kocienski[15] sulfone **9**. The synthesis of **8** began with protection of the commerically available (*R*)-(−)-Roche ester (**17**) as the TES ether (Scheme 4); reduction with DIBAl-H

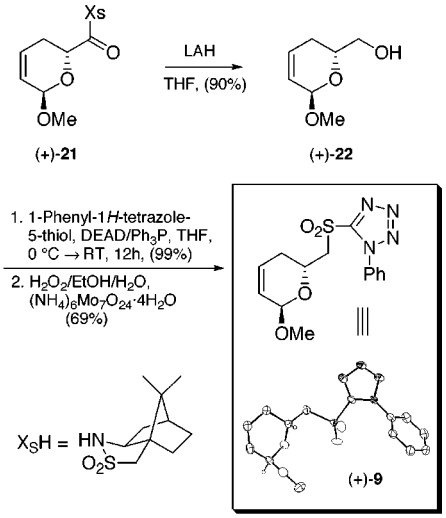
Scheme 4



at −78 °C then furnished aldehyde (−)-**18** in 86% yield. Still−Gennari Wittig[20] coupling of phosphonate **19**[21] with (−)-**18**[22] led to (+)-**20** in 79% yield; the *Z*:*E* selectivity was 8:1. A two-step reduction/oxidation sequence completed the synthesis of (+)-**8**.

To construct acetal (+)-**21**[23] (Scheme 5), the starting point for sulfone **9**, we exploited the known asymmetric hetero-Diels−Alder reaction. Acetal (+)-**21** was then reduced to

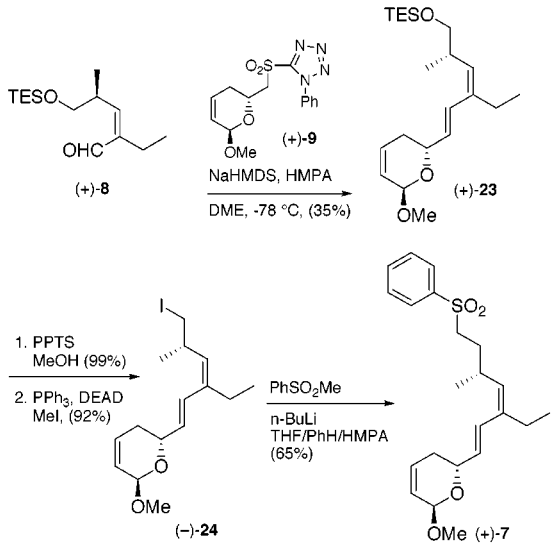
Scheme 5



the corresponding primary alcohol (+)-**22**.[23] Purification of (+)-**22** (90%) was best performed by bulb-to-bulb distillation. A Mitsunobu protocol[24] efficiently installed the phenyl tetrazole sulfide moiety (99% yield); oxidation with hydrogen peroxide−ammonium molybdate completed construction of sulfone (+)-**9** in 69% yield. X-ray analysis secured the structure of (+)-**9**.

Assembly of diene (+)-**23** was achieved by treatment of a DME solution of (+)-**8** and (+)-**9** with NaHMDS in the presence of HMPA (Scheme 6). Although the yield of (+)-

Scheme 6



23 was at best modest (ca. 35%), the *E*-olefin was the exclusive product. The low yield was due to facile β-elimination of sulfone (+)-**9** leading to decompostition. Use of

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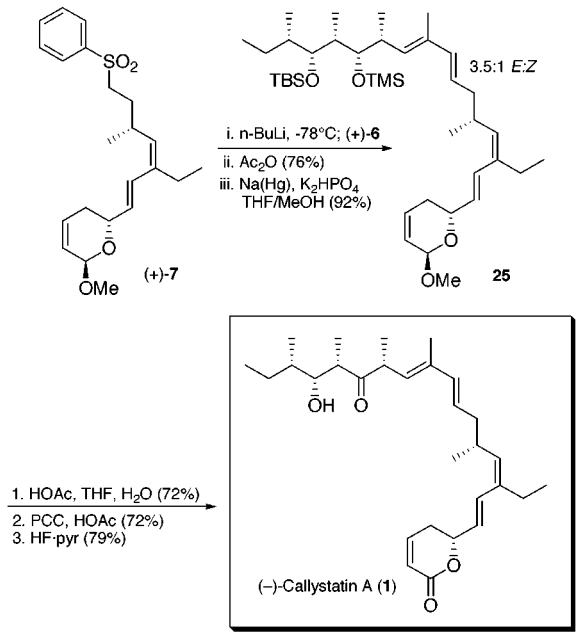
DME as solvent with 1 equiv of HMPA proved essential to minimize this competing process. Removal of the TES group (catalytic PPTS/methanol) followed by iodination (PPh_3, DEAD, iodomethane)[25] furnished (−)-**24** (91%, two steps), which was then converted to sulfone (+)-**7** in 65% yield via displacement of the iodide with the anion derived from phenyl methyl sulfone.

With the stage set to assemble the complete callystatin carbon skeleton (Scheme 7), addition of the lithium anion

Scheme 7



derived from sulfone (+)-**7** (*n*BuLi, HMPA) to aldehyde (+)-**6** followed by acetic anhydride afforded a mixture of acetates in 76% yield. Sodium amalgam reduction cleanly led to **25** in 92% yield as a mixture of *E*:*Z* olefinic isomers (3.5:1), favoring the desired *E*-isomer. Exposure of this mixture to aqueous acetic acid in THF effected hydrolysis of both the C(17) trimethylsilyl ether and C(1) methyl acetal to furnish the corresponding lactol in 72% yield. Although the olefinic isomers proved separable at this juncture, we found that better results could be obtained when the separation was performed on the subsequent, more stable ketolactone. To arrive at the ketolactone, several oxidation protocols were examined. Ultimately we discovered that PCC activated with acetic acid provided the best yield (72%) of the penultimate precursor for callystatin A (**1**). Completion of the (−)-callystatin A (**1**) synthetic venture was then achieved by removal of the TBS ether (HF·Pyr, 79% yield); the spectral data observed for synthetic (−)-callystatin A (**1**) were identical in all respects to those reported for the natural material (e.g., ^1H and ^{13}C NMR, HRMS, optical rotation, and IR).

In summary, an effective synthesis of (−)-callystatin A (**1**) has been achieved, with the longest linear sequence requiring 15 steps. The overall yield was 2.3% with an average yield of 78% per step. Studies to probe the mode of action of (−)-callystatin A (**1**) are currently underway.

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Supporting Information Available: Spectroscopic and analytical data for compounds **1**, **7**, **14**, **20**, **23**, and **25** as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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