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COMMUNICATION

An iterative Shimizu non-aldol approach for the stereoselective synthesis of C13-C22 fragment of callystatin A†

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An efficient synthesis of the polypropionate framework of callystatin A has been achieved by utilizing the Shimizu reaction in an iterative fashion.

Drugs derived from natural products play a dominant role in the treatment of numerous diseases, particularly against cancer. Remarkable efforts have been made in the last few decades, to discover natural products exhibiting high antitumor activity. In this regard, polyketide natural products have generated a great deal of interest owing to their potent biological properties against various human tumor cell lines. During the investigation of new anticancer agents belonging to the polyketide family with a novel mode of action, extremely potent cytotoxic natural products, namely leptomycins were discovered.[1] Due to their impressive antitumor activity, members of the leptomycin family provide hope for developing therapeutically useful anticancer agents. Despite their isolation from various sources, these molecules were grouped in the same family due to their structural as well as functional similarities and named after the first biologically investigated molecule, leptomycin B **1b** (Fig. 1).[2]

In view of their interesting biological properties and challenging structural features, numerous groups have embarked on total syntheses of leptomycins. As a result, several total syntheses of members of this class have been reported in the literature.[3,4] Molecular complexity, dense functionality and the presence of numerous asymmetric centers in leptomycins have made their synthesis a challenging task. Inspired by their complex architecture coupled with interesting medicinal properties, and in continuation of our interest in the synthesis of biologically active natural and unnatural products,[5,6] especially anticancer agents, we became involved in developing a unified strategy for the synthesis of members of the leptomycin family. Structurally, leptomycins have a complex molecular framework and controlling the stereochemistry of the polypropionate unit remains the most challenging task. Most of the syntheses known for the leptomycin family involve the use of asymmetric aldol reactions, metal allyl or allenyl addition reactions to construct

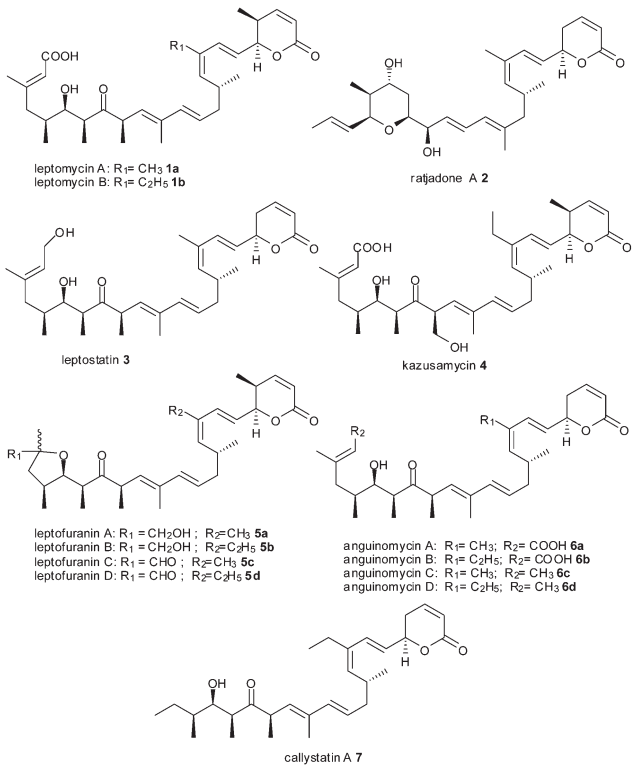

Fig. 1 Members of the leptomycin family.

the desired stereocenters of the polypropionate unit. We had earlier reported[6] a highly stereoselective formal synthesis of palmerolide A, where we utilized a Pd-catalyzed hydrogenolysis (Shimizu reaction)[7] to synthesize the *syn*-alcohol moiety. The efficacy of the Shimizu reaction prompted us to extend this rarely explored methodology in an iterative fashion to construct the complex polypropionate framework of leptomycins and herein we report an efficient synthesis of the polypropionate unit of callystatin A **7**.

Callystatin A **7** was isolated from the marine sponge, *Callyspongia truncata*, in the Nagasaki Prefecture by Kobayashi and co-workers in 1997.[8] It shows remarkable *in vitro* cytotoxicity against KB cells (IC_{50} = 0.01 ng mL^{-1}) and against L1210 cells (IC_{50} = 0.02 ng mL^{-1}). The relative and absolute stereostructures of callystatin A were established through a combination of

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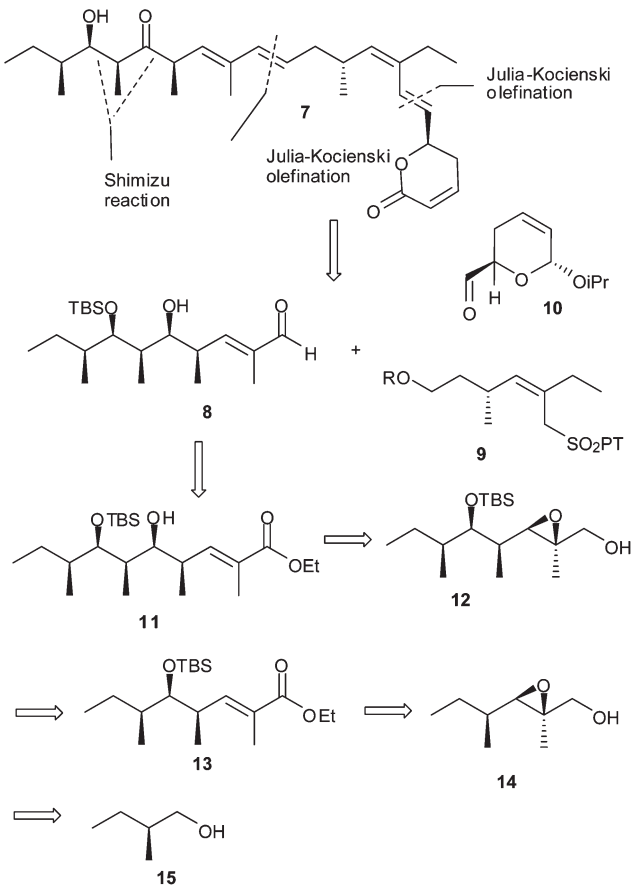
spectroscopic methods and chemical synthesis.[9] From the structural point of view, callystatin A is amply complex with several chiral centers, five double bonds, and a pyranone moiety at the peripheral position. Several total syntheses[3] and a few partial syntheses[10] of callystatin A **7** have been reported so far.

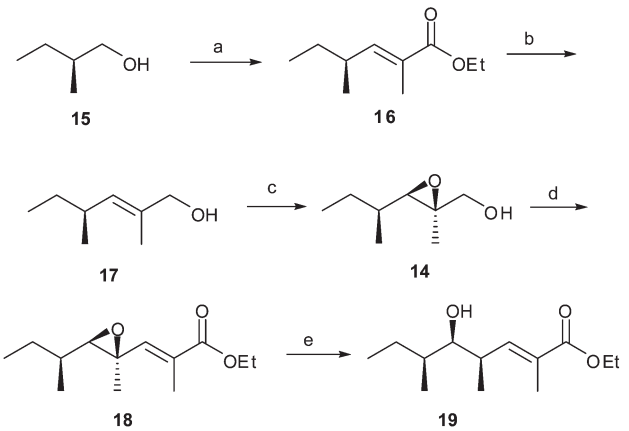
According to our designed unified approach, we envisaged that the synthesis of callystatin A **7** could be achieved by coupling three key fragments *viz.* aldehyde **8**, sulfone **9**, and pyran-aldehyde **10**, using two Julia–Kocienski olefination reactions.[11] Aldehyde **8** could be synthesized from ester **11**, which, in turn, could be obtained from epoxy alcohol **12** by employing a sequence of oxidation, Wittig olefination and Shimizu reaction of the resulting alkenyloxirane (Scheme 1). The epoxide **12** could then be obtained from the conjugated ester **13** through LAH reduction followed by Sharpless asymmetric epoxidation. Repeating the same sequence of oxidation, Wittig olefination followed by palladium-catalyzed hydrogenolysis of epoxide **14** would afford ester **13**. Alcohol **14**, in turn, could be achieved from the commercially available inexpensive amyl alcohol **15**.

As depicted in the retrosynthesis, our synthetic journey began with the preparation of alcohol **17**, starting from commercially available (*S*)-amyl alcohol **15** by following the known protocol.[12] A Sharpless epoxidation[13] of allylic alcohol **17** afforded the epoxy alcohol **14** (in 10 : 1 diastereomeric ratio by ^{1}H NMR). Upon oxidation of alcohol **14**, the resultant aldehyde was subjected to Wittig reaction to afford the conjugated ester **18**, thus setting the stage for Shimizu reaction. Pleasingly, the Pd-catalyzed opening of alkenyl oxirane **18** proceeded smoothly to deliver the *syn*-alcohol **19** in high yield (Scheme 2).

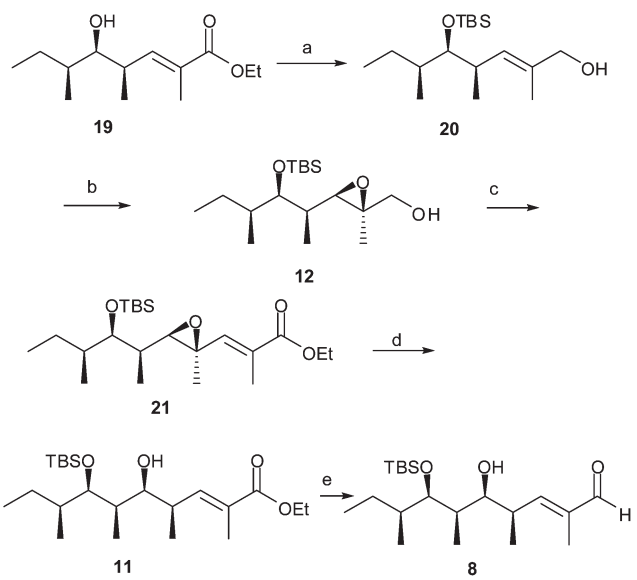
Further, protection of alcohol **19** as a TBS ether and subsequent reduction with LAH furnished allylic alcohol **20** (Scheme 3). At this stage, a substrate-controlled stereoselective epoxidation of allylic alcohol **20** was investigated. Accordingly, treatment of allylic alcohol **20** with TBHP and Ti(O^{i}Pr)$_4$



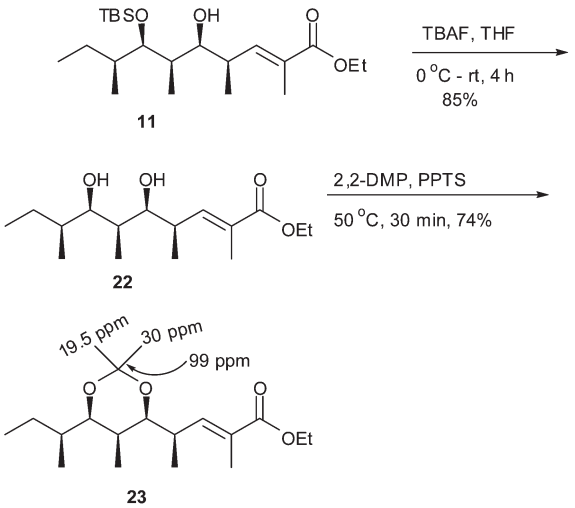
Scheme 1 Retrosynthesis of callystatin A.



Scheme 2 *Reagents and conditions*: (a) i. $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 1 h; ii. $Ph_3PC(CH_3)CO_2Et$, toluene, rt, 3 h, 56% for 2 steps; (b) LAH, Et_2O, 1 h, 0 °C–rt, 80%; (c) D-(–)-DIPT, Ti(^{i}PrO)$_4$, CH_2Cl_2, 4 Å MS, *cat*. CaH_2, TBHP, −25 °C, 4 h, 84%; (d) i. IBX, ethyl acetate, reflux, 6 h; ii. $Ph_3PC(CH_3)CO_2Et$, toluene, rt, 3 h, 71% for 2 steps; (e) $Pd_2(dba)_3CHCl_3$, HCO_2H, ^{n}Bu$_3$P, Et_3N, 1,4-dioxane, rt, 16 h, 85%.



Scheme 3 *Reagents and conditions*: (a) i. TBSOTf, Et_3N, 0 °C, 1 h, 90%; ii. LAH, Et_2O, 0 °C–rt, 2 h, 85% (b) Ti(^{i}PrO)$_4$, CH_2Cl_2, TBHP, −42 °C, 9 h, then −23 °C, 12 h, 84%, dr = 8 : 1; (c) i. IBX, ethyl acetate, reflux, 6 h; ii. $Ph_3PC(CH_3)CO_2Et$, toluene, rt, 4 h, 85% for 2 steps; (d) $Pd_2(dba)_3CHCl_3$, HCO_2H, Ph_3P, Et_3N, 1,4-dioxane, rt, 16 h, 81%; (e) i. DIBAL-H, CH_2Cl_2, −30 °C, 1 h, 90%; ii. MnO_2, CH_2Cl_2, rt, 6 h.



Scheme 4 Determination of the relative stereochemistry of the 1,3 diol.

delivered one of the epoxides stereoselectively (8 : 1 ratio by ^{1}H NMR), which was tentatively assigned as the desired isomer **12** based on precedent literature reports.[14] Oxidation of epoxy alcohol **12** using IBX delivered the corresponding aldehyde, which was immediately used for the Wittig reaction to furnish ester **21** as a single isomer. The Shimizu reaction of ester **21** afforded the known alcohol **11** having an all-*syn* polypropionate stereopentad. The spectral data of ester **11** were in good agreement with that of the previously reported one in all aspects,[10a] and also supported our tentative assignment of epoxide **12**. Reduction of conjugated ester **11** using DIBAL-H afforded the corresponding allylic alcohol, which upon chemoselective oxidation with MnO_2 furnished the desired aldehyde **8** required for the Julia–Kocienski olefination.

In order to further confirm the stereochemical outcome of the substrate-controlled epoxidation of allylic alcohol **20**, the silyl ether **11** was cleaved using TBAF (Scheme 4), and the resultant diol **22** was protected as its acetonide **23**. The ^{13}C NMR of compound **23** showed the characteristic peaks at 19.5, 30 and 99 ppm for the acetonide carbons derived from *syn*-1,3 diol,[15] suggesting that the major isomer formed during the epoxidation was indeed the desired one.

Conclusions

In conclusion, we have synthesized the more challenging stereopentad framework of callystatin A by exploring Pd-mediated hydrogenolysis of alkenyl oxirane (Shimizu reaction) in an iterative fashion. Efforts are underway to achieve the total synthesis of callystatin A and extend this unified strategy to synthesize the polypropionate framework of other leptomycins as well.

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