Asymmetric Total Synthesis of Callystatin A: Asymmetric Aldol Additions with Titanium Enolates of Acyloxazolidinethiones

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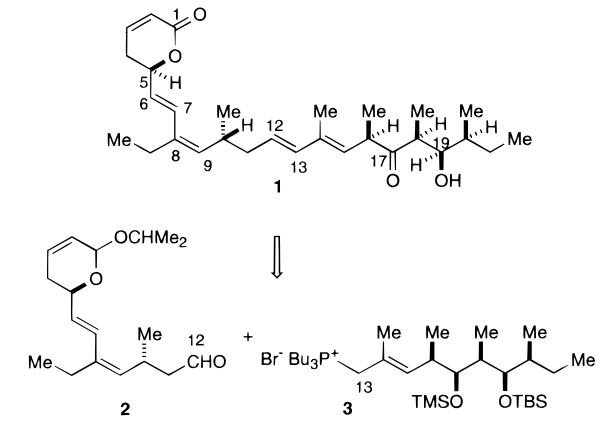
A number of highly cytotoxic polyketides, including the anguinomycins,[1] leptofuranins,[2] leptomycin,[3] and kazusamycin,[4] having similar gross chemical structures have been isolated from *Streptomyces* strains. Recently, a structurally related polyketide, callystatin A **1**, was isolated from the marine sponge, *Callyspongia truncata*, in the Nagasaki Prefecture.[5] Callystatin A shows remarkable in vitro cytotoxicity (IC_{50} = 0.01 ng/mL) against KB cells. The relative and absolute stereostructure of callystatin A was established by a combination of spectroscopic methods and chemical synthesis.[5−7] The limited quantities of callystatin A available from natural sources, as well as the possibility for carrying out syntheses and structure elucidation of the related antitumor antibiotics, prompted us to pursue a total synthesis of callystatin A.[8] Here we disclose the asymmetric total synthesis of (−)-callystatin A exploiting our recently developed asymmetric aldol protocol with chlorotitanium enolates of acyl oxazolidinethiones.[9]

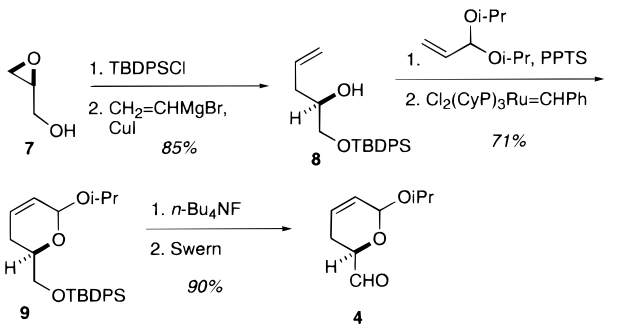
Strategically, *E*-selective olefination[10] of aldehyde **2** (Scheme 1) with the phosphorane derived from tributylphosphonium salt **3** appeared to offer the most convergent assembly of callystatin A. Aldehyde **2** representing C1 to C12 would be constructed from a similar olefination between the masked pyranone aldehyde **4** (Scheme 2) and phosphonium salt **5** (Scheme 3). The C13 to C22 propionate fragment **3** was to be constructed through consecutive asymmetric aldol additions[9] employing acyl oxazolidinethione **6** (Scheme 4).

The synthesis of aldehyde **4** began with *S*-glycidol **7** as illustrated in Scheme 2. Protection of *S*-glycidol as its TBDPS ether followed by copper-catalyzed epoxide opening with vinylmagnesium bromide provided the alcohol **8** in 85% overall yield. Conversion of the secondary alcohol to the isopropoxy propenyl ether provided a mixed acetal which was exposed to the Grubbs catalyst[11] to effect ring-closing metathesis to dihydropyran **9** (71% overall). Removal of the TBPDS protecting group with *n*-Bu_4-NF and Swern oxidation of the resultant alcohol provided a 90% yield of the requisite aldehyde **4** (C1 to C6 fragment).

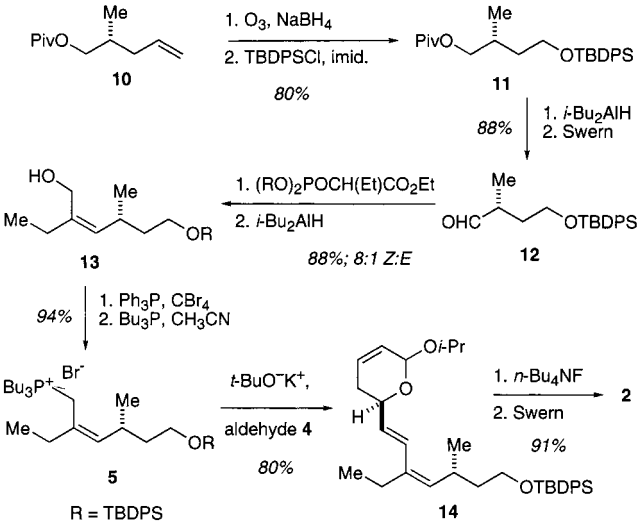
Scheme 1



Scheme 2



Scheme 3



The C7 to C12 phosphonium salt **5**, required for the olefination reaction with aldehyde **4**, was constructed as shown in Scheme 3. Oxidative cleavage of the known[12] alkene **10** followed by in situ reduction of the aldehyde and subsequent protection of the primary alcohol provided 80% of the pivalate **11**. Dibal-H reduction of the pivalate ester followed by Swern oxidation of the primary alcohol gave the aldehyde **12** in 88% overall yield. The C8−C9 *Z*-olefin was installed by utilizing Still's protocol

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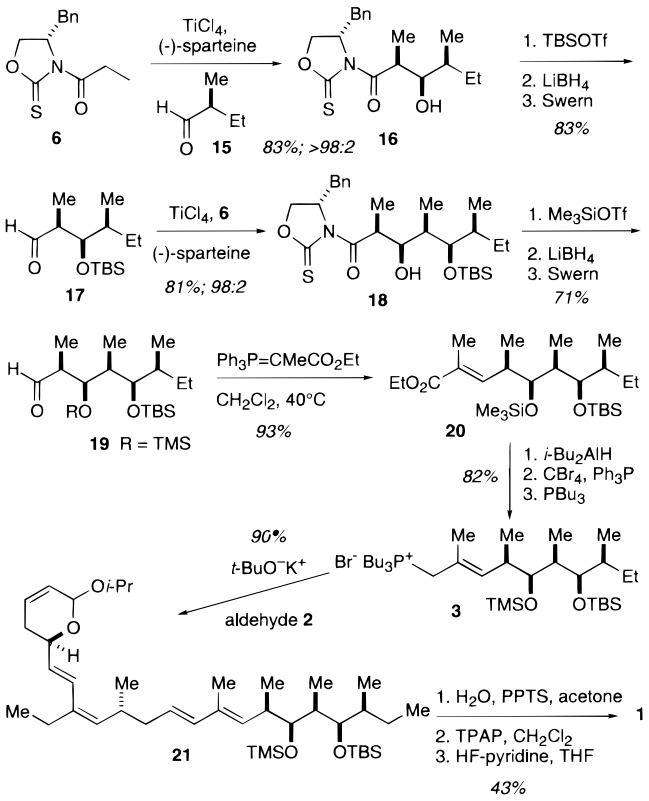
Scheme 4



for construction of *Z*-unsaturated esters.[13] Accordingly, treatment of aldehyde **12** with the required phosphonate[13] anion selectively (8:1 *E*/*Z*) produced the *Z*-unsaturated ester which was immediately reduced with Dibal-H to give 88% of the allylic alcohol **13**. The tributylphosphonium salt **5** was obtained from the alcohol **13** by conversion of the allylic alcohol to the allylic bromide and the subsequent displacement of the bromide with tributylphosphine (92% from **13**). The *E*-selective olefination of aldehyde **4** with the phosphorane derived from salt **5** was attempted with several bases in a variety of solvents. Yields were uniformly low (30% or less) when the phosphonium salt was treated with base to form the ylide followed by addition of the aldehyde.[10] However, when the base was added slowly to a mixture of the aldehyde and phosphonium salt, yields were substantially improved. The best conditions (*t*-BuOK, toluene, 0 °C) provided exclusively the *E*-olefin **14** in 80% yield from the allylic bromide. The diene **14** was readily converted to the C1 to C12 aldehyde **2** by deprotection of the C12 TBDPS ether followed by Swern oxidation (91% from **14**).

The synthesis of the C13 to C22 propionate fragment (Scheme 4) was predicated on the application of our recent success with asymmetric aldol additions using chlorotitanium enolates of acyloxazolidinethiones.[9] Thus, treatment of propionyloxazolidinethione **6** with titanium tetrachloride and (−)-sparteine followed by addition of *S*-2-methylbutanal[14] **15** resulted in the formation of the *syn*-aldol adduct **16** in 83% yield and greater than 98% de. In preparation for the second asymmetric aldol to construct the C16−C17 bond, the secondary alcohol was protected as its TBS ether, the chiral auxiliary was reductively removed with lithium borohydride, and the resultant alcohol was oxidized to the aldehyde **17** in 83% overall yield. The facile reductive removal of the oxazolidinethione auxiliary is noteworthy, given the difficulty often encountered in the reductive cleavage of oxazolidinone auxiliaries in hindered systems. Additionally, recovery of the oxazolidinethione auxiliary (>90%) by simple base extraction with aqueous NaOH further exemplifies the practicality of oxazolidinethione-mediated asymmetric processes. Execution of the second asymmetric aldol, under identical conditions to the first, produced an 81% yield of the *syn*-aldol adduct **18** (98:2 ds). At this point, orthogonal protection of the C17 hydroxyl was required to allow its selective oxidation to a carbonyl at a later stage. The TMS ether was obtained in 89% yield by exposure of alcohol **18** to TMSOTf and 2,6-lutidine. Reductive removal of the auxiliary again proceeded well, and the resultant alcohol was oxidized under Swern conditions to afford the aldehyde **19** in 71% yield for three steps. Installation of the C14−C15 *E*-olefin to produce the ester **20** was accomplished in 93% yield with high selectivity (>97:3) by the condensation of aldehyde **19** with carboethoxyethylidine-triphenylphosphorane. The ester **20** was then converted to the required phosphonium salt **3** in three steps (82% overall) as described above for the preparation of phosphonium salt **5**.

The critical assembly of the two key subunits was completed by the execution of a second *E*-selective olefination as for the construction of the C6−C7 double bond. Addition of potassium *t*-butoxide to a solution of aldehyde **2** and phosphonium salt **3** in toluene at 0 °C resulted in the exclusive formation of the *E*-alkene **21** in 90% isolated yield. Completion of the synthesis of callystatin A was accomplished by hydrolysis of the C1 acetal and the C17 trimethylsilyl ether followed by TPAP[15] oxidation of the diol to the corresponding keto-lactone and finally hydrolysis of the C19 TBS ether (43% overall for 3 steps). Synthetic callystatin A was identical in all respects (^{1}H, ^{13}C NMR; CD; IR; $[\alpha]^D$) to that reported for natural (−)-callystatin A.[5−7]

In summary, a highly efficient and selective total synthesis of (−)-callystatin A has been accomplished. The synthesis hinges on a ring-closing metathesis for the construction of the pyranone fragment, two consecutive acyl oxazolidinethione asymmetric aldol additions to prepare the propionate segment, and two *E*-selective olefinations of tributylphosphonium ylides to efficiently assemble the three key subunits.

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Supporting Information Available: Experimental procedures for compounds **1**−**5**, **8**, **9**, **11**−**14**, **16**−**21** and spectral data (^{1}H, ^{13}C, IR) for compounds **1**, **2**, **4**, **8**, **9**, **11**−**14**, **16**−**21** (22 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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