Asymmetric Total Synthesis of (−)-Callystatin A Employing the SAMP/RAMP Hydrazine Alkylation Methodology

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ABSTRACT

The asymmetric total synthesis of (−)-callystatin A has been achieved. The key steps generating the stereogenic centers rely on the asymmetric α-alkylation of aldehydes or ketones exploiting the SAMP/RAMP hydrazine alkylation methodology, as well as an enzymatic enantioselective reduction of a 3,5-dioxocarboxylate. For the construction of the alkene moieties, highly selective Wittig or Horner–Wadsworth–Emmons reactions were employed.

Callystatin A is a polyketide marine natural product isolated by Kobayashi et al. from the sponge Callyspongia truncata that shows remarkably high cytotoxic activity (IC50 = 0.01 ng/mL against KB tumor cells). Shortly thereafter, the Kobayashi group confirmed the absolute configuration of this product via partial and total synthesis and also reported the preparation of several structural analogues, which led to further insight on structure–activity relationships. Subsequently, the total synthesis of (−)-callystatin A was reported by Crimmins and King and most recently by the groups of Smith, Kalesse, and Marshall.

The limited quantities of (−)-callystatin A available from natural sources, together with the possibility of preparing analogues with improved biological activities, show the imperative need for total synthesis. In this context, and as an opportunity to demonstrate the scope and efficiency of our SAMP/RAMP hydrazine alkylation methodology to-

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together with an enzymatic enantioselective reduction developed recently, we resolved to engage in the task of pursuing its total synthesis.

Our retrosynthetic plan is shown in Scheme 1 and includes disconnections of the C_6–C_7 and C_12–C_13 double bonds, which can be built up by means of a highly E-selective Wittig olefination between allyltributylphosphorus ylide derived from bromide and aldehyde 2 and between ylide derived from 4 with the aldehyde obtained by Swern oxidation of the hydroxyl group present in 3, respectively. Aldehyde 2 should be accessible from ketoester 5, which can be prepared by enantioselective reduction of a 6-chloro-3,5-dioxohexanoate. With respect to bromide 3, it can be obtained by selective olefination of functionalized aldehyde 6, which is a suitable compound to be prepared by asymmetric α-alkylation of the corresponding (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone. Finally, stereopentad 4 can be synthesized by means of a syn-selective aldol reaction between the enolate derived from 7 and aldehyde 8, both also suitable to be obtained as single enantiomers by SAMP/RAMP hydrazone alkylation procedures.

For the synthesis of aldehyde 2 (Scheme 2) we exploited the already published enantioselective enzymatic reduction of 3,5-dioxocarboxylates catalyzed by baker’s yeast. Therefore, reduction of tert-butyl 6-chloro-3,5-dioxohexanoate proceeded with virtually full regiocontrol and high enantioselectivity, affording the hydroxyketoester 5, which was easily converted into chlorinated δ-lactone 9 (94% ee by HPLC) as described in Scheme 2. DIBAL-H reduction of 9 and subsequent acetylation provided chloroacetal 10, which upon chloroacetoxy substitution reaction with tetraubutylammonium acetate (TBAA) followed by hydrolysis of the ester moiety afforded hydroxyacetal 11 in good yield. The key synthetic intermediate 2 was obtained after treatment of 11 under standard Swern oxidation conditions.

Next we proceeded to the synthesis of the synthetic intermediate 3, which started with the asymmetric α-alkylation of aldehyde 12 via its corresponding SAMP hydrazone 13 (Scheme 3). Lithiation of 13 with LDA in THF at 0 °C followed by alkylation with iodomethane at −100 °C.
afforded the α-alkylated hydrazone in >95% de as indicated by 13C NMR analysis of the crude reaction mixture. Ozonolysis of this alkylated hydrazone cleanly yielded aldehyde 6. For the selective installation of the double bond in the α,β-unsaturated ester 14, a Horner–Wadsworth–Emmons procedure was employed using different modified phosphonate reagents. Still–Gennari13 coupling with phosphonate 15a yielded the desired product with moderate diastereoselectivity (Z/E ratio of 8:1); however, it was greatly improved (34:1) by changing to the modified reagent 15b in both cases with comparable yields. Subsequent DIBAL-H reduction of the ester moiety followed by bromination with CBr4/PPh3 in acetonitrile provided the allylic bromide 3. The ee of the final compound was checked at the allylic alcohol stage (after DIBAL-H reduction of 14) and was found to be >98% by GC analysis.

For the synthesis of the stereopentad 4 (Scheme 4)15 we proceeded first with the asymmetric alkylation of 3-pentanone via its (R)-1-amino-2-methoxymethylpyrrolidine (RAMP) hydrazone derivative 17 with benzylxoymethyl chloride (BOMCl), yielding ketone 7 (96% ee by GC analysis) after clean removal of the chiral auxiliary by a standard ozonolysis procedure. The asymmetric synthesis of aldehyde 8 was performed in an analogous way by alkylation of butanal-RAMP hydrazone 16 with iodomethane. Subsequent Sn(II)-mediated mismatched aldol reaction16 between 7 and 8 proceeded smoothly to provide hydroxyketone 18 in 87% yield and excellent diastereoselectivity (Scheme 4). After protection of the hydroxyl moiety as its TBS ether, removal of the benzyl group by hydrogenolysis, and DIBAL-H diastereoselective reduction of the obtained β-hydroxyketone, it was possible to obtain compound 19 as a stereodefined single isomer after column chromatography. Swern oxidation of 19 followed by Wittig olefination with Ph3P=CH(CH3)CO2-Et furnished α,β-unsaturated ester 20 in good yield and in a fully selective way favoring the desired E isomer. Subsequent DIBAL-H reduction and bromination with CBr4/PPh3 in the presence of 2,6-lutidine afforded the target stereopentad 4. In this case, the presence of a base such as 2,6-lutidine in the bromination reaction was necessary in order to avoid deprotection of the TBS ether.

Finally, we proceeded to the assembly of the obtained synthetic intermediates in order to build up the skeleton of (−)-callystatin A (Scheme 5). First, the allylic bromide 3 was converted into the tributylphosphonium salt 21, and subsequently a Wittig reaction was performed by reacting it with aldehyde 2 in the presence of KO'Bu to afford the triene.
in good yield and as a single diastereoisomer. Next, deprotection of the alcohol moiety with TBAF in THF, followed by Swern oxidation of the primary alcohol, furnished cleanly aldehyde 23, which was then coupled with allylic bromide 4 using again a Wittig reaction. However, in this case the use of KOtBu as the base that promotes the formation of the phosphorus ylide did not afford the olefination product and other bases had to be tested. In this context, the use of LiCH₂S(O)CH₃ was found to give the best results concerning both yield and diastereoselectivity leading to pentaene 24, as a single E isomer. Afterward, PCC/HOAc treatment of 24 proceeded with oxidation of the free alcohol functionality and concomitant hydrolysis/oxidation of the acetal moiety. The asymmetric synthesis of (−)-callystatin A was completed with the deprotection of the TBS ether with HF·pyridine in THF.

In summary, a highly efficient asymmetric total synthesis of (−)-callystatin A has been accomplished. A very important feature of this synthesis is the creation of the stereogenic centers in the first stages by using the SAMP/RAMP hydrazone alkylation protocol together with an enantioselective enzymatic reduction. In this context it should be noted that this constitutes the first non-ex-chiral pool synthesis of this cytotoxic polyketide. It is also noteworthy that the formation of C–C double bonds during the synthesis has been performed with a very high degree of diastereoselection. Consequently, this total synthesis can be favorably compared with other published routes3,5–8 and is efficient enough to allow the preparation of other modified analogues.

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Supporting Information Available: Spectroscopic and analytical data for key compounds 6–8, 14, 18, 22, 24, and (−)-callystatin A and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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