ORGANIC LETTERS

2002
Vol. 4, No. 6
1023−1026

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

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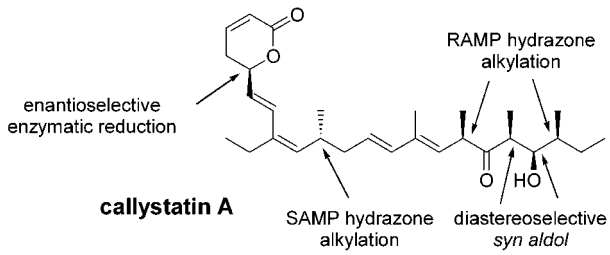
Received January 24, 2002

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 hydrazone 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 (IC_{50} = 0.01 ng/mL against KB tumor cells).[1] Shortly thereafter, the Kobayashi group confirmed the absolute configuration of this product via partial[2] and total synthesis[3] and also reported the preparation of several structural analogues, which led to further insight on structure−activity relationships.[4] Subsequently, the total synthesis of (−)-callystatin A was reported by Crimmins and King[5] and most recently by the groups of Smith,[6] Kalesse,[7] and Marshall.[8]

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 hydrazone alkylation methodology[9] to-

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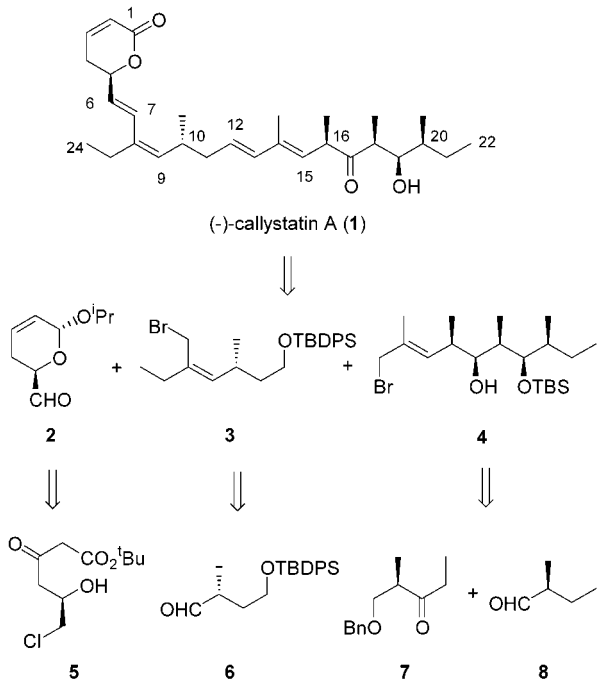
10.1021/ol0256116 CCC: $22.00
Published on Web 02/16/2002

Scheme 1



gether with an enzymatic enantioselective reduction developed recently,[10] we resolved to engage in the task of pursuing its total synthesis.[11]

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[12] between allyltributylphosphorus ylide derived from bromide **3** 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.[10b] Therefore, reduction of *tert*-butyl 6-chloro-3,5-dioxohexanoate proceeded with virtually full regiocontrol and high

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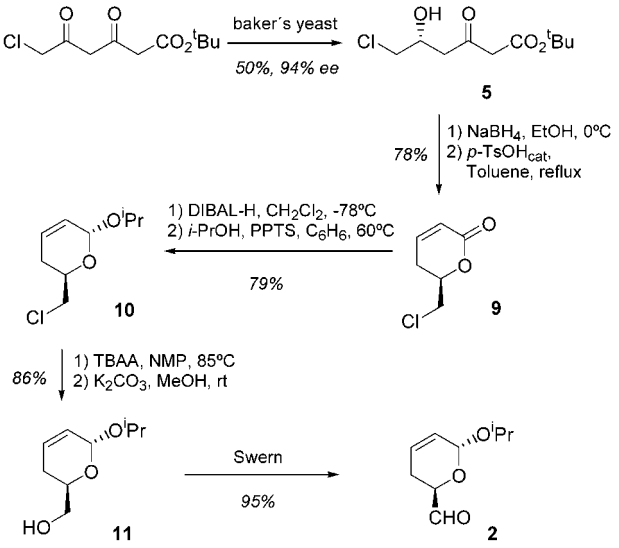
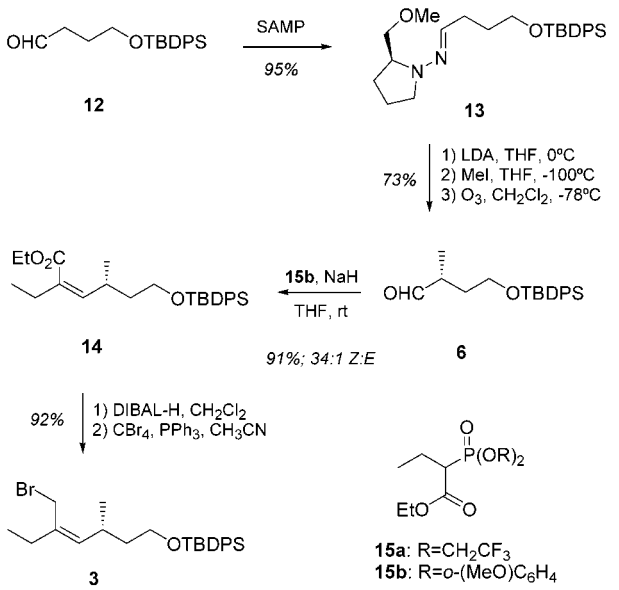
Scheme 2



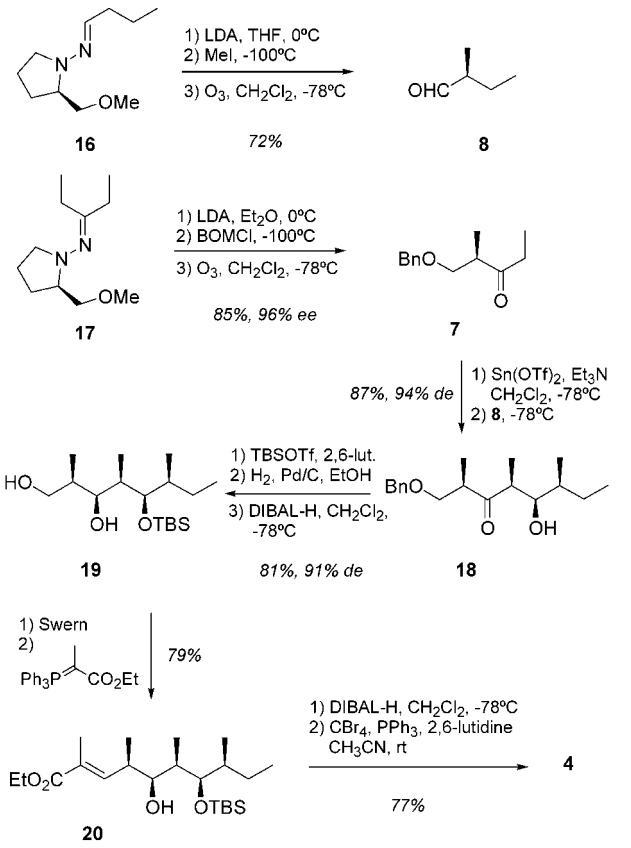
enantioselectivity, affording the hydroxyketoester **5**, which was easily converted into chlorinated δ-lactone **9** (94% ee by HPLC) as described in Scheme 2. DIBAL-H reduction of **9** and subsequent acetalization provided chloroacetal **10**, which upon chloroacetoxy substitution reaction with tetrabutylamonium 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

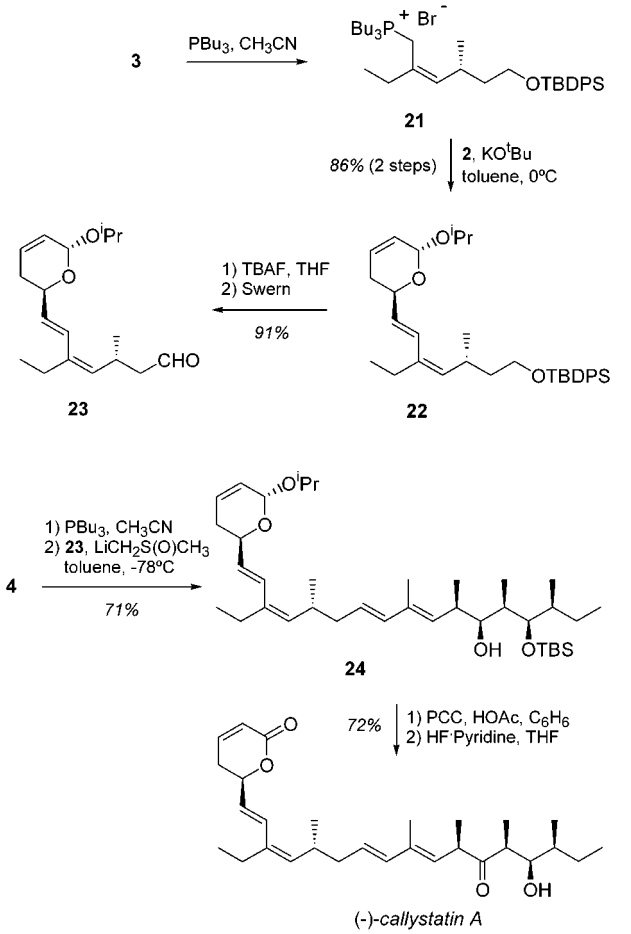
Scheme 3



Scheme 4



Scheme 5



afforded the α-alkylated hydrazone in >95% de as indicated by ^{13}C 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−Gennari[13] coupling with phosphonate **15a** yielded the desired product with moderate diastereoselectivity (*Z*/*E* ratio of 8:1);[5] however, it was greatly improved (34:1) by changing to the modified reagent **15b**[14] in both cases with comparable yields. Subsequent DIBAL-H reduction of the ester moiety followed by bromination with CBr_4/PPh_3 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 benzyloxymethyl 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 reaction[16] 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 $Ph_3P{=}C(CH_3)CO_2$-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 CBr_4/PPh_3 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^{t}Bu to afford the triene

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22 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 KO^{t}Bu 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 $LiCH_2S(O)CH_3$ 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 routes[3,5−8] and is efficient enough to allow the preparation of other modified analogues.

Acknowledgment. This work has been generously supported by the Deutsche Forschungsgemeinschaft (Sonderforschungbereich 380) and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG, and Aventis for the donation of chemicals. J.L.V. thanks the Basque Government (programas de perfeccionamiento y movilidad de personal investigador de la UPV/EHU) for financial support.

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.

OL0256116

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