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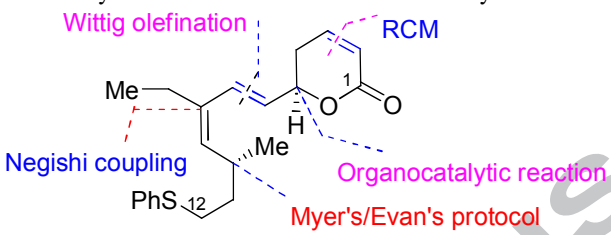

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Stereoselective synthesis of the C1-C12 subunit of (-)-callystatin A

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ABSTRACT

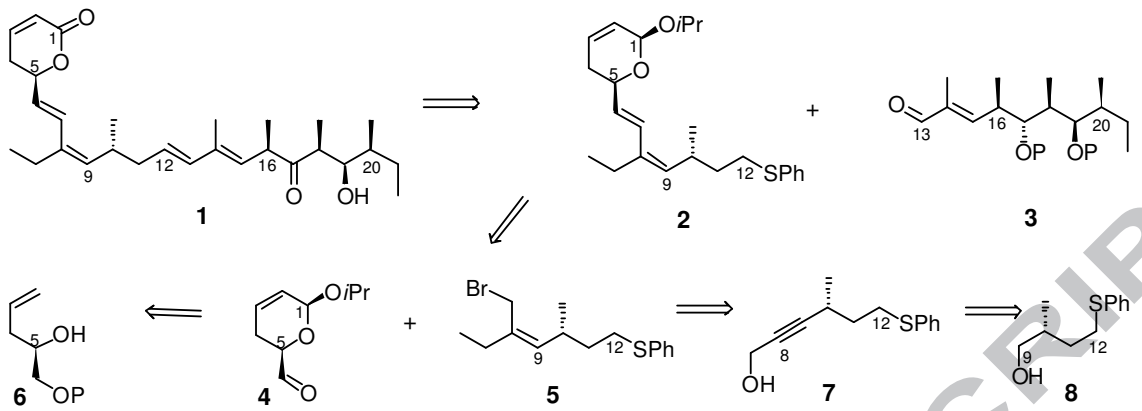
A stereoselective synthesis of the C1-C12 fragment of callystatin A is disclosed. The two stereocenters at C5 and C10 were created by an organocatalytic reaction and a diasteroselective alkylation respectively. The trisubstituted double bond was introduced by a hydroxy directed hydrostannylation followed by Negishi reaction. The lactone ring resulted from a ring-closing metathesis reaction.

(–)-Callystatin A 1, was isolated by Kobayashi and co-workers from a marine sponge, *Callyspongia truncata*.[1] Callystatin exhibits remarkable cytotoxicity against KB (IC_{50} = 10 pg mL^{-1}) and L1210 (IC_{50} = 20 pg mL^{-1}) cell lines which is attributed to its inhibition of CRM1 (chromosome region maintenance 1) protein.[2] The structure of callystatin consists of an unsaturated δ-lactone, two (*Z*, *E*)- and (*E*, *E*)-1,3-diene units, a stereogenic center at C10 and a polypropionate subunit incorporating four chiral centers.

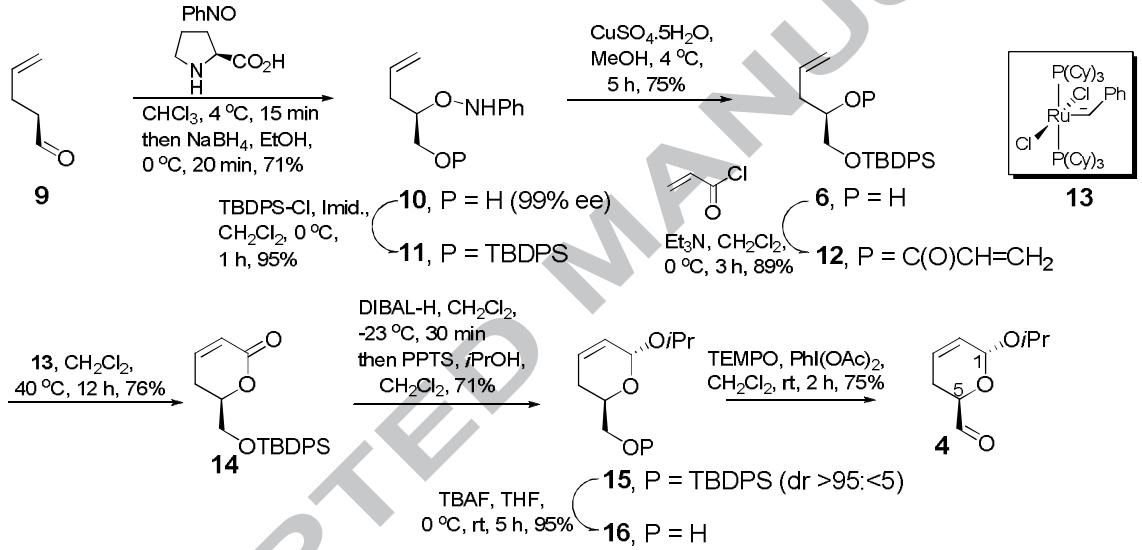
Its potent cytotoxicity combined with its complex structure has stimulated much attention leading to several total syntheses.[3] We disclose herein, our efforts toward the stereoselective synthesis of the C1-C12 subunit of callystatin. By a retrosynthetic disconnection, callystatin was envisioned to be synthesized by the union of the sulfone derived from 2 and aldehyde 3, employing the Julia-olefination, Scheme 1. The stereoselective synthesis of aldehyde 3 by a non-aldol approach was recently described.[4] The sulfide 2 was envisaged to be obtained by a Wittig olefination between aldehyde 4 and the phosphonium salt derived from bromide 5. The aldehyde 4 can be obtained from homoallyl alcohol 6 and bromide 5 was envisioned to be obtained from alkyne 7 which inturn can be traced to sulfide 8.

The synthesis began from commercially available 4-pentenal **9** which was subjected to L-proline catalyzed aminooxylation using nitrosobenzene[5] and reduction using sodium borohydride in the same pot to afford alcohol **10** (99% ee). Protection of the carbinol under standard conditions as its silyl ether **11** followed by cleavage of the O-N bond[6] furnished alcohol **6**. The acrylate ester **12** obtained from **6** was subjected to ring-closing metathesis reaction using Grubbs' first generation catalyst **13** to furnish lactone **14**.[7] Reduction to lactal using DIBAL-H and acetal formation using isopropanol and catalytic quantity of PPTS delivered compound **15** (dr >95:<5). Deprotection of the silyl ether using TBAF yielded alcohol **16** which on oxidation using TEMPO and PhI(OAc)[8] yielded aldehyde **4**, Scheme **2**.

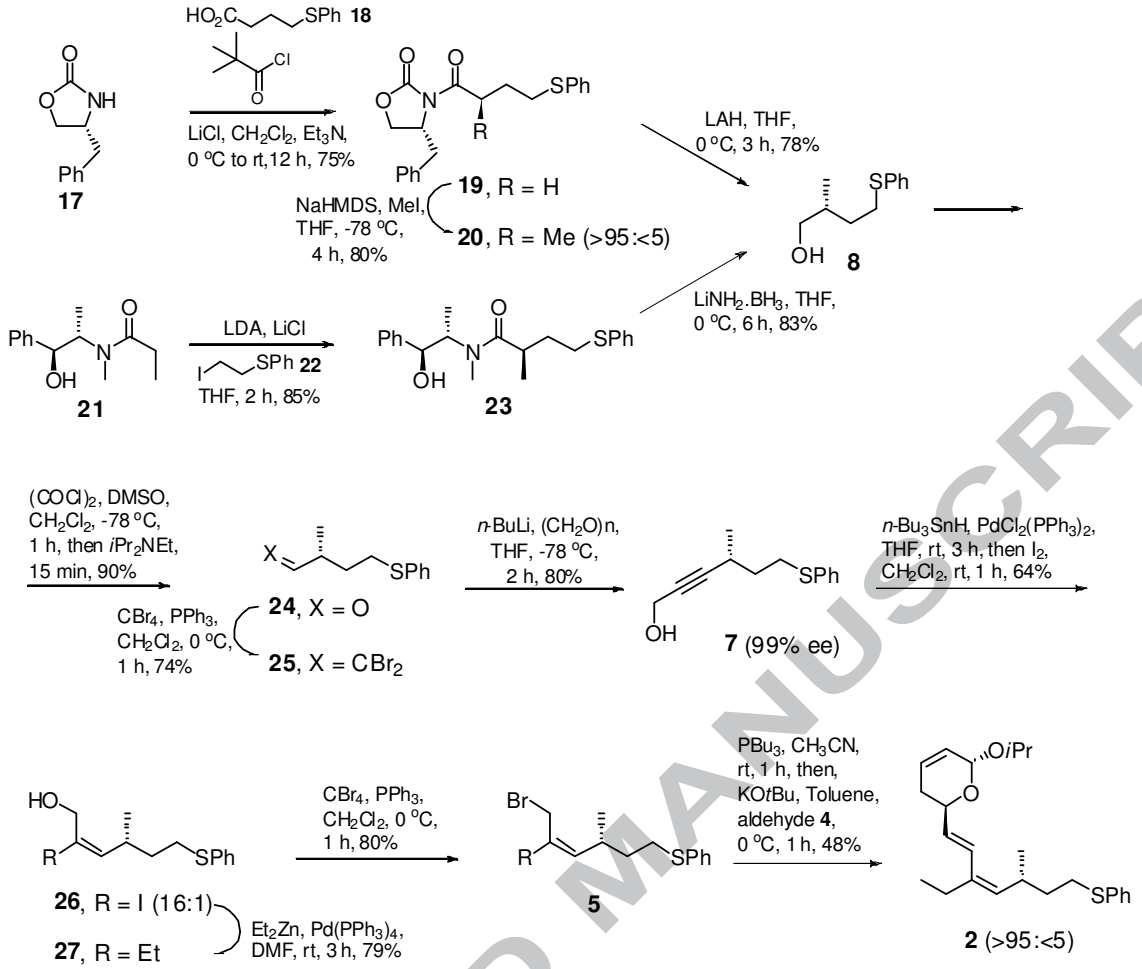
The alcohol **8** was synthesized by a diastereoselective alkylation. In the initial attempt, imide **19**,[9] prepared by the reaction of oxazolidine **17** with the mixed anhydride prepared from carboxylic acid **18**,[10] was subjected to methylation to furnish compound **20** (dr >95:<5). Reductive cleavage using LAH yielded alcohol **8** and **17**. In another approach, propionamide derivative **21**, prepared using Myer's auxiliary,[11] was subjected to alkylation with 2-thiophenyl iodoethane **22**, to yield compound **23**. Reductive cleavage of the auxiliary[12] using $LiNH_2.BH_3$ furnished alcohol **8**. While the temperature had to be maintained around -78 °C using imide **19**, the alkylation could be carried out at 0 °C using amide **21**. Oxidation of the carbinol using Swern prootocol[13] afforded aldehyde **24**. Homologation using Corey-Fuchs protocol[14] furnished dibromoalkene **25**. Alkyne formation using *n*-BuLi in the presence of an excess of paraformaldehyde yielded propargylic alcohol **7** (99% ee), Scheme **3**. A highly regio- and stereoselective hydrostannylation of alkyne was exploited for the creation of the (Z)-trisubstituted alkene. Thus treatment of **7** with tributyltin hydride in the presence of Pd(II)[15] followed by iodine quench yielded allyl alcohol **26** (regioisomer ratio 16:1). Negishi coupling[16] of **26** and diethylzinc using Pd(0) furnished alkene **27** in good yield. The alcohol **27** was transformed to bromide **5** under Mitsunobu conditions using CBr_4.[17] Further phosphonium salt formation by reaction of **5** with tributylphosphine and reaction of the corresponding ylide generated following a reported procedure,[3b] with aldehyde **4** furnished diene sulfide **2** (*E*:*Z* = >95:<5), corresponding to the C1-C12 subunit of callystatin A.



Scheme 1. Retrosynthetic disconnection of callystatin A.



Scheme 2. Synthesis of aldehyde **4**.



Scheme 3. Synthesis of sulfide **2**.

In conclusion, we have devised a stereoselective route to the C1-C12 fragment of callystatin A employing organocatalytic reaction to introduce the C5 stereocenter, a diastereoselective auxiliary controlled alkylation to introduce the C10 stereocenter. Ring-closing metathesis, hydroxy directed regio- and stereoselective hydrostannylation and Negishi coupling are other metal catalyzed/promoted reactions that have been used to advantage. The C6-C7 double bond was introduced by a Wittig olefination. Efforts are in progress to complete the synthesis of callystatin A.

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Supplementary Material

Deatailed experimental procedures are available as supplementary material.