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# A Convergent Approach to (−)-Callystatin A Based on Local Symmetry

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(−)-Callystatin A **1** is a natural polypropionate belonging to the Leptomycin family that was isolated by Kobayashi et al. in 1997[1] from a marine sponge, *Callyspongia truncata*, in very small amounts (1 mg for 1 kg of sponge). This natural product exhibits picomolar cytotoxic activity against several cancer cell lines ($IC_{50} = 10\ pg\,mL^{-1}$ against the KB cell line and $20\ pg\,mL^{-1}$ against the L1210 cell line). The mode of action of (−)-callystatin A, common to the leptomycin family, consists in the specific inhibition of the CRM1 (chromosome region maintenance 1) protein, which is responsible for the exportation of macromolecules from the nucleus to the cytoplasm of eukaryotic cells. Mechanistically, the δ-lactone moiety acts as a Michael acceptor with the cysteine 528 residue of CRM1.[2] The covalent adduct then prevents the formation of the exporting complex formed between CRM1, the macromolecule to be exported, and a cofactor, RanGTP.[3] The structure of (−)-callystatin A includes an unsaturated δ-lactone, two (*Z*,*E*)- and (*E*,*E*)-1,3-diene units, an isolated stereogenic center at C10 and a polypropionate fragment including four stereogenic centers (Figure 1).

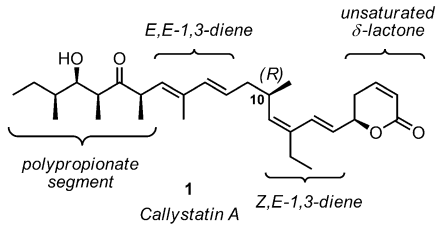


Figure 1. Structure of (−)-callystatin A **1**.

Due to its remarkable cytotoxic activity combined with its complex structure, several groups[4] have focused their attention to the synthesis of (−)-callystatin A. Nearly all the reported total syntheses have employed a convergent approach based on the formation of the diene segments through metal-mediated cross-coupling and/or olefination reactions and hence on the disconnection of the natural product in three fragments. Chiral pool and diastereoselective aldolization reactions with chiral auxiliaries were extensively used to control the stereogenic centers. However, a chiral pool could be particularly expensive in some cases and to resort to chiral auxiliaries requires additional steps for their introduction and removal. Among the enantioselective solutions to control stereogenic centers, catalytic desymmetrizations of prochiral or *meso* compounds avoid these drawbacks. Hence, the exploitation of hidden symmetry in the target molecule represents a valuable alternative approach for the synthetic chemist.[5] We recently demonstrated the strength of hidden-symmetry-based strategy in the synthesis of polypropionate natural products.[6] This straightforward approach provides valuable building blocks bearing several stereogenic centers[7] by desymmetrization of a *meso* intermediate.

Herein, we report a new synthetic approach en route to the synthesis of (−)-callystatin A exploiting the local symmetry. We particularly focused our efforts on the catalytic enantiocontrol of strategic stereogenic centers, thus avoiding the need for a chiral pool or chiral auxiliaries. In this preliminary study, the synthesis of each fragment is described and their coupling is examined.

Due to the sensitivity of the unsaturated δ-lactone, we planned a late construction of this subunit (Scheme 1). Akita's procedure of isomerization/lactonization,[8] which converts *E*-δ-hydroxy-α,β-unsaturated carboxylic acids directly into dihydropyrones, led us to consider compound **2** as a plausible intermediate to reach the natural product. From that, two strategic disconnections could be proposed: the C7−C8 bond (formed through a Stille cross-coupling) and the C12−C13 bond (formed through a modified Julia olefination), leading to three fragments. The pivotal local symmetry present on the west fragment **3** would arise from the *meso* diol **6**. The central fragment **4** and the east fragment **5** could come from itaconic acid **7** and enyne **8**, respectively.

The synthesis of the west fragment **3** started with the enzymatic desymmetrization of *meso* diol **6**, which was obtained in three steps from methacroleine **9**[9] (Scheme 2). The conditions of asymmetric acetylation, described by Chênevert and Courchesne[10] employing *Candida rugosa*, were slightly modified to furnish monoacetate **10** quantitatively

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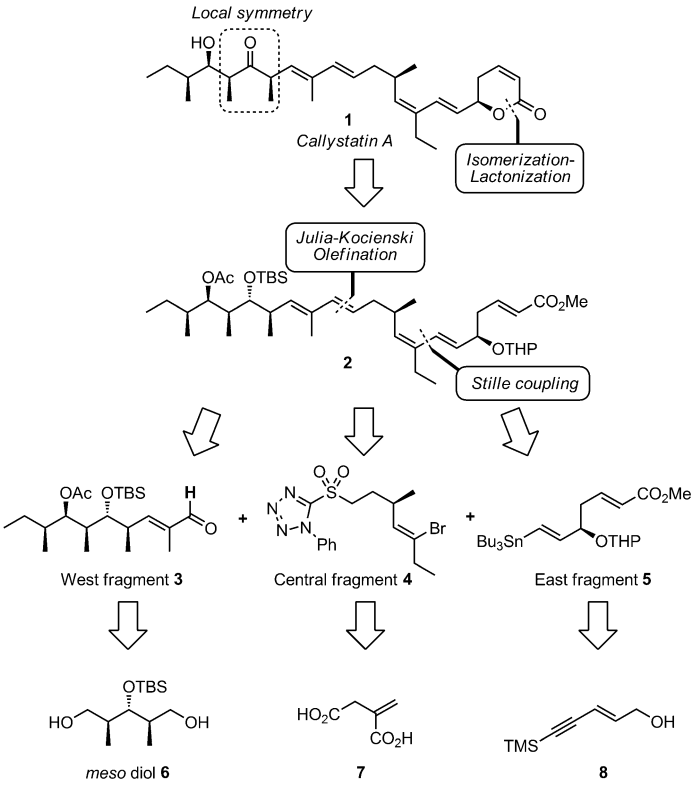


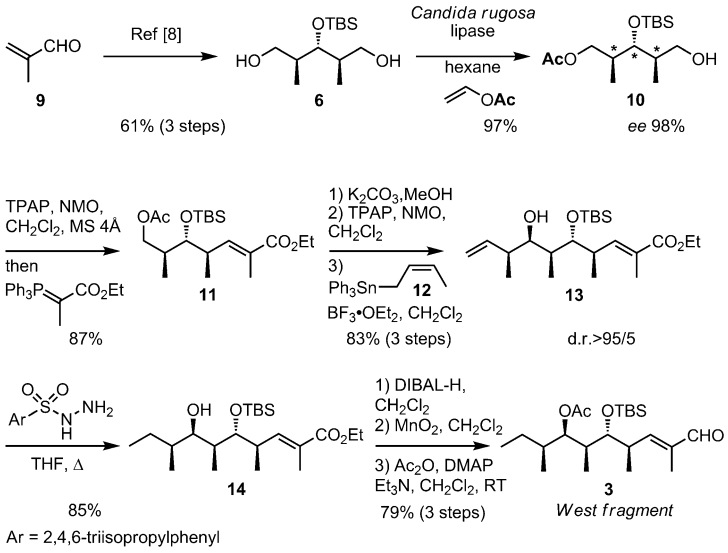

Scheme 1. Retrosynthetic plan.

with an enantiomeric excess of 98%. After oxidation using TPAP/NMO and in situ Wittig olefination under Ley's conditions,[11] α,β-unsaturated ester **11** was obtained in 87% yield.

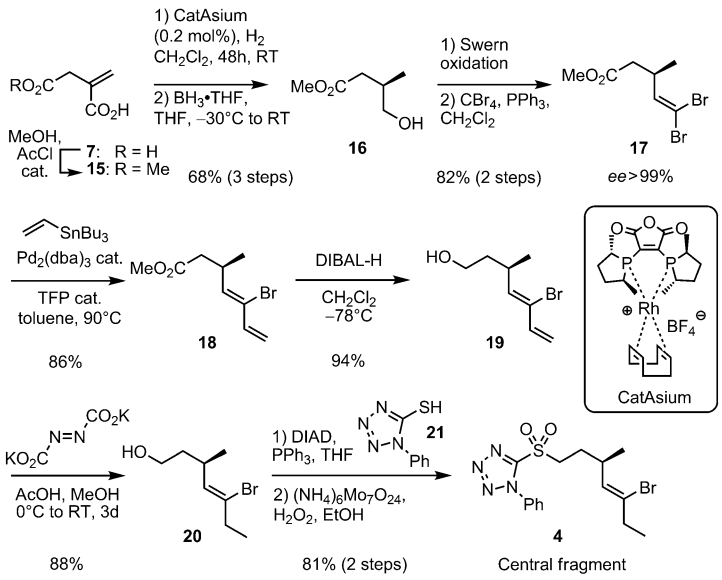
To homologate and introduce the two other stereogenic centers of the fragment, a mild saponification was carried out followed by a TPAP/NMO oxidation and a Keck crotylation.[12] This last reaction performed in the presence of $BF_3{\cdot}Et_2O$, with crotyl reagent **12** smoothly gave, through an opened transition state, the Felkin addition product **13** in good yield and excellent diastereoselectivity (diastereomeric ratio (d.r.) > 95:5).[13] Functional group transformations including chemoselective reduction of the terminal double bond with a diimide precursor,[14] DIBAL-H reduction of the ester function, oxidation of the corresponding allylic alcohol with $MnO_2$ and acetylation, afforded the west fragment **3** in 28.7% overall yield over twelve steps.

The synthesis of the central fragment **4** (Scheme 3) began with the chemoselective esterification of itaconic acid **7** followed by a highly enantioselective hydrogenation (enantiomeric excess (*ee*) = 99%) performed with 0.2 mol% of CatAsium,[15] which is rarely employed in total synthesis.[16] The hydrogenated product was reduced into corresponding alcohol **16** with $BH_3{\cdot}THF$ in good yield over three steps from acid **7**. The oxidation of hydroxyester **16** under Swern's conditions[17] into the corresponding aldehyde followed by a Ramirez's olefination[18] allowed the formation of dibromoalkene **17** without any racemization during this two-step process. A stereoselective Stille cross-coupling[19] between intermediate **17** and vinyltributylstannane gave, under mild conditions, diene **18** which was reduced with DIBAL-H into the alcohol **19**. Finally, the central fragment **4** was obtained after four additional steps: chemoselective reduction of diene **19** into vinylbromide **20** using a diimide source, substitution of the corresponding alcohol **20** with thiol **21**, under Mitsunobu's conditions, and oxidation of the sulfide into sulfone. The central fragment **4** was obtained after ten steps in 32% overall yield.

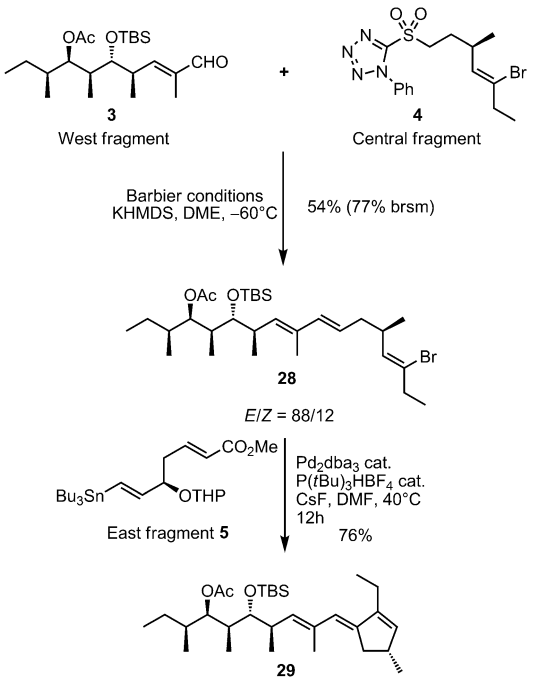
The east fragment **5**, precursor of the unsaturated δ-lactone, was synthesized starting from ethylpropiolate **22** (Scheme 4). Following Trost's procedure,[20] hydroiodination of its triple bond followed by an isomerization furnished *E*-ethyl-3-iodoacrylate. This last intermediate was coupled with trimethylsilylacetylene through a Sonogashira reaction before a DIBAL-H reduction providing enyne **8**. Subsequently, a Katsuki–Sharpless epoxidation[21] transformed allylic alcohol **8** into epoxy-alcohol **24** in 74% yield with 88% *ee*. Then, alcohol **24** was oxidized using TEMPO/PhI-$(OAc)_2$ yielding the corresponding sensitive aldehyde which was directly submitted to a Wittig olefination to afford vinyloxirane **25** in good yield. A mild and selective $Pd^0$-catalyzed reduction using tributyltin hydride converted **25** in δ-hydroxy-α,β-unsaturated ester **26**. Removal of the alkyne trimethylsilyl group and protection of the hydroxy function as THP acetal led to




Scheme 2. Synthesis of the west fragment **3**.

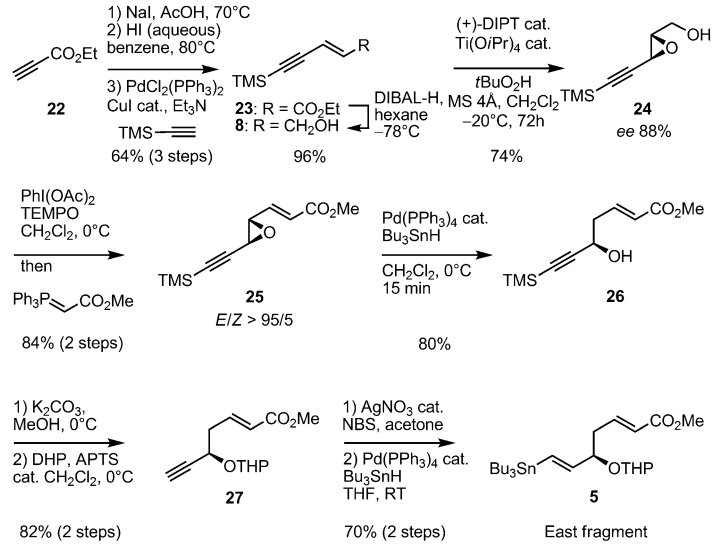



Scheme 3. Synthesis of the central fragment **4**.




Scheme 5. Couplings: Julia–Kocienski olefination then Stille cross-coupling.

the terminal alkyne **27** in 87% yield. Finally, the east fragment **5** was obtained by a two-step procedure developed by Guibé and Balavoine for regioselective hydrostannylation.[22,23] This sequence provided the east fragment **5** in 17.5% overall yield over twelve steps.




Scheme 4. Synthesis of the east fragment **5**.

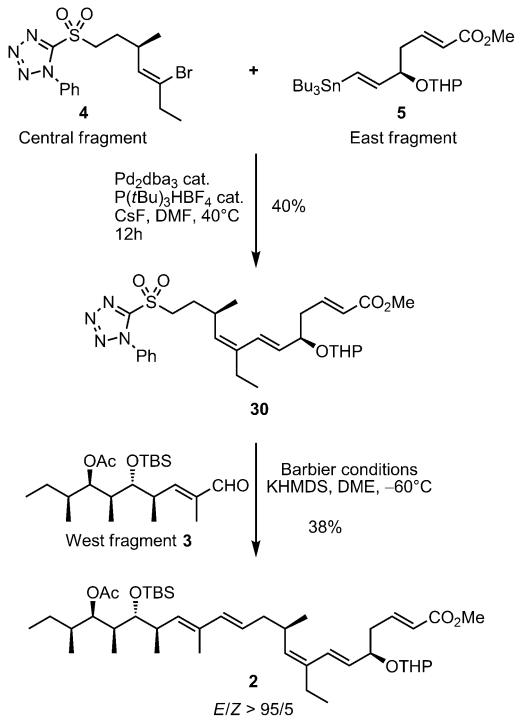
With the three fragments in hand, we next examined the crucial couplings steps towards the completion of the carbon skeleton of callystatin A. The Julia–Kocienski olefination between the west fragment **3** and the central fragment **4** followed by Stille cross-coupling with the east fragment **5** was first envisioned (Scheme 5). Olefination under Barbier conditions was employed for the olefination (KHMDS as base in DME)[24] affording triene **28** in 54% (77% based on recovered sulfone) with a good stereoselectivity in favor of the desired *E* isomer (*E*/*Z* = 88:12).

Rapid screening of Stille cross-coupling[25] conditions underlined that the THP acetal protecting group in the east fragment **5** was necessary for the success of the reaction.[26] Moreover, only the use of the bulky and electron-rich tri-*tert*-butylphosphine,[27] was able to provide the cross-coupling product.

However, the transposition of these conditions to the assembly of **28** with the east fragment **5** did not afford the desired callystatin skeleton but the alkylidene-cyclopentene **29** resulting from an intramolecular Heck coupling.

To circumvent this drawback, the inversion of the coupling sequence was examined (Scheme 6). The cross-coupling between the central fragment **4** and the east fragment **5** under Fu's conditions[27] afforded the desired sulfone **30** in moderate yield. This product was submitted to a Julia–Kocienski olefination with the west fragment **3** providing compound **2** in 38% yield with an excellent stereoselectivity (*E*/*Z* > 95:5). With this preliminary study, the three fragments were coupled to obtain the carbon skeleton of the natural product thus validating our approach.

In conclusion, we have developed a convergent synthetic approach reaching the complete carbon skeleton and controlling all stereogenic centers and double bonds configurations. Based on the pivotal local symmetry, which has not been exploited in previous total syntheses, three stereogenic centers were introduced at once, and only three catalytic enantioselective reactions were employed to obtain intermediate **2**. Our first coupling study revealed the crucial importance of the order of the final couplings. These results validate our strategy, despite the protecting group obsta-




Scheme 6. Couplings: Stille cross-coupling then Julia–Kocienski olefination.

cle,[28] and progress towards the completion of the synthesis of (−)-callystatin A will be presented in due course.

## Acknowledgements

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**Keywords:** cross-coupling · desymmetrization · Julia olefination · local symmetry · *meso* compounds · natural products

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[28] As anticipated, an acetyl shift occurred during the deprotection of the silylether of intermediate **2** giving an inseparable mixture of isomers. Indeed, initially, we had tried to introduce a benzoyl group, which is less inclined to undergo a possible shift during the deprotection, instead of acetyl group, which is more labile in the west fragment. Unfortunately, under classical conditions (BzCl, $Et_3N$, DMAP cat., $CH_2Cl_2$, 0 °C to RT) or more sophisticated conditions (BzCl, TMEDA, MS 4 Å, −78 °C to RT, T. Sano, K. Ohashi, T. Oriyama, *Synthesis* **1999**, 1141 – 1144) we were not able to introduce the benzoyl group on the hydroxyl group presumably because of a very hindered position. To validate our strategy we therefore used the west fragment **3**.

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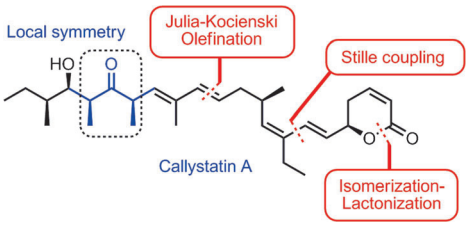
Synthetic Methods






**The key is symmetry!** A convergent synthetic approach of the highly cytotoxic natural product (−)-callystatin A was developed assembling three fragments through Julia–Kocienski olefination and Stille cross-coupling. The new strategy relies on a pivotal local symmetry of the target molecule. In this preliminary study, particular attention was devoted to facilitate the catalytic enantiocontrol of strategic stereogenic centers present in each of the fragments.