Natural Product Synthesis

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Total Synthesis of Callystatin A by Titanium-Mediated Reductive Alkyne–Alkyne Cross-Coupling**

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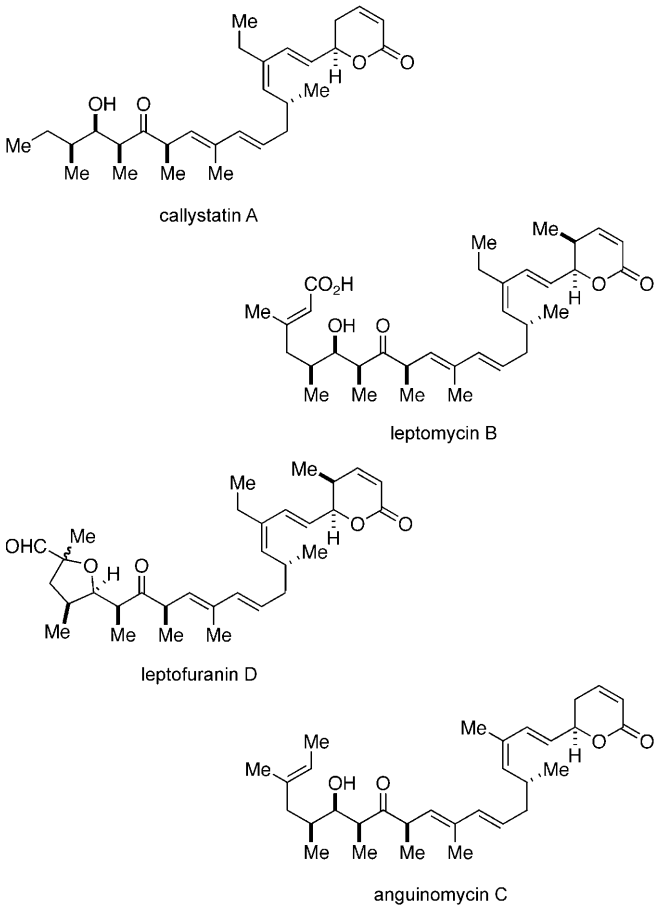
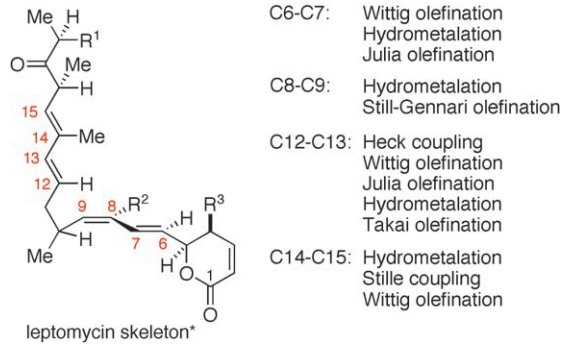
Members of the leptomcyin family of natural products possess potent cell-cycle-regulating properties, in addition to apoptotic, antifungal, and antiviral activities (Scheme 1).[1] The origin of these properties is thought to derive from the known propensity of these natural products to modulate the function of the exportin chromosomal region maintenance 1 (CRM1) and to inhibit nuclear export. [2] Although many members of this class possess impressive antitumor activity, their general toxicity has defined a barrier for clinical development.[3] Recently, novel natural and non-natural leptomycins have been identified which have significantly varied toxicity profiles, thus providing hope for the development of this class of compounds as therapeutically relevant antitumor agents.[4] Herein, we describe a powerful approach to the assembly of the leptomycin skeleton by application of a titanium-mediated reductive alkyne–alkyne cross-coupling reaction.[5] While providing a novel strategy for the total synthesis of callystatin A,[6] these studies highlight the functional group compatibility and the advantages of titanium alkoxide-mediated reductive cross-coupling processes in complex molecule synthesis.

The interesting structures and impressive biological activities of the leptomycins have served to inspire many organic chemists. Not surprisingly, no fewer than 15 total syntheses of members of this class have been reported to date.[7] Aside from demonstrating that these targets can be accessed synthetically, these contributions help define the complex issues that challenge any synthetic pathway aimed at accessing the highly unsaturated stereodefined skeleton of the leptomycins. Although the tetrahedral stereochemistry has typically been addressed with existing aldol, allylmetal, and allenylmetal methodology, the stereochemistry of the acyclic olefins has been established by a variety of methods (Scheme 2): 1) olefination processes (Wittig, Julia, Takai, and Still–Genari), 2) hydrometalation reactions, and 3) palladium-catalyzed coupling reactions (namely, Heck). Other palladium-catalyzed cross-coupling reactions have been used to assemble the leptomycin skeleton, however, these processes require the use of stereodefined olefinic coupling partners that are typically generated by other stereoselective reactions.



Scheme 1. Representative leptomycin natural products.



Scheme 2. Methods employed for establishing the stereodefined olefins common to the leptomycin skeleton. *Drawn to highlight the conformational consequence of the stereodefined acyclic olefins.

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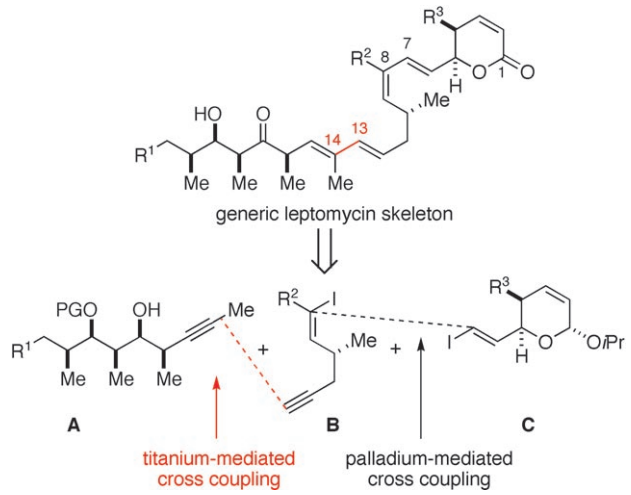


Scheme 3. Key bond constructions targeted for the convergent synthesis of the leptomycins. PG = protecting group.

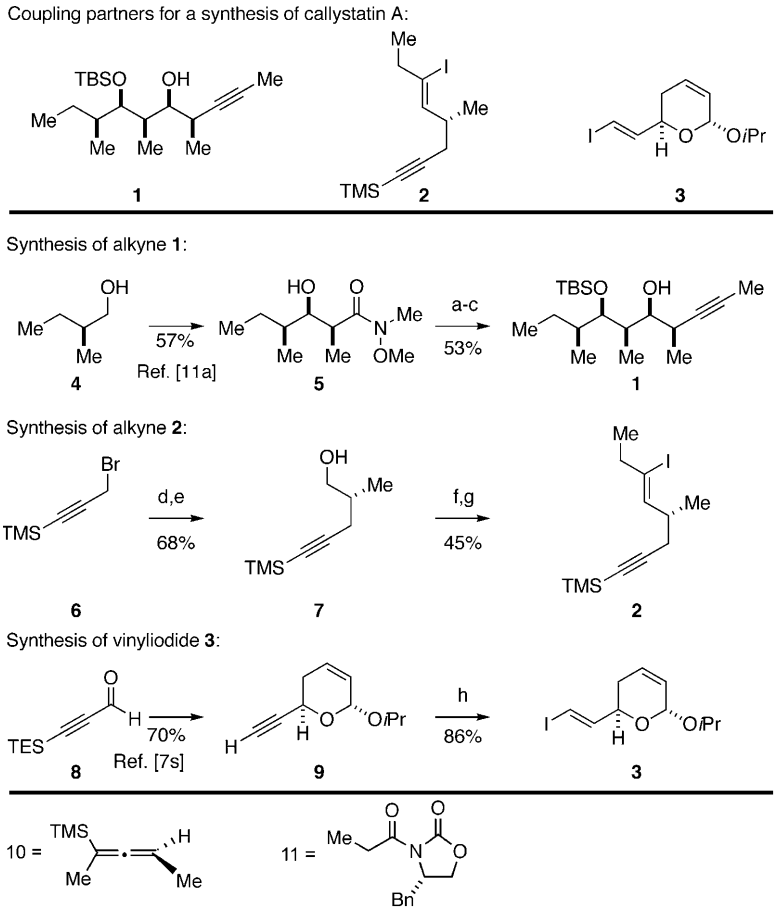
Although successful, these techniques have been proven to require numerous functional group manipulations that significantly impact any synthetic route to the leptomycins.

With the goal of defining a concise, modular synthetic pathway to the leptomycin family that would allow for the facile incorporation of widely varying functionality about the central leptomycin tetraene, we aimed to realize the coupling process described in Scheme 3. Assembly of the generic leptomycin skeleton was envisioned through sequential cross-coupling reactions: palladium-catalyzed coupling of the C8–C13-containing subunit **B** with the C1–C7-containing subunit **C**, and subsequent titanium-mediated reductive cross-coupling with the alkyne-containing subunit **A**. This last coupling process would establish the C13–C14 bond, while simultaneously installing the configuration of each stereodefined olefin of the C12–C15 1,3-diene—a single-step process that avoids multistep functional group manipulations. We describe the successful implementation of the general synthetic plan depicted in Scheme 3, which culminates in a concise total synthesis of callystatin A.

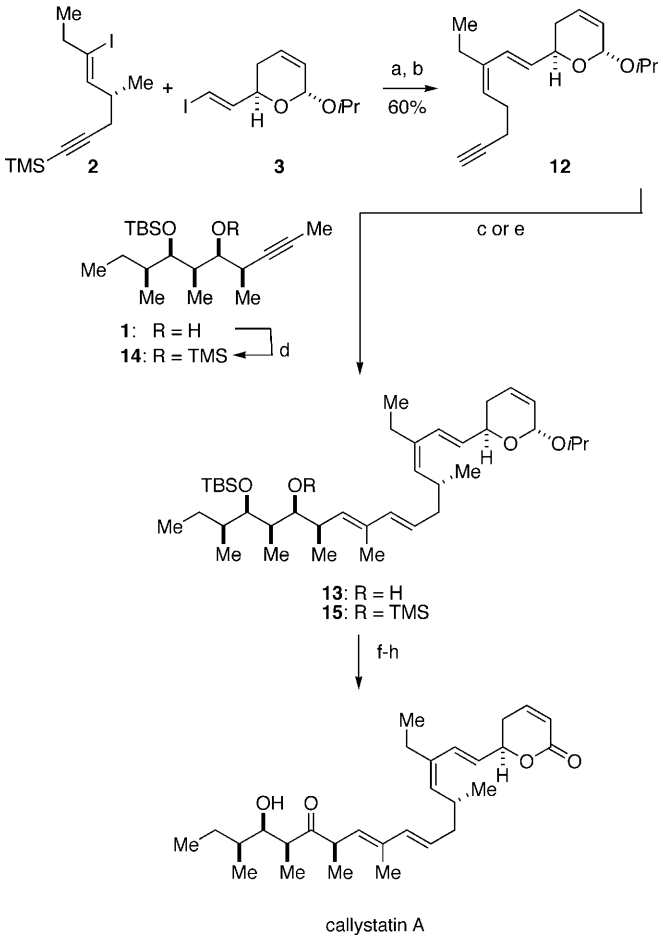
The modular plan delineated in Scheme 3, along with the structure of callystatin A, called for the preparation of coupling partners **1–3** (Scheme 4). These relatively simple substrates were generated in a straightforward manner.

The preparation of the C14–C22 coupling partner **1** was achieved from the commercially available chiral alcohol **4**, by using a combination of established aldol and propargylation methodology[8] This six-step sequence directly provides **1** without the need for further functionalization. The C8–C13 coupling partner **2** was prepared through: 1) diastereoselective alkylation of TMS-propargylbromide **6**,[9] 2) reduction, 3) oxidation, and 4) olefination. Although this sequence of steps provides access to **2**, the olefination reaction did not proceed with high stereoselection, despite previous reports describing stereoselective reactions with related phosphonium salts.[10] Although **2** can be prepared in a stereoselective fashion by a lengthier route,[11] we opted to employ this four-step sequence to access the desired coupling partner, as HPLC methods were effective for the separation of the isomeric vinyliodides. Finally, coupling partner **3** was prepared by hydrozirconation of the terminal alkyne **9**, itself available in three steps from aldehyde **8**.[7s]

With concise routes to coupling partners **1–3** defined, we focused our attention on a sequential process for their coupling. As anticipated, the palladium-catalyzed cross-coupling of **2** and **3** proceeded uneventfully and furnished a selective pathway to the polyunsaturated alkyne **12** (Scheme 5).[12] This reaction was performed by initial conversion of vinyliodide **2** into the corresponding vinylzinc reagent, and subsequent palladium-catalyzed coupling with **3**.



Scheme 4. Preparation of the coupling partners **1–3**. Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2 (82%); b) DIBAL-H, THF, −78 °C; c) **10**, $TiCl_4$, CH_2Cl_2, −78 °C (65% over 2 steps, *ds* 7:1); d) **11**, NaHMDS, −78 °C; then **6** (75%); e) $LiBH_4$, Et_2O, H_2O (91%); f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; g) 1. $Ph_3P(Pr)Br$ (Pr = propyl), *n*BuLi, THF; 2. I_2, THF; 3. NaHMDS; 4. addition of aldehyde (45%; *E*/*Z* 1.7:1); h) $[Cp_2ZrHCl]$, THF; then I_2 (86%). Bn = benzyl, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.



Scheme 5. Sequential cross-coupling and completion of a total synthesis of callystatin A. Reagents and conditions: a) **2**, $ZnCl_2$, *t*BuLi, Et_2O; then **3**, $[Pd(PPh_3)_4]$ (72%); b) TBAF, THF (83%); c) **1**, *n*BuLi, $ClTi(OiPr)_3$, *c*-C_5H_9MgCl, toluene (−78 to −30°C); then −78°C and add **12**, warm to −30°C; then NH_4Cl(aq) (43%; r.r. 3:1); d) TMSOTf, 2,6-lutidine, CH_2Cl_2 (89%); e) **14**, $ClTi(OiPr)_3$, *c*-C_5H_9MgCl, toluene (−78 to −30°C); then −78°C and add **12**, warm to −30°C; then NH_4Cl(aq) (75%; r.r. 5:1); f) PPTS, H_2O, acetone (71%); g) PCC, AcOH, M.S. (3 Å), benzene (83%); h) HF·py, py, THF (41%). M.S. = molecular sieves, PCC = pyridinium chlorochromate, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine, TBAF = *tetra-n*-butylammonium fluoride.

Titanium-mediated reductive cross-coupling provided a convenient stereoselective process for the union of **12** with **1**. Although coupling of the homopropargylic alcohol **1** with **12** was successful, to provide a 43% yield of **13**, we found that the use of TMS ether **14** was optimal in this cross-coupling reaction.[5a] In this case, **15** was produced in 75% yield as a 5:1 mixture of regioisomeric products. The success of this complex reductive cross-coupling is noteworthy for the following reasons: 1) aside from providing the desired regioisomer as the major product, no competing reaction processes were observed between **14** and **12**, thereby leaving all of the stereodefined olefins of **12** intact, 2) the potentially sensitive allylic acetal was unaffected under the reaction conditions employed, and 3) the cross-coupling reaction unites the complex fragments **12** and **14**, while simultaneously establishing the stereochemistry of the C12–C15 trisubstituted diene. In summary, this sequence of steps represents a particularly concise synthetic pathway to the highly unsaturated and stereodefined skeleton of the leptomycins.

With the sequential coupling reactions defined, we converted **15** into callystatin A through a simple three-step sequence: 1) simultaneous removal of the TMS ether and allylic acetal (PPTS, H_2O, acetone),[7b] 2) oxidation to the keto lactone (PCC, AcOH, M.S. (3 Å), benzene),[7c] and 3) removal of the TBS ether (HF·py, py, THF).[7l]

Overall, we have reported the application of a complex titanium-mediated reductive alkyne–alkyne cross-coupling reaction in the context of a total synthesis of callystatin A. The sequence described proceeds in only 11 steps from **4** (longest linear sequence) or 10 steps from **6** or **8**, and validates our proposed modular route to the assembly of the stereochemically complex, highly unsaturated skeleton common to the leptomycins (Scheme 3). The synthesis of a collection of non-natural leptomycin-inspired molecules, enabled by the advances described in this manuscript, is anticipated to provide a unique opportunity for future discovery at the chemistry/medicine interface.

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