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Application of Two Direct C(sp^3)−H Functionalizations for Total Synthesis of (+)-Lactacystin

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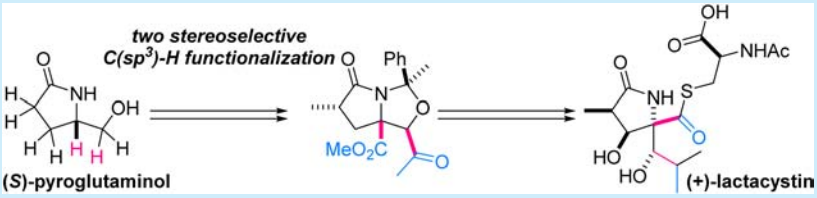
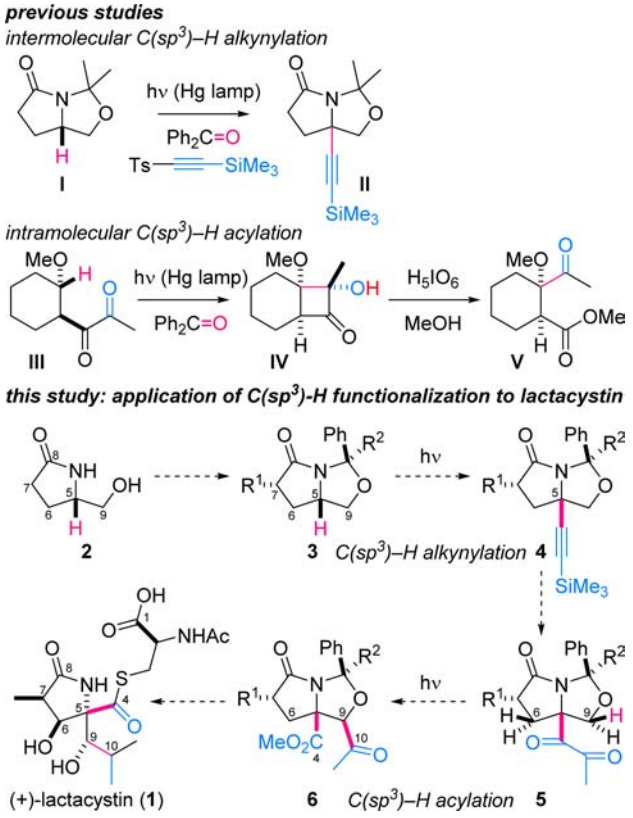
Supporting Information



ABSTRACT: Herein, we report a new synthetic route from (*S*)-pyroglutaminol to (+)-lactacystin, a potent inhibitor of the 20S proteasome. The photoinduced intermolecular C(sp^3)−H alkynylation and intramolecular C(sp^3)−H acylation chemo- and stereoselectively constructed the tetra- and trisubstituted carbon centers, respectively. The obtained bicycle was transformed into the target compound in a concise manner. The present total synthesis demonstrates the power of the direct C(sp^3)−H functionalizations for the assembly of multiple functionalized structures of natural products.

(+)-Lactacystin (**1**, Scheme 1), isolated from *Streptomyces* sp. OM-6519,[1] possesses neurite outgrowth activity in the murine neuroblastoma cell line Neuro-2a. A detailed investigation of the mode of biological action revealed that **1** irreversibly inhibits the proteolytic activity of the 20S proteasome.[2] Since the proteasome machinery plays an essential role in cell cycle control, differentiation, apoptosis, antigen processing, and immune response, proteasome inhibitors have emerged as important candidates for the development of pharmaceuticals[3] and new biological tools for the study of proteasome functions.[4] Accordingly, **1** has attracted significant attention as a synthetic target, and a number of total syntheses have been reported to date.[5−7]

Scheme 1. Synthetic Plan of (+)-Lactacystin



Direct transformation of C(sp^3)−H bonds to C(sp^3)−C bonds eliminates the need for preactivation steps and thus permits the design of simpler synthetic schemes.[8] Recently, we developed photochemically induced intra- and intermolecular C(sp^3)−H functionalizations and established their chemoselectivities (Scheme 1).[9−11] While the intermolecular C−H alkynylation employs $Ph_2C{=}O$ and 1-tosyl-2-(trimethylsilyl)-acetylene (**I** → **II**),[9e] the intramolecular C−H acylation consists of the Norrish−Yang cyclization[12] of a 1,2-diketone (**III** → **IV**) and subsequent oxidative ring-opening reaction (**IV** → **V**).[9a] In both reactions, the electrophilic oxyl radical photochemically generated from the carbonyl group chemoselectively cleaves the most electron-rich bond in the molecule (nitrogen-substituted > oxygen-substituted > aliphatic carbons), and the resultant carbon radical forms a new C−C bond. The mildness, simplicity, and predictability are highly advantageous features of these protocols for development of novel routes to complex natural products. Herein we describe construction of the multiply substituted structure of (+)-lactacystin (**1**) by combined use of these two powerful C(sp^3)−H functionalizations.

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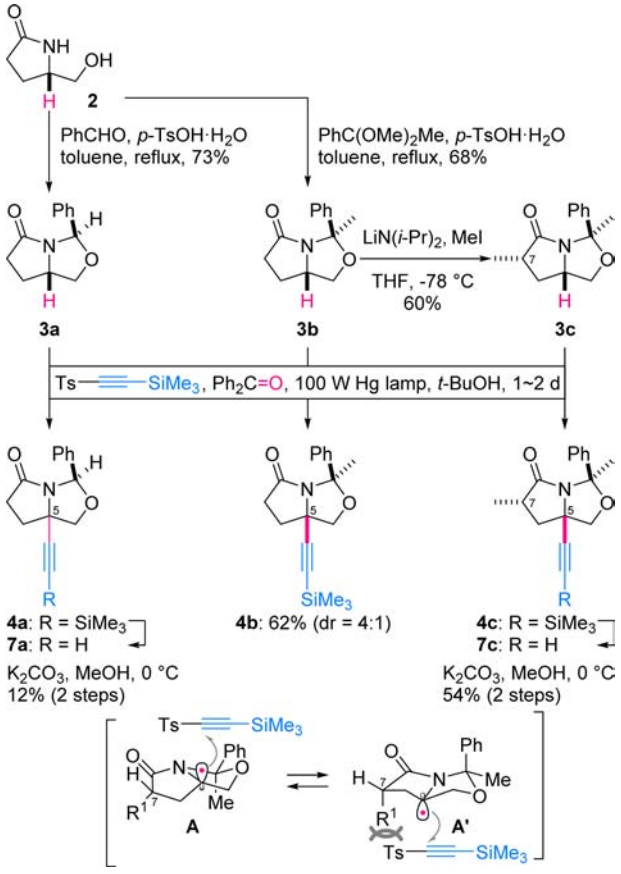
In planning the total synthesis, we correlated the C5−9 core skeleton of **1** to the structure of commercially available (*S*)-pyroglutaminol (**2**, Scheme 1). The chemo- and stereoselective C(sp^3)−H alkynylation of bicyclic lactam **3**, prepared from **2**, was expected to occur at the most electron-rich N-substituted C5-carbon to produce **4**. Alkyne **4** would be converted to 1,2-diketone **5**. Transfer of the two carbon unit of **5** to the most electron-rich O-substituted C9-carbon would be attained by utilizing the intramolecular C(sp^3)−H acylation, leading to **6**. In this way, both the C5- and C9-functional groups would be efficiently introduced by the C(sp^3)−H functionalizations at the correct oxidation levels. Once the highly substituted **6** is obtained, the targeted **1** would be synthesized through standard functional group manipulations at C4, 6, 7, and 10.

To realize the challenging chemo- and stereoselective C5-alkynylation, the three bicyclic structures **3a−c** were prepared (Scheme 2). First, formation of the benzylidene acetal from

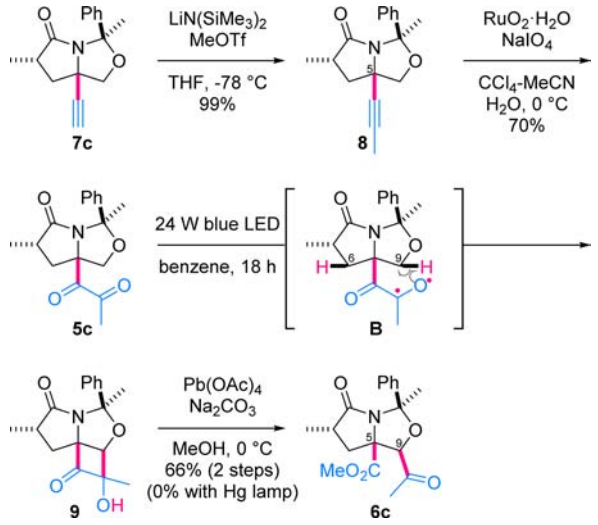
Scheme 2. Stereoselective C(sp^3)−H Alkynylation



(*S*)-pyroglutaminol (**2**) afforded **3a**[13] as a single stereoisomer. The mixture of **3a**, 1-tosyl-2-(trimethylsilyl)acetylene, and $Ph_2C{=}O$ was subjected to photoirradiation. Although the alkynylated adduct **4a** was indeed obtained, the yield was low (**7a**, 12%) after removal of the Me_3Si group. Not only the electron-rich N-substituted methine but also the *N*,*O*-acetal methine appeared to react with the photoexcited $Ph_2C{=}O$. Therefore, the alternative substrate **3b** with no acetal methine was prepared through the acid-induced trans-acetalization between **2** and acetophenone dimethyl acetal.[14] The same photoinduced alkynylation conditions transformed **3b** into **4b** in 62% yield. Thus, the chemoselectivity was significantly improved by changing the substrate from **3a** to **3b**, but the stereoselectivity was moderate (dr at C5 = 4:1). To affect the stereochemical outcome, one more stereocenter was introduced to **3b** via base-promoted methylation to produce **3c**. When **3c** was irradiated by a mercury lamp in the presence of 1-tosyl-2-(trimethylsilyl)-acetylene (1.5 equiv) and $Ph_2C{=}O$ (0.5 equiv) in *t*-BuOH, the C5-tetrasubstituted carbon of **4c** was stereoselectively constructed, and the subsequent desilylation of **4c** gave rise to terminal alkyne **7c** in 54% yield over two steps. Therefore, the stereochemical information at C5 that was once lost upon radical formation was effectively regenerated by influence of the two proximal stereocenters.[15] The higher requisite stereoselectivity from **3c** than from **3b** would be rationalized by considering the two equilibrating conformers of the resultant tertiary radicals **A** and **A′**. Since the unfavorable steric interaction between **A′** and the acetylene would be enhanced by the additional C7-methyl group of **3c** (R^1 = Me), **4c** is exclusively generated via the less shielded radical **A**.

To prepare for the next stereoselective C(sp^3)−H functionalization, diketone **5c** was synthesized from **7c** (Scheme 3).

Scheme 3. Synthesis of the Key Intermediate 6c



Methylation of terminal alkyne **7c** using $LiN(SiMe_3)_2$ and MeOTf afforded **8**. Internal alkyne **8** was then oxidized to 1,2-diketone **5c** by the action of catalytic RuO_2 and stoichiometric $NaIO_4$.[16] Compound **5c** was next irradiated with a mercury lamp for the Norrish−Yang cyclization. However, the reaction resulted in a complex mixture, presumably due to undesired reaction pathways associated with concomitant photoexcitation of monoketone **9** with UV light (<360 nm). For selective photoactivation of the diketone moiety (λ_{max} = 433 nm) of **5c**,[17] a blue LED was alternatively applied because it emits light of longer wavelength (approximately 460 nm) than the mercury lamp. Consequently, compound **5c** was smoothly transformed into the cis-fused cyclobutanone **9** in a chemo- and stereoselective manner. The site-selective H-abstraction of **B** at C9 over C6 in this reaction reflected the more electron-rich nature of the ethereal C(sp^3)−H bond in comparison to the aliphatic C−H bond. Finally, the oxidative ring-opening reaction of **9** using $Pb(OAc)_4$ and Na_2CO_3 resulted in ketoester **6c** as a single isomer in 66% yield over two steps.[18] Hence, stereoselective introductions of the two vicinal C5- and C9-centers were realized by the two C−H bond functionalizations.

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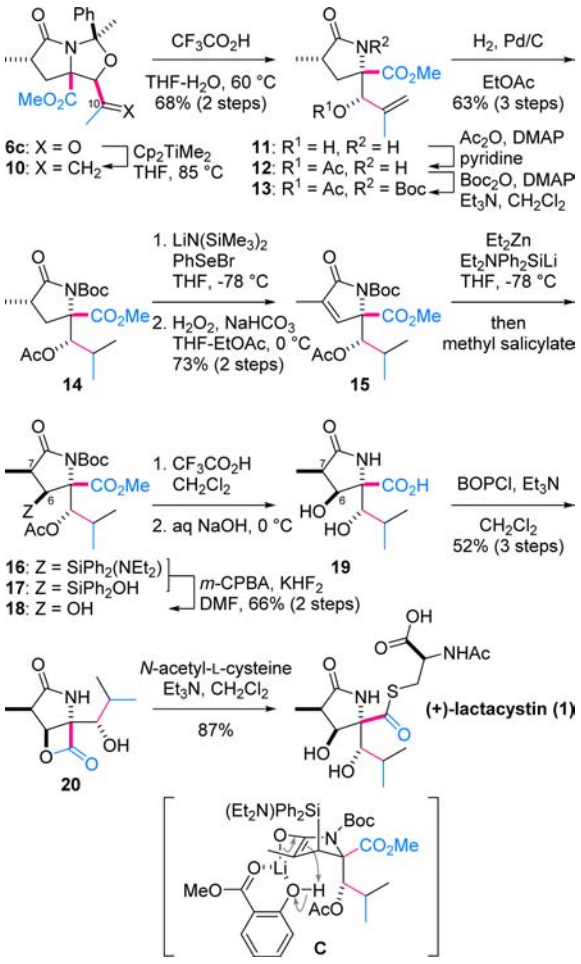
The highly branched structure of **6c** was converted to (+)-lactacystin (**1**) through homologation at C10, construction of C6,7-stereocenters, and attachment of the cysteine moiety (Scheme 4). Thus, olefination of the C10-ketone in **6c** with

Scheme 4. Total Synthesis of (+)-Lactacystin



Petasis reagent[19] and subsequent acidic removal of the *N,O*-acetal afforded allylic alcohol **11**. The liberated hydroxy and amide groups of **11** were in turn capped with the acetyl and Boc groups, respectively, leading to **13**. Hydrogenation of **13** formed the saturated branched carbon chain of **14**.

Prior to stereoselective construction of the C6,7-centers, the α,β-unsaturated lactam **15** was prepared by α-selenylation of **14** and subsequent selenoxide elimination (**14** → **15**). 1,4-Addition of (diethylamino)diphenylsilyllithium[5j,20] to **15** in the presence of diethylzinc[21] proceeded from the opposite face of the large C5-chain to install the C6-stereochemistry, and the resultant enolate **C** was protonated by methyl salicylate[22] from the opposite face of the bulky silyl group to introduce the C7-stereochemistry, leading to a mixture of **16** and **17** after the workup.[23] Tamao oxidation[24] of **16** and **17** with *m*-CPBA gave rise to **18** as the sole stereoisomer.

The total synthesis of (+)-lactacystin (**1**) was accomplished through condensation with cysteine. Detachment of the Boc group of **18** with CF_3CO_2H, followed by hydrolysis of the acetate and methyl ester, furnished β-hydroxy carboxylic acid **19**. Lastly, β-lactone formation from **19** using bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOPCl)[5a] afforded compound **20**, which was treated with *N*-acetyl-L-cysteine in the presence of Et_3N, delivering **1**. The physical data of synthetic **1** (^1H and ^{13}C NMR, IR, and $[\alpha]_D$) were in complete agreement with those previously reported.[1b,5]

In conclusion, a novel route to (+)-lactacystin (**1**) from (*S*)-pyroglutaminol (**2**) has been established by judicious application of intermolecular C−H alkynylation (**3c** → **4c**) and intramolecular C−H acylation (**5c** → **6c**). These reactions realized unique C−C bond formations, which were otherwise difficult to attain, and simplified the assembly of the branched carboskeleton of **6c**, which was efficiently derivatized into the targeted **1**. The present total synthesis demonstrates the high applicability of the two C(sp^3)−H functionalizations to form the complex intermediates and the high predictability of their chemoselectivities (N-substituted > O-substituted > aliphatic carbons). Further applications of these and other direct reactions[9] for construction of diverse structures of natural products and pharmaceuticals are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) The ultraviolet/visible spectrum of diketone **5c** and monoketone **9** showed absorption maximum (λ_{max}) of 433 and 340 nm, respectively. See the Supporting Information for details.

(18) C9-epimerization was observed without addition of Na_2CO_3.

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