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Short and Versatile Route to a Key Intermediate for Lactacystin Synthesis

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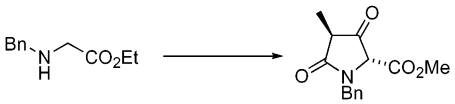
ABSTRACT

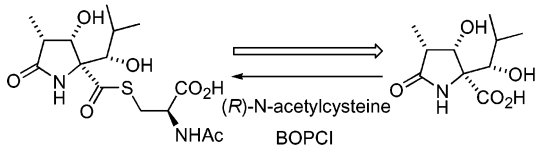


A key intermediate 14 for the synthesis of lactacystin 1 has been constructed in four steps and 33% overall yield. The key steps involve cyclization of a suitably functionalized glutamic acid derivative and concomitant alkylation of the resulting *β*,*β*-diketoester system, C-acylation of the cyclic α-amidoketone 9, and decarboxylbenzylation of 12. Alkylation of a related *β*,*β*-diketoester 5 was additionally achieved with several electrophiles.

In 1991, Omura reported the isolation of (+)-lactacystin **1**, a novel amino acid metabolite from a *Streptomyces* species.[3] The compound inhibits cell growth and also induces neurite outgrowth in the murine neuroblastoma cell line (Neuro 2a), prompting study of the usefulness of the compound in treating neurologically related diseases such as Alzheimer's.[4] The specific target of lactacystin is the 20S proteasome,[5] part of the 28 protein complex responsible for the normal turnover of cellular proteins, the removal of damaged proteins, and control of cell growth and metabolism.[6] Due to its unique ability to inhibit the activity of the 20S proteasome, the compound is in great demand in many laboratories today, and several synthetic approaches to the compound have been reported [7] and reviewed.[8] This paper reports the synthesis of a key intermediate **14** for lactacystin synthesis in just four steps without any column chromatography.

Retrosynthesis of lactacystin by disconnection at the thiol ester linkage leads to the principal synthetic target molecule, the α-substituted pyroglutamic acid **2**. Corey has shown that this may be coupled with (*R*)-*N*-acetylcysteine without hydroxy group protection in one step (Scheme 1).[7]

Scheme 1



Our synthetic approach to **2** began with condensation between *N*-benzyl glycine ethyl ester and benzyl malonyl chloride to give the amide **3** in 83% yield (Scheme 2).[9] Similar reaction with ethyl malonyl chloride gave the corresponding amide **4** in 91% yield. Dieckmann cyclization of diester **4** with sodium/methanol under reflux gave methyl *N*-benzylpyrrolidin-2,4-dione 3-carboxylate **5** in 88% yield.

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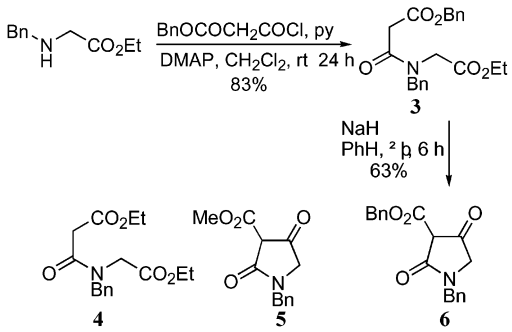
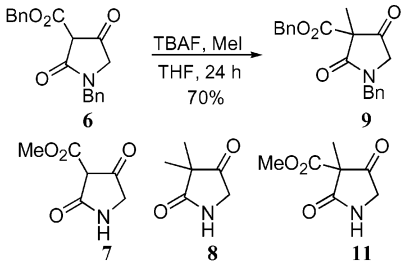
Initial attempts using sodium/benzyl alcohol for the cyclization of **3** gave only a low yield of the pyrrolidin-2,4-dione 3-carboxylate **6** (14%), but treatment of **3** with sodium hydride in benzene furnished **6** in 63% yield.

Scheme 2



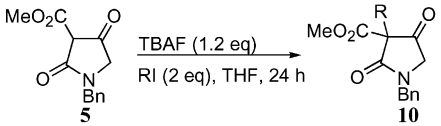
Introduction of the required methyl group into 3-positions of **5** and **6** proved to be extremely troublesome, as the compounds are poorly soluble in common organic solvents. Standard methods such as NaH/MeI, K_2CO_3/MeI, and ^{t}BuOK/BuOH/MeI failed to give any of the desired methylated products. Fedorynski has reported the alkylation of malonates and related materials in good yield using potassium or sodium carbonates in the presence of tetraalkylammonium salts or crown ethers at elevated temperatures,[10] but use of this system in acetonitrile was also unsuccessful in our hands; the major product of treatment of methyl pyrrolidin-2,4-dione 3-carboxylate **7** with potassium carbonate and tetrabutylammonium bromide in acetonitrile under reflux was 3,3-dimethylpyrrolidin-2,4-dione **8**, presumably formed through decarboxymethylation of the ester group.[11] We had previously observed similar decarboxylation of **8** upon simple heating in acetonitrile. Fortunately, we were able to overcome this problem by treatment of **6**, **5**, and **7** with tetrabutylammonium fluoride/MeI in THF solution to give **9** (70%), **10** (R = Me, 77%), and **11** (82%), respectively, in very good yields (e.g., Scheme 3).

Scheme 3



Alkylation of such β,β-diketoester systems appears to be very uncommon in the literature. To investigate the efficiency of the reaction, we have carried out the alkylation of this system using several different electrophiles, using **5** as the substrate, to give **10** as products (Scheme 4, Table).

Scheme 4

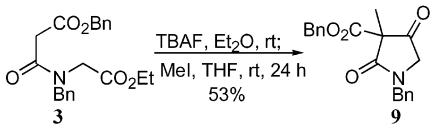


Alkylation of 5 using TBAF/RI

R	yield (%)
Me	77
Et	63
$PhCH_2$	89
CH_2=$CHCH_2$	60
PhCH=$CHCH_2$	64
EtO_2CCH_2	46

We subsequently discovered that treatment of **3** with tetrabutylammonium fluoride in ether at room-temperature induces cyclization and enolate formation to give the enolate of **6**, which may be treated with iodomethane in THF to lead directly from **3** to **9** in 53% yield (Scheme 5).

Scheme 5



Having successfully prepared the methylated compound **9**, the next step required the introduction of a methyl ester function adjacent to the nitrogen atom by acylation at the carbon of the corresponding enol or enolate. This carboxymethylation reaction also proved to be problematic because the compound undergoes O-acylation in most reaction systems (for example, with ethyl chloroformate using LDA,

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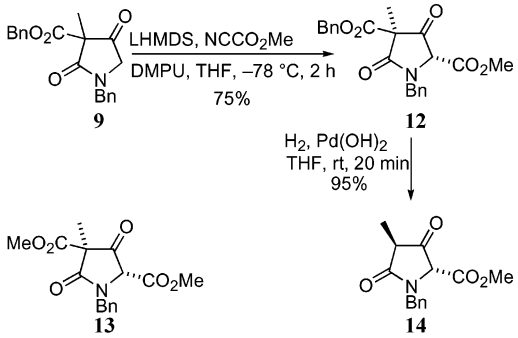
Scheme 6



NaH, KOt-Bu, or LiOt-Bu as a base). By using Mander's reagent, however, we were able to carry out C-acylation of **9** to give **12** as a 5:1 mixture of diastereoisomers, with no competing O-acylation (Scheme 6).[12] C-Acylation of **10** (R = Me) takes place under similar conditions to give **13** in 76% yield as a 2:1 diastereoisomeric mixture.

Removal of the ester benzyl group of **12** by hydrogenolysis and concomitant decarboxylation was achieved in 20 min at room temperature with $Pd(OH)_2$/THF to give **14** in 95% yield (Scheme 6). Further studies toward the elaboration of **13** and **14** for a total synthesis of lactacystin are currently under investigation in our laboratories.

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