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A Short and Efficient Synthesis of (−)-7-Methylomuralide, a Potent Proteasome Inhibitor

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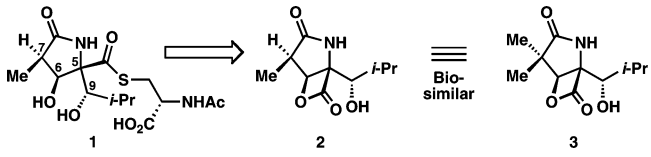
Lactacystin (**1**) was discovered by Õmura et al.[1] using an in vitro screen for secondary metabolites that exhibit nerve growth factor-like activity against a murine neuronal cell line. Subsequently, it was determined that the observed stimulation of neurite outgrowth shown by **1** stemmed from its inhibition of the 20S proteasome by acylation mainly at the N-terminal threonine of the β5 (chymotryptic) subunit.[2] The active small molecule in this process is the β-lactone omuralide[3] (*clasto*-lactacystin, **2**), of which **1** is actually a precursor.[2,4]

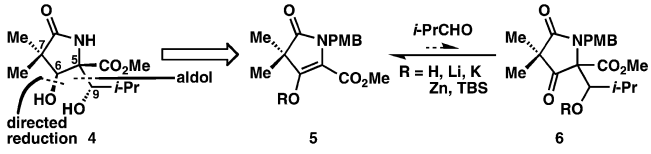
Proteasome inhibition constitutes a useful means of modulating and studying a variety of cellular processes, including mitosis, heat-shock response, and antigen presentation.[5] Of current clinical interest is the effect of proteasome inhibition on cancer cells, as it has been demonstrated to lead to cell-cycle arrest and apoptosis by preventing the degradation of I-κ B and ultimately hindering transcription.[6] Consequently, several proteasome inhibitors are being clinically evaluated for the treatment of hematological malignancies. Velcade (bortezomib) is one such drug currently prescribed for multiple myeloma.[7]

Both **1** and **2** are commercially available through purveyors of fine chemicals. However, their high cost ($1500/mg and $2360/mg, respectively; Sigma-Aldrich) and the lengthy syntheses required for their preparation underscore the need for simpler and more economical routes to this class of proteasome inhibitor. Herein, we report a concise synthesis of 7-methylomuralide (**3**), a simpler but nearly equipotent analogue[3] of **2**, using a route that allows for the rapid and inexpensive preparation of this important molecule.



1 2 3

The potency of **3** has inspired two prior syntheses from these laboratories (13−15 steps).[8] However, to maximize material throughput, a shorter route to **3** was envisaged whereby intermediate **4** could be accessed through only two stereogenic reactions: directed reduction of C6 and a stereoselective aldol reaction to establish C5 and C9. Unfortunately, initial attempts at direct bond formation with isobutyraldehyde failed because of the instability of aldol product **6**, which undergoes rapid reversion to the starting material (see below) under a variety of conditions (Figure 1).



4 5 6

Figure 1. Direct aldol route to **4** (unfavorable).

However, it was possible to override this tendency for reverse aldolization by using as intermediates the imides **7a**−**c** (Figure 2A). These were synthesized in one step by treating the corresponding *N*-carbamoyl glycine *O*-methyl esters with 3.1 equiv of LHMDS and 1.1 equiv of dimethylmalonyl dichloride (see Scheme 1 and the Supporting Information). Reaction of the Boc-imide **7a** with base and isobutyraldehyde gave solely and in excellent yield aldol ester **9a** (mp 136−138 °C), the structure of which was determined by X-ray crystallographic analysis (see inset **9a** in Figure 2A). The diastereoselectivity of this aldol reaction is opposite to that required for the synthesis of **3**. This problem was overcome by the use of the trichloroethoxycarbonyl (Troc)-imide **7c** and a 25-fold excess of isobutyraldehyde, which afforded the required aldol carbonate ester **8c** (mp 116−118 °C) in 70% isolated yield and >10:1 predominance over the diastereomer **9c**. In the case of benzyl carbamate **7b**, the aldol/acyl migration reaction[9] is not strongly diastereoselective between the **8** and **9** diastereomers (Figure 2A). The X-ray crystal structure of **8b** (mp 136−138 °C) is shown in Figure 2A; aldol esters **8b** and **8c** were correlated by conversion to the acid[8a] corresponding to (±)-**3** (see below). The dependence of the stereoselectivity on aldehyde concentration for **7c** is a good indication that the rate-determining step in the formation of **8c** is the aldol reaction while that in the formation of **9c** is the acyl-transfer reaction (Figure 2B).

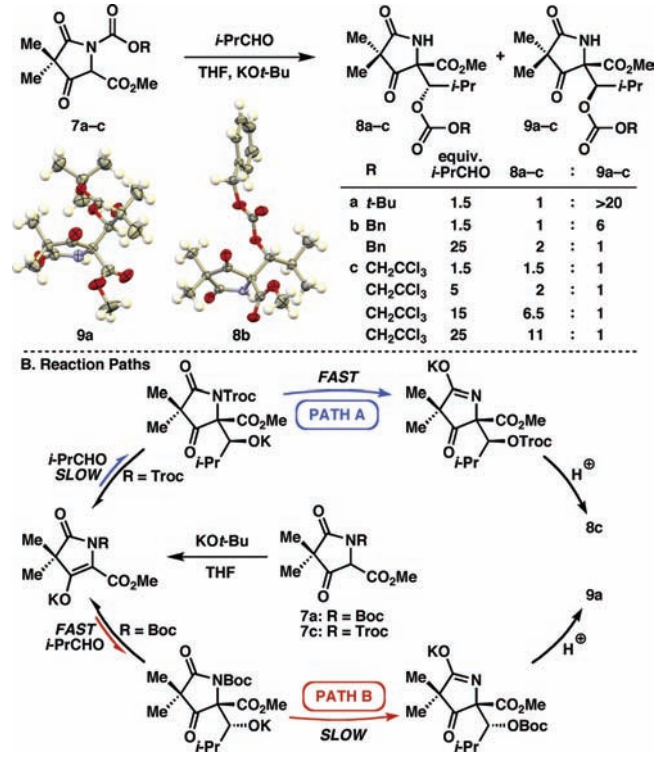
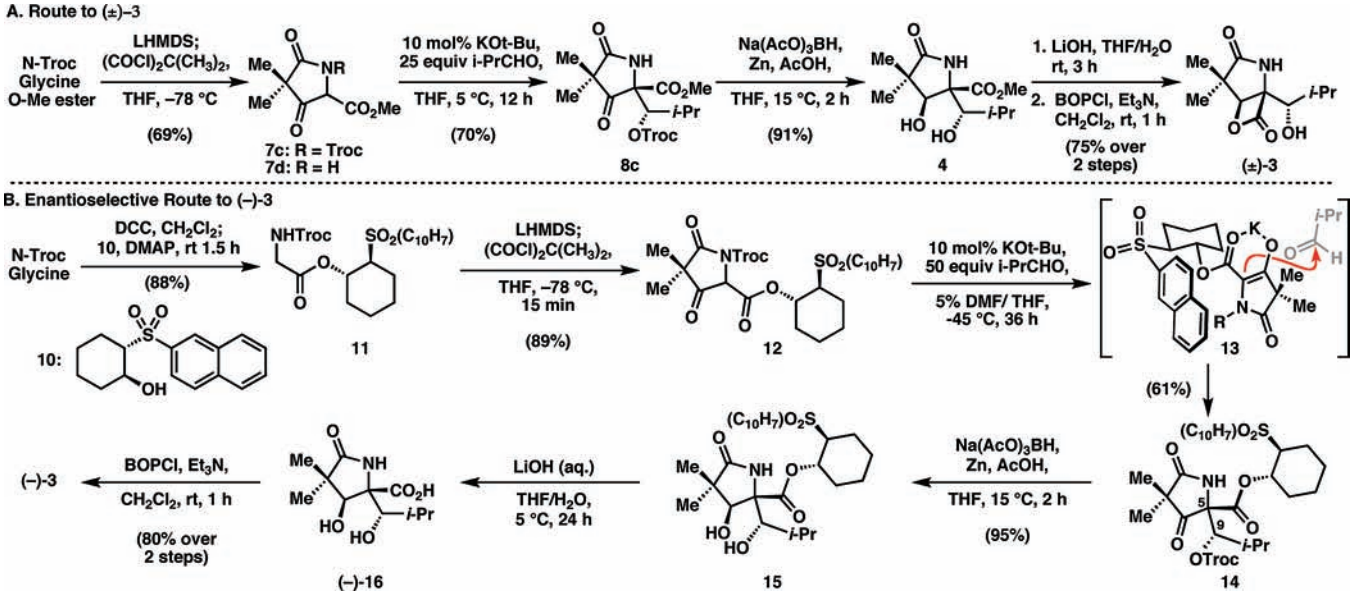


Figure 2. Major pathways for diastereoselective tandem aldol/acyl-transfer reactions of **7a** and **7c**.

10.1021/ja901400q CCC: $40.75

Scheme 1. Straightforward Routes to (±)-**3** and (−)-**3** in Five and Six Steps, Respectively



In accord with previous observations, the alcohol derived from **8c** by Troc removal with zinc metal proved unstable due to retro-aldol cleavage and was never detected; only lactam **7d** (Scheme 1A) could be isolated from the reaction mixture. However, when the same reaction was conducted in the presence of sodium triacetoxyborohydride (10 equiv), the nascent alcohol was efficiently trapped as the boronate by displacement of an acetate ligand on boron. This borohydride derivative then internally reduced the adjacent ketone function, producing dihydroxy ester **4** diastereoselectively and in excellent yield (91%). Saponification and lactonization[4,8] yielded (±)-**3**, whose spectroscopic characteristics were identical to those previously reported.[8]

In order to synthesize enantiomerically pure lactone (−)-**3**, it was necessary to render the tandem aldol/acyl-transfer step asymmetric. To this end, we turned to the practical chiral directing group **10** (Scheme 1B), which was previously developed in these laboratories for enantioselective Diels−Alder reactions of unsaturated esters and enantioselective alkylation of ester enolates.[10] It was anticipated that van der Waals interactions similar to those described in previous studies would organize the pretransition state assembly for aldol bond formation. Use of the controller **10** in the key aldol reaction was predicted to provide the required absolute configuration for the synthesis of (−)-**3**.

The controller was appended by carbodiimide-mediated coupling of enantiomerically pure alcohol **10**[10] with *N*-Troc glycine. Lactam formation (**11** → **12**) was effected in even higher yield (89%) than in the route shown in Scheme 1A via a deep red intermediate (possibly the dianion of **11**).

The **10**-based controller effectively screened one face of enolate **13** in the aldol reaction in favor of diastereomer **14** (8:1 selectivity at C5). This selectivity can be attributed to the previously proposed[10] van der Waals attraction between the electron-rich potassium enolate and the appendant electron-poor 2-naphthylsulfone, which favors the pretransition state assembly **13**. Even though the selectivity due to differentiation of the prochiral aldehydic carbon was 4:1, overall the reaction was efficient enough to provide isomer **14** (mp 178−180 °C) in 61% yield after recrystallization from methanol, which removed the three minor diastereomeric impurities.

The subsequent tandem Troc removal/intramolecular reduction also proceeded in high yield (95%) to afford diol **15**, which could be saponified to (−)-**16** (with **10** being recovered quantitatively) and lactonized to form optically pure lactone (−)-**3**.[8b]

In summary, short, practical and scalable syntheses of (±)-**3** and (−)-**3** have been developed. The approach relies on three consecutive tandem reaction pairs to establish all of the carbons and the stereochemistry of the target molecule, vastly simplifying the synthetic scheme to a mere five or six steps from glycine carbamates. Of note is the use of chiral directing group **10** to control the absolute stereochemistry of the key aldol reaction, suggesting that this easily prepared chiral controller may be considerably more useful than previously indicated.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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