ORGANIC LETTERS

2001
Vol. 3, No. 9
1395−1397

A Novel Enantioselective Synthetic Route to Omuralide Analogues with the Potential for Species Selectivity in Proteasome Inhibition

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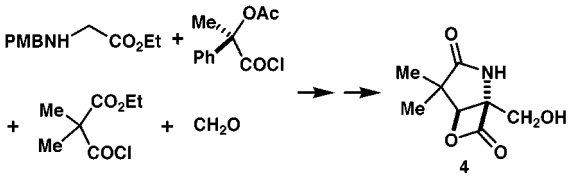
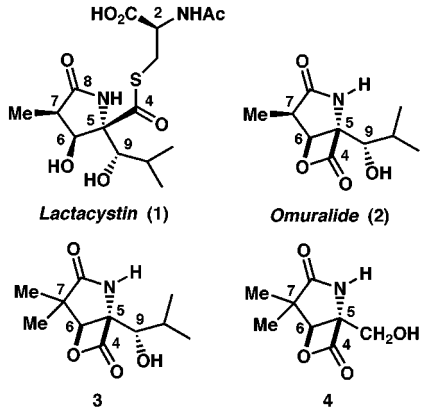
Received February 23, 2001

ABSTRACT



The building blocks shown can be combined for an enantioselective construction of the simplified omuralide analogue 4 in nine steps, with the use of (*R*)-atrolactic acid as a recoverable chiral controller.

Lactacystin (**1**) and the corresponding β-lactone, omuralide (**2**), exhibit a remarkably selective and potent irreversible inhibition of proteasome function.[1,2] Since proteasomes degrade many, if not most, of the proteins in cells, including misfolded proteins,[3] and proteins involved in cell cycle progression[4] and regulation of gene transcription,[5] **1** and **2** have emerged as important biochemical tools. Totally synthetic **1** and **2**[6,7] have been used as reagents in hundreds



of laboratories because of their unequalled selectivity and effectiveness. The β-lactone **2** inactivates the 20 *S* proteasome at a much faster rate than does lactacystin (**1**), with a major source of inactivation being through acylation of the *N*-terminal threonine subunit, a key catalytic component.[1b,8] An extensive series of synthetic and biological studies has

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(2) For general reviews on proteasomes, see: (a) Voges, D.; Zwickl, P.; Baumeister, W. *Annu. Rev. Biochem.* **1999**, *69*, 1015. (b) Coux, O.; Tanaka, K.; Goldberg, A. L. *Annu. Rev. Biochem.* **1996**, *65*, 801. (c) Bogyo, M.; Gaczynska, M.; Ploegh, H. L. *Biopolymers Peptide Sci.* **1997**, *43*, 269.

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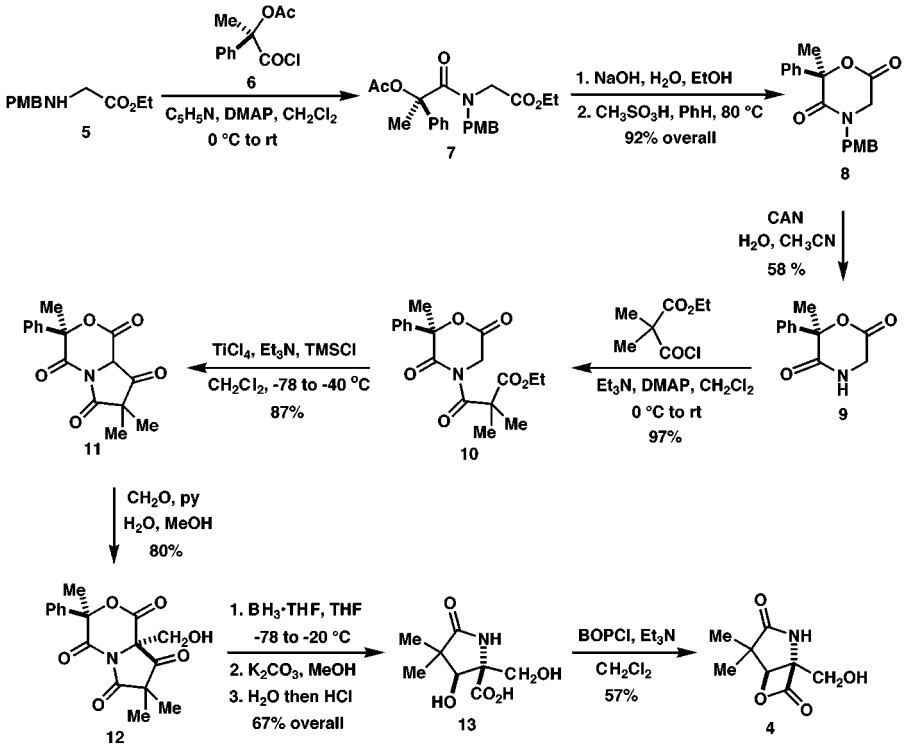
10.1021/ol015757p CCC: $20.00
Published on Web 03/27/2001

Scheme 1



provided a clear correlation between chemical structure and rate of irreversible inactivation[1a] of the mammalian (bovine) proteasome.[9] The (*S*)-1-hydroxyisobutyl side chain attached to C(5) was found to be critical to activity, as well as the γ-lactam and β-lactone subunits. However, the methyl group attached to C(7) could be replaced by Et, *i*-Pr, *n*-Bu, or CH_2Ph without loss of activity. Furthermore, the 7,7-dimethyl analogue **3** had nearly the same (0.75×) activity as **2**.[10] The objective of the present research, the synthesis of the simplified omuralide analogue **4**, derived from the knowledge of these structure−activity correlations for the mammalian proteasome and the fact that **1** and **2** block development of the malaria parasite (*Plasmodium* sp.)[11] and the trypanosomal parasite (*Trypanosoma cruzi*).[12] Unfortunately, the concentrations of **1** and **2** required to inhibit the development of these parasites to the pathological stage also inactivate the mammalian proteasome and cause unacceptable toxicity. We therefore undertook the synthesis of omuralide analogues such as **4** which clearly would be less toxic to humans[9] in the hope of finding compounds which more effectively exploit the differences between human and parasite proteasomes. Such a molecule with a therapeutic index of ca. 10^3−10^4 could in principle provide a cure for malaria and other parasite-caused diseases.

The synthesis of the target molecule **4** is outlined in Scheme 1. Coupling of *N*-*p*-methoxybenzylglycine ethyl ester (**5**)[13] with (*R*)-*O*-acetylatrolactoyl chloride (**6**)[14] in the presence of pyridine and 4-(dimethylamino)pyridine in CH_2Cl_2 at 0−23 °C provided the amide ester **7** which was deacetylated by NaOH in aqueous ethanol and lactonized by heating at reflux in benzene with methanesulfonic acid (8 mol %) for 30 min to afford **8** in 92% overall yield from **5**. Oxidative cleavage of the PMB group with ceric ammonium nitrate in aqueous acetonitrile at 23 °C generated the lactam **9** (58%). *N*-Acylation of **9** with the monoester monoacid chloride of dimethylmalonic acid gave the coupling product **10** (97%) which underwent Dieckmann cyclization to **11** (87%) when treated with $TiCl_4$−Et_3N−Me_3SiCl at −40 °C in CH_2Cl_2.[15] Intermediate **11**, which exists in solution

(9) For reviews on structure−activity correlations for a large series of omuralide analogues, see: (a) Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1. (b) Corey, E. J.; Li, W.-D. Z.; Nagamitsu, T.; Fenteany, G. *Tetrahedron* **1999**, *55*, 3305. (c) Masse, C. E.; Morgan, A. J.; Adams, J.; Panek, J. S. *Eur. J. Org. Chem.* **2000**, 2513.

(10) Corey, E. J.; Li, W.-D. Z. *Tetrahedron Lett.* **1998**, *39*, 7475.

(11) Gantt, S. M.; Myung, J. M.; Briones, M. R. S.; Li, W.-D.; Corey, E. J.; Omura, S.; Nussenzweig, V.; Sinnis, P. *Antimicrob. Agents Chemother.* **1998**, *42*, 2731.

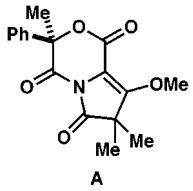
(12) Gonzalez, J.; Ramalho-Pinto, F. J.; Frevert, U.; Ghiso, J.; Tomlinson, J.; Scharfstein, J.; Corey, E. J.; Nussenzweig, V. *J. Exp. Med.* **1996**, *184*, 1909.

(13) Miknis, G. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 536.

(14) (*R*)-Atrolactic acid was obtained from the commercially available racemate (Acros) by the following sequence: (1) precipitation of the (*S*)-enantiomer as the salt with (*S*)-(−)-α-methylbenzylamine from water, (2) extractive isolation of the remaining enriched (*R*)-atrolactic acid from the acidified filtrate, and (3) crystallization of the salt of (*R*)-atrolactic acid and (*R*)-(+)-α-methylbenzylamine from hot water. See: Smith, L. *J. Prakt. Chem.* **1911**, *115*, 731. (*R*)-Atrolactic acid of >99% ee was obtained from this salt by extraction from acidic water and a single recrystallization from hot toluene. (*R*)-Atrolactic acid was acetylated by stirring with acetyl chloride at 23 °C for 1.5 h and the resulting acid was converted into the acid chloride **6** by reaction with oxalyl chloride in benzene with dimethylformamide (3 mol %) as catalyst.

(15) (a) Patek, M. *Collect. Czech. Chem. Commun.* **1989**, *54*, 1223. (b) Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Tetrahedron Lett.* **1999**, *68*, 1015.

along with the enol tautomer, was fully characterized as the enol ether **A** obtained by the action of diazomethane in ether.



A

Hydroxymethylation of **11** occurred smoothly upon reaction with 10 equiv of aqueous formaldehyde and pyridine (10 mol %) in aqueous methanol at 23 °C to form **12** stereoselectively in 80% yield. The face selectivity of the hydroxymethylation is controlled by the difference in steric screening (C_6H_5 > CH_3) due to the atrolactic derived stereocenter.

Treatment of **12** with borane−tetrahydrofuran complex resulted in conversion to diol **B** of high diastereomeric purity (>95%). Nuclear Overhauser difference measurements revealed that **B** possessed the desired configurations at C(8) and C(8a) (Figure 1). Selective removal of the atrolactic acid controller without compromising the γ-lactam ring in **B** was accomplished by treatment with potassium carbonate in methanol to afford dihydroxy acid **13** in 67% yield from **12**. These two operations were conveniently carried out in one flask. The separation of **13** and atrolactic acid (for reuse) was accomplished simply by trituration of the crude product with chloroform, which dissolves the latter. Treatment of the triethylammonium salt of **13** with bis(2-oxo-3-oxazolidinonyl)phosphinic chloride (BOPCl) in CH_2Cl_2 at 23 °C provided β-lactone **4** in 57% yield after chromatography on silica gel.

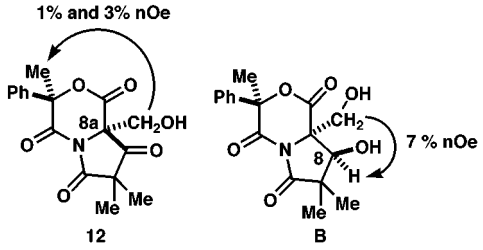


Figure 1. Assignment of relative stereochemistry of **12** and **B**.

The synthesis of **4** which is outlined in Scheme 1 utilizes a novel chiral glycine equivalent (**9**) for enantiocontrol. The brevity and efficiency of the synthesis allow ready access to **4** and related analogues. The facile recovery of the chiral controller (*R*)-atrolactic acid for reuse adds to the practicality of this approach.

Acknowledgment. This work was assisted financially by a research grant from Pfizer Inc. and a Canadian NSERC postdoctoral fellowship to S.N.C.

Supporting Information Available: Full experimental procedures for the synthesis of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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