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New Entry to Convertible Isocyanides for the Ugi Reaction and Its Application to the Stereocontrolled Formal Total Synthesis of the Proteasome Inhibitor Omuralide§

Cynthia B. Gilley, Matthew J. Buller, and Yoshihisa Kobayashi*

Department of Chemistry and Biochemistry, University of California, San Diego,
9500 Gilman Drive, Mail Code 0343, La Jolla, California 92093-0343

ykoba@chem.ucsd.edu

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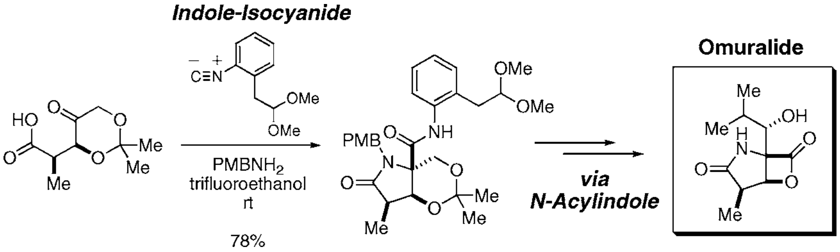
ABSTRACT



The development of a new convertible isocyanide, *indole-isocyanide*, for ready access to pyroglutamic acids culminated in the formal total synthesis of the proteasome inhibitor omuralide featuring a stereocontrolled Ugi reaction. Indole-isocyanide was named after the facilitation of hydrolysis of the resulting 2-(2,2-dimethoxyethyl)anilide via an *N*-acylindole intermediate obtained by the Ugi multicomponent condensation reaction followed by the indole formation.

Omuralide (**1**), derived from the natural product lactacystin (**2**),[1] has been shown to be a selective inhibitor of the *20S* proteasome found in mammalian and bacterial cells.[2] A great deal of attention has been devoted recently to proteasome inhibition as a novel therapeutic target in human cancer due to the distinctly different mechanism of action from known chemotherapeutics.[3] In 2003, FDA approval of Velcade for the treatment of multiple myeloma validated proteasome inhibition as a novel cancer therapy.[4] A structurally related and more potent proteasome inhibitor, salinosporamide A (**3**), was reported by Fenical recently.[5]

The combination of the unique biological profile and the structural complexity of omuralide (**1**)[6] and salinosporamide A (**3**)[7] has led to intense research efforts by synthetic chemists. Both molecules share a fused γ-lactam−β-lactone core structure which could easily be obtained from a

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§ In memory of Dr. Kenji Koga.

(1) (a) Omura, S.; Fujimoto, T.; Otoguru, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113−116. (b) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117−118.

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(3) (a) Fenteany, G. A.; Standaert, R. F.; Reichard, G. A.; Corey, E. J.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3358−3362. (b) Fenteany, G. A.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726−731.

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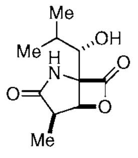
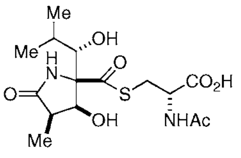
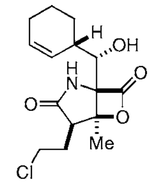
10.1021/ol701446y CCC: $37.00



Omuralide (1)



Lactacystin (2)

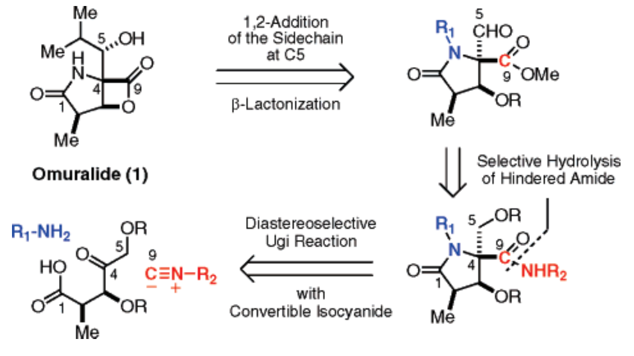


Salinosporamide A (3)

pyroglutamic acid derivative. We envisioned utilizing the Ugi multicomponent condensation reaction to form the γ-lactam ring of omuralide (**1**) from a densely functionalized γ-ketoacid (Scheme 1). The challenging aspects to this strategy are the stereoselective construction of the α-carbon (C4 in the carbon numbering of omuralide) and selective cleavage of the sterically more hindered C-terminal *exo*-amide (C9 vs C1) of the Ugi product. Although numerous reports of the Ugi reaction of levulinic acid (**4**) to prepare pyroglutamic acid amides have been published,[8] the inherent challenges described above have prohibited its general utility in natural product synthesis.

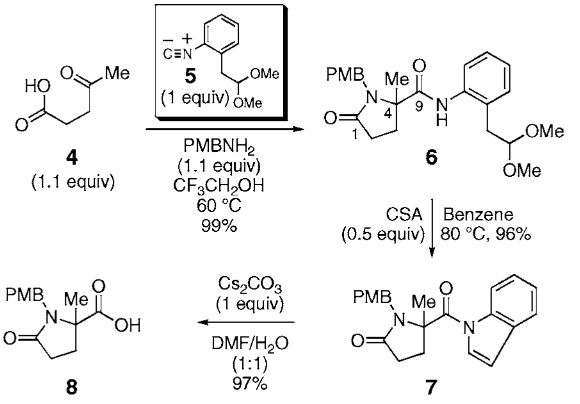
Armstrong developed 1-cyclohexenyl isocyanide to allow the facile hydrolysis of the C-terminal amide via azlactone under mild acidic conditions.[9b] This process is effective for most Ugi products, except the pyroglutamic acid amide and the related lactam amides which cannot form the activated intermediate. Ugi's convertible isocyanide,[10] activated via *N*-acyloxazolidinone, was ineffective for the hydrolysis due to steric hindrance surrounding the resultant amide. Therefore, design modification of the convertible isocyanide was required for efficient access to pyroglutamic acids employing the Ugi reaction.

Scheme 1. Overall Strategy toward the Synthesis of Omuralide (**1**)



We report 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**5**) as a convertible isocyanide which readily affords pyroglutamic acids via the Ugi reaction (Scheme 2).[11,12] The initial Ugi product, anilide **6**, derived from levulinic acid (**4**), is readily converted to the corresponding carboxylic acid **8** via *N*-acylindole **7** under mild conditions. This privileged ability of the 2-(2,2-dimethoxyethyl)anilide **6**, originally reported by Fukuyama,[13] has proven to be effective even with the

Scheme 2. Synthesis of 2-Methylpyroglutamic Acid by Ugi Reaction with Convertible Isocyanide **5**



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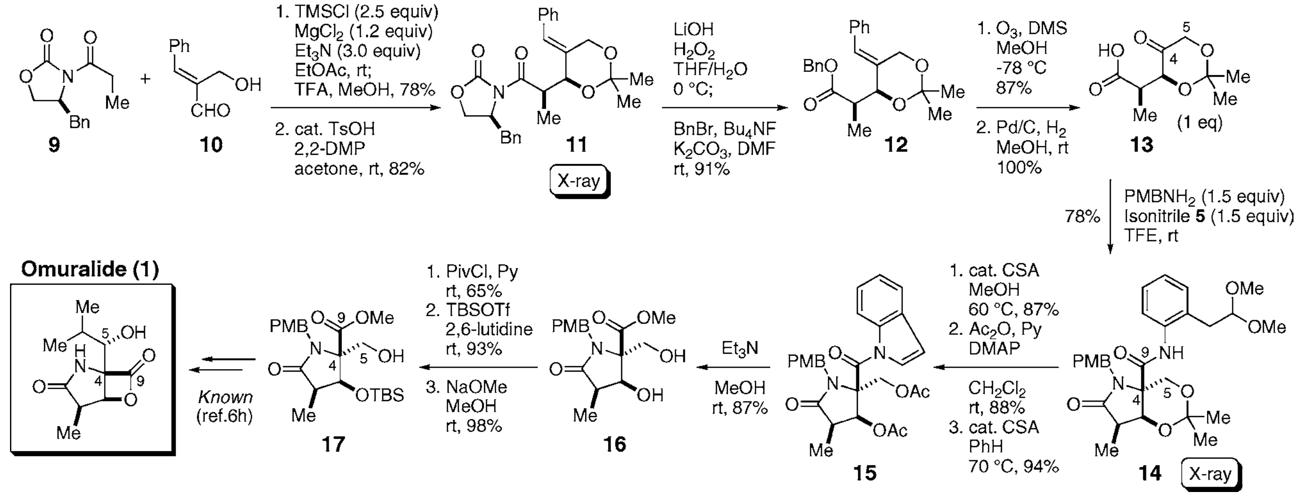
Scheme 3. Formal Total Synthesis of Omuralide (1) Featuring Stereoselective Ugi Reaction with Convertible Isocyanide **5**



hindered amide. To our knowledge, this is the first demonstration of the isocyanide in the Ugi reaction. The subsequent selective hydrolysis of the sterically more hindered *exo*-amide proves the concept as a convertible isocyanide. With the methodology to efficiently access pyroglutamic acid derivatives, we intended to show the utility of the isocyanide **5** in the synthesis of omuralide (**1**) as a platform to investigate the general applicability in natural product synthesis.

After preliminary studies,[14] it was realized that γ-ketoacid **13** would be a key precursor of a stereocontrolled Ugi reaction to reach Corey's intermediate **17**[6h,15] for the formal total synthesis of omuralide (**1**) (Scheme 3). We then embarked on the investigation of an efficient enantioselective synthesis of chiral ketoacid **13**. Because of the mild conditions of the Evans *anti*-selective aldol reaction of acyloxazolidinone **9**,[16] we believed it possible to use α-(hydroxymethyl)cinnamaldehyde **10**[17] directly in the aldol reaction without protection of the primary alcohol in advance. By modifying the original reaction conditions to include an extra equivalent of TMSCl and Et_3N to protect the free alcohol in situ, as well as including an additional equivalent of $MgCl_2$, the aldol reaction proceeded smoothly to afford the resulting 1,3-diol adduct in 78% yield as a 10:1 diastereomixture. The diol was protected as the acetonide to give **11** isolated as a single diastereomer. It was unambiguously assigned as the required *anti*-aldol product by X-ray crystallography,[18] which is consistent with the literature.[16] Lithium peroxide mediated hydrolysis of the chiral auxiliary and benzyl protection of the resultant carboxylic acid gave **12** in 91% yield. Ozonolysis of the *exo*-olefin followed by hydrogenolysis of the benzyl ester provided the Ugi precursor ketoacid **13**, which was then subjected to the Ugi reaction with the isocyanide **5** without purification. It should be noted that ketoacid **13** exists as a single diastereomer of a hemiketal at C4 (**13a**). The ^{13}C NMR chemical shift of C4 clearly indicated the hemiketal carbon instead of an intact carbonyl group (Figure 1).[19]

Much to our delight, the Ugi reaction of ketoacid **13** with isocyanide **5** and *p*-methoxybenzylamine in 2,2,2-trifluoroethanol furnished γ-lactam **14** in 78% yield as a single diastereomer. The relative stereochemistry of the resulting stereocenter C4 of the Ugi product **14** was unambiguously assigned by X-ray crystallography.[20] At this time we believe the diastereoselectivity arises due to the preference of small

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(9) For convertible isocyanides, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. See pp 3183−3184 and refs therein. (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574−2583. (c) Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. *Synlett* **2004**, 41−44. (d) Rikimaru, K.; Mori, K.; Kan, T.; Fukuyama, T. *Chem. Commun.* **2005**, 394−396. (e) Pirrung, M. C.; Ghorai, S. *J. Am. Chem. Soc.* **2006**, *128*, 11772−11773.

(10) Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411−7420.

(11) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Abstracts of Papers*, Presented at the 232th National Meeting of American Chemical Society, San Francisco, CA, United States, September 10−14, 2006; ORGN-739.

(12) Preparation of isocyanide **5** and the application to synthesis of quinoline is reported. Kobayashi, K.; Yoneda, K.; Mizumoto, T.; Umakoshi, H.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **2003**, *44*, 4733−4736. Our execution of the preparative synthesis (10 g scale) of isocyanide **5** is reported in the Supporting Information.

(13) (a) Arai, E.; Tokuyama, H.; Linsell, M. S.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 71−74. (b) Greene, T. W.; Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: New York, 1999; p 640.

(14) Kobayashi, Y.; Gilley, C. B.; Ozboya, K.; Ju, L. *Abstracts of Papers*, Presented at the 229th National Meeting of American Chemical Society, San Diego, CA, United States, March 13−17, 2005; ORGN-566.

(15) The compound **17** was obtained by Corey (ref 6h) in 10 steps from the known compound in 30% overall yield (89% per step) and by us in 14 steps from **10** in 14% overall yield (87% per step).

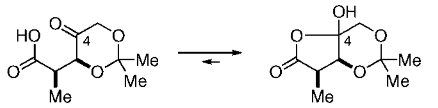
(16) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393.

(17) Compound **10** was prepared in one step starting from the known allyl alcohol (Doi, T.; Hirabayashi, K.; Kokubo, M.; Komagata, T.; Yamamoto, K.; Takahashi, T. *J. Org. Chem.* **1996**, *61*, 8360−8361). For experimental procedures, see Supporting Information. The synthesis of **10** by DIBALH reduction of (*Z*)-2-cyano-3-phenyl-2-propen-1-ol is previously reported without spectroscopic data: Campi, E. M.; Dyall, K.; Fallon, G.; Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Synthesis* **1990**, 855−856.

(18) CCDC 634646 contains the supplementary crystallographic data of **11**. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(1223)336033 or deposit@ccdc.cam.ac.uk.

(19) Mondon, A.; Menz, H.; Zander, J. *Chem. Ber.* **1963**, *96*, 826−839.

(20) CCDC 634644 contains the supplementary crystallographic data of **14**.



13
Not detected
by ^{1}H and ^{13}C NMR

13a
Single Diastereomer
C4 of hemiketal: δ 99.8 ppm

Figure 1. Observed structure of γ-ketoacid **13**.

nucleophiles to approach the carbonyl group of 1,3-dioxan-4-ones exclusively from the axial direction.[21]

To circumvent certain undesired side reactions,[22] we decided to selectively remove the acetonide protecting group before forming the indole. The treatment of the Ugi product **14** with catalytic CSA in MeOH furnished the corresponding diol without formation of *N*-acylindole. The resulting diol was protected as a diacetate, which was stable under the acid-catalyzed indole formation conditions that afforded the desired *N*-acylindole **15**. Direct conversion to the methyl ester diol **16** occurred in 87% yield by stirring in a 10:1 MeOH/Et_3N mixture overnight at room temperature. The following sequence led to the completion of the formal total synthesis of omuralide: selective pivaloate formation of the primary alcohol of **16**, subsequent TBS protection of the remaining secondary alcohol, and NaOMe-mediated removal of the pivaloate. The conversion of **17** to omuralide (**1**) was reported by Corey.[6h]

In this paper, we introduced the isocyanide **5** as a convertible isocyanide. To our knowledge, this is the first demonstration of the isocyanide in the Ugi reaction. The resulting anilide is amenable to facile hydrolysis to yield a free pyroglutamic acid via *N*-acylindole. The feasibility and applicability of this methodology were proven by its use in the stereocontrolled formal total synthesis of omuralide (**1**). This Ugi strategy with the isocyanide for the synthesis of pyroglutamic acids would be applicable to the synthesis of a structurally related natural product, salinosporamide A (**3**), as well as others containing a pyroglutamic acid moiety. We propose to name this convertible isocyanide as *indole-isocyanide* after the facilitation of hydrolysis of the resulting anilide via *N*-acylindole intermediate.[23]

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Supporting Information Available: Characterization data for all new compounds and CIF files of X-ray crystallographic analysis of both compounds **11** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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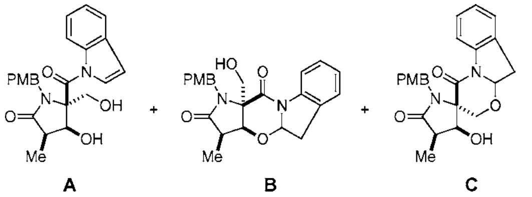
[21] Jochims, J. C.; Kobayashi, Y.; Skrzelewski, E. *Tetrahedron Lett.* **1974**, *7*, 571−574.

[22] Despite numerous attempts to form the *N*-acylindole from Ugi product anilide **14**, we were unsuccessful because the reaction was always complicated by acetonide deprotection and undesired *N*,*O*-acetal formation with both primary and secondary alcohols which was unexpectedly facile from this substrate (0.3 equiv of CSA, benzene, rt, 63% of the mixture of *N*-acylindole **A**, and bicyclic *N*,*O*-acetal **B** and **C** as shown below).



Ratio A:B:C = 1:1:2

[23] Although the structure of the isocyanide **5** does not contain an indole itself before Ugi reaction, we believe the name appropriately describes the function and character as a convertible isocyanide. Moreover, we are currently developing a series of convertible isocyanides which could systematically be named by using this format indicating the activation method for the hydrolysis of the resulting amide derived from isocyanide in Ugi/Passerini multicomponent condensation reactions. Gilley, C. B.; Kobayashi, Y., unpublished results.