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2-Nitrophenyl Isocyanide as a Versatile Convertible Isocyanide: Rapid Access to a Fused γ-Lactam β-Lactone Bicycle

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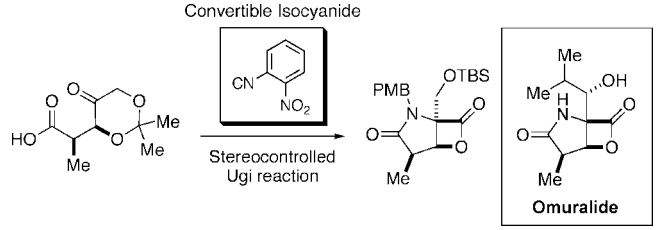

2-Nitrophenyl isocyanide is introduced as a convertible isocyanide with demonstration of its feasibility and applicability in an efficient synthesis of the fused γ-lactam β-lactone bicycle of proteasome inhibitor omuralide. Starting from a linear keto acid precursor, the fused γ-lactam β-lactone bicycle was prepared in four steps by a sequential biscyclization strategy; a stereocontrolled Ugi reaction and the concomitant direct β-lactonization following the formation of an *N*-acylbenzotriazole intermediate. The *N*-acylbenzotriazole is amenable to intra- or intermolecular attack from a variety of nucleophiles with a catalytic amount of base to form the pyroglutamic acid derivatives.

Introduction

A fused γ-lactam β-lactone bicyclic ring system is the common core structure found in a growing number of potent proteasome inhibitors including omuralide (*clasto*-lactacystin-β-lactone, **1**),[1] salinosporamides A and B (**2** and **3**),[2] and cinnabaramides A−C (**4**−**6**, Figure 1).[3] Due to the recent validation of proteasome inhibition as a novel therapeutic target for cancer,[4] these natural products are emerging as an important class of drugs that offer potential new therapies. Salinosporamide A (**2**), a marine natural product produced by the recently described obligate marine bacterium *Salinispora tropica*, is a potent anticancer agent that recently entered phase I human clinical trials for the treatment of multiple myeloma.[5] X-ray crystallographic studies have demonstrated that the β-oxygen atom of the *N*-terminal threonine of the 20*S* proteasome is

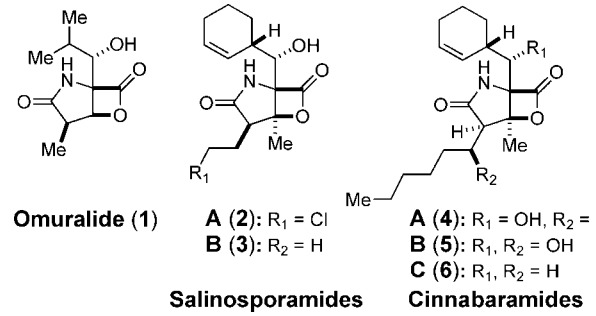

FIGURE 1. Proteasome inhibitors containing fused γ-lactam β-lactone bicyclic ring.

(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.

(2) Isolation of salinosporamide A: (a) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355–357. For congeners of salinosporamide A, see: (b) Williams, P. G.; Buchanan, G. O.; Feling, R. H.; Kauffman, C. A.; Jensen, P. R. *J. Org. Chem.* **2005**, *70*, 6196–6203. (c) Stadler, M.; Bitzer, J.; Mayer-Bartschmid, A.; Mueller, H.; Benet-Buchholz, J.; Gantner, F.; Tichy, H. V.; Reinemer, P.; Bacon, K. B. *J. Nat. Prod.* **2007**, *70*, 246–252. (d) Reed, K. A.; Manam, R. R.; Mitchell, S. S.; Xu, J.; Teisan, S.; Chao, T. H.; Deyanat-Yazdi, G.; Neuteboom, S. T. C.; Lam, K. S.; Potts, B. C. M. *J. Nat. Prod.* **2007**, *70*, 269–276.

(3) Cinnabaramides, A.-G.; Stadler, M.; Bitzer, J.; Mayer-Bartschmid, A.; Muller, H.; Benet-Buchholz, J.; Gantner, F.; Tichy, H. V.; Reinemer, P.; Bacon, K. B. *J. Nat. Prod.* **2007**, *70*, 246–52.

(4) Kyle, R. A.; Rajkumar, S. V. *N. Engl. J. Med.* **2004**, *351*, 1860–1873.

(5) (a) Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velonkar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T. H.; Neuteboom, S. T.; Richardson, P.; Palladino, M. A.; Anderson, K. C. *Cancer Cell* **2005**, *8*, 407–419. (b) Macherla, V. R.; Michell, S. S.; Manam, R. R.; Reed, K. A.; Chao, T. H.; Nicholson, B.; Deyanat-Yazdi, G.; Mai, B.; Jensen, P. R.; Fenical, W.; Neuteboom, S. T. C.; Lam, K. S.; Palladino, M. A.; Potts, B. C. M. *J. Med. Chem.* **2005**, *48*, 3684–3687.

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selectively acylated by the β-lactone moieties of both omuralide[6] and salinosporamide A.[7]

To date, a series of total syntheses of omuralide (**1**)[8] and salinosporamide A (**2**)[9] have been reported, with a number of routes showing the isopropyl or cyclohex-2-enylcarbinol side chains of the heterobicyclic core structure introduced in the late stage via an aldehyde intermediate. Romo recently reported a diastereocontrolled 1,2-addition of a cyclohexenyl zinc reagent even in the presence of the preformed β-lactone.[10] With methodology already established to introduce those side chains in the late stage, we sought the rapid construction of the common core fused γ-lactam β-lactone bicyclic ring system starting from a linear precursor through two consecutive ring formation steps.

For the initial γ-lactam formation, we chose to utilize the Ugi 4-center 3-component (4C-3C) condensation reaction because it affords pyroglutamic acid amide derivatives from readily accessible γ-keto acids.[11] We recently described a formal total synthesis of omuralide (**1**) employing a stereocontrolled Ugi reaction as the key step.[12a] We reported the development of a convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl)-benzene (**7**) (Figure 2), for its utility in the Ugi reaction and demonstrated the selective cleavage of the resultant *C*-terminal amide bond of **7a** derived from the isocyanide **7**.[11a,12b,c] The sterically hindered *exo*-anilide was successfully converted to a methyl ester via methanolysis of an *N*-acylindole **7b**. However, the direct intramolecular conversion of the activated *N*-acylindole intermediate to the β-lactone (and concurrent expulsion of indole) was never realized. In addition, the acidic conditions required to form the *N*-acylindole intermediate were not compatible with the adjacent unprotected alcohols causing unwanted side products.[13]

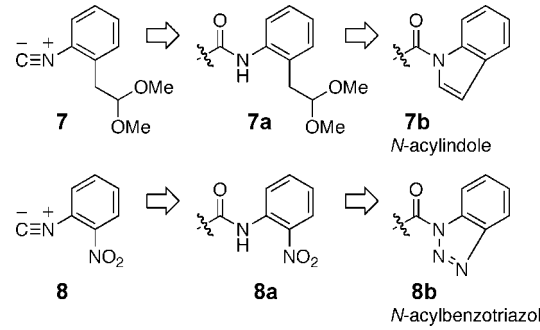

FIGURE 2. Structures of convertible isocyanides 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**7**) and 2-nitrophenyl isocyanide (**8**).

Results and Discussion

Design of Convertible Isocyanide. We then sought an alternative convertible isocyanide **8** which would allow for the conversion of the Ugi product amide **8a** to the corresponding β-lactone via its appropriate activation (i.e., **8b**, Figure 2). It should satisfy the following requirements: (a) quick and easy preparation from an inexpensive commercially available material, (b) mild activation conditions that are compatible with unprotected functional groups, (c) enhanced activation of the carbonyl group, and (d) spontaneous formation of the β-lactone when generated.

Our strategy was to access the fused γ-lactam β-lactone bicyclic ring system (compound **9**) of omuralide (**1**) via an *N*-acylbenzotriazole (*N*-acylBt) **10**, instead of *N*-acylindole (Scheme 1). The presence of two additional electronegative nitrogen atoms in benzotriazole, compared with the carbon atoms in indole, should make it a better leaving group. Indeed, the proton on the nitrogen atom of benzotriazole (pK_a 11.9 in DMSO) is more acidic then that of indole (pK_a 20.95).[14] Also, *N*-acylbenzotriazoles are known as stable non-moisture-sensitive acid chloride equivalents. They have been used as acylating agents for the preparation of esters, amides, Weinreb amides, *C*-acylated heterocycles, *N*-acylsulfonamides, acyl azides, ketones, β-keto esters, and β-diketones, as well as acyl ketones, cyanides, and sulfones.[15] Therefore, we speculated the enhanced activation of the carbonyl group would allow for direct β-lactone

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(7) Groll, M.; Huber, R.; Potts, B. C. M. J. *Am. Chem. Soc.* **2006**, *128*, 5136–5141.

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(9) For salinosporamide A total syntheses, see: (a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230–6231. (b) Reddy, L. R.; Fournier, J. F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699–2701. (c) Reddy, L. R.; Fournier, J. F.; Reddy, B. V. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8974–8976. (d) Endo, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 8298–8299. (e) Mullholand, N. P.; Pattenden, G.; Walters, I. A. S. *Org. Biomol. Chem.* **2006**, *4*, 2845–2846. (f) Ling, T.; Macherla, V. R.; Manam, R. R.; McArthur, K. A.; Potts, B. C. M. *Org. Lett.* **2007**, *9*, 2289–2292.

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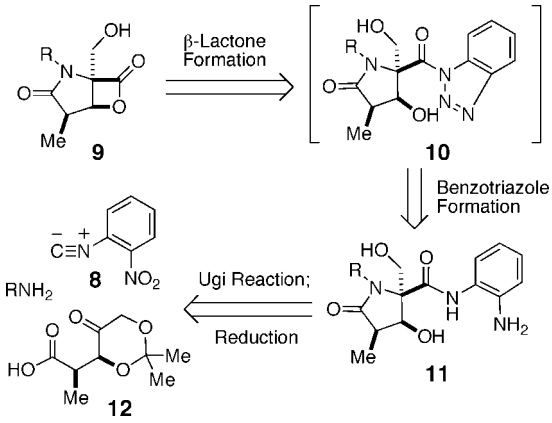
(12) (a) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631–3634. (b) Vamos, M.; Ozboya, K.; Kobayashi, Y. *Synlett* **2007**, 1595–1599. (c) Kreye, O.; Westermann, B.; Wessjohann, L. A. *Synlett* **2007**, 3188–3192.

(13) The acidic conditions required to activate the (2,2-dimethoxyethyl)anilide to the *N*-acylindole intermediate with the convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl)benzene, in our previous synthesis caused unwanted *N,O*-acetal formation as the major product by reaction with the unprotected alcohols (see ref 12a).

(14) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

(15) For recent reviews on the application of *N*-acylbenzotriazoles in organic synthesis, see: (a) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, *11*, 1656–1665. (b) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409–548.

SCHEME 1. Retrosynthetic Analysis of Fused γ-Lactam β-Lactone Bicyclic Ring 9



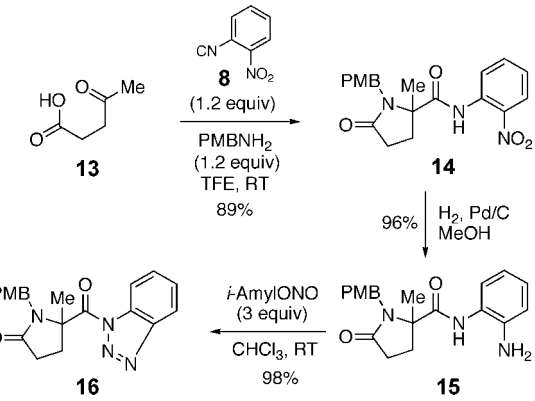
formation, when the *N*-acylBt is generated in the presence of a hydroxyl group at the β position. Synthetically, benzotriazole is a convenient byproduct after the coupling reaction, because the relatively low pK_a allows for simple removal by extraction with aqueous alkaline solution (1 N NaOH).

N-acylBt **10** could be generated in situ from the diazotization of *o*-aminoanilide **11** by 5-*endo-dig* cyclization of the amide nitrogen.[16] The *o*-aminoanilide **11** could have derived from the diastereoselective Ugi reaction of γ-keto acid **12** with 2-nitrophenyl isocyanide (**8**) and *p*-methoxybenzylamine.[17] Upon investigation, it was found that isocyanide **8** is a readily available solid which can be prepared in two steps (87%) from 2-nitroaniline and has been reported as a ligand of a metal complex previously.[18]

Ugi Reaction with 2-Nitrophenyl Isocyanide. We report here 2-nitrophenyl isocyanide (**8**) as a convertible isocyanide. The rapid construction of the fused γ-lactam β-lactone bicyclic ring system of omuralide (**1**) is introduced via a diastereoselective Ugi reaction of cyclic β,δ-dihydroxy-γ-keto acids with isocyanide **8**. In addition, it readily affords ester, thioester, primary amide, and ketone derivatives of pyroglutamic acid via the Ugi reaction of levulinic acid. A similar isocyanide, 4-methoxy-2-nitrophenyl isocyanide,[19] was introduced previously as a hydrolyzable isocyanide in the Ugi 4-component condensation reaction. Due to the activation of the amide bond of the resulting Ugi product anilide, via the electron-withdrawing *o*-nitro group, direct hydrolysis was achieved without additional activation. However, rather harsh basic conditions (6 equiv of LiOH in refluxing MeOH, 3 h) are required for the hydrolysis of the anilide.

In order to quickly ascertain whether 2-nitrophenyl isocyanide (**8**) would be an effective convertible isocyanide, allowing for the synthesis of a series of pyroglutamic acid derivatives, we sought to prepare *N*-acylBt **16** starting from commercially available levulinic acid (**13**) (Scheme 2). The initial *o*-nitroanilide **14**, derived from the Ugi reaction of levulinic acid (**13**)

SCHEME 2. Synthesis of *N*-Acylbenzotriazole 16



with *p*-methoxybenzylamine and isocyanide **8**, is readily converted to the corresponding *N*-acylBt **16** through hydrogenolysis of the nitro group to the aniline **15** and subsequent diazotization of the amino group followed by 5-*endo-dig* cyclization of the anilide toward the diazonium salt. The *N*-acylBt **16** is an isolable solid, which is purified by SiO_2 column chromatography. Interestingly, the resulting isoamyl alcohol did not react with the *N*-acylBt to afford the corresponding isoamyl ester during the reaction, probably due to the steric hindrance of **16** and also the so-called Newman's rule of six (regarding isoamyl alcohol).[20] Methanolysis of *N*-acylBt **16** occurred with a catalytic amount of Et_3N in DCM/MeOH (2:1) at room temperature in 10 min. The corresponding pure methyl ester (**21a** in Table 1) was obtained in 94% yield after basic aqueous extraction (1 N NaOH) of benzotriazole without the need for further purification.

Synthesis of the Fused γ-Lactam β-Lactone Bicycle. Having established 2-nitrophenyl isocyanide (**8**) as a convertible isocyanide, we undertook our original goal of the stereocontrolled synthesis of the common γ-lactam β-lactone bicyclic core among known proteasome inhibitors. The remaining challenges were the stereoselective formation of the fully substituted carbon (C4 of omuralide) during the Ugi reaction, the compatibility of unprotected functional groups during the conversion of the nitroanilide to an *N*-acylBt, and the intramolecular β-lactone formation with the activated *N*-acylBt. We chose omuralide core bicycle **20** as a probe to evaluate the feasibility and applicability of isocyanide **8** in natural product synthesis (Scheme 3). The enantioselective preparation of **12** was previously reported in our synthesis of omuralide (**1**).[12a]

The Ugi 4C-3C reaction of functionalized chiral γ-keto acid **12** with isocyanide **8** furnished γ-lactam **17** in 67% yield as a single diastereomer. The relative stereochemistry of the resulting stereocenter of Ugi product **17** was unambiguously assigned by X-ray crystallography (Figure 3).[21] As expected, axial attack of the isocyanide toward the iminium intermediate exclusively furnished the desired isomer **17**. Attempted hydrolysis of the *o*-nitroanilide under basic conditions did not provide the corresponding carboxylic acid presumably due to steric hindrance.[19]

Methanolysis of **17** with a catalytic amount of CSA smoothly deprotected the acetonide moiety to give the free 1,3-diol **18** in 90% yield. Fortunately, the transfer of the nitrobenzene functionality onto the resulting alcohols via a Meisenheimer

(16) (a) Katritzky, A. R.; Ji, F. B.; Fan, W. Q.; Beretta, P.; Bertoldi, M. *J. Heterocycl. Chem.* **1992**, *29*, 1519–1523. (b) Plummer, B. F.; Russell, S. R.; Reese, W. G.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1991**, *56*, 3219–23. (c) Hart, H.; Ok, D. *J. Org. Chem.* **1986**, *51*, 979–986.

(17) We expected a single diastereomer in the Ugi reaction of ketacid **11** based on our previous studies (see ref 12a).

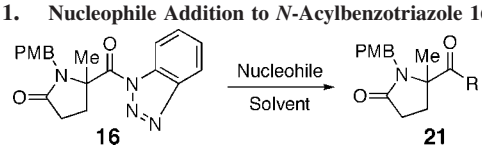
(18) Hahn, F. E.; Plumed, C. G.; Muender, M.; Luegger, T. *Chem. Eur. J.* **2004**, *10*, 6285–6293.

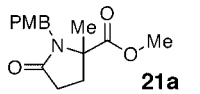
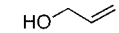
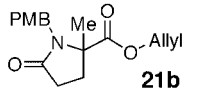
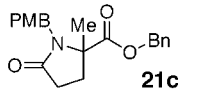
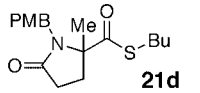
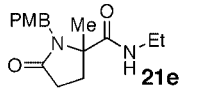
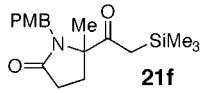
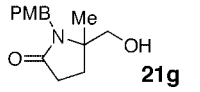
(19) (a) Maison, W.; Schlemminger, I.; Westerhoff, O.; Martens, J. *Bioorg. Med. Chem. Lett.* **2000**, *8*, 1343–1360. (b) Maison, W.; Schlemminger, I.; Westerhoff, O.; Martens, J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 581–584.

(20) Newman, M. S. *J. Am. Chem. Soc.* **1950**, *72*, 4783–4786.

(21) The CIF file of the X-ray analysis of compound **17** is available in the Supporting Information.

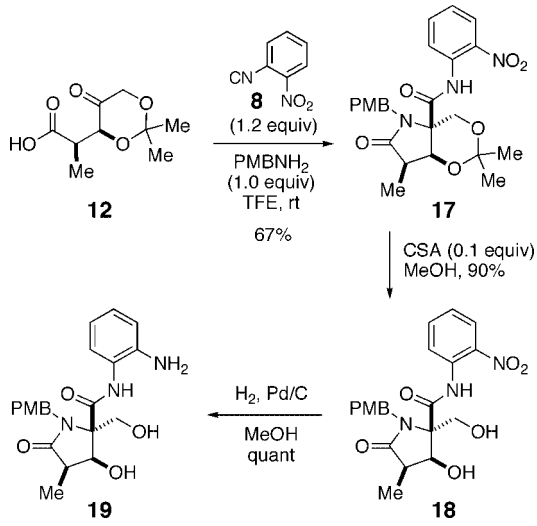
TABLE 1. Nucleophile Addition to *N*-Acylbenzotriazole 16



Entry	Nucleophile	Product	Yield
1	MeOH	 **21a**	94%[a,f]
2		 **21b**	90%[b]
3	BnOH	 **21c**	84%[b]
4	BuSH	 **21d**	99%[b]
5	$EtNH_2$	 **21e**	97%[c]
6		 **21f**	97%[d,e]
7	$NaBH_4$	 **21g**	79%[e,f]

[a] 0.1 equiv Et_3N; rt. [b] 1.1 equiv nucleophile; 0.1 equiv Et_3N; DCM, rt. [c] 1.1 equiv $EtNH_2$; DCM, rt. [d] 3.0 equiv nucleophile; THF. [e] 0 °C to rt. [f] DCM/MeOH (2:1).

SCHEME 3. Stereocontrolled Ugi Reaction with Keto Acid 12 and Convertible Isocyanide 8



complex, known as the Smiles rearrangement,[22] did not occur (although it could readily happen under basic conditions). Hydrogenolysis of the nitro group provided *o*-aminoanilide **19** as a precursor of the *N*-acylBt in quantitative yield.[23] In addition, we are aware that aminoanilide **19** could be a precursor to form

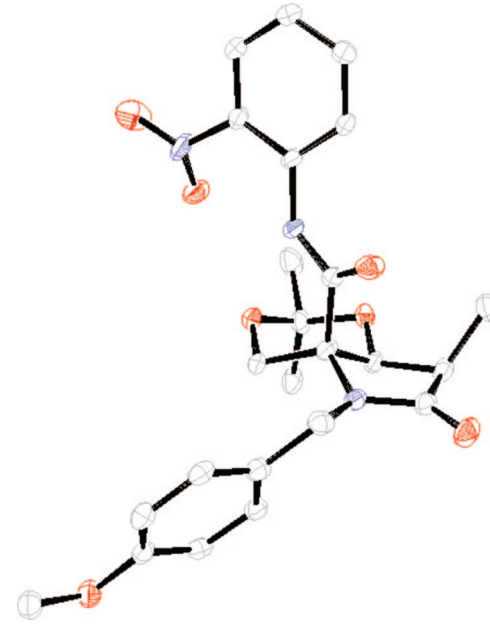


FIGURE 3. ORTEP figure of Ugi product **17**.

an *N*-acylbenzoimidazole[24] (pK_a 16.4, between an indole and a benzotriazole).

Diazotization of the aniline **19** and subsequent benzotriazole formation **19a** by 5-*endo-dig* cyclization of amide at the ortho position occurred smoothly under the neutral conditions mediated by isoamyl nitrite in chloroform at room temperature. The mild nature of the reaction allowed efficient conversion even in the presence of the unprotected diols without any side reactions.[13] The formation of the *N*-acylBt **19a** was indicated by TLC without β-lactone formation at that moment. Again, the isoamyl alcohol formed during nitrosonation of the aniline **19** did not react with the resulting *N*-acylBt **19a** in situ to afford the corresponding isoamyl ester.

As designed, fused γ-lactam β-lactone formation occurred in situ with the addition of a catalytic amount of triethylamine (0.1 equiv). Spiro-γ-lactam β-lactone formation was not detected. The remaining primary alcohol of the γ-lactam β-lactone bicycle **19b**[8j] and the resulting isoamyl alcohol were protected as a TBS ether, and then the core fused γ-lactam β-lactone bicycle **20** was isolated in 71% yield in one pot (three steps from **19**). In summary, the synthesis of the fused γ-lactam β-lactone bicycle of omuralide (**1**) was achieved via a stereocontrolled Ugi 4C-3C condensation reaction with isocyanide **8**. The subsequent *N*-acylBt formation was compatible with the unprotected alcohols, and direct β-lactonization occurred. These results show the superior activation of the carbonyl group provided by the *N*-acylBt, compared to the *N*-acylindole.

Utility of *N*-Acylbenzotriazole. Table 1 shows the synthetic utility of the *N*-acylbenzotriazole **16**. Conversion of **16** into 2-methylpyroglutamic acid esters **21a**−**c** (entry 1−3), thioester **21d** (entry 4), amide **21e** (entry 5), and ketone **21f** (entry 6)

(22) For use of the smiles rearrangement in Ugi reactions, see: (a) El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7691. (b) El Kaïm, L.; Gizolme, M.; Grimaud, L. *Org. Lett.* **2006**, *8*, 2051–2053. (c) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169–4180.

(23) Alternative conditions for the reduction of the nitro group are as follows: $SnCl_2$ HCl, EtOH, heat. These conditions are compatible with the presence of unsaturated bonds as well as other functionality not compatible with hydrogenolysis.

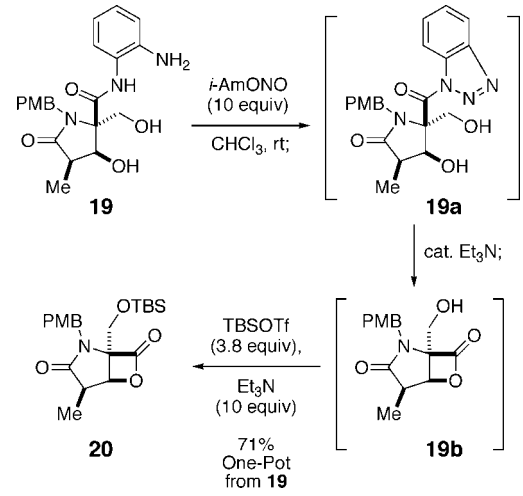
(24) Tanaka, K.; Shimazak, M.; Murakami, Y. *Chem. Pharm. Bull.* **1982**, *30*, 2714–2722.

derivatives as well as the reduction to its hydroxymethyl derivative **21g** (entry 7) are described. In general, primary oxo-, thio-, and amine-containing nucleophiles (1.1 equiv) displace benzotriazole with a catalytic amount of triethylamine (0.1 equiv) in dichloromethane at room temperature. The reactions were complete within 10 min, and excellent yields of the corresponding adducts were obtained (84−99%). In addition, when employing volatile nucleophiles (entries 1, 4−6) the products were obtained in pure form without SiO_2 column chromatography because the resulting benzotriazole could be extracted by washing with aqueous alkaline solution.

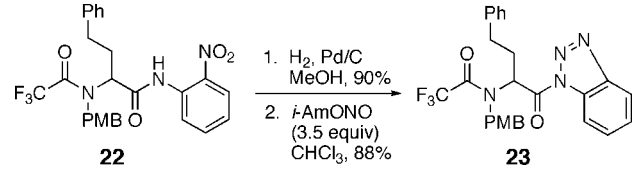
The nucleophilic addition of secondary and tertiary alcohols and amines failed presumably due to the steric hindrance of the substrate. On the other hand, trimethylsilylmethylmagnesium chloride was efficiently added to *N*-acylBt **16** yielding the corresponding α-silyloxy ketone in 97% yield. However, the addition of other Grignard and alkyllithium species to **16** resulted predominantly in formation of the corresponding tertiary alcohol by addition of 2 equiv of the reagent, which is in contrast to previously reported results using similar, but less hindered, substrates.[25] Allylmagnesium bromide, lithium phenylacetylide, and 2-lithiothiophene gave the corresponding tertiary alcohol in 78%, 65%, and 78% yield, respectively. It may be that the steric congestion at the neighboring fully substituted carbon causes the collapse of the proposed tetrahedral intermediate (similar to the case with Weinreb amides), which normally allows for preferential formation of ketones over tertiary alcohols. This table indicates the reactivity and versatility of *N*-acylbenzotriazoles, which are effective even with the hindered pyroglutamic amides.

Synthesis of Amino Acid. We further explored the utility of this methodology to extend to linear Ugi products. The conformational flexibility of the linear system provided the possibility of azlactone/ müchnone formation, similar to that reported by Armstrong with the "universal isocyanide".[26] Anilide **22**, derived from the Ugi reaction of hydrocinnamaldehyde with 2-nitrophenyl isocyanide **8**, *p*-methoxybenzylamine, and trifluoroacetic acid (65% yield), was converted to *N*-acylBt **23** by hydrogenolysis and subsequent benzotriazole formation (Scheme 5). Interestingly, the formation of an azalactone intermediate and subsequent hydrolysis was not observed. Instead, the *N*-acylBt **23** was isolable and stable to flash column chromatography. Most likely, the suppression of the azalactone formation was possible due to the neutral conditions employed to generate the *N*-acylbenzotriazole and the poor nucleophilicity of the carbonyl group of the trifluoroacetamide. The synthetic utility of *N*-acylbenzotriazole species of this type, including direct peptide coupling, has been shown previously.[25,27] Typically, *N*-acylbenzotriazoles are prepared via the direct acylation of benzotriazole itself, instead of derivatization from *o*-amino anilides.[16]

SCHEME 4. Synthesis of Fused γ-Lactam β-Lactone Bicycle 20



SCHEME 5. Synthesis of *N*-Acylbenzotriazole 23 Derived from Linear Ugi Product 22



Conclusions

In this paper, we introduced 2-nitrophenyl isocyanide (**8**) as a convertible isocyanide and demonstrated its feasibility and applicability in efficient synthesis of the fused γ-lactam β-lactone bicycle of omuralide (**1**). To our knowledge, this is the first demonstration of the isocyanide as a convertible isocyanide in the Ugi reaction. The resulting sterically hindered anilide can be converted under mild neutral conditions to an *N*-acylbenzotriazole, which is known as a stable acid chloride equivalent. Staring from the linear γ-keto acid precursor, the fused γ-lactam β-lactone bicycle was prepared only in four steps by a sequential biscyclization strategy: a stereocontrolled Ugi reaction and the concomitant direct β-lactonization following the formation of *N*-acylbenzotriazole intermediate. The *N*-acylbenzotriazole is amenable to intra- or intermolecular attack from a variety of nucleophiles with a catalytic amount of base to form the coupling products of the pyroglutamic acid derivatives. Conveniently, after the coupling reaction, the resulting benzotriazole can be readily removed from the reaction mixture by extraction with 1 N NaOH. Owing to the mild nature of the reaction conditions, as well as the high compatibility with other functional groups, the applicability of this methodology will be extended to the synthesis of other natural products, which contain a fused γ-lactam β-lactone bicycle as the core structure. Application to total synthesis of salinosporamide A (**2**) will be reported in due course.

Experimental Section

1-(4-Methoxybenzyl)-2-methyl-*N*-(2-nitrophenyl)-5-oxopyrrolidine-2-carboxamide (14). To a solution of levulinic acid (**13**) (152 mg, 1.31 mmol, 1.0 equiv) in TFE (5 mL) were added *p*-methoxybenzylamine (216 mg, 1.58 mmol, 1.2 equiv) and isocyanide **8** (243 mg, 1.64 mmol, 1.2 equiv) at room temperature. The

(25) Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. *J. Org. Chem.* **2006**, *71*, 9861–9864.

(26) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574–2583.

(27) (a) Katritzky, A. R.; Angrish, P. *Synthesis* **2006**, *24*, 4135–4142. (b) Katritzky, A. R.; Meher, G.; Angrish, P. *Chem. Biol. Drug Des.* **2006**, *68*, 326–333. (c) Katritzky, A. R.; Todadze, E.; Shestopalov, A. A.; Cusido, J.; Angrish, P. *Chem. Biol. Drug Des.* **2006**, *68*, 42–47. (d) atritzky, A. R.; Todadze, E.; Cusido, J.; Angrish, P.; Shestopalov, A. A. *Chem. Biol. Drug Des.* **2006**, *68*, 37–41. (e) Katritzky, A. R.; Angrish, P.; Suzuki, K. *Synthesis* **2006**, *3*, 411–424. (f) Katritzky, A. R.; Jiang, R.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4993–5000. (g) Katritzky, A. R.; Angrish, P.; Huer, D.; Suzuki, K. *Synthesis* **2005**, *3*, 397–402. (h) Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Synthesis* **2004**, *16*, 2645–2652. (i) Katritzky, A. R.; Shestopalov, A. A.; Suzuki, K. *Synthesis* **2004**, *11*, 1806–1813.

reaction mixture was stirred overnight and then concentrated in vacuo. The crude mixture was applied directly to flash chromatography (30−75% EtOAc/hexanes) to yield 445 mg (89%) of **14** as a viscous orange oil: R_f (75% EtOAc/hexanes) = 0.53; HRMS (EI) *m*/*z* calcd for $C_{20}H_{21}N_4O_5$ (M^+) 383.1476, found 383.1474; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.47 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.8 Hz, 1H), 7.11−7.15 (m, 3H), 6.56 (d, J = 8.4 Hz, 2H), 4.53 (d, J = 14.8 Hz, 1H), 4.37 (d, J = 15.2, Hz 1H), 3.55 (s, 3H), 2.64−2.73 (m, 1H), 2.48−2.56 (m, 1H), 2.32−2.39 (m, 1H), 1.96−2.07 (m, 1H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 175.6, 172.9, 159.0, 136.5, 136.0, 134.3, 130.1, 129.1, 125.9, 123.8, 121.8, 113.9, 67.8, 55.2, 44.1, 33.0, 29.5, 22.8; IR (film, cm^{-1}) 2937, 1693, 1608, 1581, 1499, 1398, 1250, 1173, 1037, 742.

1-(4-Methoxybenzyl)-*N*-(2-aminophenyl)-2-methyl-5-oxopyrrolidine-2-carboxamide (15). To a solution of **14** (445 mg, 1.16 mmol, 1.0 equiv) in MeOH (30 mL) was added ∼10% by weight Pd/C at room temperature. A balloon of H_2 was applied, and the reaction mixture was stirred for 2 h. The mixture was then filtered through Celite and washed with methanol. Concentration in vacuo yielded 394 mg (96%) of **15** as a white solid which was used without further purification: R_f (75% EtOAc/hexanes) = 0.18; mp = 47−52 °C; HRMS (EI) *m*/*z* calcd for $C_{20}H_{23}N_3O_3$ (M^+) 353.1734, found 353.1730; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.97 (s, 1H), 7.24 (d, J = 9.4 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 6.78−6.81 (m, 3H), 6.67−6.72 (m, 2H), 4.62 (d, J = 15.2, 1H), 4.36 (d, J = 15.2, 1H), 3.74 (s, 3H), 3.64 (s, 2H), 2.54−2.63 (m, 1H), 2.41−2.50 (m, 2H), 1.96−2.03 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 176.5, 172.3, 159.4, 140.9, 129.9, 129.9, 127.4, 125.3, 124.1, 119.6, 118.7, 114.5, 68.3, 55.5, 44.5, 34.1, 29.8, 23.4; IR (film, cm^{-1}) 2969, 2060, 1667, 1501, 1449, 1404, 1248, 1186, 1029, 750.

1-(4-Methoxybenzyl)-2-methyl-2-(*N*-acylbenzotriazol)-5-oxopyrrolidine (16). To a solution of anilide **15** (363 mg, 1.03 mmol, 1.0 equiv) in $CHCl_3$ (10 mL) was added isoamyl nitrite (0.4 mL, 2.99 mmol, 3.0 equiv) at room temperature. The reaction mixture was stirred overnight and then concentrated in vacuo. The crude mixture was applied directly to flash chromatography (50−75% EtOAc/hexanes) to yield 365 mg (98%) of *N*-acylbenzotriazole **16** as a yellow solid: R_f (75% EtOAc/hexanes) = 0.50; mp = 136−139 °C; HRMS (EI) *m*/*z* calcd for $C_{20}H_{20}N_4O_3$ (M^+) 364.1530, found 364.1535; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.02 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.27 (d, J = 8.8 Hz, 2H), 4.80 (d, J = 14.8 Hz, 1H), 4.15 (d, J = 14.8 Hz, 1H), 3.41 (s, 3H), 2.85−2.98 (m, 2H), 2.59−2.68 (m, 1H), 2.17−2.26 (m, 1H), 1.83 (s, 3H)); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 175.9, 172.5, 158.6, 130.4, 129.9, 127.8, 126.3, 120.0, 114.8, 113.4, 68.1, 55.0, 43.7, 31.3, 29.7, 25.0; IR (film, cm^{-1}) 2995, 2943, 1724, 1689, 1522, 1398, 1363, 1239, 1033, 959, 757.

(4a*R*,7*R*,7a*S*)-5-(4-Methoxybenzyl)hexahydro-2,2,7-trimethyl-*N*-(2-nitrophenyl)-6-oxo[1,3]dioxino[5,4-*b*]pyrrole-4a-carboxamide (17). To a solution of γ-keto acid **12** (98.0 mg, 0.485 mmol, 1.0 equiv) in TFE (2 mL) were added *p*-methoxybenzylamine (66.5 mg, 0.485 mmol, 1.0 equiv) and isocyanide **8** (86.0 mg, 0.581 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred overnight and then concentrated to yield a red-brown oil. The mixture was purified by flash chromatography (30−50% EtOAc/hexanes) to yield 153 mg (67%) of anilide **17** as a yellow solid which was a single diastereomer: R_f (50% EtOAc/hexanes) = 0.40; mp = 68−71 °C; $[\alpha]^{25}_D$ = +15 (c = 0.020, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{24}H_{27}N_3O_7$ (M^+) 469.1844, found 469.1836; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 11.46 (s, 1H), 8.63 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.26 (m, 1H), 7.16 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.0, Hz 2H), 5.11 (d, J = 14.5 Hz, 1H), 4.45 (d, J = 8.5 Hz, 1H), 3.84 (m, 2H), 3.80 (s, 3H), 3.64 (d, J = 11.5 Hz, 1H), 2.86 (quint., J = 8.5 Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H), 1.26 (d, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.0, 171.0, 159.6, 135.4, 133.4, 130.3, 129.4, 125.9, 124.5, 124.3, 114.3, 103.7, 76.1, 69.3, 65.3, 55.5, 45.3, 38.8, 29.3, 19.5, 9.8; IR (film, cm^{-1}) 2998, 2942, 2917, 2886, 1711, 1608, 1583, 1513, 1434, 1345, 1274, 1250, 1180, 738.

(2*R*,3*S*,4*R*)-1-(4-Methoxybenzyl)-3-hydroxy-2-(hydroxymethyl)-4-methyl-*N*-(2-nitrophenyl)-5-oxopyrrolidine-2-carboxamide (18). To a solution of **17** (130.5 mg, 0.278 mmol, 1.0 equiv) in MeOH (3 mL) was added camphorsulfonic acid (7 mg, 0.03 mmol, 0.1 equiv). The reaction mixture was heated to 70 °C with stirring for 1 h. After being cooled to room temperature, the mixture concentrated and purified directly by flash chromatography (50−75% EtOAc/hexanes) to yield 107 mg (90%) of diol **18** as a yellow solid: R_f (75% EtOAc/hexanes) = 0.15; mp = 72−75 °C; $[\alpha]^{25}_D$ = +28 (c = 0.014, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{21}H_{23}N_3O_7$ (M^+) 429.1531, found 429.1526; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.63 (d, J = 8.8 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.24 (m, 2H), 6.72 (d, J = 8.4 Hz, 2H), 5.01 (d, J = 15.2 Hz, 1H), 4.71 (dd, J = 5.6, 8.0 Hz, 1H), 4.18 (d, J = 15.2 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, J = 6.8, 12.0 Hz, 1H), 2.86 (quint, J = 7.6 Hz, 1H), 2.50 (d, J = 5.2 Hz, 1H), 2.25 (t, J = 6.0 Hz, 1H), 1.29 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.3, 170.1, 159.3, 137.5, 135.8, 133.6, 130.0, 129.7, 125.9, 129.7, 125.9, 124.2, 122.8, 114.3, 75.3, 71.4, 64.0, 55.4, 45.2, 40.6, 9.6; IR (film, cm^{-1}) 3340, 2942, 1670, 1607, 1583, 1505, 1437, 1340, 1272, 1233, 1175, 1029, 738.

(2*R*,3*S*,4*R*)-1-(4-Methoxybenzyl)-*N*-(2-aminophenyl)-3-hydroxy-2-(hydroxymethyl)-4-methyl-5-oxopyrrolidine-2-carboxamide (19). To a solution of diol **18** (95.1 mg, 0.221 mmol, 1.0 equiv) in MeOH (6 mL) was added ∼10% by weight activated palladium on carbon. The flask was fitted with a rubber septum, and a balloon of H_2 gas was introduced at room temperature with stirring. After 30 min, N_2 gas was flushed through the reaction mixture, and the palladium was removed by filtration through Celite. The clear solution was concentrated to yield 88.4 mg of *o*-aminoanilide **19** (100%) as a clear oil which was used without further purification: R_f (100% EtOAc) = 0.18; $[\alpha]^{25}_D$ = +8.3 (c = 0.021, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{21}H_{25}N_3O_5$ (M^+) 399.1789, found 399.1792; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.15 (s, 1H), 7.22 (d, J = 6.8 Hz, 2H), 7.03 (t, J = 5.6 Hz, 1H), 6.79 (d, J = 7.4 Hz, 2H), 6.72 (t, J = 6.0 Hz, 1H), 6.66 (d, J = 6.0 Hz, 1H), 4.83 (d, J = 15.2 Hz, 1H), 4.49 (d, J = 7.2 Hz, 1H), 4.17 (d, J = 14.8 Hz, 1H), 3.80−3.67 (m, 6H), 3.44 (d, J = 12.0 Hz, 1H), 2.72 (quint., J = 8.0 Hz, 1H), 1.17 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.7, 170.2, 159.3, 140.8, 129.9, 129.7, 128.4, 127.3, 122.9, 119.8, 117.9, 114.4, 74.9, 71.1, 64.0, 55.5, 45.4, 40.5, 9.6; IR (film, cm^{-1}) 3369, 3010, 2932, 2825, 1670, 1612, 1510, 1456, 1408, 1296, 1238, 1175, 1029, 748.

(1*S*,2*R*,5*R*)-4-(4-Methoxybenzyl)-5-(*tert*-butylsilyloxymethyl)-2-methyl-7-oxa-4-azabicyclo[3.2.0]heptane-3,6-dione (20). To a solution of *o*-aminoanilide **19** (9.1 mg, 0.023 mmol, 1.0 equiv) in $CHCl_3$ (1 mL) was added isoamyl nitrite (0.03 mL, 0.22 mmol, 10 equiv) at room temperature. The reaction mixture was stirred for 5 min, and after detection of *N*-acylbenzotriazole **19a** by TLC analysis, triethylamine (0.01 mL) was added to form β-lactone **19b**. The reaction mixture was stirred an additional 5 min, and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.02 mL, 0.087 mmol, 3.8 equiv) and additional triethylamine (0.02 mL, 0.22 mmol, 10 equiv total) were added. The reaction mixture was stirred for 1 h and then diluted with ethyl acetate (5 mL) and washed with brine (2 × 5 mL). After drying with sodium sulfate, the solution was concentrated and purified by preparative thin-layer chromatography (30% EtOAc/hexanes) to yield 6.5 mg (71%) of β-lactone **20** as a clear oil: R_f (30% EtOAc/hexanes) = 0.39; $[\alpha]^{25}_D$ = −31 (c = 0.016, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{21}H_{31}N_1O_5Si_1$ (M^+) 405.1966, found 405.1973; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.19 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.03 (d, J = 6.0 Hz, 1H), 4.85 (d, J = 15.2 Hz, 1H), 4.22 (d, J = 15.2 Hz, 1H), 3.90 (d, J = 10.8 Hz, 1H), 3.79 (s. 3H), 3.43 (d, J = 10.8 Hz, 1H), 2.77 (quint., J = 7.2 Hz, 1H), 1.37 (d, J = 7.6 Hz, 3H), 0.82 (s, 9H), −0.01 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,

ppm) δ 175.2, 167.8, 159.6, 129.5, 129.1, 114.3, 81.0, 74.4, 58.5, 55.5, 44.8, 38.6, 25.8, 18.3, 8.6, −5.5, −5.5; IR (film, cm^{-1}) 2932, 2854, 1835, 1709, 1510, 1461, 1393, 1248, 1117, 835, 767.

Methyl 1-(4-Methoxybenzyl)-2-methyl-5-oxopyrrolidine-2-carboxylate (21a). To a solution of *N*-acylbenzotriazole **16** (182 mg, 0.499 mmol, 1.0 equiv) in DCM/MeOH (2/1, 3 mL) was added triethylamine (0.01 mL, 0.07 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred for 10 min and then concentrated in vacuo. The crude oil was diluted with EtOAc and washed with 1 N NaOH and brine. The solution was dried over Na_2SO_4 and concentrated in vacuo to yield 130 mg (94%) of methyl ester **21a** as a clear oil. No further purification was necessary: R_f (50% EtOAc/hexanes) = 0.29; HRMS (EI) *m/z* calcd for $C_{15}H_{19}N_1O_4$ (M^+) 277.1309, found 277.1312; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.18 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.42 (d, *J* = 15.6 Hz, 1H), 4.35 (d, *J* = 14.8 Hz, 1H), 3.76 (s, 3H), 3.44 (s, 3H), 2.52−2.60 (m, 1H), 2.40−2.47 (m, 1H), 2.25−2.31(m, 1H), 1.82−1.90 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 175.9, 174.2, 159.1, 129.9, 129.6, 113.9, 66.0, 55.5, 52.6, 43.9, 32.4, 29.9, 23.4; IR (film, cm^{-1}) 2995, 2943, 1740, 1693, 1608, 1503, 1398, 1247, 1169, 1115, 1021, 812.

2-(*N*-(4-Methoxybenzyl)-2,2,2-trifluoroacetamido)-*N*-(2-nitrophenyl)-4-phenylbutanamide (22). To a solution of hydrocinnamaldehyde, 90% (300 mg, 2.01 mmol, 1.0 equiv) in TFE (10 mL) were added *p*-methoxybenzylamine (338 mg, 2.46 mmol, 1.2 equiv) and trifluoroacetic acid (0.19 mL, 2.47 mmol, 1.2 equiv). The mixture was stirred with 4 Å molecular sieves at room temperature for 20 min, and then isocyanide **10** (365 mg, 2.46 mmol, 1.2 equiv) was added. The reaction mixture was stirred overnight and then concentrated to yield a brown oil. The mixture was purified by flash chromatography (10−30% EtOAc/hexanes) to yield 750 mg (65%) of **22** as a yellow solid: R_f (20% EtOAc/hexanes) = 0.50; mp = 95−97 °C; HRMS (EI) *m/z* calcd for $C_{26}H_{24}N_3O_5F_3$ (M^+) 515.1663, found 515.1672. The title compound exists at room temperature as a 2.2/1 mixture of rotamers. When peaks corresponding to the same proton(s) from each rotamer can be identified, they are listed separately as major and minor: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) major δ 10.4 (br s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.8 Hz, 1H), 7.14−7.31 (m, 7H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.50 (d, *J* = 15.6 Hz, 1H), 4.34 (d, *J* = 6.8 Hz, 1H), 3.71 (s, 3H), 2.64−2.74 (m, 3H), 2.10−2.15 (m, 1H); minor δ 10.6 (br s, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 2H), 4.90 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 15.6 Hz, 1H), 4.37 (d, *J* = 8.0 Hz, 1H), 3.60 (s, 3H), 2.48−2.59 (m, 3H), 1.94−2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.0, 167.0, 160.1, 157.9, 140.4, 140.1, 136.9, 135.8, 134.3, 130.5, 130.3, 129.0, 128.9, 128.8, 128.6, 126.7, 125.8, 125.4, 124.0, 123.8, 122.8, 122.1, 118.1, 115.2, 114.5, 113.8, 61.4, 60.4, 55.4, 55.2, 50.8, 47.4, 32.9, 32.5, 31.5, 29.9; IR (film, cm^{-1}) 3350, 2942, 1694, 1607, 1587, 1500, 1456, 1432, 1335, 1272, 1199, 1150, 1029, 748.

2-(*N*-(4-Methoxybenzyl)-2,2,2-trifluoroacetamido)-*N*-(2-aminophenyl)-4-phenylbutanamide (22a). To a solution of **22** (600 mg, 1.16 mmol, 1.0 equiv) in MeOH (20 mL) was added ∼10% by weight activated palladium on carbon. The flask was fitted with a rubber septum, and a balloon of H_2 gas was introduced at room temperature with stirring. After 30 min, N_2 gas was flushed through the reaction mixture, and the palladium was removed by filtration through Celite. The light yellow solution was concentrated to yield 509 mg of **22a** (90%) as a light yellow foamy solid which was used without further purification: R_f (20% EtOAc/hexanes) = 0.24; mp = 45−49 °C; HRMS (EI) *m/z* calcd for $C_{26}H_{26}N_3O_3F_3$ (M^+) 485.1921, found 485.1925; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.40 (br s, 1H), 7.23−7.33 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.00−7.05 (m, 3H), 6.84−6.89 (m, 3H), 6.68−6.78 (m, 2H), 4.76 (d, *J* = 15.5 Hz, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.14 (d, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.73 (br s, 2H), 2.62−2.68 (m, 3H), 2.13−2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.2, 160.2, 141.1, 140.4, 130.3, 129.9, 129.0, 128.7, 128.6, 127.6, 126.7, 126.1, 125.5, 123.1, 119.0, 117.5, 114.9, 61.1, 55.6, 51.9, 32.6, 29.7; IR (film, cm^{-1}) 3369, 3039, 2981, 1684, 1617, 1515, 1447, 1248, 1199, 1146, 1034, 820, 743.

***N*-(1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-1-oxo-4-phenylbutan-2-yl)-*N*-(4-methoxybenzyl)-2,2,2-trifluoroacetamide (23).** To a solution of **22a** (21.0 mg, 0.0443 mmol, 1.0 equiv) in $CHCl_3$ (1 mL) was added isoamyl nitrite (0.02 mL, 0.150 mmol, 3.5 equiv). The reaction mixture was stirred for 10 min at room temperature and then concentrated to yield a yellow oil. The mixture was purified by preparative thin-layer chromatography (20% EtOAc/hexanes) to yield 19.0 mg (88%) of **23** as a clear oil: R_f (20% EtOAc/hexanes) = 0.53; HRMS (EI) *m/z* calcd for] $C_{26}H_{23}N_4O_3F_3$ (M^+) 496.1717, found 496.1714. The title compound exists at room temperature as a 3.7/1 mixture of rotamers. When peaks corresponding to the same proton(s) from each rotamer can be identified, they are listed separately as major and minor: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) major δ 8.13 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.08−7.25 (m, 5H), 7.00 (d, *J* = 7.0 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 5.24 (dd, *J* = 5.0,8.0 Hz, 1H), 3.70 (s, 3H), 2.66−2.75 (m, 2H), 2.47−2.55 (m, 1H), 1.87−1.94 (m, 1H); minor δ 8.04 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 2H), 6.57 (d, *J* = 9.0 Hz, 2H), 6.10 (t, *J* = 6.5 Hz, 1H), 4.89 (d, *J* = 4.5 Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.8, 160.0, 146.1, 140.5, 131.3, 130.9, 130.8, 130.5, 129.3, 128.8, 128.6, 128.5, 126.9, 126.7, 126.5, 125.5, 120.5, 120.3, 114.6, 114.4, 114.0, 60.6, 55.4, 55.3, 52.0, 48.8, 33.0, 32.8, 32.7, 31.0; IR (film, cm^{-1}) 2942, 1738, 1684, 1612, 1505, 1447, 1379, 1257, 1209, 1180, 1150, 1029, 961, 835, 743.

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Supporting Information Available: Experimental procedure for compounds **21b−g**, copies of ^{1}H and ^{13}C NMR spectra of **14−20**, **21a−g**, **22**, **22a**, and **23**, and a CIF file for compound **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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