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Multicomponent Synthesis of Cyclic Depsipeptide Mimics by Ugi Reaction Including Cyclic Hemiacetals Derived from Asymmetric Organocatalysis

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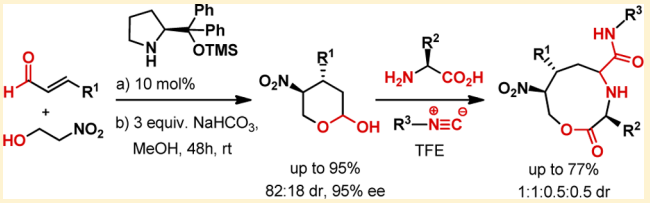
Supporting Information

ABSTRACT: The synthesis of novel cyclic depsipeptide mimics by means of an organocatalytic conjugate addition, leading to chiral cyclic hemiacetals, followed by a multicomponent reaction with α-amino acids and isocyanides, is described. The initial organocatalytic step is employed for the asymmetric derivatization of α,β-unsaturated aldehydes to 4,5-disubstituted 2-hydroxytetrahydropyrans, which are next used as chiral bifunctional substrates on the Ugi five-center three-component reaction, giving rise to nine-membered-ring lactones. This sequential approach proved to be suitable for the rapid generation of molecular complexity through the combination of aliphatic, dipeptidic, glucosidic, and lipidic isocyanides with several amino acids, thus giving access to amido-, glyco-, and lipo-depsipeptide scaffolds featuring natural product-like structures.



INTRODUCTION

Isocyanide-based multicomponent reactions (I-MCRs) traditionally stand among the most versatile methods to produce medium-sized and macrocyclic peptidomimetics.[1] These processes not only comprise great chemical efficiency and atom economy but also enable the easy implementation of the diversity-oriented synthesis (DOS) concept to cover the wider chemical space.[2] Among the I-MCRs, the Ugi four-component reaction[3]—i.e., the condensation of a primary amine, a carboxylic acid, an aldehyde/ketone, and an isocyanide, leading to *N*-substituted dipeptide—has been the most powerful synthetic tool to produce naturally occurring cyclic peptides and peptidomimetics.[1,2] An outstanding variation of the Ugi reaction is the so-called Ugi five-center four-component reaction (Ugi-5C-4CR), developed in 1996.[4] Ugi's concept behind this remarkable process was the utilization of α-amino acids as bifunctional scaffolds, leading to six-membered-ring α-adducts that evade the classic Mumm rearrangement, enabling the attack of a nucleophilic solvent like methanol. Applications of this reaction include the design of chiral ligands for asymmetric catalysis[5] and of inhibitors of metallo-amino-peptidases[6] based on the resulting 1,1′-iminodicarboxylic acid platform. Also, variants of this reaction include the Lewis acid catalyzed diastereoselective version[7] and the replacement of methanol by a further amine component for the design of a new four-component reaction, leading to 1,1′-iminodicarboxamides.[8]

An important modification of this reaction that gives access to cyclic skeletons was developed by Ugi himself using trifunctional scaffolds like the amino acid lysine.[9] In this new variant, named Ugi five-center three-component reaction (Ugi-5C-3CR), the α-adduct evolves through an intramolecular acylation of the side chain amino group, leading to an α-amino-ε-lactam derivative (Scheme 1A). The same approach was also implemented by Kim and co-workers for the synthesis of α-

Scheme 1. Synthetic Variants of the Ugi-5C-3CR with (A) a Trifunctional Amino Acid and (B and C) Two Chiral Bifunctional Substrates

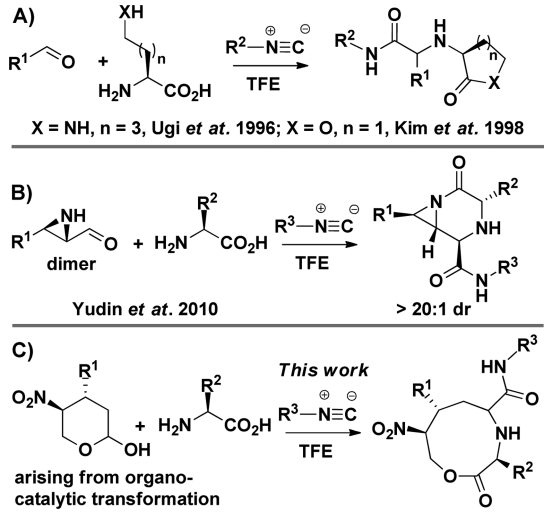


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Table 1. Screening of Reaction Conditions and Substrate Scope of the Asymmetric Conjugate Addition of Nitroethanol to α,β-Unsaturated Aldehydes, Catalyzed by Diphenylprolinol Silyl Ether

entry[a]	R	temp. (°C)	compound	yield (%)[c]	dr[d]	ee (%)[e]
1	Ph	25	**1a**	96	88:12	83
2	Ph	10	**1a**	95	82:18	95
3	Ph	−10	**1a**	95	84:10	94
4[b]	Ph	10	**1a**	50	73:27	83
5	*p*-BrC_6H_4	10	**1b**	92	84:16	92
6	*p*-$MeOC_6H_4$	10	**1c**	82	84:16	59
7	*p*-$NO_2C_6H_4$	10	**1d**	59	93:7	92
8	C_2H_5	10	**1e**	87	75:25	92

[a]Reactions using 0.9 mmol (1.5 equiv) of nitroethanol and 0.6 mmol of the α,β-unsaturated aldehyde. [b]Reaction using 5 mol % of catalyst. [c]Yield of isolated pure product. [d]dr *anti*/*syn* determined by ^{1}H NMR of the crude product. [e]Determined by chiral-phase HPLC analysis of the *anti* isomer.

aminobutyrolactones using α-homoserine as trifunctional scaffold.[10] The authors took advantage of the feasible intramolecular acylation also with a primary alcohol and designed a new variant of the Ugi-5C-3CR based on the utilization of two different bifunctional scaffolds (i.e., a glycoaldehyde and α-amino acid) along with the isocyanide component.[11] An important improvement of this latter concept was made by Yudin et al. with the development of an Ugi-5C-3CR using an aziridine aldehyde and α-amino acids.[12] Remarkably, such a chiral amphoteric scaffold enabled the highly stereoselective synthesis of pirazinones (Scheme 1B) and macrocyclic peptidomimetics, while allowing a variety of derivatizations toward cyclopeptidic architectures.[13] Just recently, both unprotected carbohydrates and α-amino acids were employed as chiral bifunctional substrates for this type of procedure, leading to the diastereoselective formation of novel cyclic glycopeptides.[14]

Herein, we describe a novel approach for the Ugi-multicomponent synthesis of cyclic depsipeptide mimics employing 4,5-disubstituted 2-hydroxytetrahydropyrans as chiral bifunctional substrates (Scheme 1C). The overall strategy involves an initial asymmetric organocatalytic conjugate addition of nitroethanol to α,β-unsaturated aldehydes, followed by an Ugi-5C-3CR, including the chiral cyclic hemiacetals and a variety of amino acids and isocyanides. Recently, we initiated a synthetic program aiming at the development of new multicomponent approaches derived from chiral hemiacetals previously generated by aminocatalytic transformations.[15] This concept is inserted in an international endeavor to combine the diversity and complexity-generating character of MCRs with the high stereoselection provided by organocatalysis.[16]

RESULTS AND DISCUSSION

Our synthetic design relying on the use of chiral hemiacetals as I-MCR inputs seeks the implementation of ideally one-pot,[15] or eventually consecutive reaction sequences, leading to complex small or medium-sized heterocyclic compounds. In this study, we implement an asymmetric conjugate addition, leading to an enantioenriched cyclic hemiacetal, as this scaffold can be included into an Ugi-5C-3CR pathway by reaction with an α-amino acid and an isocyanide. The rationale of using 2-hydroxytetrahydropyran lies at its bifunctional character, as the aldehyde group may react with the other Ugi components to form the α-adduct, while the appendage primary hydroxyl group undertakes the intramolecular acylation, leading to a completely new type of depsipeptide mimic (see Scheme 2).

We chose an efficient approach previously developed by Hayashi and co-workers as the initial organocatalytic step toward cyclic hemiacetals.[17] This process comprises the conjugate addition of nitroethanol to α,β-unsaturated aldehydes catalyzed by a diphenylprolinol silyl ether, which, after cyclization, renders the enantioenriched 4,5-disubstituted 2-hydroxytetrahydropyrans **1**. Our original idea was to perform the organocatalytic step and the I-MCR as a one-pot process, but this turned out to be impractical due to the low diastereoselectivity of the organocatalytic conjugate addition/acetalization. In their seminal paper, Hayashi and co-workers found that base-mediated isomerization (i.e., stirring in a methanolic $NaHCO_3$ solution) after hemiacetal formation significantly favors the conversion of the *cis* isomer into the more stable *trans* isomer, thus leading to a marked improvement in the diastereoselectivity. This result was corroborated by our laboratory and thus prompted the design of a sequential procedure instead of a one-pot sequence, since the excess of base would be adverse for the subsequent Ugi-5C-3CR.

However, the reported reaction conditions based on the use of 10 mol % of the chiral diarylprolinol silyl ether organocatalyst and 20 mol % of benzoic acid as cocatalyst at 25 °C did not reproduce the excellent enantioselectivity originally reported (i.e., 95% ee).[17] As shown in Table 1, good yield and diastereoselectivity were achieved with those conditions, but only up to 83% ee was obtained after several attempts (entry 1). Consequently, further screenings of the reaction conditions and substrate scope were carried out, keeping the original stoichiometry, reaction time, and solvent from the reported procedure.[17] Thus, we found that carrying out the reaction at 10 °C led to an important increment in enantiomeric excess up to 95%, while both the yield and diastereoselectivity remained high (entry 2). The decrease of the temperature to −10 °C did not lead to further improvement (entry 3), while lowering the catalyst loading to 5 mol % provoked a drop in yield and enantio- and diastereoselectivity (entry 4). The reaction conditions of entry 2, standardized for cinnamaldehyde, were also employed for the organocatalytic conjugate addition to other α,β-unsaturated aldehydes, generally resulting in good to excellent yields and stereoselectivity. A poorer enantioselectivity was

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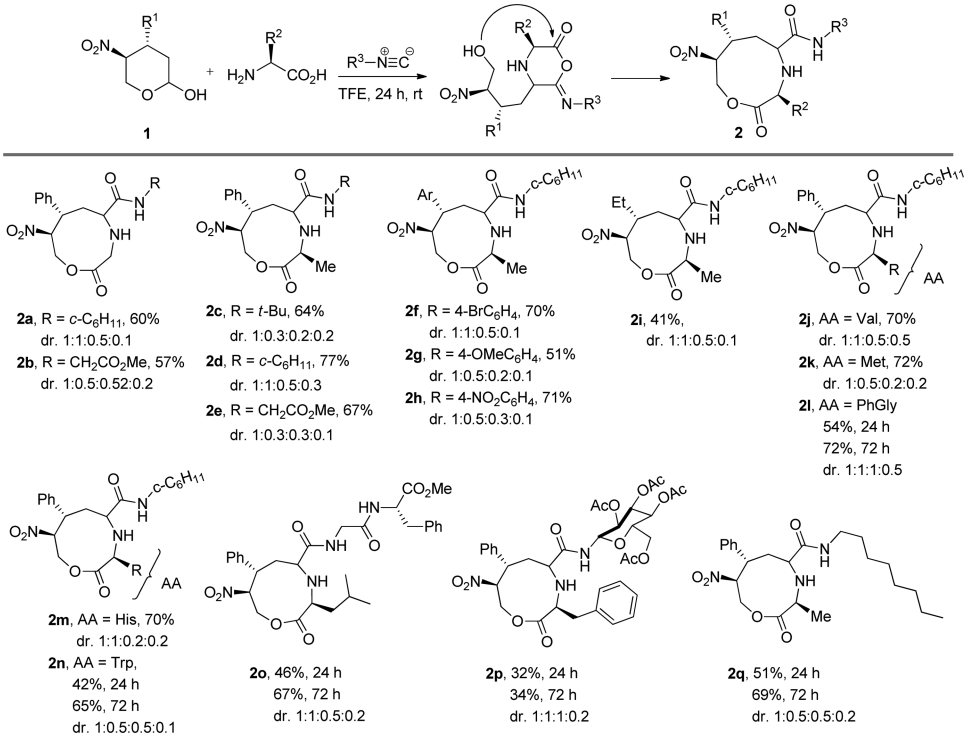
Scheme 2. Multicomponent Synthesis of Cyclic Depsipeptides by Ugi-5C-3CR between Cyclic Chiral Hemiacetals, α-Amino Acids, and Isocyanides



obtained for *p*-methoxy-cinnamaldehyde (entry 6), which also is in contradiction with the previously reported results.[17]

Once we were capable of reproducing these results and thus have access to a pool of enantioenriched 4,5-disubstituted 2-hydroxytetrahydropyrans, we turned our attention to the synthesis of cyclic depsipeptide mimics by the Ugi-5C-3CR with such chiral hemiacetals. Cyclic depsipeptides are naturally occurring peptides composed of amino acids and at least one hydroxy acid as amino acid surrogate, thus enabling the formation of a lactone bond in the cyclic skeleton. A variety of natural cyclic depsipeptides have been shown to possess antitumor, antimicrobial, and anti-inflammatory activities,[18] which makes them important targets for synthetic methods development in drug discovery approaches. I-MCRs have been used to produce macrocyclic lactams resembling naturally occurring depsipeptides,[19] but in most cases, the I-MCR is not responsible for the ring-closure step and has never been used to produce medium-sized lactone rings.

As depicted in Scheme 2, hemiacetal **1a** was initially reacted with glycine in the presence of cyclohexylisocyanide or methyl isocyanoacetate at room temperature to afford nine-membered-ring depsipeptides **2a** and **2b**, respectively, in moderate yields after 24 h of reaction. Whereas compounds **2a** and **2b** were produced with very low diastereoselectivity, this suggests that the stereogenic centers at the hemiacetal exert no stereocontrol over the Ugi-multicomponent reaction. Unfortunately, the combination of this chiral hemiacetal with chiral α-amino acids also led to poor diastereoselectivity in the formation of the new stereogenic center in compounds **2c**−**q**. However, results of marked relevance were obtained from the study of the substrate scope, which showed that a wide range of peptidic, monosaccharidic, and lipidic isocyanides could be efficiently combined with a variety of α-amino acids and hemiacetals. In all cases, the reactions were conducted at 0.25 mol·L^{-1} in trifluoroethanol (TFE), conditions that comprise the initial insolubility of the starting materials and their gradual solubilization during the first hours of reaction.

L-Alanine (Ala) was chosen to assess the reaction efficiency upon variation of the isocyanide component and 4-aryl-substituted 2-hydroxytetrahydropyrans, in all cases, providing moderate to good yields in the Ugi-5C-3CR (**2c**−**2h**, 51−77% yield). However, the use of a 2-hydroxytetrahydropyran bearing an aliphatic group in position 3 led to the lowest product yield (**2i**, 41% yield) among all hemiacetals combined with Ala. Variation of the amino acid component further proved the potential of this protocol to produce diverse natural product-like skeletons (**2j**−**2n**); as shown, either amino acids bearing aromatic and aliphatic hydrocarbon side chains such as Val, Leu, Phe, and PhGly or those having heteroatom-functionalized side chains such as Met, His, and Trp readily led to the desired nine-membered-ring lactones. Regarding the case of compounds **2k** and **2n**—derived from PhGly and Trp, respectively—that were produced only in moderate yield, parallel experiments proved that the reaction efficiency can be enhanced up to 70% yield with 72 h of reaction. However, it was not possible to further increase the reaction yield even with longer reaction times. Finally, we proved that this approach is well suited for the rapid generation of molecular complexity by the combination of a dipeptidic, a D-glucosidic, and a lipidic isocyanide with varied amino acids (**2o**, **2p**, and **2q**, respectively). For compounds **2o** and **2q**, the yield could be increased by setting up the reaction time at 72 h. For the synthesis of glycodepsipeptide **2p**, though, the yield could not be further improved with a longer reaction time.

Aiming to improve the diastereoselectivity of this reaction, we carried out experiments using 5 mol % of the Lewis acid catalyst $Ti(OCH(CH_3)_2)_4$, which was previously reported to effectively enhance the diastereoselection of the classic Ugi-5C-

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3CR of amino acids with aromatic aldehydes.[7] However, even after several attempts and screening of reaction conditions, there was no improvement in the diastereoselectivity, as it is in the case of several Ugi-multicomponent processes for which there are no available stereoselective versions.

CONCLUSIONS

We have designed and implemented a new reaction sequence combining organocatalysis and a multicomponent reaction to provide structurally novel cyclic depsipeptide mimics. The sequential approach was initiated with an asymmetric organocatalytic conjugate addition of nitroethanol to α,β-unsaturated aldehydes, followed by base-mediated isomerization to the *trans* isomer of 4,5-disubstituted 2-hydroxytetrahydropyrans. Such enantiomerically enriched cyclic hemiacetals were combined in an Ugi reaction with a wide variety of α-amino acids and isocyanides of aliphatic, peptidic, glycosidic, and lipidic nature to produce polysubstituted nine-membered-ring lactones featuring natural product-like architectures. Whereas the multicomponent step showed poor diastereoselectivity, the overall strategy proved a remarkable complexity-generating ability with the creation of three new stereocenters and the incorporation of four components into the final cyclic depsipeptide scaffolds. The presence of a nitro group makes these compounds suitable for further derivatization such as reduction and coupling to amino acids for enlarging the peptide chain by the western part. Overall, the synthetic scope of this method further proves the potential of combining the organocatalytic functionalization of carbonyls with their subsequent multicomponent derivatization.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in parts per million relative to the residual solvent signals of tetramethylsilane (TMS), and coupling constants (J) are reported in hertz. High-resolution ESI mass spectra were obtained from a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer, an RF-only hexapole ion guide, and an external electrospray ion source. Flash column chromatography was carried out using silica gel 60 (230−400 mesh), and analytical thin-layer chromatography (TLC) was performed using silica gel aluminum sheets. HPLC chromatograms were obtained on an apparatus with a LC-10AT Pump, SPD-10A UV−vis Detector, SCL-10A System Controller, using a Chiralpak AD-H (4,6 mmØ × 250 mmL, particle size 5 μm). Optical rotations were measured with a polarimeter at 589 nm, 23 °C.

General Procedure for the Organocatalytic Conjugate Addition. Diphenylprolinol silylether (0.06 mmol, 10 mol %) and the α,β-unsaturated aldehyde (0.6 mmol, 1.0 equiv) were dissolved in MeOH (1.2 mL). The solution was cooled to 10 °C, and $PhCO_2H$ (0.12 mmol, 20 mol %) and 2-nitroethanol (0.9 mmol, 3.0 equiv) were added. The reaction mixture was stirred for 24 h at 10 °C, then treated with $NaHCO_3$ (3.0 mmol, 5.0 equiv) and stirred for another 48 h at room temperature. The resulting mixture was quenched with phosphate buffer (pH 7.0), and the organic material was extracted with AcOEt (3 × 3 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc as eluent to furnish the corresponding 5-nitro-4-aryl-2-hydroxytetrahydropyran. The NMR and physical data of chiral 2-hydroxytetrahydropyrans are in agreement with published data;[17] see the Supporting Information. The enantiomeric excess was determined by chiral-phase HPLC analysis through comparison with the authentic racemic material. Assignment of the stereoisomers was performed by comparison with literature data.[17]

General Procedure for the Ugi-5C-3CR. To a suspension of the corresponding 4,5-disubstituted 2-hydroxytetrahydropyran (0.25 mmol) and the α-amino acid (0.25 mmol) in TFE (1 mL) was added slowly the isocyanide component (0.25 mmol). The resulting mixture was stirred for 24 h at 25 °C. The volatiles were removed under pressure, and the crude product was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc as eluent. The diastereomeric ratio of final compounds was determined by ^{1}H NMR.

Compound ***2a***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), glycine (18.7 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2a** (57 mg, 60%) as a colorless oil. R_f = 0.25 (*n*-hexane/EtOAc 1:1). Four diastereomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39−7.23 (m, 5H), 7.04, 6.96, 6.76 (3 × d, J = 8.4 Hz, 1H), 4.76 (m, 1H), 4.49 (m, 1H), 4.44−4.37 (m, 1H), 3.88−3.74 (m, 1H), 3.69−3.48 (m, 1H), 3.38, 3.30, 3.24, 3.18 (4 × d, J = 18.0 Hz, 2H), 2.85, 2.75, 2.68 (3 × dd, J = 8.8, 3.6 Hz, J = 8.8, 5.1 Hz, J = 10.4, 2.6 Hz, 1H), 2.33, 2.18, 1.97 (3 × m, 2H), 1.88−1.55 (m, 6H), 1.34 (m, 2H), 1.21−1.03 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 171.5, 170.9, 170.3, 137.7, 137.0, 129.5, 129.4, 129.2, 129.1, 128.4, 128.3, 128.2, 94.0, 93.3, 62.7, 62.4, 61.6, 61.2, 60.88, 60.79, 60.5, 60.4, 60.2, 60.0, 48.7, 48.6, 48.1, 47.9, 43.2, 42.9, 37.1, 36.09, 34.4, 33.0, 25.55, 24.83. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{20}H_{26}N_3O_5$: 388.18779, found 388.18710.

Compound ***2b***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), glycine (18.7 mg, 0.25 mmol), and methylisocyanoacetate (22.7 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2b** (54 mg, 57%) as a colorless oil. R_f = 0.23 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56, 7.47 (2 × t, J = 5.8 Hz, 1H), 7.40−7.23 (m, 5H), 4.83−4.74 (m, 1H), 4.53−4.47 (m, 1H), 4.41 (q, J = 8.4 Hz, 1H), 4.06, 4.02, 3.99, 3.93 (4 × d, J = 6.4 Hz, 2H), 3.82, 3.54 (m, 1H), 3.75, 3.74, 3.73 (3 × s, 3H), 3.63−3.48, 3.44, 3.36, 3.27 (4 × d, J = 18.1 Hz, 2H), 3.00, 2.95, 2.88, 2.80 (4 × dd, J = 7.7, 5.7 Hz, J = 9.0, 3.6 Hz, J = 8.6, 4.9 Hz, J = 10.4, 2.6 Hz, 1H), 2.34, 2.16, 2.00, 1.78 (4 × m, 2H), 1.43, 1.34, 1.26 (3 × s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.6, 173.1, 170.95, 170.4, 170.3, 137.5, 136.9, 129.5, 129.4, 129.2, 129.1, 128.4, 128.4, 94.0, 62.7, 62.3, 61.6, 60.9, 60.8, 60.5, 60.4, 59.9, 59.7, 52.5, 48.6, 43.0, 42.7, 40.9, 40.7, 36.5, 35.9. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{17}H_{20}N_3O_7$: 378.13067, found 378.13116.

Compound ***2c***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-alanine (22.3 mg, 0.25 mmol), and *tert*-butylisocyanide (28 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2c** (60 mg, 64%) as a colorless oil. R_f = 0.57 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44−7.18 (m, 5H), 7.04, 6.82, 6.65 (s, 1H), 4.79−4.74 (m, 1H), 4.40, 4.29 (2 × m, 2H), 3.83 (m, 1H), 3.52 (m, 1H), 3.19−3.12 (m, 1H), 2.87, 2.76, 2.67, 2.56 (4 × dd, J = 8.2, 3.5 Hz, J = 7.3, 6.3 Hz, J = 10.3, 2.7, J = 9.4, 4.8 Hz, 1H), 2.37, 2.18, 1.98, 1.82 (4 × dd, J = 14.5, 12.0, 2.7 Hz, 2H), 1.33, 1.28 (2 × s, 9H, CH_3), 1.22, 1.17, 1.03 (3 × d, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5, 172.5, 172.0, 137.7, 136.9, 129.7, 129.2, 129.0, 128.5, 128.4, 128.1, 94.0, 93.9, 93.4, 62.4, 61.7, 60.8, 60.7, 60.4, 60.3, 59.7, 59.2, 58.7, 55.2, 50.9, 50.7, 43.0, 42.8, 42.4, 37.9, 35.4, 29.8, 28.7, 28.6, 28.4, 19.5, 18.4. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{19}H_{26}N_3O_5$: 376.18779, found 376.18704

Compound ***2d***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-alanine (22.3 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2d** (78 mg, 77%) as a colorless oil. R_f = 0.50 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46−7.20 (m, 5H, Ph), 7.25, 7.02, 6.84, 6.72 (4 × d, J = 8.3 Hz,

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J. Org. Chem. 2016, 81, 803−809

1H), 4.77 (m, 1H, H-8), 4.21−4.12 (m, 2H, H-9), 3.82 (m, 1H, H-7), 3.69−3.62 (m, 1H, H-13), 3.21−3.19 (m, 1H, H-3), 2.96, 2.82, 2.78, 2.65 (4 × dd, J = 7.9, 3.7 Hz, J = 7.6, 5.9 Hz, J = 10.2, 2.8 Hz, J = 9.2, 4.8 Hz, 1H), 2.38, 2.18, 2.03 (3 × m, 2H, H-6), 1.94−1.56 (m, 6H), 1.36−1.00 (m, 5H), 1.22, 1.14, 0.99 (3 × d, J = 7.1 Hz, 3H, H-10). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5, 173.1, 173.0 (*C*═O, *C*-2), 172.4, 172.2, 171.8 (*C*═O, *C*-11), 138.3, 137.6, 137.0 (*C*, *C*-19), 129.6, 129.3, 129.2, 129.0, 128.5, 128.4, 128.1 (*C*H, *C*-20−24), 94.1, 94.0, 93.5 (*C*H, *C*-8), 62.5, 62.4, 61.8, 60.7, 60.4, 60.3 (CH_2, *C*-9), 59.7, 59.2, 59.1, 58.6 (*C*H, *C*-5), 55.3, 55.1 (*C*H, *C*-3), 48.3, 48.1, 47.7 (*C*H, *C*-13), 43.0, 42.8, 42.4 (*C*H, *C*-7), 37.6, 36.4, 35.3 (CH_2, *C*-6), 33.5, 33.0, 32.7 (CH_2), 25.5, 24.8 (CH_2), 19.4, 19.3, 18.4, 18.1 (CH_3, *C*-10). HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{21}H_{28}N_3O_5$: 402.20344, found 402.20197.

Compound ***2e***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-alanine (22.3 mg, 0.25 mmol), and methylisocyanoacetate (22.7 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2e** (65.9 mg, 67%) as a light yellow oil. R_f = 0.20 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68, 7.51 (2 × t, J = 6.0 Hz, 1H), 7.42−7.23 (m, 5H), 4.77 (m, 1H), 4.54, 4.41 (2 × m, 2H), 4.29−4.22 (m, 1H), 3.95 (t, J = 5.8 Hz, 1H), 3.75, 3.72, 3.71 (4 × s, 1H), 3.65−3.43 (m, 2H), 3.27 (m, 1H), 3.04, 2.94, 2.87, 2.79 (4 × dd, J = 8.3, 3.6 Hz, J = 7.7, 5.5 Hz, J = 10.1, 2.8 Hz, J = 8.9, 4.8 Hz, 1H), 2.42, 2.27, 1.95, 1.83 (m, 2H), 1.47, 1.42, 1.17, 1.05 (4 × d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.2, 174.0, 173.7, 173.24, 173.20, 171.3, 170.2, 137.5, 136.9, 129.7, 129.3, 129.2, 128.6, 128.5, 128.4, 128.2, 94.1, 93.9, 93.6, 93.5, 62.5, 62.3, 61.8, 61.7, 60.9, 60.7, 60.5, 60.3, 59.0, 58.4, 56.3, 55.4, 55.0, 54.8, 52.6, 52.5, 52.4, 42.8, 42.7, 42.4, 42.0, 41.0, 40.9, 40.7, 40.3, 37.0, 35.2, 33.7, 32.2, 21.1, 19.4, 18.3, 18.1, 16.9, 14.2. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{18}H_{22}N_3O_7$: 392.14632, found 392.14630.

Compound ***2f***. 4-(4-Bromophenyl)-5-nitrotetrahydro-2*H*-pyran-2-ol (**1b**, 32.3 mg, 0.125 mmol), L-alanine (22.3 mg, 0.125 mmol), and cyclohexylisocyanide (14 μL, 0.125 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2f** (84 mg, 70%) as a colorless oil. R_f = 0.30 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53, 7.49, 7.48 (3 × d, J = 8.4 Hz, 2H), 7.20, 7.15, 7.11 (3 × d, J = 8.4 Hz, 2H), 6.94, 6.89, 6.77 (3 × d, J = 8.1 Hz, 1H), 4.71 (m, 1H), 4.49−4.42 (m, 2H), 4.25 (m, 1H), 4.12 (m, 1H), 3.77 (m, 1H), 3.60 (m, 1H), 3.52 (m, 1H), 3.19 (m 1H), 2.95, 2.75, 2.61 (3 × dd, J = 7.7, 4.4 Hz, J = 10.1, 2.9 Hz, J = 9.9, 4.5 Hz, 1H), 2.33, 2.12, 2.03 (3 × m, 2H), 1.79 (m, 2H), 1.35 (m, 4H), 1.24, 1.19, 1.11 (3 × d, J = 7.2 Hz, 3H, CH_3), 1.28−1.07 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 172.0, 171.5, 137.3, 136.6, 136.1, 132.8, 132.5, 132.4, 130.3, 130.1, 93.6, 93.4, 92.9, 62.2, 61.7, 60.9, 60.5, 58.9, 58.6, 55.4, 55.1, 48.2, 47.7, 42.2, 42.1, 41.8, 37.5, 35.4, 33.0, 32.8, 25.5, 24.8, 19.6, 18.5, 18.3. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{21}H_{27}BrN_3O_5$: 480.11396, found 480.11322.

Compound ***2g***. 4-(4-Methoxyphenyl)-5-nitrotetrahydro-2*H*-pyran-2-ol (**1c**, 63.3 mg, 0.25 mmol), L-alanine (22.3 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2g** (57 mg, 51%) as a colorless oil. R_f = 0.50 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20, 7.16, 7.13 (3 × d, J = 8.8 Hz, 2H), 6.91, 6.88, 6.87 (3 × d, J = 8.7 Hz, 2H), 7.07, 6.83 (d, J = 8.2 Hz, 1H), 4.71 (m, 1H), 4.52 (m, 1H), 4.39 (m, 1H), 4.31−4.20 (m, 1H), 4.16−4.10 (m, 1H), 3.81, 3.79, 3.78 (3 × s, 3H), 3.58 (m, 1H), 3.35 (m, 1H), 3.24−3.12 (m, 1H), 2.95, 2.85, 2.78, 2.68 (4 × dd, J = 8.1, 3.6 Hz, J = 11.5, 6.2 Hz, J = 10.1, 2.5 Hz, J = 9.1, 4.8 Hz, 1H), 2.38, 2.20, 2.05 (3 × m, 2H), 1.91−1.56 (m, 6H), 1.43−1.03 (m, 5H), 1.22, 1.17, 1.06 (3 × d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.6, 173.2, 172.4, 171.8, 159.6, 159.3, 129.5, 129.4, 128.5, 115.0, 114.7, 114.6, 94.1, 93.6, 62.5, 62.4, 61.8, 60.8, 60.5, 59.2, 58.78, 58.70, 58.5, 55.4, 55.3, 55.2, 48.1, 47.7, 42.3, 42.0, 41.7, 37.6, 35.4, 33.7, 33.0, 32.8, 29.8, 25.5, 24.8, 19.5, 18.4, 18.2. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{22}H_{30}N_3O_6$: 432.21401, found 432.21249.

Compound ***2h***. 4-(4-Nitrophenyl)-5-nitrotetrahydro-2*H*-pyran-2-ol (**1d**, 67 mg, 0.25 mmol), L-alanine (22.3 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2h** (45 mg, 71%) as a colorless oil. R_f = 0.30 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19, 8.17, 8.14 (3 × d, J = 8.7 Hz, 2H), 7.47, 7.43, 7.36 (3 × d, J = 8.8 Hz, 2H), 6.92, 6.89, 6.82 (3 × d, J = 8.7 Hz, 1H, NH), 4.70 (m, 1H), 4.43, 4.19 (m, 2H), 3.64 (m, 1H), 3.54 (m, 1H), 3.19 (q, J = 7.2 Hz, 1H), 3.10, 2.85, 2.66, 2.49 (4 × dd, J = 14.7, 6.6 Hz, J = 8.2, 4.8 Hz, J = 9.8, 3.2 Hz, J = 10.2, 4.3 Hz, 1H), 2.31, 2.11, 1.90 (3 × m, 2H), 1.90−1.50 (m, 6H), 1.19, 1.15, 1.10 (3 × d, J = 7.1 Hz, 3H, CH_3), 1.36−0.99 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.6, 173.0, 171.7, 171.2, 147.8, 147.6, 145.1, 144.8, 129.6, 129.5, 129.4, 124.5, 124.2, 124.1, 93.0, 92.8, 92.4, 61.9, 58.6, 58.3, 55.3, 54.9, 48.1, 47.6, 42.1, 37.3, 35.6, 33.0, 32.9, 32.7, 25.4, 24.7, 19.5, 18.3, 18.2. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{21}H_{27}N_4O_7$: 447.18852, found 447.18777.

Compound ***2i***. 4-Ethyl-5-nitrotetrahydro-2*H*-pyran-2-ol (**1e**, 15 mg, 0.07 mmol), L-alanine (5 mg, 0.07 mmol), and cyclohexylisocyanide (7 μL, 0.07 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2i** (10.2 mg, 41%) as a colorless oil. R_f = 0.50 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11, 7.06, 6.92, 6.73 (d, J = 8.8 Hz, 1H), 4.84−4.36 (m, 2H), 4.25−4.00 (m, 1H), 3.89 (m, 1H), 3.73 (m, 1H), 3.50, 3.35 (2 × m, 1H), 3.27, 3.16, 3.07, 2.98 (4 × dd, J = 8.0, 6.1 Hz, J = 13.3, 6.9 Hz, J = 8.2, 5.6 Hz, 1H), 2.22 (m, 1H), 1.97−1.09 (m, 13H), 1.40, 1.36 (2 × d, J = 7.0 Hz, 3H), 0.97 (dt, J = 14.4, 4.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0, 173.9(*C*═O), 172.8, 172.8 (*C*═O), 90.9, 90.5, 90.2 (*C*H), 61.2, 61.0, 60.8 (CH_2), 59.8, 58.7 (*C*H), 55.4, 55.2 (*C*H), 48.0, 47.8, 47.2 (*C*H), 37.4, 37.2, 36.8 (*C*H), 34.9, 34.6 (CH_2), 33.1, 32.8 (CH_2), 25.5, 24.9, 24.8 (CH_2), 24.3, 23.7, 23.3, 23.1 (CH_2), 19.7, 18.0 (CH_3), 11.1, 11.0, 10.8 (CH_3). HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{17}H_{28}N_3O_5$: 354.20344, found 354.20346.

Compound ***2j***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-valine (29.3 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2j** (75 mg, 70%) as a colorless oil. R_f = 0.45 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42−7.19 (m, 5H), 7.05, 6.91, 6.58 (d, J = 8.8 Hz, 1H), 4.79−4.70 (m, 1H), 4.51, 4.35 (2 × dd, J = 12.7, 8.5 Hz, 1H), 4.21−4.06 (m, 1H), 3.89−3.75 (m, 1H), 3.73−3.50 (m, 1H), 2.97, 2.89, 2.70, 2.59 (4 × dd, J = 9.9, 2.7 Hz, J = 9.6, 4.8 Hz, 1H), 2.32, 2.18, 2.08 (3 × ddd, J = 14.5, 11.8, 2.9 Hz, 3H), 1.93−1.60 (m, 6H), 1.45−0.76 (m, 5H), 1.04 (d, J = 6.8 Hz, 1H), 0.97, 0.90, 0.80 (3 × d, J = 6.9 Hz, 6H), 0.92, 0.77 (2 × d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.9, 172.6, 172.4, 171.6, 137.4, 129.6, 129.2, 128.6, 128.5, 128.4, 128.1, 94.1, 93.9, 66.4, 65.6, 62.50, 60.57, 60.1, 59.2, 48.2, 47.8, 43.0, 42.8, 38.0, 36.3, 33.1, 32.8, 31.8, 31.3, 25.6, 24.8, 19.8, 18.7, 18.4, 17.4. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{23}H_{32}N_3O_5$: 430.23474; found 430.23441.

Compound ***2k***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-methionine (37.3 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2k** (75 mg, 72%) as a colorless oil. R_f = 0.45 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46−7.19 (m, 5H), 6.86, 6.82, 6.48 (3 × d, J = 8.3 Hz, 1H), 4.74 (m, 1H), 4.51 (dd, J = 12.7, 8.4 Hz, 1H), 4.40 (dd, J = 12.7, 8.4 Hz, 1H), 4.22, 4.12 (2 × dd, J = 16.7, 8.4 Hz, 1H), 3.78 (m, 1H), 3.69−3.50 (m, 2H), 3.31 (m, 1H), 2.74, 2.65, 2.54, 2.50 (4 × dd, J = 12.8, 8.1 Hz, J = 11.9, 5.9 Hz, J = 8.3, 5.1 Hz, J = 8.3, 5.1 Hz, 1H), 2.31, 2.09 (2 × m, 1H), 2.07, 2.05, 2.04, 2.03 (4 × s, 3H), 1.67 (m, 8H), 1.23 (m, 6H).

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J. Org. Chem. 2016, 81, 803−809

^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 172.1, 137.3, 129.7, 129.2, 128.6, 128.4, 93.9, 62.5, 59.2, 58.9, 48.3, 42.7, 36.3, 33.1, 32.90, 32.10, 30.0, 25.5, 24.9, 15.3. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{23}H_{32}N_3O_5S$: 462.20627, found 462.20670.

Compound ***2l***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-phenylglycine (37.8 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2l** (63 mg, 54%) as a colorless oil. R_f = 0.40 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49−6.88 (m, 10H), 4.95−4.61 (m, 1H), 4.58−4.21 (m, 1H), 4.21−3.91 (m, 1H), 3.84 (m, 1H), 3.73−3.41 (m, 1H), 3.37−2.69 (m, 3H), 2.68−2.22 (m, 1H), 2.00−1.45 (m, 7H), 1.44−0.91 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 171.6, 137.9, 129.8, 129.2, 129.0, 128.9, 128.3, 128.1, 127.5, 93.4, 62.3, 61.7, 51.1, 48.9, 48.2, 47.2, 43.3, 42.3, 39.2, 34.7, 33.1, 32.6, 25.5, 24.8. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{26}H_{30}N_3O_5$: 464.21800, found 464.21838.

Compound ***2m***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-histidine (38.8 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2m** (82 mg, 70%) as an orange solid. Mp = 96−99 °C. R_f = 0.45 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70, 7.68, 6.94, 6.91 (4 × s, 1H), 7.54, 7.51, 6.77, 6.72 (4 × d, J = 2.98 Hz, 1H), 7.45−7.25 (m, 5H), 7.09, 7.00 (2 × d, J = 6.9 Hz, 1H), 4.73 (m, 1H), 4.54−4.40 (m, 1H), 4.36−4.24 (m, 1H), 4.01 (m, 1H), 3.81, 3.71 (2 × d, J = 8.6 Hz, 2H), 3.64−3.36 (m, 2H), 3.25−2.95 (m, 1H), 2.91, 2.81, 2.71, 2.65 (4 × dd, J = 14.5, 8.7 Hz, J = 7.9 Hz, 10.5 Hz, 1H), 2.36, 2.25 (2 × m, 2H), 1.94−1.56 (m, 6H), 1.36−1.00 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 172.9, 172.6, 137.9, 137.1, 137.1, 136.1, 135.3, 129.5, 129.1, 128.9, 128.3, 128.1, 128.0, 124.2, 121.4, 116.1, 112.7, 94.5, 94.5, 94.4, 62.3, 61.6, 61.3, 60.7, 60.4, 60.0, 59.6, 48.3, 43.0, 42.6, 37.2, 36.0, 32.9, 32.8, 32.6, 30.5, 25.5, 25.4, 24.93, 24.89. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{24}H_{30}N_5O_5$: 468.22469, found 468.22278.

Compound ***2n***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-tryptophan (51.1 mg, 0.25 mmol), and cyclohexylisocyanide (31 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2n** (54 mg, 42%) as a yellow solid. Mp = 90−95 °C. R_f = 0.10 (Hex/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77, 8.26, 8.07 (3 × s, 1H), 7.70−7.64 (m, 1H), 7.51−7.41 (m, 1H), 7.39−7.05 (m, 7H), 7.01, 6.59 (d, J = 6.6 Hz, 1H, $NH_{(amide)}$), 6.35, 6.33, 6.32 (3 × s, 1H), 4.77−4.69 (m, 1H), 4.53, 4.32 (2 × m, 2H), 4.54−4.38 (m, 1H), 2.88, 2.81, 2.74, 2.64 (4 × dd, J = 14.5, 10.4 Hz, J = 10.6, 3.9 Hz, J = 14.6, 9.6 Hz, J = 9.3, 4.7 Hz, 1H), 2.40, 2.20 (2 × m, 2H), 1.86−1.41 (m, 8H), 1.38−1.05 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.2, 173.0, 172.6, 171.8, 138.2, 137.2, 136.7, 136.4, 129.1, 128.9, 128.6, 128.2, 127.2, 123.6, 123.2, 122.8, 122.5, 120.1, 118.7, 118.5, 112.1, 111.6, 111.0, 110.2, 93.6, 93.5, 93.5, 61.9, 61.7, 61.3, 61.30, 60.33, 59.7, 48.3, 47.5, 47.2, 43.2, 42.4, 36.4, 34.7, 33.1, 32.6, 32.0, 29.7, 29.3, 25.5, 24.8. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{29}H_{33}N_4O_5$: 517.24564, found 517.24359.

Compound ***2o***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 27.9 mg, 0.1 mmol), L-leucine (16.4 mg, 0.1 mmol), and CN-Gly-Phe-OMe[15] (30.8 mg, 0.1 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2o** (26.8 mg, 46%) as a yellow solid. Mp = 82−86 °C. R_f = 0.15 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (dt, J = 10.5, 5.3 Hz, 1H), 7.44−6.98 (m, 10H), 6.65, 6.54, 6.43, 6.36 (4 × d, J = 6.8 Hz, 1H), 4.93−4.66 (m, 1H), 4.48−4.20 (m, 1H), 4.16−3.93 (m, 1H), 3.73, 3.70, 3.69 (3 × s, 3H), 3.87−3.44 (m, 1H), 3.26−2.96 (m, 1H), 3.08, 2.84, 2.73, 2.70 (4 × dd, J = 14.0, 5.9 Hz, 1H), (d, J = 4.9 Hz, 1H), (dd, J = 8.9, 3.5 Hz, 1H), (dd, J = 10.4, 2.9 Hz, 1H), 2.41, 2.18, 2.00 (3 × m, 2H), 1.81−1.15 (m, 5H), 0.93, 0.90 (2 × d, J = 6.4 Hz, 3H), 0.87, 0.80 (2 × d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 173.3, 171.8, 171.6, 170.5, 168.6, 137.0, 135.88, 135.85, 129.8, 129.5, 129.3, 129.2, 128.7, 128.6, 128.5, 127.4, 127.3, 127.1, 93.9, 93.9, 93.8, 62.5, 62.3, 59.5, 59.3, 59.1, 53.5, 53.4, 53.1, 52.6, 52.5, 52.4, 43.1, 42.8, 42.6, 37.90, 37.86, 37.1, 36.4, 24.8, 24.7, 22.8, 22.6, 22.5. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{30}H_{37}N_4O_8$: 581.26031; found 581.26169.

Compound ***2p***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-phenylalanine (41.3 mg, 0.25 mmol), and β-D-glucosyl isocyanide[20] (89.3 mg, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2p** (58.2 mg, 32%) as a light yellow solid. Mp = 91−96 °C. R_f = 0.5 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45−7.22 (m, 10H), 7.00, 6.83 (2 × d, J = 9.2 Hz, 1H, *NH*), 5.28 (dd, J = 15.2, 5.7 Hz, 1H), 5.12 (dd, J = 9.3 Hz, 1H), 5.07 (m, 1H), 4.87 (dd, J = 9.5 Hz, 1H), 4.61 (m, 1H), 4.50 (dd, J = 12.7, 8.5 Hz, 1H), 4.32−4.21 (m, 2H), 4.05 (dd, J = 12.4, 2.0 Hz, 1H), 3.78 (m, 1H), 3.68 (dd, J = 12.4, 8.3 Hz, 1H), 3.45 (dd, J = 12.4, 2.0 Hz, 1H), 3.17−3.10 (m, 1H), 2.99, 2.78, 2.59 (3 × dd, J = 13.8, 4.7 Hz, J = 13.7, 9.0 Hz, J = 10.9, 4.1 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.65 (d, J = 7.4 Hz, 3H), 1.53−1.10 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.2, 171.9, 171.1, 170.7, 170.0, 169.6, 137.0, 136.7, 129.79, 129.71, 128.9, 128.5, 128.1, 127.3, 93.8, 78.3, 73.7, 72.8, 70.7, 68.1, 62.5, 61.6, 60.6, 58.8, 42.2, 39.2, 36.8, 20.7. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{35}H_{40}N_3O_{14}$: 726.25103; found 726.25049.

Compound ***2q***. 5-Nitro-4-phenyl-tetrahydro-2*H*-pyran-2-ol (**1a**, 55.8 mg, 0.25 mmol), L-alanine (22.3 mg, 0.25 mmol), and *n*-octylisocyanide[15] (44 μL, 0.25 mmol) were reacted in TFE (1 mL) according to the general Ugi-5C-3CR-based procedure. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded **2q** (55 mg, 51%) as a colorless oil. R_f = 0.50 (*n*-hexane/EtOAc 1:1). Four diastereoisomers were detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42−7.19 (m, 5H), 7.12, 6.96, 6.86 (3 × t, J = 5.6 Hz, 1H), 4.77 (m, 1H), 4.51, 4.40 (2 × m, 2H), 4.28 (m, 1H), 3.82 (m, 1H), 3.53 (m, 1H), 3.23 (m, 1H), 2.98, 2.87, 2.78, 2.69 (4 × dd, J = 7.6, 3.8 Hz, J = 11.2, 5.1 Hz, J = 10.1, 2.7 Hz, J = 9.0, 4.9 Hz, 1H), 2.38, 2.18, 1.86, 1.78 (4 × m, 2H), 1.45 (m, 2H), 1.27 (br. s, 8H), 1.21, 1.15, 1.00 (3 × d, J = 7.0 Hz, 3H, CH_3), 0.88 (t, J = 7.1, 3.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.6, 173.3, 173.2, 173.1, 172.6, 138.4, 137.7, 137.0, 129.6, 129.4, 129.2, 129.1, 128.9, 128.6, 128.5, 128.4, 128.1, 127.3, 94.1, 94.0, 93.5, 62.5, 62.4, 61.8, 60.8, 60.7, 60.5, 60.3, 59.3, 59.1, 58.6, 55.4, 55.2, 55.1, 43.2, 43.0, 42.8, 42.4, 39.6, 39.4, 39.1, 37.4, 35.3, 33.4, 31.8, 29.59, 29.52, 29.3, 27.0, 22.7, 19.4, 18.4, 18.1, 14.1. HRMS (ESI-FT-ICR) $[M - H]^-$ calcd. for $C_{23}H_{34}N_3O_5$: 432.25039; found 432.25018.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02158.

^{1}H, ^{13}C NMR, and HRMS (ESI-FT-ICR) *m*/*z* spectra of medium-sized cyclic peptidomimetics and chiral-phase HPLC analysis of Michael adducts (PDF)

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Notes

The authors declare no competing financial interest.

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