JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

From Amino Acids to Nature-Inspired Molecular Scaffolds: Incorporation of Medium-Sized Bridged Heterocycles into a Peptide Backbone

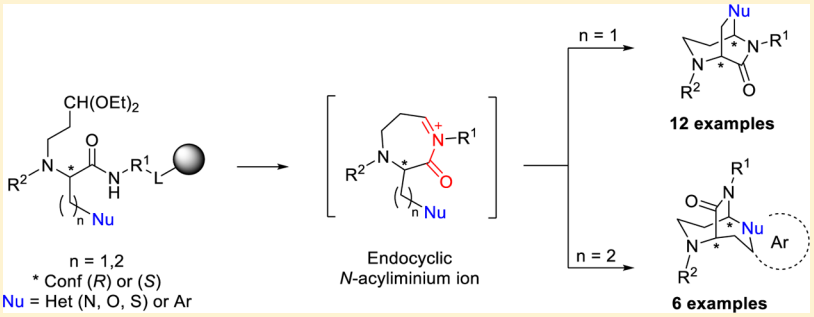
Agustina La-Venia,[||,†] Pilar Ventosa-Andrés,[||,†] Ludmila Hradilová,[‡] and Viktor Krchňák*[,†,§]

[†]Department of Organic Chemistry, Faculty of Science, Institute of Molecular and Translational Medicine, Palacky University, 17. Listopadu 12, 771 46 Olomouc, Czech Republic

[‡]Farmak, Na vlčinci 16/3, Klášterní Hradisko, 779 00 Olomouc, Czech Republic

[§]Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Center, Notre Dame, Indiana 46556, United States

Supporting Information



ABSTRACT: Novel molecular scaffolds comprising two to four bridged and fused heterocycles were synthesized from amino acids using seven-membered endocyclic *N*-acyliminium ions as key intermediates in acid-mediated tandem reactions with internal nucleophiles. This complexity-generating synthesis proceeds with high efficiency and with full stereocontrol of the newly generated stereogenic center. These results have extended the scope of medium-sized cyclic iminium ion chemistry, making it applicable as a regio- and stereoselective synthetic strategy for the generation of complex polycyclic structures. Furthermore, its compatibility with the traditional Merrifield synthesis of peptides on solid supports allowed the incorporation of the previously unexplored conformationally restricted cyclic systems into peptides without a need to independently synthesize the scaffold.

INTRODUCTION

Natural products possess immense chemical diversity, biochemical specificity, and other molecular properties that make them an indispensable source of structural motifs for drug discovery.[1,2] Taking into account this important role, new synthetic routes have been developed to access natural product-like libraries via conventional or diversity-oriented synthesis (DOS). The DOS approach is aimed at exploring the natural-product-based chemical space that is currently unoccupied by conventional combinatorial chemistry. This challenge is addressed through the creation of structural diversity in terms of appendages, functional groups, stereochemistry, and molecular skeletons.[3−6] The use of sequential complexity-generating reactions that proceed from simple starting materials to diverse and structurally complex compounds is one of the most useful strategies and has been denoted as tandem reactions. Because of their high atom economy, greater selectivity, and ability to form multiple bonds in one-pot reactions, tandem or sequential processes have been used for the efficient synthesis of highly complex products.[7−9]

Medium-sized heterocyclic rings (seven- to nine-membered) are a particularly valuable class of scaffolds that can be found in the structures of numerous biologically active natural products and drugs as well as in key intermediates of a wide range of complex syntheses. These heterocycles are considered to be difficult to synthesize because of unfavorable enthalpies and entropies, especially in synthetic routes involving the direct closure of such rings; therefore, their synthesis remains a challenge for organic chemists.[10−12] Currently, several methodologies are available for their construction, including the direct cyclization of an acyclic precursor or ring expansion by fragmentation and rearrangement.[13−17] The use of tandem reactions leading to these challenging heterocyclic molecular scaffolds is an elegant strategy in both solution chemistry and solid-supported synthesis.[18,19]

In addition, a successful approach in the search for peptidomimetics relies on the synthesis of peptides containing conformational restrictions on their backbones and exhibiting

Received: August 27, 2014
Published: October 1, 2014

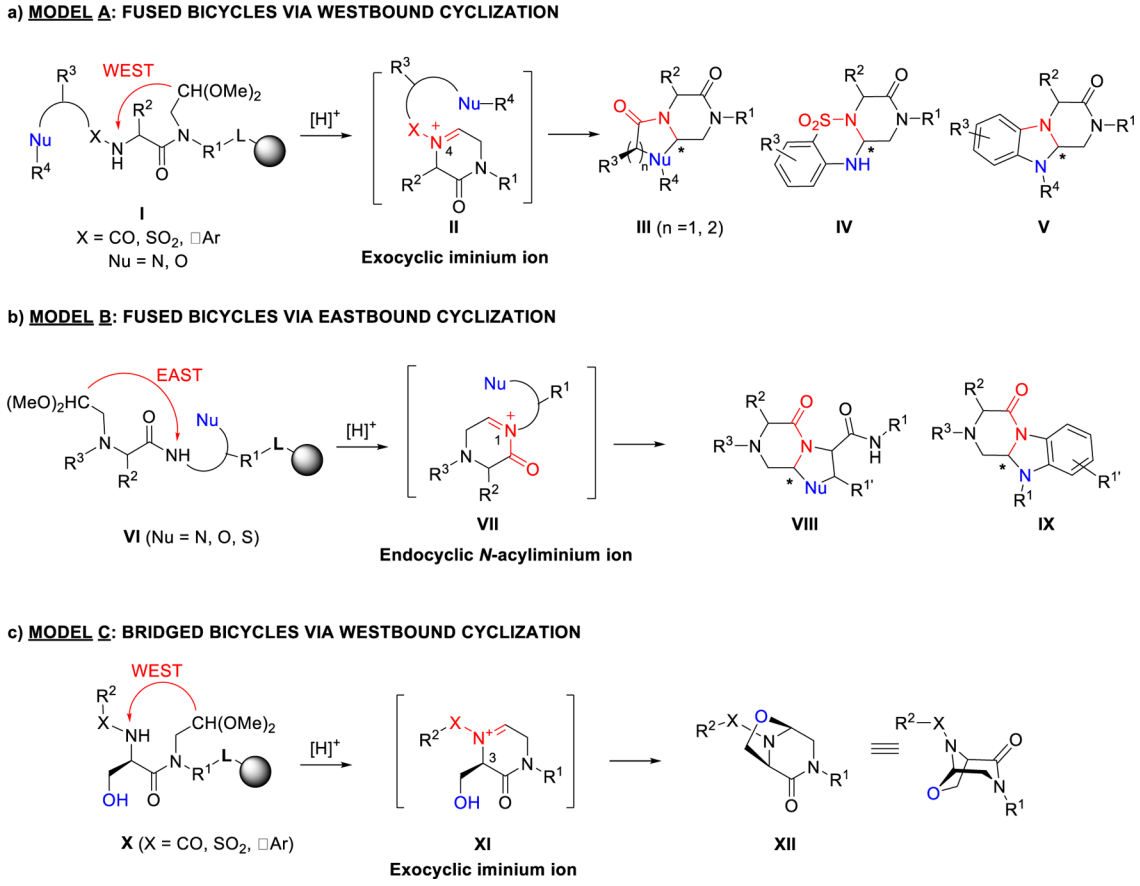


Figure 1. Reported synthetic methodology and structures of fused and bridged heterocycles via 6-membered cyclic iminium ions.

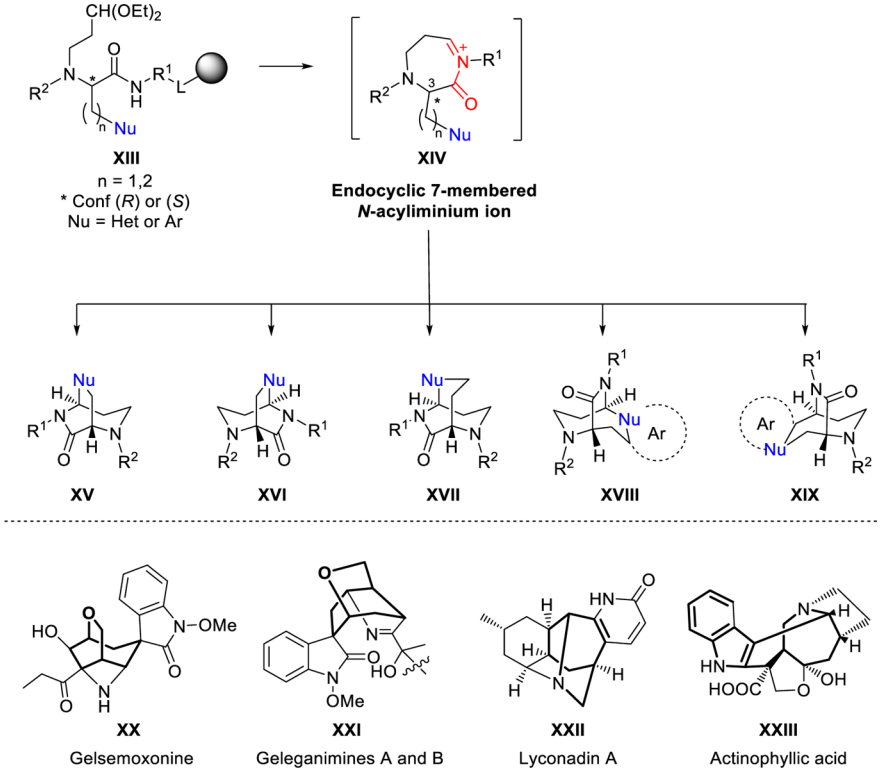
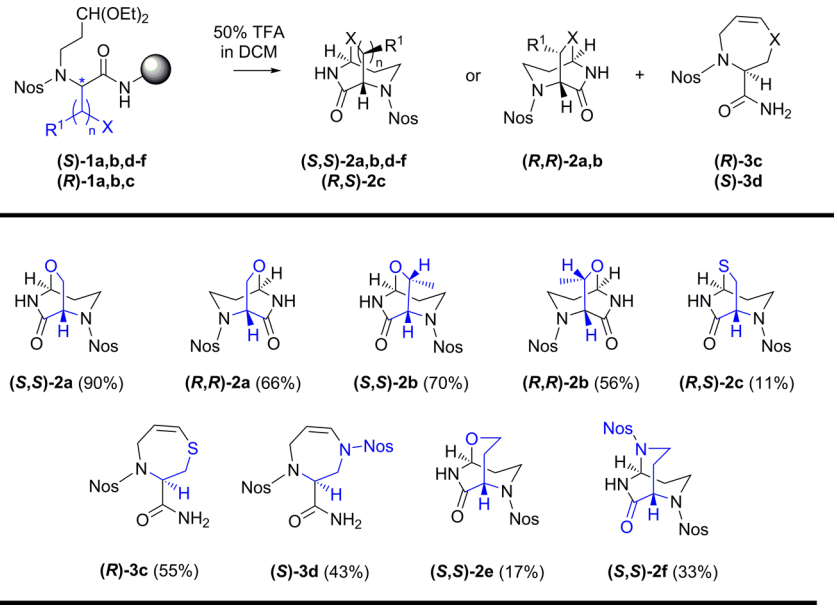


Figure 2. Bridged-designed scaffolds (**XV**–**XIX**) and representative natural products (**XX**–**XXIII**).

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378–10389

Scheme 1. Scope and Limitations of the Cyclization Reaction Using Heteroatom Nucleophiles



enhanced biological properties, which are related to their affinity and selectivity toward a given receptor. Such constrained moieties have commonly been achieved by the incorporation of ring systems into the peptide chain. In particular, the introduction of small- and medium-sized rings in a peptide sequence is intriguing because such rings are able to stabilize β-turn conformations, which are commonly found in bioactive peptides and are the most frequently occurring secondary structure in proteins.[20−22]

Our recent research has been focused on the synthesis of diverse fused and bridged bicyclic molecular scaffolds via tandem iminium-ion cyclization-nucleophilic addition on a solid support as the key chemical transformation (Figure 1). This efficient strategy encompassed the formation of 6-membered cyclic iminium ions (**II**, **VII**, and **XI**) from linear peptide-derived intermediates (**I**, **VI**, and **X**). The cyclic iminium ions were formed from a peptide amide and an aldehyde. The protected aldehyde was attached via a two-carbon spacer to an α-amino acid amino group. The formation of the fused or bridged bicycles depends on the location of the internal nucleophile in the iminium-ion intermediate. Fused bicycles (**III**−**V**, **VIII**, and **IX**) are formed when the internal nucleophile is attached via a spacer to the nitrogen involved in the iminium ion (*N*-position 1 or *N*-position 4 in models A and B, Figure 1a,b). In contrast, when the nucleophile is attached to position C-3 of the 6-membered cyclic iminium ion, the bridged systems (**XII**) are produced instead (model C, Figure 1c). The length of the spacer determines the size of the fused/bridged heterocycle. The complete regioselectivity of the reaction (via westbound or eastbound cyclization) is achieved by the appropriate choice of building blocks. Moreover, the formation of the new asymmetric carbon is generated with complete stereocontrol.[23−28]

The synthesis of medium-sized fused bicycles via iminium-ion chemistry has typically been used to form 5- or 6-membered cyclic *N*-acyliminium ion intermediates, followed by nucleophilic attack to close the second larger ring (from 5- to 8-membered rings).[29−31] However, the use of 7-membered *N*-acyliminium ion intermediates has been sparsely studied.[32−34] Therefore, we extended our ongoing research aimed at the chemistry of iminium ions and explored the scope and limitations of medium-sized cyclic iminium ions. In this research article, we report the synthesis of diverse bridged molecular scaffolds (**XV**-**XIX**) using seven-membered endocyclic *N*-acyliminium ions (**XIV**) as the key intermediates in a complexity-generating synthetic route that is compatible with the traditional Merrifield synthesis of peptides on solid supports (Figure 2). These bridged scaffolds possess complex 3D structures contained in several natural products such as gelsemoxonine (**XX**),[35] lyconadins (**XXI**),[36] and indol alkaloids such as geleganimine (**XXII**)[37] and actinophyllic acid (**XXIII**).[38]

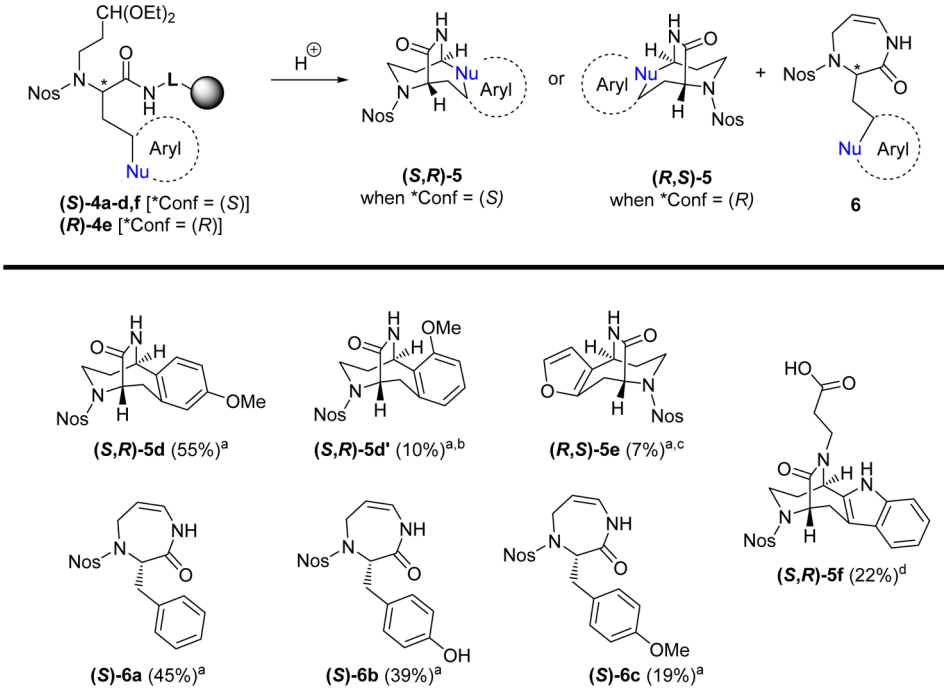
Target molecular scaffolds were prepared from acyclic precursors containing an acetal-protected aldehyde attached via a three-carbon spacer to an amide nitrogen and an internal nucleophile present on various amino acids (**XIII**, Figure 2). This internal nucleophile is connected to position C-3 of the *N*-acyliminium ion intermediate. The precursors have five points of diversification, including the following: nucleophile (heteroatom or aryl), length of the lateral chain and absolute configuration of the amino acid, R^1 substituents and R^2 substituents. All of these modifications provided diverse and complex structures prepared in a straightforward synthetic route from simple starting materials.

RESULTS AND DISCUSSION

All of the polymer-supported acyclic precursors were synthesized using standard solid-phase chemistry protocols and commercially available building blocks, as described in our previous reports.[23−28] Briefly, Rink amide[39] and Wang resins[40] were acylated with natural and non-natural Fmoc-α-amino acids containing N, O, or S nucleophiles in their lateral chains, such as Ser(*t*Bu), Thr(*t*Bu), Cys(Trt), HSer(Trt), Dap(Alloc), and Dab(Alloc). Removal of the Fmoc protecting group followed by activation with a 4-nitrobenzenesulfonyl (4-Nos) group led to resin-bound sulfonamides, which were subjected to the Mitsunobu reaction using 3,3-dietoxy-1-propanol as the masked aldehyde to obtain the desired linear precursors **1** (Scheme 1). The final acidic treatment of the supported acyclic compounds **1** triggered several reactions in one pot, including release from the resin, removal of the protecting groups (masked aldehyde and

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

Scheme 2. Scope and Limitations of Cyclization Reactions with Carbon Nucleophiles



[a]Treatment with 50% TFA in DCM, 2 h. [b]Minor isomer (7-OMe)-Ph due to steric hindrance. [c]Decomposed in acidic media. [d]Cleavage of the linear compound using 0.1 M NaOH in THF:MeOH (1:1), followed by purification of the linear precursor and finally overnight treatment with 50% TFA in DCM.

protected nucleophile) and formation of the endocyclic *N*-acyliminiun ion followed by internal nucleophilic addition, providing the target molecular scaffolds **2**.

C-Heteroatom Bond Formation. The acyclic intermediates derived from *t*Bu-protected L-Ser [(*S*)-**1a**] and D-Ser [(*R*)-**1a**] were selected as model compounds to study the tandem cyclizations and stereochemistry. After 2 h of treatment with 50% TFA, (1*S*,5*S*)-6-oxa-2,9-diazabicyclo[3.2.2]nonan-8-one [(*S*,*S*)-**2a**] and (1*R*,5*R*)-6-oxa-2,9-diazabicyclo[3.2.2]nonan-8-one [(*R*,*R*)-**2a**] were formed in excellent overall yields (90% and 66%, respectively). A new stereogenic center with a defined stereochemistry was generated, and its configuration depended exclusively on the stereochemistry of the amino acid present on the linear precursor. Whereas L-amino acids led to the (*S*)-configuration for the new stereocenter, D-amino acids promoted the opposite (*R*)-configuration. With the aim of studying the mechanism of the reaction, we conducted a kinetic study on the L-Ser linear model (*S*)-**1a**. Surprisingly, because the reaction was accomplished after 30 min of acid treatment, we hypothesized that the *t*-butyl protecting group was cleaved from the amino acid under the Mitsunobu conditions. We later confirmed this hypothesis using ^{1}H NMR spectrometry.

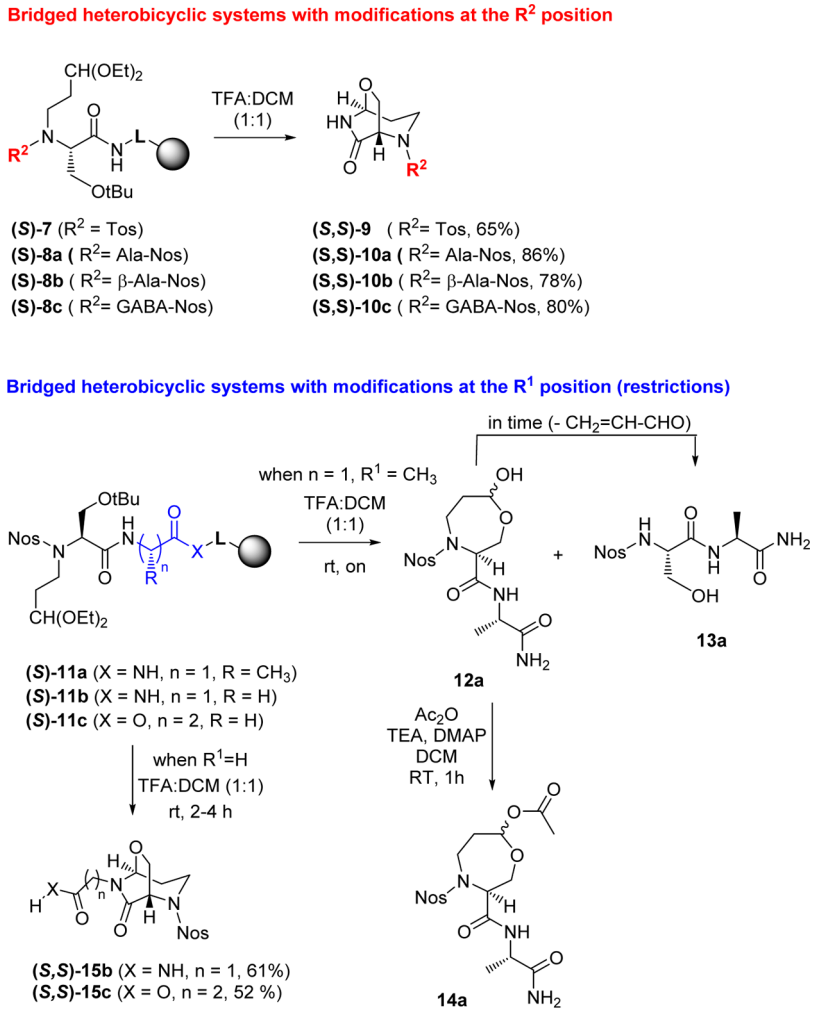
Encouraged by the smooth formation of bridged scaffolds by the Ser-derived model compounds, we addressed the scope and limitations of the acid-mediated cyclization of precursors derived from amino acids with different heteroatom nucleophiles, the stereochemistry at the α-carbon and the length of the lateral chain. Linear intermediates derived from L-Thr [(*S*)-**1b**] and D-Thr [(*R*)-**1b**] were treated with 50% TFA in DCM to give the corresponding bridged compounds (*S*,*S*)-**2b** and (*R*,*R*)-**2b** in good yields (70 and 56%, respectively). The S-nucleophile L-Cys precursor (*R*)-**1c** provided the corresponding (1*R*,5*S*)-6-thia-2,9-diazabicyclo[3.2.2]nonan-8-one [(*R*,*S*)-**2c**] in 11% yield, along with the alkene-derivative (*R*)-**3c** as the major product (55%). Similarly, the diaminopropionic acid (L-Dap) with its N-nucleophile protected/activated as Nos [(*S*)-**1d**] led to the enamide (*S*)-**3d** (43%) as the main product, because of competition between the formation of the *N*-sulfonyliminium and *N*-acyliminium ions, with both of them driving the formation of seven-membered rings. An increase in the length of the side chain to two carbons (n = 2) successfully provided (1*S*,5*S*)-6,9-diazabicyclo[3.3.2]decan-10-ones [(*S*,*S*)-**2e**] and [(*S*,*S*)-**2f**] with the generation of entirely new stereogenic centers with (*S*)-configurations. The L-HSer lineal precursor (*S*)-**1e** led to the corresponding bridged product (*S*,*S*)-**2e** in 17% yield, whereas the incorporation of Nos-protected diaminobutyric acid (L-Dab) yielded 2,6,9-triazabicyclo[3.3.2]decan-10-one [(*S*,*S*)-**2f**] as a single product (33%). In contrast to the case of Dap derivatives, the larger 8-membered *N*-sulfonyliminium ion is less favored, and the corresponding enamide (*S*)-**3f** was not observed.

The ^{1}H NMR spectra of compounds **2** and **3** showed the presence of the secondary amide as a doublet at 8.37−8.93 ppm and the proton on the new (bridged) stereogenic carbon as a multiplet at 4.67−5.21 ppm; the signals of this secondary amide and proton served as diagnostic signals for the bridged system. Accordingly, the ^{13}C NMR spectra showed the corresponding bridged carbons at 58.0−77.8 ppm.

C−C Bond Formation. Afterward, inspired by the *N*-acyliminium Pictet−Spengler reaction,[41−43] we synthesized Phe and Trp-derived linear intermediates [**4a**−**f**] to evaluate the formation of a new C−C bond during the formation of the second ring (Scheme 2). The polymer-supported substrates with an unsubstituted phenyl or with a phenyl with an electron-donating group in its *para* position as an internal nucleophile [(*S*)-**4a-c**] generated the corresponding 7-membered enamides [(*S*)-**6a-c**]. However, a different substitution pattern in the

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

Scheme 3. Incorporation of Amino Acids into the Amino (R^2) and Carboxy (R^1) Termini



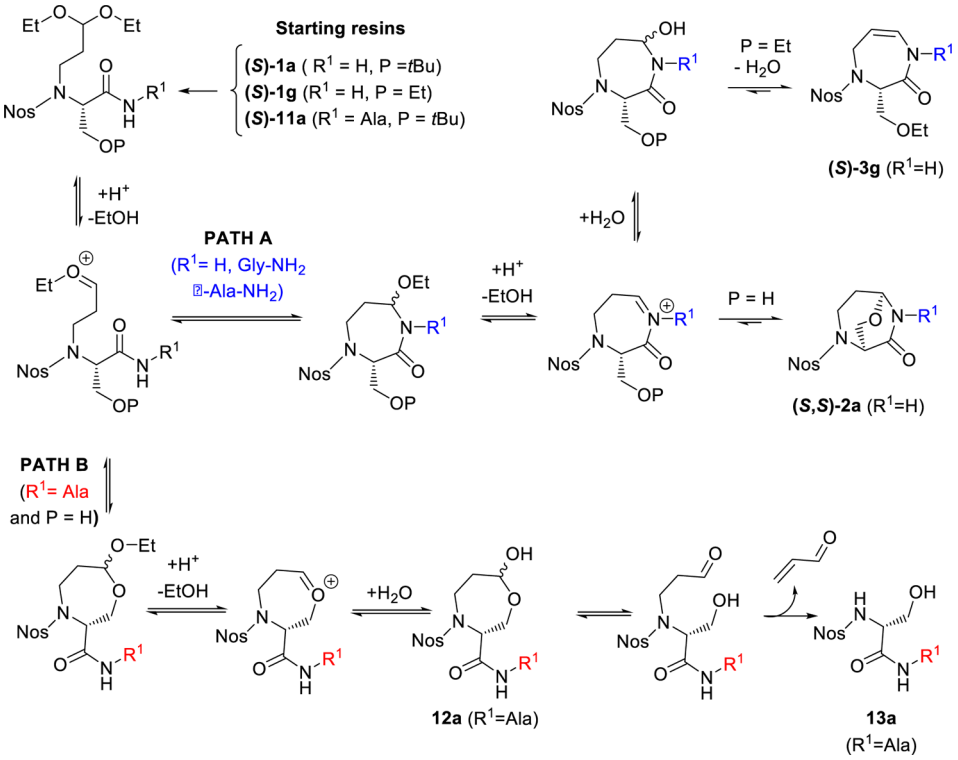
aromatic group of phenylalanine with an electron-donating group in the *meta* position [(*S*)-**4d**] enhanced the nucleophilicity of the phenyl ring and promoted closure of the second ring, leading to the corresponding mixture of the isomeric 1,2,3,4,5,6-hexahydro-6,2-(epiminomethano)benzo[*d*]azocin-12-ones [(*S*,*R*)-**5d** and (*S*,*R*)-**5d**′] in total yields of 55% and 10%, respectively. In this case, because two nonequivalent carbons were activated, two regioisomers were obtained, both with full stereocontrol of the nucleophilic attack. As expected, the major isomer (*S*,*R*)-**5d** contained the OMe group in the less sterically hindered position. Similarly, the more nucleophilic aromatic groups furyl and indolyl present in the lateral chain [(*R*)-**4e** and (*S*)-**4f**] achieved the bridged bicyclic products under acidic treatment with complete control of the stereoselectivity of the new chiral carbon. Unfortunately, because of the instability of furyl under acidic conditions, compound (*R*,*S*)-**5e** was obtained with a low yield (7%). In particular, the presence of Trp in the linear supported substrates required a base-labile linker and a modified procedure, which consisted of cleavage of the protected intermediate from the Wang resin using 0.5 M NaOH.[24] The isolation of the highly pure product and further treatment with 50% TFA in DCM led to the corresponding indolyl-bridged compound [(*S*,*R*)-**5f**].

Incorporation of the Constrained Scaffold into a Peptide Chain. Taking into account that the bridged compounds could be considered as a constrained mimetic of an amino acid, we focused on the incorporation of the bridged scaffolds into a peptide backbone. We first addressed the effect of the amino acids present at the amino terminus (R^2) and then at the carboxy terminus (R^1) (Scheme 3). Rink resin-bound model compounds with several modifications at the R^2 position, including a Tos group [(*S*)-**7**] and N-derivatized amino acids Nos-L-Ala, Nos-*β*-Ala and Nos-GABA [(*S*)-**8a-c**] were prepared. After being treated with acid, the bridged compounds (*S*,*S*)-**9** and (*S*,*S*)-**10a-c** were regioselectively obtained with good to excellent yields (65−86%). The ^{1}H NMR spectra of compounds (*S*,*S*)-**10a-c** showed the presence of the diagnostic signals for the bridged system, such as the secondary amide as a doublet at 8.95−9.09 ppm, the bridged proton as a multiplet at 5.04−5.13 ppm and the NH-Nosyl as a broad singlet at 8.04−8.50 ppm. Accordingly, the ^{13}C NMR spectra showed the corresponding bridged carbon at approximately 78.2 ppm, as previously described. In addition, in the cases where R^2 is a Nos-amino acid [(*S*,*S*)-**10a-c**], only one regioisomer was detected. This isomer was isolated and characterized, and was determined to exhibit the same eastbound directional preference due to the formation of the endocyclic *N*-acyliminium ion intermediate with the primary amide. It is worth to mention that we observed presence of cis:trans rotamers for all *N*-acyl derivatives.

Because of the complete regioselectivity of the eastbound cyclization with the second amino acid present at the R^2 position, we prepared simple precursors with modified R^1 moieties. We

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

Scheme 4. Proposed and Confirmed Mechanism for the Formation of Bridged Bicycles (Path A) and Lactol Derivatives (Path B)



incorporated different amino acids at the carboxy terminus [(*S*)-**11a-c**]. Gly and *β*-Ala present at the carboxy terminus facilitated the formation of the cyclic iminium ion, followed by the second annulation to efficiently yield the extended bicycles with exclusive stereochemistry [(*S,S*)-**15b,c**]. However, when L-Ala was incorporated as the first amino acid of the backbone and after overnight cleavage with 50% TFA, LC/MS analysis surprisingly revealed the formation of the lactol intermediate **12a** as the major product. After semipreparative HPLC purification in ammonium acetate buffer and lyophilization, the analysis of the ^{1}H NMR spectra of the purified compound showed a mixture of lactol **12a** (78%, anomer mixture = 71:29) along with the dipeptide **13a** (19%) and traces of acrolein (3.5%). This result could be due to the base-induced elimination of acrolein from the aldehyde, which is in equilibrium with the hemiacetals in aqueous solution.[44,45] Acetylation of lactol **12a** under standard conditions afforded the corresponding acetate derivative **14a** with very good yield, confirming the structure of the cyclic hemiacetal.[46] This unexpected result prompted a more detailed study of the mechanism of these tandem reactions promoted by TFA.

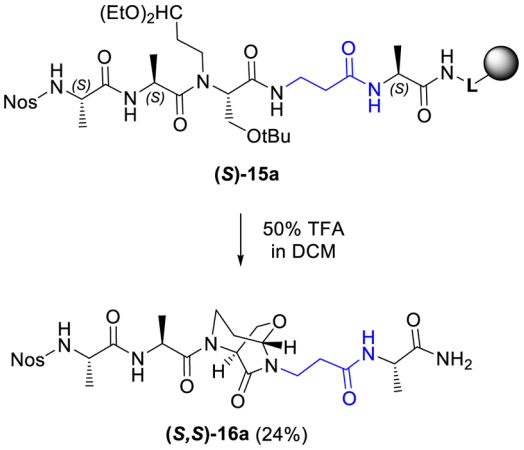
Mechanism. The time course of the cascade reaction was monitored on a simple model (*S*)-**1a** (R^1 = H) via LC/MS and ^{1}H NMR. The final bridged bicycle [(*S,S*)-**2a**] was detected by LC/MS as the main product after only 10 min of acid treatment, along with the ethoxy-group-containing intermediate, which completely disappeared after 90 min. NMR analysis revealed that the terminal amide was involved in the formation of this cyclic ethoxy intermediate, suggesting that it had been formed by the nucleophilic attack of the amide on the oxonium species formed during the acetal deprotection (path A, Scheme 4). This ethoxy intermediate can eliminate ethanol after protonation to give the *N*-acyliminium ion species, which, in turn, reacts with internal nucleophiles (P = H), thereby closing the second ring to give the expected bicycles [(*S,S*)-**2a**]. In the absence of an internal nucleophile (P = Et), another alternative is the formation of the more stable enamide [(*S*)-**3g**] via hemiazaacetals, as observed in the case of Ser(OEt) linear intermediates (*S*)-**1g**. Different models exhibited similar experimental evidence, suggesting that this mechanism is the main route of the formation of the bridged bicyclic system.

In contrast, an analogous study with the Ala-derived substrate (*S*)-**11a** (R^1 = Ala) pointed to an alternative mechanism (path B, Scheme 4). The cyclic ethoxy intermediates were formed from the oxonium species by ring closure with the free alcohol of Ser, which, as previously mentioned, had been deprotected under Mitsunobu conditions. This cyclic ethoxy acetal can be hydrolyzed to the corresponding lactol **12a**, which proved to be unstable because of the equilibrium with the lineal aldehyde that underwent dealkylation in basic media to give dipeptide **13a**, as previously described.[44,45] Fortunately, the acetylation of the lactol **12a** efficiently afforded the stable acetate derivative **14a** (Scheme 3), confirming the structure of the cyclic hemiacetals.[46]

Finally, we introduced a bridged heterobicycle during traditional Merrifield peptide synthesis to demonstrate the feasibility of this scaffold as a peptide backbone constraint and to gain insight into its potential significance as an inducer of peptide secondary structures (*β*-turns). Taking into account the restrictions previously detailed in Scheme 3, we designed a model pentapeptide derivative with the suggested incorporation of *β*-Ala as a neighboring amino acid of the Ser (shown in blue in Scheme 5). Therefore, a simple pentapeptide model (*S,S*)-**16a** (Nos-Ala-Ala-Bridged-bicycle-*β*-Ala-Ala-NH$_2$) was prepared in satisfactory yield from the lineal precursor (*S*)-**15a** after treatment with 50% TFA in DCM, with complete regioselectivity and with full control of the stereochemistry (Scheme 5).

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

Scheme 5. Synthesis of a Pentapeptide Derivative (*S,S*)-16a Containing an O-Bridged Bicycle



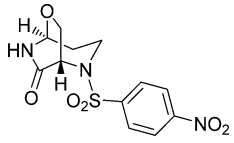
CONCLUSION

The synthesis of diverse medium-sized bridged molecular scaffolds via tandem reactions promoted by TFA with 7-membered endocyclic *N*-acyliminium ions as key intermediates was described. The complex heterocyclic compounds were synthesized with moderate to excellent total yields and with full stereocontrol of the newly generated asymmetric carbon from simple starting materials, whose syntheses were straightforward. This strategy enables the generation of 7- and 8-membered bridged-heterobicycles in addition to the possibility of variability in the heteroatom involved in the second cyclization, including N, O, and S. Furthermore, the use of electron-rich aromatic rings provided complex tri- and tetracycles via C−C bond formation. Additionally, the bridged heterocyclic scaffold was incorporated into the backbone of a model peptide, demonstrating the applicability of this synthetic strategy in the generation of larger molecules. Further work to explore the potential of these bridged molecular scaffolds as inductors of secondary structures is currently in progress.

EXPERIMENTAL SECTION

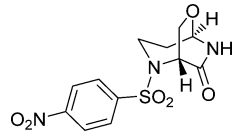
The solid-phase syntheses were performed in plastic reaction vessels (syringes, each equipped with a porous disc) using a manually operated synthesizer. The volume of the wash solvent was 10 mL per 1 g of resin. For washing, the resin slurry was shaken with fresh solvent for at least 1 min before changing the solvent. Commercially available Rink resin (100−200 mesh, 0.66 mmol/g) and Wang resin (100−200 mesh, 1.0 mmol/g) were used. The yields of the crude products were calculated with respect to the loading of the first building block. The reaction conditions for the individual steps of the synthesis have been reported in previous communications.[27,28]

Analytical Data of Individual Compounds. *(1S,5S)-2-((4-Nitrophenyl)sulfonyl)-6-oxa-2,9-diazabicyclo[3.2.2]nonan-8-one [**(S,S)-2a**].*



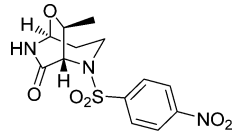
Yield 24.0 mg (90%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.94 (d, J = 4.4 Hz, 1 H), 8.42 (d, J = 9.2 Hz, 2 H), 8.11 (d, J = 8.8 Hz, 2 H), 5.06 (ddd, J = 5.5, 4.2, 3.1 Hz, 1 H), 4.42−4.46 (m, 1 H), 3.98−4.04 (m, 1 H), 3.92−3.97 (m, 1 H), 3.60 (dt, J = 12.9, 5.4 Hz, 1 H), 3.04 (ddd, J = 12.8, 8.2, 4.8 Hz, 1 H), 2.00−2.09 (m, 1 H), 1.89−1.98 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 164.4, 150.0, 143.2, 129.0, 124.6, 77.8, 66.2, 58.1, 40.8, 35.0. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}N_3NaO_6S$ [M + Na]$^+$ 350.0417, found 350.0428.

*(1R,5R)-2-((4-Nitrophenyl)sulfonyl)-6-oxa-2,9-diazabicyclo[3.2.2]nonan-8-one [**(R,R)-2a**].*



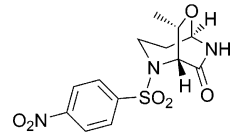
Yield 11 mg (66%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.92 (d, J = 3.9 Hz, 1 H), 8.40 (d, J = 9.2 Hz, 2 H), 8.10 (d, J = 9.2 Hz, 2 H), 5.08−5.02 (m, 1 H), 4.44−4.39 (m, 1 H), 3.99 (dd, J = 3.5, 11.5 Hz, 1 H), 3.93 (dd, J = 1.5, 11.9 Hz, 1 H), 3.58 (td, J = 5.4, 12.9 Hz, 1 H), 3.02 (ddd, J = 4.8, 8.3, 13.2 Hz, 1 H), 2.08−1.98 (m, 1 H), 1.96−1.86 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 164.4, 150.0, 143.2, 129.0, 124.6, 77.8, 66.1, 58.1, 40.8, 35.0. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{14}N_3O_6S$ [M + H]$^+$ 328.0598, found 328.0589.

*(1S,5S,7R)-7-Methyl-2-((4-nitrophenyl)sulfonyl)-6-oxa-2,9-diazabicyclo[3.2.2]nonan-8-one [**(S,S)-2b**].*



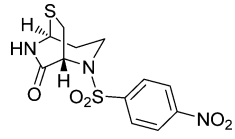
Yield 12 mg (70%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.83 (d, J = 3.9 Hz, 1 H), 8.42 (d, J = 9.2 Hz, 2 H), 8.09 (d, J = 9.2 Hz, 2 H), 5.02 (dt, J = 1.5, 5.2 Hz, 1 H), 4.28 (s, 1 H), 4.02 (dq, J = 3.1, 6.3 Hz, 1 H), 3.72−3.61 (m, 1 H), 2.55−2.41 (m, 1 H), 2.09−1.87 (m, 2 H), 1.19 (d, J = 6.1 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ(ppm) 164.7, 150.1, 142.6, 129.3, 124.6, 77.6, 70.5, 62.7, 40.4, 36.4, 18.0. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{16}N_3O_6S$ [M + H]$^+$ 342.0754, found 342.0720.

*(1R,5R,7S)-7-Methyl-2-((4-nitrophenyl)sulfonyl)-6-oxa-2,9-diazabicyclo[3.2.2]nonan-8-one [**(R,R)-2b**].*



Yield 11.3 mg (56%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.84 (d, J = 3.9 Hz, 1 H), 8.44 (d, J = 8.8 Hz, 2 H), 8.11 (d, J = 9.2 Hz, 2 H), 5.03 (td, J = 5.0, 1.3 Hz, 1 H), 4.30 (s, 1 H), 4.04 (qd, J = 6.3, 2.6 Hz, 1 H), 3.65−3.72 (m, 1 H), 2.46−2.54 (m, 1 H), 1.93−2.07 (m, 2 H), 1.21 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 164.7, 150.1, 142.6, 129.2, 124.6, 77.6, 70.5, 62.7, 40.4, 36.4, 17.9. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{16}N_3O_6S$ [M + H]$^+$ 342.0754, found 342.0767.

*(1R,5S)-2-((4-Nitrophenyl)sulfonyl)-6-thia-2,9-diazabicyclo[3.2.2]nonan-8-one [**(R,S)-2c**].*

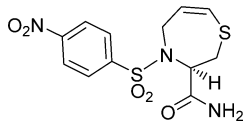


Yield 4.2 mg (11%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.93 (d, J = 7.5 Hz, 1 H), 8.42 (d, J = 8.8 Hz,

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

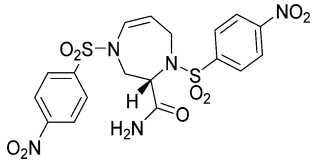
2 H), 8.12 (d, J = 8.8 Hz, 2 H), 4.70−4.78 (m, 2 H), 3.90 (dt, J = 13.8, 3.8 Hz, 1 H), 3.60 (ddd, J = 14.3, 9.0, 5.7 Hz, 1 H), 3.21 (dd, J = 13.6, 5.3 Hz, 1 H), 2.96 (dd, J = 13.6, 1.8 Hz, 1 H), 1.87−1.93 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 168.1, 150.0, 143.8, 128.7, 124.8, 58.0, 52.4, 42.4, 37.2, 27.6. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}N_3NaO_5S_2$ $[M + Na]^+$ 366.0189, found 366.0216

*(R)-4-((4-Nitrophenyl)sulfonyl)-2,3,4,5-tetrahydro-1,4-thiazepine-3-carboxamide [**(R)-3c**].*



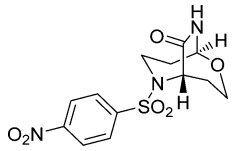
Yield 20.9 mg (55%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.35 (d, J = 9.2 Hz, 2 H), 8.04 (d, J = 9.2 Hz, 2 H), 7.52 (s, 1 H), 7.28 (s, 1 H), 5.86−5.94 (m, 1 H), 5.54−5.62 (m, 1 H), 4.63 (dd, J = 11.8, 4.8 Hz, 1 H), 4.44 (dt, J = 19.3, 2.6 Hz, 1 H), 4.35 (dd, J = 19.3, 6.1 Hz, 1 H), 3.36 (dd, J = 14.9, 11.8 Hz, 1 H), 3.08 (ddd, J = 14.9, 4.8, 0.9 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 170.5, 149.6, 145.2, 128.7, 124.0, 123.9, 123.2, 61.4, 43.0, 34.9. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}N_3NaO_5S_2$ $[M + Na]^+$ 366.0189, found 366.0218.

*1,4-bis((4-Nitrophenyl)sulfonyl)-2,3,4,7-tetrahydro-1H-1,4-diazepine-2-carboxamide [**(S)-3d**].*



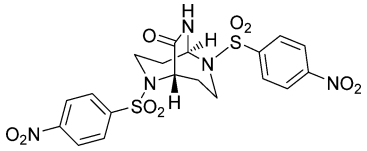
Yield 9 mg (43%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.35 (d, J = 8.8 Hz, 2 H), 8.34 (d, J = 9.2 Hz, 2 H), 8.06 (d, J = 8.8 Hz, 2 H), 8.02 (d, J = 9.2 Hz, 2 H), 7.82 (s, 1 H), 7.40 (s, 1 H), 6.22 (d, J = 8.8 Hz, 1 H), 4.87 (ddd, J = 3.9, 5.3, 8.8 Hz, 1 H), 4.57 (dd, J = 5.5, 11.6 Hz, 1 H), 4.30 (d, J = 3.9 Hz, 2 H), 4.01 (dd, J = 5.7, 14.9 Hz, 1 H), 3.45 (dd, J = 11.4, 14.9 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 169.2, 150.2, 149.7, 144.7, 143.0, 128.9, 128.7, 128.4, 124.9, 124.3, 108.6, 59.2, 49.7, 42.0. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}N_5O_9S_2$ $[M + H]^+$ 512.0546, found 512.0587.

*(1S,5S)-6-((4-Nitrophenyl)sulfonyl)-2-oxa-6,9-diazabicyclo[3.3.2]decan-10-one [**(S,S)-2e**].*



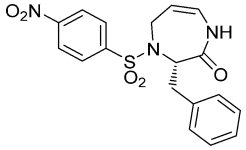
Yield 4.0 mg (17%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.60 (d, J = 5.7 Hz, 1 H), 8.43 (d, J = 8.8 Hz, 2 H), 8.11 (d, J = 8.8 Hz, 2 H), 4.82 (td, J = 6.4, 2.6 Hz, 1 H), 4.44 (td, J = 4.5, 1.5 Hz, 1 H), 3.98−4.06 (m, 1 H), 3.75−3.82 (m, 1 H), 3.58−3.66 (m, 1 H), 3.09 (ddd, J = 13.4, 9.0, 3.9 Hz, 1 H), 2.14−2.23 (m, 1 H), 1.88−1.98 (m, 2 H), 1.71 (ddt, J = 15.1, 6.6, 4.1 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 170.4, 150.0, 143.5, 128.7, 124.8, 75.9, 61.4, 58.7, 41.4, 31.7, 29.8. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{15}N_3NaO_6S$ $[M + Na]^+$ 364.0574, found 364.0571.

*(1S,5S)-2,6-Bis((4-nitrophenyl)sulfonyl)-2,6,9-triazabicyclo-[3.3.2]decan-10-one [**(S,S)-2f**].*



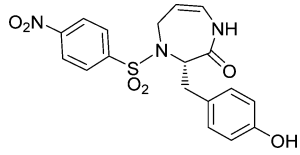
Yield 7.2 mg (33%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.67−8.62 (m, 1 H), 8.39 (d, J = 8.8 Hz, 2 H), 8.37 (d, J = 9.2 Hz, 2 H), 8.08 (d, J = 8.8 Hz, 2 H), 8.07 (d, J = 9.2 Hz, 2 H), 5.22 (dt, J = 3.1, 7.0 Hz, 1 H), 4.40 (t, J = 4.2 Hz, 1 H), 3.78−3.56 (m, 2 H), 3.29−3.09 (m, 2 H), 2.23−2.09 (m, 1 H), 2.04−1.93 (m, 1 H), 1.80−1.68 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 169.7, 150.0, 143.9, 143.2, 128.7, 124.8, 124.8, 60.7, 60.5, 41.3, 39.8 (hide in the DMSO signal), 33.0, 27.5. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{20}N_5O_9S_2$ $[M + H]^+$ 526.0697, found 526.0702.

*(S)-3-Benzyl-4-((4-nitrophenyl)sulfonyl)-1,3,4,5-tetrahydro-2H-1,4-diazepin-2-one [**(S)-6a**].*



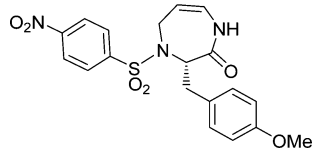
Yield 13 mg (45%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.93 (d, J = 6.1 Hz, 1 H), 8.25 (d, J = 9.2 Hz, 2 H), 7.84 (d, J = 9.2 Hz, 2 H), 7.21−7.14 (m, 5 H), 5.54 (tdd, J = 1.8, 6.1, 10.5 Hz, 1 H), 4.87 (ddd, J = 2.2, 4.6, 10.5 Hz, 1 H), 4.70 (dd, J = 6.1, 10.1 Hz, 1 H), 4.31 (dd, J = 4.4, 19.7 Hz, 1 H), 3.87 (td, J = 2.2, 19.7 Hz, 1 H), 3.04 (dd, J = 6.6, 14.6 Hz, 1 H), 3.02 (dd, J = 10.5, 14.6 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 171.6, 149.7, 144.1, 135.7, 128.7, 128.4, 126.7, 124.2, 122.2, 107.6, 63.0, 52.2, 43.1, 33.2. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}N_3O_5S$ $[M + H]^+$ 388.0967, found 388.0992.

*(S)-3-(4-Hydroxybenzyl)-4-((4-nitrophenyl)sulfonyl)-1,3,4,5-tetrahydro-2H-1,4-diazepin-2-one [**(S)-6b**].*



Yield 12.0 mg (39%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.27 (s, 1 H), 8.94 (d, J = 6.1 Hz, 1 H), 8.26 (d, J = 9.2 Hz, 2 H), 7.82 (d, J = 8.8 Hz, 2 H), 6.93 (d, J = 8.8 Hz, 2 H), 6.55 (d, J = 8.8 Hz, 2 H), 5.57 (ddt, J = 10.3, 6.1, 2.2 Hz, 1 H), 4.89 (ddd, J = 10.4, 4.8, 2.2 Hz, 1 H), 4.63 (dd, J = 10.3, 5.9 Hz, 1 H), 4.33 (dd, J = 19.7, 4.8 Hz, 1 H), 3.86 (dt, J = 19.3, 2.2 Hz, 1 H), 2.94 (dd, J = 14.5, 6.1 Hz, 1 H), 2.87 (dd, J = 14.5, 10.3 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 171.9, 156.3, 149.5, 144.3, 129.6, 128.3, 125.4, 124.2, 122.2, 115.2, 107.6, 63.4, 42.8, 32.4. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{17}N_3NaO_6S$ $[M + Na]^+$ 426.0730, found 426.0722.

*(S)-3-(4-Methoxybenzyl)-4-((4-nitrophenyl)sulfonyl)-1,3,4,5-tetrahydro-2H-1,4-diazepin-2-one [**(S)-6c**].*

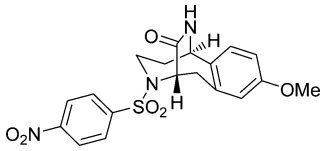


Yield 4.7 mg (19%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.97 (d, J = 6.1 Hz, 1 H), 8.25 (d, J = 8.8 Hz,

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

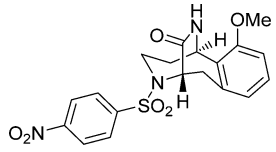
2 H), 7.82 (d, J = 8.8 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 6.71 (d, J = 8.3 Hz, 2 H), 5.59 (ddt, J = 10.1, 6.1, 1.9 Hz, 1 H), 4.91 (ddd, J = 10.1, 4.6, 2.2, 1 H), 4.64 (dd, J = 9.9, 6.4 Hz, 1 H), 4.35 (dd, J = 19.5, 4.6 Hz, 1 H), 3.89 (dt, J = 19.3, 2.2 Hz, 1 H), 3.68 (s, 3 H), 2.99 (dd, J = 14.6, 6.1 Hz, 1 H), 2.94 (dd, J = 14.9, 10.1 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm)171.9, 158.0, 149.5, 144.3, 129.7, 128.3, 127.3, 124.2, 122.2, 113.7, 107.7, 63.4, 54.9, 42.9, 32.3. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{19}N_3NaO_6S$ $[M + Na]^+$ 440.0887, found 440.0856.

*(2S,6R)-9-Methoxy-3-((4-nitrophenyl)sulfonyl)-1,2,3,4,5,6-hexahydro-6,2-(epiminomethano)benzo[d]azocin-12-one [**(S,R)-5d**].*



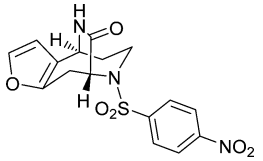
Yield 11.5 mg (55%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.39−8.45 (m, 3 H), 8.12 (d, J = 9.2 Hz, 2 H), 7.04 (d, J = 8.3 Hz, 1 H), 6.67−6.72 (m, 2 H), 4.67−4.72 (m, 1 H), 4.27 (ddd, J = 7.5, 5.3, 2.2 Hz, 1 H), 3.90−3.98 (m, 1 H), 3.68 (s, 3 H), 3.44 (dd, J = 19.3, 5.7 Hz, 1 H), 3.08 (ddd, J = 15.0, 12.6, 2.6 Hz, 1 H), 2.91 (dd, J = 19.5, 2.9 Hz, 1 H), 1.80−1.89 (m, 1 H), 1.69−1.77 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 171.3, 158.2, 149.9, 145.1, 137.1, 129.9, 128.7, 128.5, 124.8, 115.0, 112.1, 59.8, 55.0, 52.3, 40.5, 35.1, 32.0. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{20}N_3O_6S$ $[M + H]^+$ 418.1067, found 418.1057.

*(2S,6R)-7-Methoxy-3-((4-nitrophenyl)sulfonyl)-1,2,3,4,5,6-hexahydro-6,2-(epiminomethano)benzo[d]azocin-12-one [**(S,R)-5d′**].*



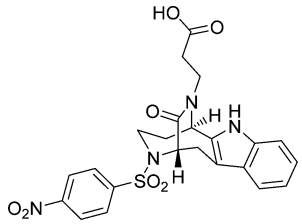
Yield 2.1 mg (10%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.41 (d, J = 9.2 Hz, 2 H), 8.33 (dd, J = 7.7, 1.5 Hz, 1 H), 8.12 (d, J = 8.8 Hz, 2 H), 7.15 (t, J = 8.1 Hz, 1 H), 6.82 (d, J = 7.9 Hz, 1 H), 6.71 (d, J = 7.9 Hz, 1 H), 4.96 (ddd, J = 7.8, 5.2, 2.9 Hz, 1 H), 4.65−4.69 (m, 1 H), 3.92 (dt, J = 14.7, 3.0 Hz, 1 H), 3.48 (dd, J = 19.5, 5.5 Hz, 1 H), 3.05 (ddd, J = 14.8, 12.6, 2.4 Hz, 1 H), 2.90 (dd, J = 19.7, 3.1 Hz, 1 H), 1.81−1.90 (m, 1 H), 1.61−1.68 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 171.6, 154.9, 149.9, 145.0, 137.4, 128.5, 127.9, 124.8, 124.8, 122.3, 108.4, 59.6, 55.8, 43.1, 41.0, 33.3, 31.9. HRMS (ESI-TOF) m/z calcd for $C_{19}H_{20}N_3O_6S$ $[M + H]^+$ 418.1067, found 418.1043.

*(4S,8R)-7-((4-Nitrophenyl)sulfonyl)-4,5,6,7,8,9-hexahydro-4,8-(epiminomethano)furo[2,3-d]azocin-10-one [**(R,S)-5e**].*



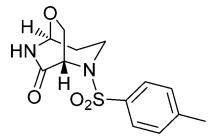
Yield 1.9 mg (7%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.37−8.43 (m, 3 H), 8.12 (d, J = 8.8 Hz, 2 H), 7.47 (d, J = 1.8 Hz, 1 H), 6.33 (d, J = 1.8 Hz, 1 H), 4.85−4.89 (m, 1 H), 4.20 (ddd, J = 7.3, 4.9, 2.6 Hz, 1 H), 3.96 (dt, J = 15.0, 3.2 Hz, 1 H), 3.27−3.34 (m, 1 H overlapped with water), 3.19 (ddd, J = 15.1, 12.3, 2.9 Hz, 1 H), 2.78 (dd, J = 18.9, 2.6 Hz, 1 H), 1.75−1.86 (m, 1 H), 1.63 (ddt, J = 14.3, 5.0, 2.6 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 171.7, 149.9, 148.3, 144.9, 141.0, 128.5, 124.8, 119.8, 110.1, 58.8, 44.6, 40.7, 32.9, 26.7. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{16}N_3O_6S$ $[M + H]^+$ 378.0754, found 378.0743.

*(2S,6R)-3-((4-Nitrophenyl)sulfonyl)-2,3,4,5,6,7-hexahydro-1H-6,2-(epiminomethano) azocino[5,4-b]indol-13-one [**(S,R)-5f**].*



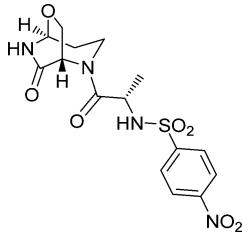
Yield 4.4 mg (22%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6)) δ (ppm) 10.92 (s, 1 H), 8.40 (d, J = 9.2 Hz, 2 H), 8.08 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 7.9 Hz, 1 H), 7.28 (d, J = 7.9 Hz, 1 H), 7.05 (t, J = 7.9 Hz, 1 H), 6.95 (t, J = 7.9 Hz, 1 H), 5.07 (dd, J = 2.0, 5.9 Hz, 1 H), 4.75 (dd, J = 2.4, 5.0 Hz, 1 H), 3.96 (d, J = 14.9 Hz, 1 H), 3.52−3.19 (m, 4 H, below water signal), 2.87 (dd, J = 2.4, 18.2 Hz, 1 H), 2.11−2.04 (m, 2 H), 2.00−1.90 (m, 1 H), 1.77−1.66 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 172.7, 170.3, 149.9, 145.3, 134.4, 132.4, 128.5, 127.2, 124.8, 121.6, 118.8, 117.9, 111.3, 107.4, 60.3, 54.2, 45.3, 40.7, 32.7, 32.1, 24.7. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{22}N_4O_7S$ $[M + H]^+$ 499.1287, found 499.1281.

*((1S,5S)-2-Tosyl-6-oxa-2,9-diazabicyclo[3.2.2]nonan-8-one [**(S,S)-9**].*



Yield 12.3 mg (65%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (d, J = 4.4 Hz, 1 H), 7.71 (d, J = 8.3 Hz, 2 H), 7.42 (d, J = 7.9 Hz, 2 H), 5.02−5.06 (m, 1 H), 4.37−4.40 (m, 1 H), 3.96 (dd, J = 11.4, 3.5 Hz, 1 H), 3.84 (dd, J = 11.6, 1.1 Hz, 1 H), 3.46 (dt, J = 12.7, 5.5 Hz, 1 H), 2.93 (ddd, J = 13.0, 8.4, 4.8 Hz, 1 H), 2.40 (s, 3 H), 1.96−2.06 (m, 1 H), 1.86−1.94 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 164.7, 143.6, 134.8, 129.8, 127.3, 77.8, 66.2, 58.1, 40.5, 35.1, 21.0. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{17}N_2O_4S$ $[M + H]^+$ 297.0904, found 297.0926.

*4-Nitro-N-((S)-1-oxo-1-((1S,5S)-8-oxo-6-oxa-2,9-diazabicyclo[3.2.2]nonan-2-yl)propan-2-yl)benzenesulfonamide [**(S,S)-10a**].*

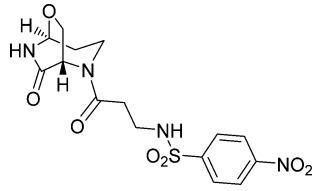


Yield 14 mg (86%) of amorphous solid. Rotamers cis/trans = 30:70. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) *Trans rotamer*: 8.98 (dd, J = 1.4, 5.3 Hz, 1 H), 8.50 (br. s., 1 H), 8.37 (d, J = 9.0 Hz, 2 H), 8.02 (d, J = 9.0 Hz, 2 H), 5.18−5.00 (m, 1 H), 4.48 (q, J = 7.0 Hz, 1 H), 4.46−4.43 (m, 1 H), 3.88 (td, J = 4.1, 14.5 Hz, 1 H), 3.68 (dd, J = 2.9, 11.2 Hz, 1 H), 3.37 (dd, J = 1.2, 10.5 Hz, 1

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

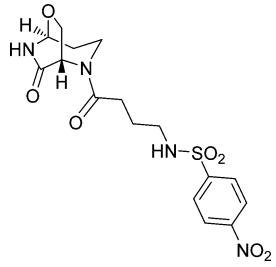
H), 3.17−3.03 (m, 1 H), 1.95−1.87 (m, 2 H), 1.09 (d, J = 6.7 Hz, 3 H). Cis rotamer: 9.09 (d, J = 4.3 Hz, 1 H), 8.50 (br. s., 1 H), 8.31 (d, J = 8.6 Hz, 2 H), 7.98 (d, J = 9.0 Hz, 2 H), 5.12−5.05 (m, 1 H), 4.58 (q, J = 7.1 Hz, 1 H), 4.35−4.32 (m, 1 H), 4.24 (d, J = 11.7 Hz, 1 H), 4.00 (dd, J = 3.5, 11.7 Hz, 1 H), 3.58 (td, J = 5.0, 13.8 Hz, 1 H), 3.30−3.19 (m, 1 H), 1.87−1.77 (m, 1 H), 1.42−1.27 (m, 1 H), 1.17 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) Trans rotamer: 169.4, 165.9, 149.5, 146.7, 128.2, 124.4, 78.2, 64.8, 56.5, 49.0, 40.5, 36.5, 18.6. Cis rotamer: 170.0, 166.8, 149.4, 146.2, 128.5, 124.0, 77.9, 64.9, 56.3, 49.2, 40.6, 36.6, 19.3. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{18}N_4NaO_7S$ [M + Na]$^+$ 421.0788, found 421.0778.

*4-Nitro-N-(3-oxo-3-((1S,5S)-8-oxo-6-oxa-2,9-diazabicyclo-[3.2.2]nonan-2-yl)propyl) benzenesulfonamide [**(S,S)-10b**].*



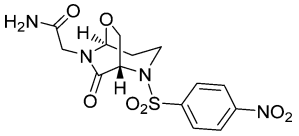
Yield 14.0 mg (78%) of amorphous solid. Rotamers cis/trans = 40:60. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) Trans rotamer: 8.97 (d, J = 3.9 Hz, 1 H), 8.40 (d, J = 8.8 Hz, 2 H), 8.04 (d, J = 9.2 Hz, 2 H), 8.21−7.86 (m, 1 H), 5.14−5.05 (m, 1 H), 4.74 (d, J = 1.8 Hz, 1 H), 3.87−3.85 (m, 3 H), 3.14 (ddd, J = 5.3, 9.2, 14.5 Hz, 1 H), 3.07−2.97 (m, 2 H), 2.70−2.54 (m, 2 H), 1.98−1.90 (m, 2 H). Cis rotamer: 8.95−8.90 (m, 1 H), 8.40 (d, J = 8.8 Hz, 2 H), 8.03 (d, J = 9.2 Hz, 2 H), 8.21−7.86 (m, 1 H), 5.14−5.05 (m, 1 H), 4.39−4.31 (m, 1 H), 4.23 (d, J = 11.8 Hz, 1 H), 3.97 (dd, J = 3.5, 11.8 Hz, 1 H), 3.92−3.80 (m, 1 H), 3.49 (ddd, J = 4.8, 9.3, 14.4 Hz, 1 H), 3.07−2.97 (m, 2 H), 2.70−2.54 (m, 2 H), 1.98−1.90 (m, 1 H), 1.76−1.62 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) Trans rotamer: 168.7, 166.1, 149.6, 146.0, 128.1, 124.6, 78.2, 65.5, 55.5, 38.8, 36.0, 34.9, 33.1. Cis rotamer: 169.1, 167.1, 149.6, 146.0, 128.1, 124.6, 78.1, 64.9, 56.6, 38.8, 36.1, 34.9, 33.3. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{18}N_4NaO_7S$ [M + Na]$^+$ 421.0788, found 421.0770.

*4-Nitro-N-(4-oxo-4-((1S,5S)-8-oxo-6-oxa-2,9-diazabicyclo-[3.2.2]nonan-2-yl)butyl) benzenesulfonamide [**(S,S)-10c**.*



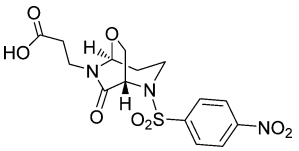
Yield 24.0 mg (80%) of amorphous solid. Rotamers cis/trans = 40:60. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) Trans rotamer: 8.95 (d, J = 3.1 Hz, 1H), 8.41 (d, J = 9.2 Hz, 2 H), 8.02 (d, J = 8.8 Hz, 2 H), 8.09−7.87 (m, 1 H), 5.13−5.04 (m, 1 H), 4.75 (d, J = 2.2 Hz, 1 H), 3.84 (d, J = 2.2 Hz, 1 H), 3.80−3.66 (m, 2 H), 3.14 (ddd, J = 5.7, 8.9, 14.4 Hz, 1 H), 2.82 (q, J = 7.0 Hz, 2 H), 2.44−2.30 (m, 2 H), 1.99−1.91 (m, 2 H),1.65−1.53 (m, 2 H). Cis rotamer: 8.95 (d, J = 3.1 Hz, 1H), 8.40 (d, J = 9.2 Hz, 2 H), 8.02 (d, J = 8.8 Hz, 2 H), 8.09−7.87 (m, 1 H), 5.13−5.04 (m, 1 H), 4.41−4.32 (m, 1 H), 4.21 (d, J = 11.4 Hz, 1 H), 3.97 (dd, J = 3.5, 11.8 Hz, 1 H), 3.80−3.66 (m, 1 H), 3.58 (ddd, J = 5.0, 8.7, 13.9 Hz, 1 H), 2.82 (q, J = 7.0 Hz, 2 H), 2.44−2.30 (m, 2 H), 1.99−1.91 (m, 1 H),1.78−1.66 (m, 1 H), 1.65−1.53 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) Trans rotamer: 170.3, 166.3, 149.5, 146.1, 128.1, 124.6, 78.2, 65.5, 55.5, 42.1, 36.1, 35.0, 29.6, 24.7. Cis rotamer: 170.7, 167.0, 149.5, 146.1, 128.1, 124.6, 78.1, 65.2, 56.8, 42.2, 36.0, 35.0, 29.6, 24.7. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{20}N_4O_7S$ [M + H]$^+$ 413.1131, found 413.1125.

*2-((1S,5S)-2-((4-Nitrophenyl)sulfonyl)-8-oxo-6-oxa-2,9-diazabicyclo[3.2.2]nonan-9-yl)acetic acid [**(S,S)-15b**].*



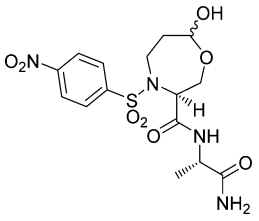
Yield 15 mg (61%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.39 (d, J = 8.8 Hz, 2 H), 8.09 (d, J = 8.8 Hz, 2 H), 7.35 (s, 1 H), 6.99 (s, 1 H), 5.21 (dd, J = 2.4, 4.6 Hz, 1 H), 4.56 (dd, J = 0.9, 3.6 Hz, 1 H), 4.05 (d, J = 16.7 Hz, 1 H), 4.03 (dd, J = 3.6, 11.4 Hz, 1 H), 3.94 (dd, J = 0.9, 11.4 Hz, 1 H), 3.72 (d, J = 16.7 Hz, 1 H), 3.59 (td, J = 5.3, 13.0 Hz, 1 H), 3.17 (ddd, J = 4.6, 8.7, 13.0 Hz, 1 H), 2.27 (qd, J = 4.8, 14.5 Hz, 1 H), 2.01−1.91 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 169.2, 163.3, 150.0, 143.3, 128.9, 124.6, 84.4, 66.6, 57.6, 47.5, 40.6, 33.8. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{16}N_4NaO_7S$ [M + Na]$^+$ 407.0637, found 407.0618.

*3-((1S,5S)-2-((4-Nitrophenyl)sulfonyl)-8-oxo-6-oxa-2,9-diazabicyclo[3.2.2]nonan-9-yl) propanoic acid [**(S,S)-15c**].*



Yield 12 mg (52%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.40 (d, J = 8.8 Hz, 2 H), 8.08 (d, J = 8.8 Hz, 2 H), 5.27 (t, J = 3.5 Hz, 1 H), 4.55−4.50 (m, 1 H), 4.00−3.96 (m, 2 H), 3.58 (td, J = 5.7, 13.2 Hz, 1 H), 3.41 (td, J = 7.0, 14.0 Hz, 1 H), 3.32 (td, J = 7.0, 14.0 Hz, 1 H), 3.03 (td, J = 6.9, 13.5 Hz, 1 H), 2.25 (t, J = 7.0 Hz, 2 H), 2.02−1.95 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 172.5, 163.2, 150.0, 143.3, 129.0, 124.6, 83.8, 66.2, 57.4, 41.0, 40.7, 33.6, 32.6. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{17}N_3NaO_8S$ [M + Na]$^+$ 422.0629, found 422.0635.

*(3S,7S)-N-((S)-1-Amino-1-oxopropan-2-yl)-7-hydroxy-4-((4-nitrophenyl)sulfonyl)-1,4-oxazepane-3-carboxamide [**12a**].*

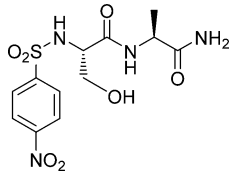


Yield 28 mg (42%) of amorphous solid. Crude purity = 69%. RT = 2.50 min, Mixture of anomers (78%), dealkylated product (18.5%), and acrolein (3.5%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) Major anomer: (71%) 8.37 (d, J = 9.2 Hz, 2 H), 8.12 (d, J = 7.0 Hz, 1 H), 8.01 (d, J = 9.2 Hz, 2 H), 7.19 (br. s., 1 H), 6.99 (br. s., 1 H), 6.38 (d, J = 4.8 Hz, 1 H), 4.81 (td, J = 4.8, 8.8 Hz, 1 H), 4.66 (dd, J = 4.0, 6.4 Hz, 1 H), 4.05 (quin, J = 7.0 Hz, 1 H), 3.99 (dd, J = 4.0, 13.8 Hz, 1 H), 3.74 (dd, J = 6.4, 13.8 Hz, 1 H), 3.71−3.64 (m, 1 H), 3.53 (dd, J = 11.2, 14.5 Hz, 1 H), 2.01−1.92 (m, 1 H), 1.61−1.48 (m, 1 H), 1.15 (d, J = 7.0 Hz, 3 H) Minor anomer: (29%) 8.39−8.33 (m, 2 H), 8.23 (d, J = 7.5 Hz, 1 H), 8.04−7.99 (m, 2 H), 7.24 (br. s., 1 H), 6.94 (br. s., 1 H),

dx.doi.org/10.1021/jo501983j | J. Org. Chem. 2014, 79, 10378−10389

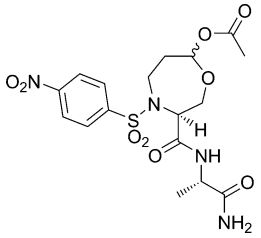
6.44 (d, J = 4.4 Hz, 1 H), 4.99 (td, J = 3.0, 4.4 Hz, 1 H), 4.63 (dd, J = 5.5, 9.6 Hz, 1 H), 4.15 (dd, J = 9.6, 13.6 Hz, 1 H), 3.88 (quin, J = 7.0 Hz, 1 H), 3.70−3.65 (m, 2 H), 3.58 (dd, J = 5.5, 13.6 Hz, 1 H), 1.72−1.65 (m, 2 H), 1.14 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) Major anomer: 173.8, 167.7, 149.6, 145.5, 128.4, 124.4, 96.2, 62.4, 59.9, 47.9, 40.4, 37.1, 18.5. Minor anomer: 173.8, 167.7, 149.6, 145.5, 128.5, 124.4, 92.2, 60.5, 58.9, 48.0, 41.1, 37.6, 18.2. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{21}N_4O_8S$ $[M + H]^+$ 417.1075, found 417.1079.

*(S)-N-((S)-1-Amino-1-oxopropan-2-yl)-3-hydroxy-2-((4-nitrophenyl)sulfonamido) propanamide [**13a**].*



^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.32 (d, J = 9.2 Hz, 2 H), 8.13 (d, J = 7.5 Hz, 1 H), 7.98 (d, J = 8.8 Hz, 2 H), 7.19 (s, 1 H), 7.02 (s, 1 H), 3.92 (quin, J = 7.2 Hz, 1 H), 3.77 (t, J = 6.4 Hz, 1 H), 3.39 (d, J = 6.6 Hz, 3 H), 1.06 (d, J = 7.5 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 174.1, 168.2, 149.4, 146.9, 128.2, 124.1, 62.5, 58.6, 48.8, 21.2. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{17}N_4O_7S$ $[M + H]^+$ 361.0812, found 361.0808.

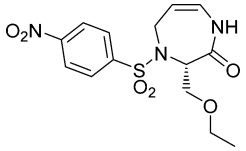
*(3S)-3-(((S)-1-Amino-1-oxopropan-2-yl)carbamoyl)-4-((4-nitrophenyl)sulfonyl)-1,4-oxazepan-7-yl acetate [**14a**].*



A solution of crude lactol **12a** (0.06 mmol) in DCM (4 mL) was treated with 4-dimethylaminopyridine (76 mg, 0.063 mmol), TEA (69 μL, 0.49 mmol), acetic anhydride (24 μL, 0.25 mmol). The reaction mixture was allowed to stir for 1 h then concentrated in vacuo. The resulting yellow oil was purified by semipreparative HPLC to afford acetal **14a** (as a 2.75:1 mixture of anomers) as an amorphous solid.

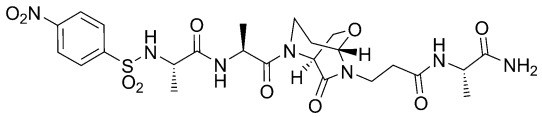
Yield 8 mg (28%) of amorphous solid. Crude purity = 75%. RT = 0.87 (22%) and 0.92 (78%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) Major anomer: 8.36 (d, J = 9.2 Hz, 2 H), 8.11 (d, J = 7.4 Hz, 1 H), 7.99 (d, J = 9.2 Hz, 2 H), 7.19 (br. s., 1 H), 6.98 (br. s., 1 H), 5.77 (dd, J = 5.2, 8.6 Hz, 1 H), 4.70−4.66 (m, 1 H), 4.08 (dd, J = 3.3, 13.8 Hz, 1 H), 4.04 (quin, J = 7.0 Hz, 1 H), 3.94 (dd, J = 5.2, 13.7 Hz, 1 H), 3.82−3.73 (m, 1 H), 3.62 (dd, J = 10.9, 14.3 Hz, 1 H), 2.19−2.10 (m, 1 H), 1.95 (s, 3 H), 1.84−1.73 (m, 1 H), 1.12 (d, J = 7.0 Hz, 3 H). Minor anomer: 8.38 (d, J = 8.8 Hz, 2 H), 8.29 (d, J = 7.0 Hz, 1 H), 8.04 (d, J = 8.8 Hz, 2 H), 7.25 (br. s, 1 H), 6.97 (br. s, 1 H), 4.72 (dd, J = 4.8, 8.8 Hz, 1 H), 4.06 (dd, J = 9.7, 14.0 Hz, 1 H), 4.00 (quin, J = 7.0 Hz, 1 H), 3.84−3.69 (m, 4 H), 2.01 (s, 3 H), 1.94−1.88 (m, 2 H), 1.14 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) Major anomer: 173.6, 168.7, 167.0, 149.7, 145.2, 128.5, 124.5, 94.6, 64.5, 59.2, 47.9, 41.0, 34.0, 20.9, 18.6. Minor anomer: 172.2, 169.0, 167.6, 149.7, 145.2, 129.0, 124.6, 92.4, 62.3, 60.1, 48.0, 40.6, 35.2, 20.8, 18.3. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{22}N_4NaO_9S$ $[M + Na]^+$ 481.1000, found 481.0974.

*(S)-3-(Ethoxymethyl)-4-((4-nitrophenyl)sulfonyl)-1,3,4,5-tetrahydro-2H-1,4-diazepin-2-one [**(S)-3g**].*



Yield 4.4 mg (22%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.00 (d, J = 6.3 Hz, 1 H), 8.38 (d, J = 9.2 Hz, 2 H), 8.04 (d, J = 9.2 Hz, 2 H), 5.48−5.54 (m, 1 H), 4.84−4.91 (m, 1 H), 4.63 (dd, J = 9.7, 4.6 Hz, 1 H), 4.39 (dd, J = 18.9, 4.6 Hz, 1 H), 3.79 (d, J = 18.9 Hz, 1 H), 3.74 (t, J = 10.3 Hz, 1 H), 3.60 (dd, J = 10.9, 4.6 Hz, 1 H), 3.26−3.39 (m, 2 H), 0.90 (t, J = 6.9 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 170.2, 149.8, 144.4, 128.7, 124.3, 122.2, 107.7, 65.5, 65.2, 61.9, 43.1, 14.7. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{17}N_3NaO_6S$ $[M + Na]^+$ 378.0730, found 378.0710.

*N-((S)-1-Amino-1-oxopropan-2-yl)-3-((1S,5S)-2-(((4-nitrophenyl)sulfonyl)-L-alanyl-L-alanyl)-8-oxo-6-oxa-2,9-diazabicyclo[3.2.2]nonan-9-yl)propanamide [**(S,S)-16a**].*



Yield 24.4 mg (24%) of amorphous solid. Rotamers cis/trans = 21:79. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) Trans rotamer: 8.37 (d, J = 8.8 Hz, 2 H), 8.26 (d, J = 7.0 Hz, 1 H), 8.04 (d, J = 7.9 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 2 H), 7.27 (br. s., 1 H), 6.95 (br. s., 1 H), 5.24 (d, J = 4.8 Hz, 1 H), 4.78 (d, J = 3.1 Hz, 1 H), 4.51 (quin, J = 7.0 Hz, 1 H), 4.16 (quin, J = 7.0 Hz, 1 H), 3.95 (quin, J = 7.0 Hz, 1 H), 3.95−3.84 (m, 1 H), 3.78 (d, J = 11.0 Hz, 1 H), 3.74−3.58 (m, 2 H), 3.49−3.37 (m, 1 H), 3.04−2.91 (m, 1 H), 2.43−2.28 (m, 2 H), 2.11−1.97 (m, 1 H), 1.93−1.75 (m, 1 H), 1.15 (d, J = 7.0 Hz, 3 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 174.2, 170.2, 170.2, 169.6, 164.2, 149.5, 146.8, 128.1, 124.3, 84.4, 65.8, 55.4, 51.5, 47.9, 44.8, 41.7, 39.1, 34.9, 34.0, 19.1, 18.3, 17.2. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{33}N_7O_{10}S$ $[M + H]^+$ 612.2088, found 612.2087.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vkrchnak@nd.edu.

Author Contributions

‖A.L.-V. and P.V.-A. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Department of Chemistry and Biochemistry, University of Notre Dame, by the projects P207/12/0473 from Czech Science Foundation (GACR), CZ.1.07/2.3.00/30.0060 and 1.07/2.3.00/30.0004 from the European Social Fund. We gratefully appreciate the use of the NMR facility at the University of Notre Dame.

REFERENCES

(1) Harvey, A. L. *Drug Discovery Today* **2008**, *13*, 894−901.
(2) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141−2153.
(3) Spandl, R. J.; Diaz-Gavilan, M.; O'Connell, K. M.; Thomas, G. L.; Spring, D. R. *Chem. Rec.* **2008**, *8*, 129−142.
(4) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.
(5) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.
(6) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867−3870.
(7) Pulici, M.; Cervi, G.; Martina, K.; Quartieri, F. *Comb. Chem. High Throughput. Screen.* **2003**, *6*, 693−727.
(8) Taylor, S. J.; Taylor, A. M.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1681−1685.
(9) Sello, J. K.; Andreana, P. R.; Lee, D.; Schreiber, S. L. *Org. Lett.* **2003**, *5*, 4125−4127.
(10) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, *2000*, 3117−3125.
(11) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.
(12) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744−8754.
(13) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740−5750.
(14) Piscopio, A. D.; Robinson, J. E. *Curr. Opin. Chem. Biol.* **2004**, *8*, 245−254.
(15) Nubbemeyer, U. In *Stereoselective Heterocyclic Synthesis III*, 216th ed.; Metz, P., Ed.; Springer: Berlin Heidelberg, 2001; pp 125−196.
(16) Shiina, I. *Chem. Rev.* **2006**, *107*, 239−273.
(17) Pflantz, R.; Tielmann, P.; Rossle, M.; Hoenke, C.; Christoffers, J. *Eur. J. Org. Chem.* **2007**, *2007*, 3227−3238.
(18) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya, P. *Chem. Rev.* **2009**, *109*, 1999−2060.
(19) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186.
(20) Fustero, S.; Mateu, N.; Albert, L.; Acena, J. L. *J. Org. Chem.* **2009**, *74*, 4429−4432.
(21) Lampariello, L. R.; Piras, D.; Rodriquez, M.; Taddei, M. *J. Org. Chem.* **2003**, *68*, 7893−7895.
(22) Lecinska, P.; Corres, N.; Moreno, D.; Garcia-Valverde, M.; Marcaccini, S.; Torroba, T. *Tetrahedron* **2010**, *66*, 6783−6788.
(23) Ventosa-Andres, P.; Hradilova, L.; Krchnák, V. *ACS Comb. Sci.* **2014**, *16*, 359−366.
(24) Schütznerová, E.; Oliver, A. G.; Zajícek, J.; Krchnák, V. *Eur. J. Org. Chem.* **2013**, *2013*, 3158−3165.
(25) La Venia, A.; Dolensky, B.; Krchnák, V. *ACS Comb. Sci.* **2013**, *15*, 162−167.
(26) La Venia, A.; Lemrova, B.; Krchnák, V. *ACS Comb. Sci.* **2013**, *15*, 59−72.
(27) Cankarova, N.; Krchnák, V. *J. Org. Chem.* **2012**, *77*, 5687−5695.
(28) Cankarova, N.; La Venia, A.; Krchnák, V. *ACS Comb. Sci.* **2014**, *16*, 293−302.
(29) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628.
(30) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.
(31) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311−2352.
(32) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Brown, B.; Ryono, D. E.; Bird, J. E.; Asaad, M. M.; Schaeffer, T. R.; Trippodo, N. C. *J. Med. Chem.* **1996**, *39*, 494−502.
(33) Shi, Y.; Wilmot, J. T.; Nordstrom, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313−14320.
(34) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; DiMarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348−2355.
(35) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 17634−17637.
(36) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3243−3247.
(37) Qu, J.; Fang, L.; Ren, X. D.; Liu, Y.; Yu, S. S.; Li, L.; Bao, X. Q.; Zhang, D.; Li, Y.; Ma, S. G. *J. Nat. Prod.* **2013**, *76*, 2203−2209.
(38) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568−7569.
(39) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787−3790.
(40) Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.
(41) Stockigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538−8564.
(42) Nielsen, T. E.; Diness, F. F.; Meldal, M. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 801−814.
(43) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842.
(44) Gandon, L. A.; Russell, A. G.; Snaith, J. S. *Org. Biomol. Chem.* **2004**, *2*, 2270−2271.
(45) Gandon, L. A.; Russell, A. G.; Guveli, T.; Brodwolf, A. E.; Kariuki, B. M.; Spencer, N.; Snaith, J. S. *J. Org. Chem.* **2006**, *71*, 5198−5207.
(46) Beaver, M. G.; Billings, S. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2082−2086.

NOTE ADDED AFTER ASAP PUBLICATION

An Me group configuration was corrected in Scheme 1 and in the structure for [(*R*,*R*)-**2b**] on October 16, 2014.