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Polymer-Supported Stereoselective Synthesis of Tetrahydro-2*H*-oxazolo[3,2-*a*]pyrazin-5(3*H*)-ones from *N*-(2-Oxo-ethyl)-Derivatized Dipeptides via Eastbound Iminiums

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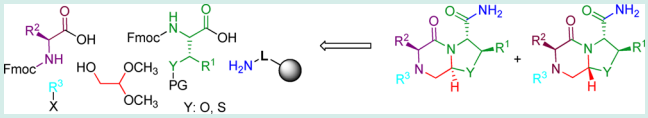
Supporting Information

ABSTRACT: Polymer-supported *N*-(2-oxo-ethyl)-derivatized Ser/Thr/Cys-containing dipeptides were synthesized and subjected to acid-mediated tandem *N*-acylium ion cyclization−nucleophilic addition to yield tetrahydro-2*H*-oxazolo-[3,2-*a*]pyrazin-5(3*H*)-ones. The reaction conditions and building-block combinations for stereoselective synthesis of the newly formed asymmetric carbon were developed. The synthesis was fully compatible with solid-phase peptide synthesis, and the products serve as conformationally constrained peptidomimetics. The traceless synthesis of bicycles is also reported as part of this work.



KEYWORDS: *fused heterocycles, iminium, solid-phase synthesis, stereoselectivity*

INTRODUCTION

Several compound collections commonly used for high-throughput screening in drug discovery have been analyzed and their structural features have been compared with current drugs and natural products. The analysis revealed statistically significant deficiencies of specific features. In addition to limited diversity, the compound decks suffered from a low frequency of sp^3 carbons (compound "flatness") and mostly absence of asymmetric carbons.[1−3] Specifically, only 6% of compounds were prepared by asymmetric synthesis.[1] To enhance structural diversity and enrich the screening decks with compounds possessing underrepresented features, our ongoing research is focused on the development of synthetic routes to heterocycles with 3D topography and formation of asymmetric carbons with full stereocontrol.[4−7]

Tandem *N*-acylium ion cyclization−nucleophilic addition is a powerful strategy for synthesis of diverse fused ring systems,[8−10] including conformational constraints in peptides.[11−14] Typically, a cyclic iminium is formed from an aldehyde attached via a two-carbon spacer to an amide nitrogen (**I**, Scheme 1). The cyclic iminium can be formed in two directions: either toward the peptide amino terminus (**II**) (referred to as westbound) or toward the peptide carboxyl terminus (eastbound, iminium **III**).[5] The directions are based on the standard peptide/protein nomenclature with the N-terminal amino acid on the left side.

Cyclizations in both directions have been reported in the literature;[15] however, the westbound direction has been used more frequently.[16−18] When both directions of iminium formation are possible, the westbound direction is favored.[5] In the eastbound cyclization direction, N, O, S, and C internal nucleophiles have been used to close the fused ring.[19−21]

Oxygen has previously served as an internal nucleophile in the preparation of five-,[21−23] six-,[24] and seven-membered rings.[25,26] Analogous 6 + 5 fused heterocycles that contain a 2-oxopiperazine ring have also been synthesized using a one-pot strategy in solution.[22] Oxazolo[3,2-*a*]pyrazin-5-ones (**VI**) have also been prepared from 3-aza-1,5-diketoacids (**IV**) and amino alcohols (**V**) (Scheme 2).[23]

We have already reported the polymer-supported synthesis of 6-oxa-3,8-diazabicyclo[3.2.1]octan-2-ones (**VII**)[6] and tetrahydropyrazino[2,1-*b*][1,3]oxazine-4,7(6*H*,8*H*)-diones (**VIII**)[5] via westbound tandem *N*-acylium ion cyclization−nucleophilic addition using Ser and Thr as key building blocks to provide the oxygen internal nucleophile (Scheme 3). Here, we describe the expansion of this chemistry for the synthesis of tetrahydro-2*H*-oxazolo[3,2-*a*]pyrazin-5(3*H*)-ones (**IX**). In addition to Ser and Thr, we also included Cys and compared the results with O- and S-nucleophiles. Although the synthesis of oxazolo[3,2-*a*]pyrazin-5-ones has already been reported,[23] we used a different synthetic strategy and prepared compounds with different substitution patterns. The synthetic route reported here allows the incorporation of bicyclic scaffolds as a peptide constraint during traditional peptide synthesis.

RESULTS AND DISCUSSION

The solid-phase synthesis of acyclic precursors **5** that contain O- and S-nucleophiles was performed using traditional peptide synthesis protocols (Scheme 4). Rink amide resin (**1**) was

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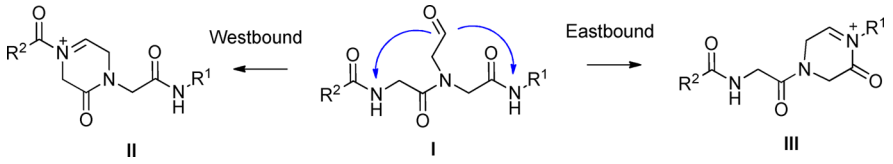
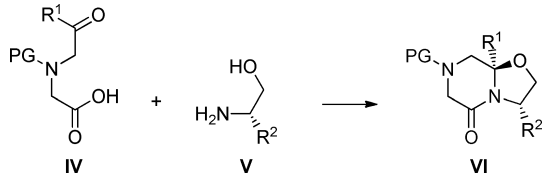
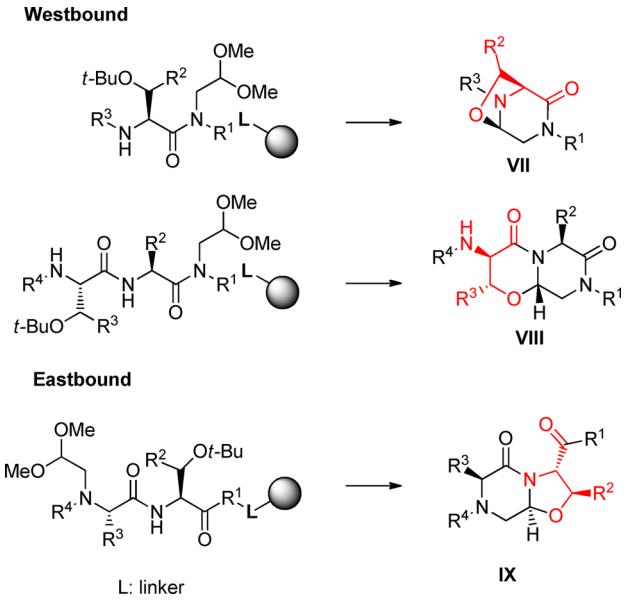
Scheme 1. Eastbound and Westbound Directions of Iminium Formation



Scheme 2. Synthesis of Oxazolo[3,2-*a*]pyrazin-5-ones



Scheme 3. Reported and New Solid-Phase Syntheses of Fused Rings using Ser and Thr (Shown in Red) as Key Building Blocks



acylated with Fmoc-Ser(*t*Bu)-OH, Fmoc-Thr(*t*Bu)-OH, and Fmoc-Cys(Trt)-OH (resin **2**), followed by acylation with a set of L- and D-α-amino acids (**3**) to evaluate the effect of their chirality and the R^2 substituent on the stereochemistry of the target compounds. The protected aldehyde was incorporated via the Fukuyama variation[27] of the Mitsunobu reaction[28] with glycolaldehyde dimethyl acetal on 4-nitrobenzenesulfonyl (4-Nos) derivatized resin (**4**)[4] to obtain the resin-bound acyclic substrates **5**.

Upon acid-mediated unmasking of protection groups and cleavage of the acyclic intermediates from the resin, the cyclic *N*-acyliminium ions were formed. The presence of O- or S-nucleophiles facilitated the formation of the fused ring, and two diastereomers were formed depending on the direction of the nucleophilic attack. The new chiral carbon (C8a) was formed either with an (*S*)-configuration (diastereomer **A,** compounds **6** and **8**) or the opposite configuration (*R*) (diastereomer **B,** compounds **7** and **9**) (Figure 1).

The absolute configuration of the new chiral center at C8a was unambiguously assigned using the NMR spectra of compounds **6-O(1,1,1)**, **6-O(1,2,1)**, **6-O(1,2,2)**, **6-O(1,4,1)**, **6-O(2,2,1)**, **7-O(1,4,1)**, **7-S(1,2,1)**, **8-S(1,5,1)**, **8-S(1,3,1)**, **8-O(1,3,1)**, **8-O(1,5,1)**, and **9-S(1,5,1)**. First, the chemical shifts were unambiguously assigned to individual atoms based on gCOSY, gHSQC, and gHMBC NMR spectra. Subsequent analyses of the NOE interactions (NOESY1D spectra) enabled estimation of the absolute configuration at C8a. Specifically, the NOE interactions between the substituents at C6 and the hydrogen at C8a were decisive (Figure 2). The configurations of the other compounds were derived based on the similarity of their characteristic signals (chemical shifts and size of interaction constants; see Table S1 in the Supporting Information).

The effect of individual factors was evaluated on a set of model compounds with the 4-Nos group in the R^3 position. The stereochemistry of the fused ring was influenced by the chirality of the amino acids, the character of the R^2 side chain, and the presence of Ser, Thr, or Cys derivatives (Table 1). The results indicated that the stereocontrol was mainly directed by the (*S*)-configuration of the first amino acid (Ser, Thr, or Cys), which favored the formation of the new stereocenter with an (*S*)-configuration. This stereocontrol was evident in substrates with no substituent at the R^2 position, such as **5-O(1,1,1)** (entry 1) and **5-S(1,1,1)** (entry 13), both of which formed with high stereoselectivity. However, the stereo-outcome was also strongly influenced by the nature of the R^2 group. Figure 1 portrays a model compound with the R^2 originating from L-amino acids and where the nucleophilic attack occurred through the same face of the R^2 group. As evident in the figure, the stereoselectivity decreased because of the steric hindrance. In contrast, the D-amino acid-derived model exhibited a synergic effect, which reinforced the controlled direction of the second ring closure.

As expected from the previous analysis, we observed full stereocontrol for the Ser derivatives with R^2 = H or a small alkyl group, such as methyl. The stereocontrol was independent of the absolute configuration of the second amino acid (R^2 substituent) because of insignificant steric repulsion (e.g., substrates **5-O(1,1,1)**, **5-O(1,2,1)**, and **5-O(1,3,1)**, entries 1 to 3). However, the stereochemistry of the newly formed chiral carbon was influenced by the presence of bulkier alkyl groups (such as isopropyl, entries 6 and 7) in the R^2 position and was dependent on the R^2 chirality. We observed complete stereochemical control for the compound with the (*R*)-configuration (**8-O(1,5,1)**, entry 7), whereas the opposite (*S*)-configuration (L-Val, entry 6) unfavorably influenced the stereochemistry and resulted in the formation of a mixture of diastereomers (**6-O(1,4,1)** and **7-O(1,4,1)** as well as the enamide **10(1,4,1)**). In addition, the exchange of 4-Nos for 2-Nos at R^3 hindered the formation of major stereoisomer **6** and produced a small amount of **7** as well (entry 4, substrate **5-O(1,2,2)**).

The polymer-supported precursors prepared using Thr as the C-terminal amino acid incorporated a methyl group and an additional stereocenter, which disfavored the stereoselectivity of the reaction and led to a mixture of products (entries 9 to 12). The probable reason for this decreased selectivity was the presence of bulkier side chains in close proximity to the internal nucleophile. This proximity influenced the stereoselectivity in a

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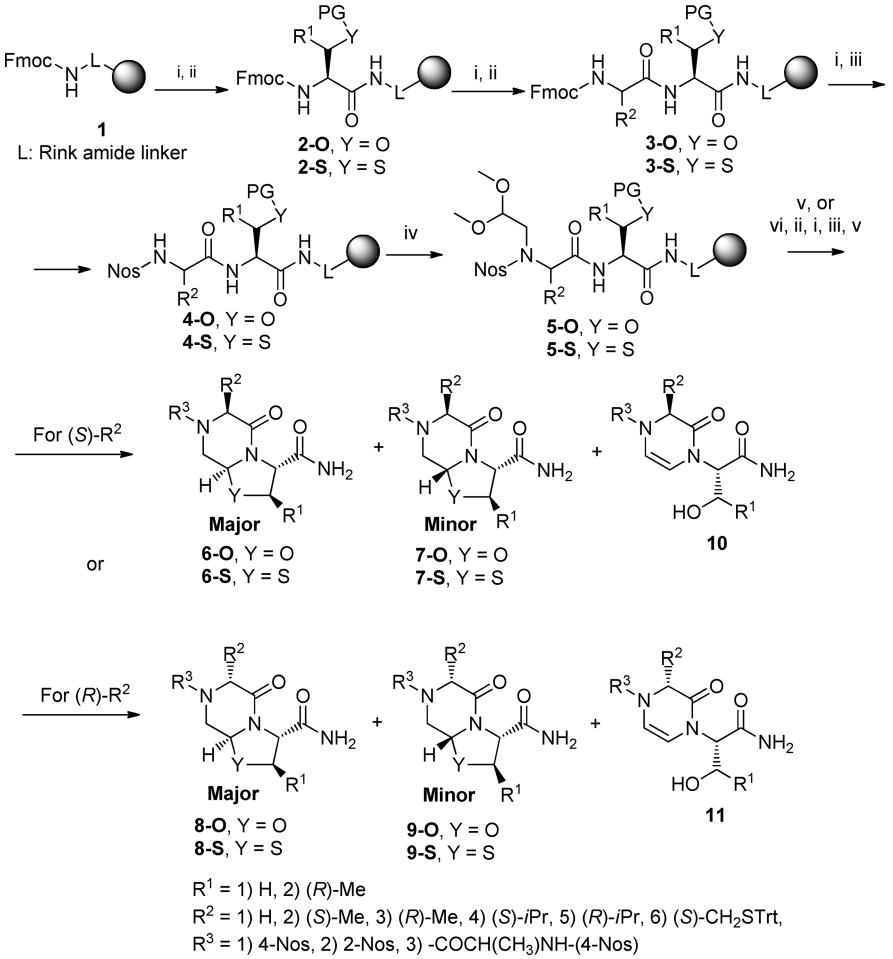
Scheme 4. Polymer-Supported Synthesis of Ser/Thr/Cys Bicyclic Compounds[a]



[a]Reagents and conditions: (i) piperidine (50% v/v), DMF, rt, 20 min; (ii) Fmoc-AA, HOBt, DIC, DCM, rt, 16 h; (iii) 2-methylbenzenesulfonyl chloride (2-Nos-Cl) or 4-methylbenzenesulfonyl chloride (4-Nos-Cl), lutidine, DCM, rt, 16 h; (iv) glycolaldehyde dimethyl acetal, DIAD, PPh_3, anhydrous THF, 50°C, 16 h; (v) TFA (50%), DCM, rt, 2−3 h; (vi) mercaptoethanol, DBU, DMF, rt, 10 min. Note: individual compounds are identified by a number followed by the type of nucleophile (O or S) (e.g., **6-O(R¹,R²,R³)**). For R numbering, see Table 1.

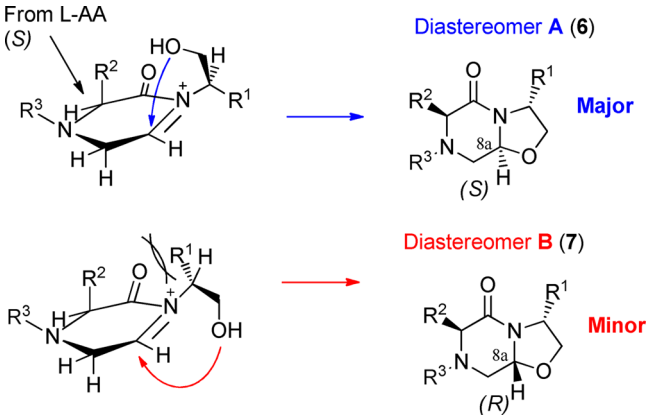


Figure 1. Formation of diastereomers **A** and **B** [for (*S*)-R^2 series].

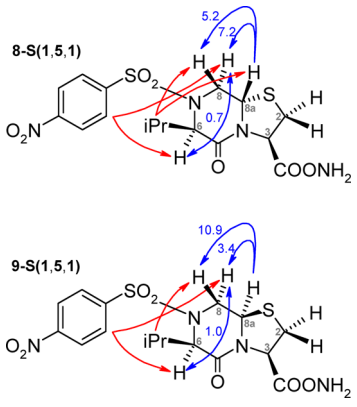


Figure 2. Decisive NOE interactions (red) and the coupling interactions (blue) for assignment of the absolute configuration at C8a using **8-S(1,5,1)** and **9-S(1,5,1)**.

manner similar to that of bulkier side chains on L-amino acids (R^2) (entry 6). Surprisingly, an opposite effect for R^2 was observed: only the combination of Thr with L-Ala in the second position resulted in significant stereocontrol (entry 10, **6-O(2,2,1)**).

Cys-derived substrates exhibited an analogous chemoselectivity in the outcome of the final product (entries 13 to 18). However, when the mixture of both fused diastereomers was produced, we observed a lower selectivity toward stereoisomers **6** and **8** than that observed with Ser-derived compounds (compare substrates **5-S(1,2,1)** (entry 14), **5-S(1,2,2)** (entry 16), and **5-S(1,5,1)** (entry 18) with **5-O(1,2,1)** (entry 2), **5-O(1,2,2)**

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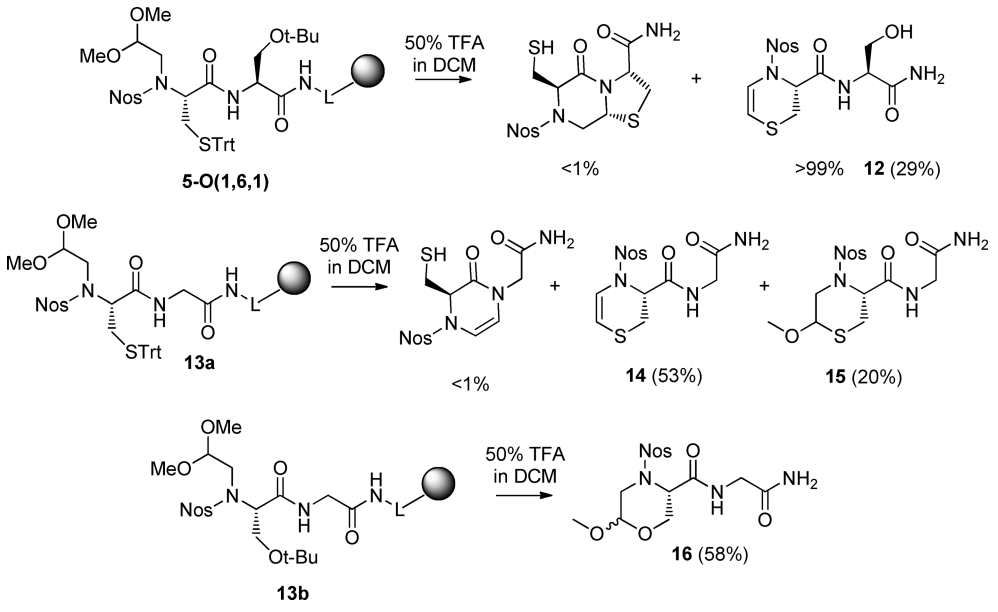
Table 1. Effect of Derivatization (R^1, R^2, and R^3) on Product Distribution

entry	substrate	R^1	R^2	R^3	ratio[a] 6:7:10 or 8:9:11	total yield[b] (%)
1	**5-O(1,1,1)**	H	H	4-Nos	99:<1:0	**6-O(1,1,1)** 10%
2	**5-O(1,2,1)**	H	(*S*)-CH_3	4-Nos	99:<1:0	**6-O(1,2,1)** 75%
3	**5-O(1,3,1)**	H	(*R*)-CH_3	4-Nos	99:<1:0	**8-O(1,3,1)** 67%
4	**5-O(1,2,2)**	H	(*S*)-CH_3	2-Nos	85:15:0	**6-O(1,2,2)** 27%
5	**5-O(1,2,3)**	H	(*S*)-CH_3	4-Nos-Ala	95% of 17[c]	**17** 52%
6	**5-O(1,4,1)**	H	(*S*)-$CH(CH_3)_2$	4-Nos	50:22:28	**6-O(1,4,1)**[d] 35%
						7-O(1,4,1) 28%
						10(1,4,1)[d] 26%
7	**5-O(1,5,1)**	H	(*R*)-$CH(CH_3)_2$	4-Nos	99:<1:0	**8-O(1,5,1)** 40%
8	**5-O(1,6,1)**	H	(*S*)-CH_2STrt	4-Nos	95% of 12[e]	**12** 29%
9	**5-O(2,1,1)**	(*R*)-CH_3	H	4-Nos	52:32:16	**6-O(2,1,1)** 20%
10	**5-O(2,2,1)**	(*R*)-CH_3	(*S*)-CH_3	4-Nos	99:<1:0	**6-O(2,2,1)** 66%
11	**5-O(2,3,1)**	(*R*)-CH_3	(*R*)-CH_3	4-Nos	83:17:00	**8-O(2,3,1)** 33%
12	**5-O(2,4,1)**	(*R*)-CH_3	(*S*)-$CH(CH_3)_2$	4-Nos	48:27:25	**6-O(2,4,1)** 27%
						7-O(2,4,1) 8%
13	**5-S(1,1,1)**	H	H	4-Nos	99:<1:0	**6-S(1,1,1)** 11%
14	**5-S(1,2,1)**	H	(*S*)-CH_3	4-Nos	52:48:0	**6-S(1,2,1)** 13%
						7-S(1,2,1) 12%
15	**5-S(1,3,1)**	H	(*R*)-CH_3	4-Nos	99:<1:0	**8-S(1,3,1)** 12%
16	**5-S(1,2,2)**	H	(*S*)-CH_3	2-Nos	57:43:0	**6-S(1,2,2)** 14%
						7-S(1,2,2) 12%
17	**5-S(1,4,1)**	H	(*S*)-$CH(CH_3)_2$	4-Nos	54:46:0	**6-S(1,4,1)** 11%
						7-S(1,4,1) 10%
18	**5-S(1,5,1)**	H	(*R*)-$CH(CH_3)_2$	4-Nos	88:22:0	**8-S(1,5,1)** 45%
						9-S(1,5,1) 12%

[a]The relative ratio of products was estimated from LC traces at 240 nm or structures confirmed in the crude preparation by ^{1}H NMR; major products were isolated by HPLC and were fully characterized. [b]Total yield after purification by HPLC of products prepared in a 6- to 9-step synthesis. [c]NA: not applicable, westbound cyclization (see Scheme 6). [d]Products obtained as an inseparable mixture (see Scheme 5). [e]NA: not applicable, sulfur-aldehyde reaction.

Scheme 5. Regioselectivity of Products with N-Terminal Cys and Ser



(entry 4), and **5-O(1,5,1)** (entry 7), respectively). The less efficient stereocontrol in those reactions that involved sulfur as the internal nucleophile was ascribed to its pronounced nucleophilicity and larger size, which allowed the formation of the more thermodynamically stable diastereomer in a greater ratio. Nevertheless, a positive effect on stereoselectivity for the D-amino acids (R^2) was also significant in both model compounds (**5-S(1,3,1)**, entry 15, and **5-S(1,5,1)**, entry 18). The increased nucleophilicity of sulfur was also expressed in the complete absence of the enamides in all of the tested cases.

To this point, model compounds with aliphatic R^2 side chains were investigated, but we became interested in the outcome of these reactions when R^2 contained a more complex functional group, particularly nucleophiles. To evaluate the competition

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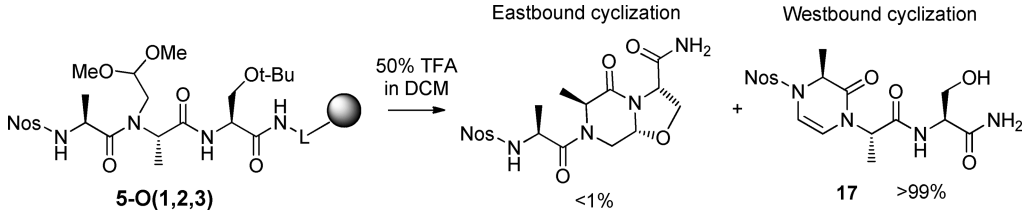
Scheme 6. Westbound Cyclization Favored



and regioselectivity of different internal nucleophiles, Ser and Cys were introduced as N-terminal amino acids. In the case of Ser incorporation (R^2 = (*S*)-CH_2O*t*-Bu), however, the Mitsunobu reaction with glycolaldehyde dimethyl acetal did not provide satisfactory conversion. In contrast, the Cys-derived substrate **5-O(1,6,1)** (entry 8) was obtained successfully. Interestingly, acid treatment yielded the olefin **12** as the major product through reaction of the sulfur with the aldehyde, and the fused ring compound was not detected (Scheme 5). To independently prove the observed regiochemistry, we prepared model compounds using C-terminal Gly (**13a**, **13b**) (Scheme 5). None of these polymer-supported substrates formed the acyliminium intermediate under acidic conditions. Furthermore, the Cys-containing dipeptide **13a** yielded an analogous compound, similar to the previous case; the main product was the unsaturated compound **14**. Interestingly, methoxythiomorpholine **15** was also isolated as a minor product. Moreover, resin-bound Ser derivative **13b** yielded a mixture of diastereomers of **16.**

Incorporation of tetrahydro-2*H*-oxazolo[3,2-*a*]pyrazin-5(3*H*)-ones as peptide mimetics during traditional Merrifield peptide synthesis by simple extension of the peptide was not possible. The addition of one amino acid to the dipeptide N-terminus followed by 4-Nos derivatization (**5-O(1,2,3)**, entry 5, Table 1) opened the possibility of westbound iminium formation (Scheme 6).[5] The olefin **17** was produced exclusively, whereas the presence of 6 + 5 fused rings was not detected. This problem can be solved through modification of the synthetic strategy and will be the subject of a future study.

Encouraged by the smooth preparation of the 6 + 5 ring system with oxygen nucleophiles, we modified the synthetic scheme and synthesized fused bicycles in a traceless manner.[29] Although the previous synthetic route was designed to incorporate the bicycles during peptide synthesis as peptidomimetics, the following route enabled access to these bicycles with no trace of a linker on the products. We evaluated the scope and limitation of this solid-phase synthesis with two different immobilizations of amino alcohols. Route **A** (Scheme 7) involved the attachment of the precursor via the oxygen nucleophile to Wang resin using Fmoc-2-aminoethanol with trichloroacetimidate activation.[30] Route **B** involved the application of the amide nitrogen for immobilization. BAL resin underwent reductive amination with 1-aminopropanol. Both routes continued with acylation of the polymer-supported amines with bromoacetic acid followed by reaction with aminoacetaldehyde dimethyl acetal. The derivatization of the resin-bound secondary amines by Tos-Cl and 4-fluoro-3-nitrobenzotrifluoride was the last synthetic step on the solid phase. Both the sulfonamide (Tos) and *N*-aryl (4-trifluoromethyl-2-nitroaryl) derivatives provided 5 + 6 as well as 6 + 6 fused heterocycles in excellent purity and yield (Table 2). Gratifyingly, the formation of the elimination product was not observed.

Scheme 7. Synthesis of Model Compounds for Cyclization with O-Nucleophiles via a Traceless Approach

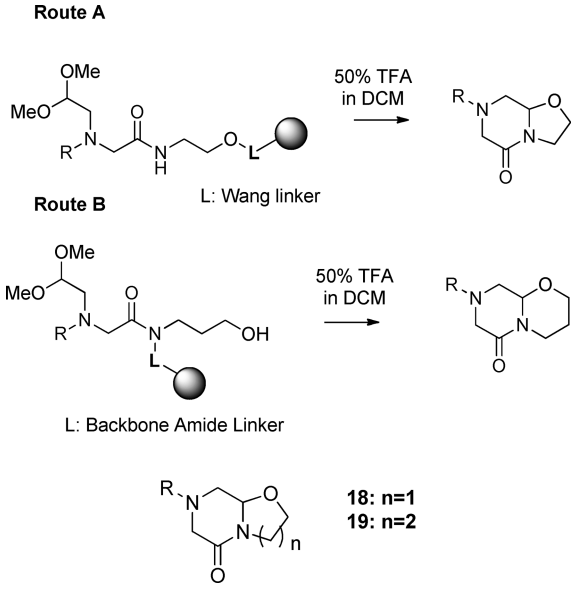
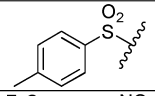
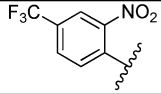
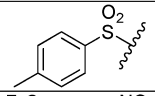
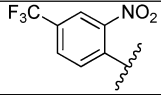


Table 2. Compounds Prepared with *O*-Nucleophiles using A and B Synthetic Routes

Entry	n	R	Purity [%]	Yield [%]
18a	1		95	74
18b	1		96	74
19a	2		91	56
19b	2		87	38

CONCLUSION

We have developed a robust polymer-supported synthetic route allowing access to fused tetrahydro-2*H*-oxazolo[3,2-*a*]pyrazin-5(3*H*)-one heterocycles and their sulfur analogs via eastbound tandem *N*-acylium ion cyclization−nucleophilic addition. The effect of amino acids and their chirality on the stereochemical outcome was studied, and compounds with full stereocontrol of the newly formed asymmetric carbon were synthesized. The synthesized compounds will serve as scaffolds for the construction of compound libraries and as peptide backbone-constrained peptidomimetics.

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EXPERIMENTAL PROCEDURES

Individual steps of the solid-phase synthesis of compounds **5**, the cleavage of target compounds from the resin, and the HPLC purification are described in a previous paper[5] and in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

Analytical data of individual compounds, tabulated NMR characteristics (Table S1), and copies of NMR spectra associated with this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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