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Polymer-Supported Stereoselective Synthesis of (1*S*,5*S*)-6-Oxa-3,8-diazabicyclo[3.2.1]octanes

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We describe a polymer-supported stereoselective synthesis of the (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octane-bridged scaffold by tandem iminium ion cyclization/nucleophilic addition reactions. A series of resin-bound acyclic intermediates bearing different substituents were prepared, and the scope and limitations of the chemical route leading to the bridged scaffold were evaluated. The Thr-derived bridged scaffold was found to be substantially more stable in acid than the Ser-derived scaffold, which was partially transformed into dihydropyrazinones. Substitution at the iminium-forming nitrogen was critical for acid stability, and the *N*-arylsulfonamides with electron-withdrawing groups yielded the highest purity of the crude products prepared by acid-mediated cleavage. The acid-labile target compounds were synthesized by nucleophile-mediated cleavage from the esterified Wang resin and cyclization in formic acid.

Introduction

Nature is the ultimate source of structural diversity for drug discovery. Natural products have always played an important role in traditional medicine and are crucial to the pharmaceutical chemistry. For example, in cancer treatment, the structures of over 60% of the drugs have a natural origin.[1,2] The search for novel, biologically active structures that mimic natural products has become an integral part of drug discovery. However, recent structural analysis of the drugs and compound libraries used in high-throughput screening has revealed significant differences in the chemical space covered by individual groups of compounds.[3] The existing compound collections typically display a low frequency of sp^3-hybridized carbons and chiral centers when compared with drugs and natural products.[4] To fill the gap in chemical space, our ongoing research is focused on the design and synthesis of compound collections that are characterized by nature-inspired, nonplanar structures (i.e., those that include sp^3 carbons) and the formation of stereogenic centers with stereocontrol.[5–7]

Nitrogen-containing heterocyclic systems, particularly alkaloids, have been the focus of medicinal chemistry for several decades.[8] The bicyclo[3.2.1]octane moiety is a core structure in many natural products including tropane alkaloids [tropane (**I**), Figure 1], a group of over 100 biologically active compounds that include atropine (**II**), cocaine (**III**), and scopolamine (**IV**).[9] These bridged bicyclic structures have pharmacological and clinical uses, for example, the local anesthetic cocaine acts as a serotonin–norepinephrine–dopamine reuptake inhibitor that leads to prolonged post-synaptic effects. The subsequent high rates of addiction to cocaine have become a worldwide problem.[10] The structure–activity relationships (SAR) of reuptake inhibitors of the dopamine transporter include tropane and piperidine analogues.[9]

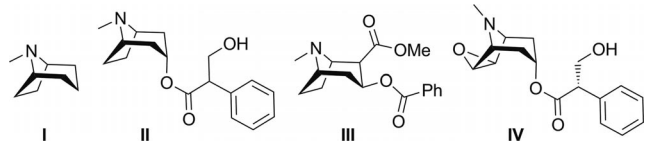

Figure 1. Bicyclo[3.2.1]octane-derived natural products **I**–**IV**.

A number of chemical routes lead to tropane-like bridged bicyclic scaffolds. The densely substituted, bridged heterocycle **V** (Figure 2) was prepared from 1,4-diphenyl-2,6-dioxopiperazine and phenyl hypochlorothioite by dipolar cycloaddition with formaldehyde.[11] Another bridged bicycle, methyl 2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-carboxylate **VI**, which is a conformationally constrained dipeptide isoster, was prepared from tartaric acid and *N*-benzylamino alcohols.[12] Guarna et al.[13] patented an analogous route for the synthesis of 3-aza-6,8-dioxabicyclo-[3.2.1]octanes **VII** from α-amino ketones and α,β-dihydroxy acid derivatives or α-amino-β-hydroxy acids. Molecumetics[14] patented the synthesis of the fused bicyclic nitroge-

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nous compounds **VIII**. The synthesis was carried out on the solid phase, and acyclic dipeptide aldehydes were cleaved from the resin and concurrently cyclized to the bicyclic derivatives **VIII**. The synthesis of (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octanes (X = O, *n* = 1) has not been documented, however, an analogous synthetic route to bridged bicycles by the addition of carbon nucleophiles has been reported.[15]

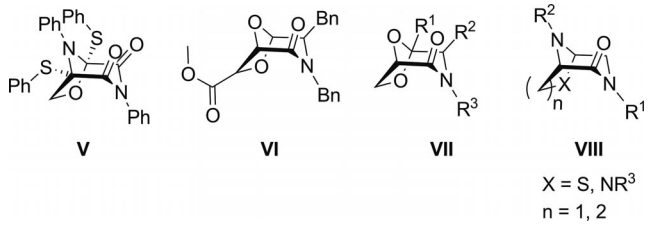


Figure 2. Synthesis of (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octane.

Among the many chemical routes used for the synthesis of natural-product-like molecules, the tandem iminium ion cyclization/nucleophilic addition represents one of the most versatile methodologies.[16–20] *N*-Acyliminium pathways were used in the solid-phase synthesis of piperidines[21] and 2-oxopiperazines,[22] fused benzimidazolopiperazines have been prepared by the acid-triggered cyclization of iminium ion intermediates,[23] and *N*-acyliminium ion chemistry led to 2,6-bridged piperazines starting from amino acids.[24] Conformational constraints have been incorporated into peptides through silylated amino acids with subsequent conversion into *N*-acyliminium ions.[25–27] *N*-Boc-1,3-oxazinane-masked aldehyde building blocks have been incorporated into peptides and used to synthesize structurally diverse bicyclic dipeptide mimetics.[28,29] Finally, diverse heterocycles have recently been prepared by the acyliminium Pictet–Spengler reaction.[30]

We describe herein the polymer-supported stereoselective synthesis of (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octanes by using a strategy compatible with the traditional Merrifield solid-phase synthesis. This strategy has allowed the synthesis of a library of natural-product-like compounds for drug discovery and the introduction of this bridged scaffold as a peptide backbone constraint.

Results and Discussion

Resin-bound acyclic intermediates were prepared on the solid phase by using linkers that allow for base- and/or acid-mediated cleavage from the resin. The acid-mediated cleavage triggered tandem iminium ion cyclization/nucleophilic addition with concurrent cleavage from the resin to yield (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octanes. The base-mediated cleavage released fully protected compounds that were deprotected and cyclized in solution.

The acyclic precursors were synthesized on polymer-supported amines (resins **1**, Figure 3). To expand the diversity of the target compounds and address any potential effects from either the immobilization or the amine-containing building block, different resin-bound amines were prepared on Rink amide,[31] Wang,[32] and backbone amide linker (BAL)[33] resins by using four types of anchoring: Carboxamide, carboxylate, amine, and ether (Figure 3). The Rink amide resin **1(1)** was used as the starting amine and was acylated with Fmoc-Tyr(*t*Bu)-OH [resin **1(2)**], the BAL resin was subjected to reductive amination with *n*-propylamine[34] [**1(3)**], and the Wang resin was esterified with Fmoc-Ala-OH followed by cleavage of the Fmoc group by using piperidine in DMF [**1(4)**]. Finally, the Wang resin was also derivatized with 1,3-diaminopropane through a carbamate linkage by using the carbonyldiimidazole (CDI) activation method[35] [**1(5)**] and with 2-(Fmoc-amino)ethanol through an ether linkage by using trichloroacetimidate activation[36] followed by Fmoc cleavage [**1(6)**].

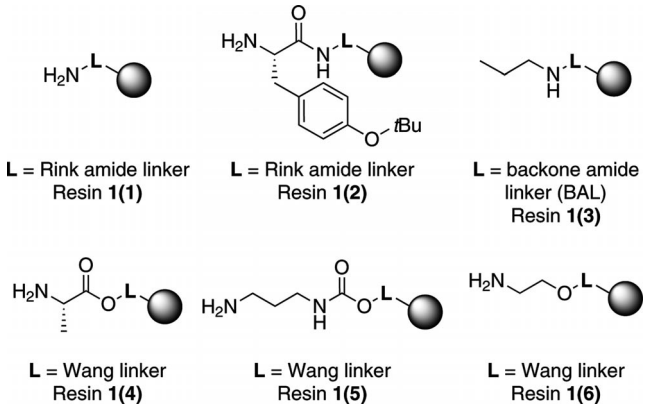
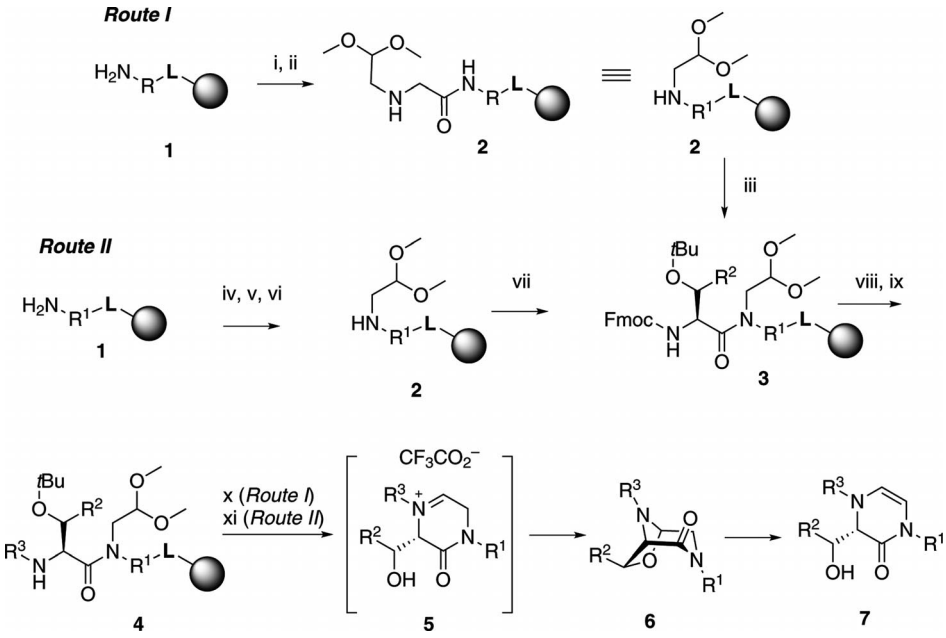


Figure 3. Polymer-supported amines **1(1)**–**1(6)**.

Two routes were used to attach the protected aldehyde. Resin-bound amines **1(1)**–**1(5)** (Figure 3) were acylated with bromoacetic acid. The protected aldehyde was introduced by nucleophilic displacement of the bromine with excess aminoacetaldehyde dimethyl acetal[37,38] to yield resin **2** (Scheme 1, Route I). As an alternative, the protected aldehyde was also attached by Route II. The resin-bound amines **1(5)** and **1(6)** were treated with 4-nitrobenzenesulfonyl chloride (4-Nos-Cl) and the 4-Nos-derivatized polymer-supported amines were subjected to Fukuyama alkylation[39] with glycolaldehyde dimethyl acetal. The 4-Nos group was subsequently cleaved. Ultimately, both routes converged to one family of compounds.

The anhydride formed from the reaction of Fmoc-Ser(*t*Bu)-OH [or Fmoc-Thr(*t*Bu)-OH] and *N*,*N*′-diisopropylcarbodiimide (DIC)[40] was then treated with the secondary amine **2** to yield the polymer-supported amide **3**. The piperidine-mediated Fmoc deprotection was followed by reaction of the polymer-supported amines with a series of reagents to introduce different R^3 substituents. Arylsulfonyl chlorides in the presence of a base produced the sulfon-



Scheme 1. Polymer-supported stereoselective synthesis of (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octane **6**. Reagents and conditions: (i) bromoacetic acid (2 equiv.), DIC (1 equiv.), DCM, 5 min, then *N*-ethyl-*N*,*N*-diisopropylamine (DIEA; 1 equiv.), room temp., 1 h; (ii) aminoacetaldehyde dimethyl acetal, DIEA, DMF, room temp., 2 h; (iii) Fmoc-amino acid (2 equiv.), DIC (1 equiv.), THF, room temp., overnight; (iv) 4-nitrobenzenesulfonyl chloride, 2,6-lutidine, DCM, room temp., overnight; (v) glycolaldehyde dimethyl acetal, PPh_3, DIAD, anhydrous THF, 0 to 50 °C, overnight, repeat; (vi) 2-mercaptoethanol, DBU, DMF, room temp., 5 min; (vii) Fmoc-Ser(*t*Bu)-OH (1 equiv.), HOBt (1 equiv.), DIC (1 equiv.), DCM/DMF (1:1), room temp., overnight; (viii) 50% piperidine in DMF, room temp., 20 min; (ix) arylsulfonyl chloride, 2,6-lutidine, DCM, room temp., overnight; (x) 50% TFA in DCM, room temp., 90 min; (xi) TFA/H_2O (95:5), room temp., 90 min.

amide resin **4**. *N*-Alkylation was carried out after activation with 4-Nos-Cl followed by reaction with 2-nitrobenzyl alcohol and *N*-(2-hydroxyethyl)phthalimide under Mitsunobu conditions.[41] The 4-Nos group was subsequently cleaved by treatment with mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[39,42] The *N*-arylation was performed with 4-fluoro-3-nitrobenzofluoride in the presence of a base.[43] *N*-Acylation was carried out with 4-methoxybenzoic acid, 4-trifluoromethylbenzoic acid, and Fmoc-Pro-OH by using conventional peptide coupling techniques with *N*-hydroxybenzotriazole (HOBt) and DIC.[44] The final cyclization of the resin-bound acyclic precursor **4** was enabled by the acid-mediated cleavage of the hydroxy and aldehyde protecting groups concurrent with cleavage from the resin with a 50% TFA solution in dichloromethane (DCM; Route I) or 5% water in TFA (Route II). The acid-assisted cleavage typically yielded two products, (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octane **6** and 3,4-dihydropyrazin-2(1*H*)-one **7** (Scheme 1).

The structure of the bridged compound **6** was confirmed by analysis of its 1D and 2D ^1H and ^{13}C NMR spectra (COSY, HSQC, and HMBC). In addition, compound **6(1,1,6)** was crystallized from an acetonitrile/DMSO solution and its structure was determined by X-ray analysis (Figure 4).

The presence of dihydropyrazinone **7** in the crude reaction mixture following the acid-mediated cleavage of the acyclic intermediate from the resin prompted us to explore

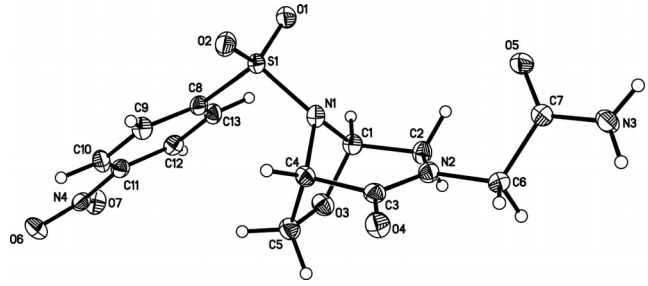


Figure 4. ORTEP drawing of the X-ray crystal structure of compound **6(1,1,6)**. Thermal displacement ellipsoids are depicted at the 50% probability level.

why this product was formed; the enamide **7** could have been formed from iminium **5**[45,46] or the partially decomposed target bridged compound **6** present in the cleavage cocktail. We tested the effect of acid concentration and exposure time on the ratio of **6** and **7** by using two model compounds **4(1,1,3)** (R^1 = CH_2CONH_2, R^2 = H, R^3 = *p*Tos; for numbering of the building blocks, see Table 1) and **4(4,1,4)** (R^1 = CH_2COOH, R^2 = H, R^3 = 4-methoxy-2-nitrophenylsulfonyl). The results are summarized in Table 1. A longer reaction time or higher TFA concentration shifted the ratio of **6**/**7** in favor of the enamide **7** (entries 1–4).

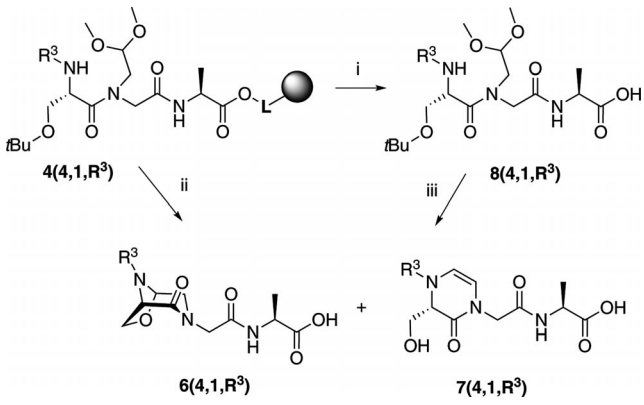
These results indicated that bicycle **6** suffered acid-mediated transformation into enamide **7** and that milder conditions were required to increase the yield of target com-

Table 1. Effect of the cleavage conditions on the ratio of products **6/7** from resins **4(4,1,4)** and **4(1,1,3)**.

Entry	Cleavage cocktail	6(4,1,4)/7(4,1,4)[a]	6(1,1,3)/7(1,1,3)
1	50% TFA/DCM, 30 min	78:22	36:64
2	50% TFA/DCM, overnight	39:61	22:78
3	100% TFA, 30 min	63:37	28:72
4	95%TFA/water, 30 min	67:33	27:73
5	NaOH, 30 min	95% of **8(4,1,4)**	n.a.[b]
6	NaOH, 30 min then formic acid, 1 h	99:1	n.a.
7	NaOH, 30 min then formic acid, overnight	58:42[c]	n.a.
8	NaOH, 30 min then 10% TFA, 1 h	75:25	n.a.
9	formic acid, 1 h, then 0.5 M NaOH, 30 min	99:1[d]	n.a.

[a] The relative ratio of products **6/7** was estimated from the LC traces at 240 nm. [b] n.a.: not applicable. [c] Contains an *O*-formyl derivative. [d] Only 17% of *t*Bu was cleaved.

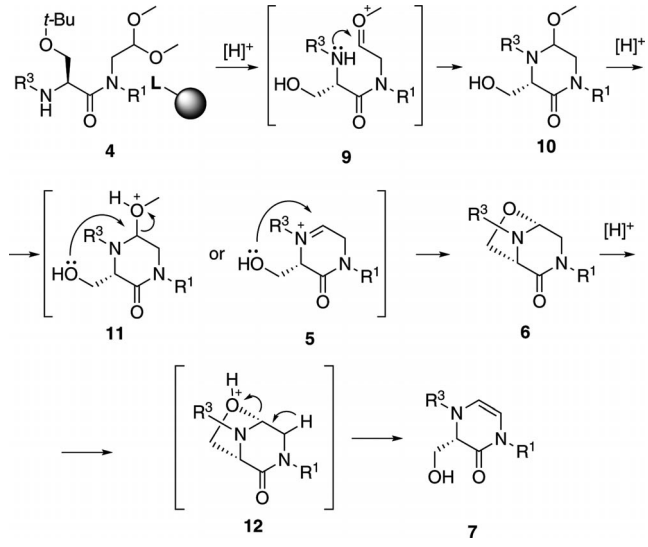
pound **6**. Cleavage from the Rink amide resin typically requires exposure to TFA and a milder acid such as formic acid (FA), often used to trigger the tandem iminium ion cyclization/nucleophilic addition reaction,[47–49] does not completely cleave the products from the Rink amide resin. However, formic acid does cleave the O*t*Bu protecting group of Ser and unmasks the aldehyde in solution. Model experiments indicated that a solution of Fmoc-Ser(*t*Bu)-OH in FA contain Fmoc-Ser-OH (50%), Fmoc-Ser(*O*-formyl)-OH (43%), and Fmoc-Ser(*t*Bu)-OH (7%) after 1 h, which corresponds to 93% cleavage of the *t*Bu group. We synthesized model compound **4(4,1,4)** immobilized on the Wang resin through an ester linkage (Scheme 2). We then cleaved the protected intermediate **8(4,1,4)** from the resin **4(4,1,4)** with 0.5 M NaOH and isolated the highly pure product **8(4,1,4)** (entry 5). When **8(4,1,4)** was exposed to formic acid for 1 h, the bridged compound **6** was formed exclusively (entry 6). Treatment of **8(4,1,4)** with formic acid overnight led to 42% of the enamide **7** (entry 7), thus confirming that



Scheme 2. Acid- and base-mediated cleavage of **4(4,1,R^3)**. Reagents and conditions: (i) 0.5 M NaOH in MeOH/THF (1:1), room temp., 30 min; (ii) 50% TFA in DCM, room temp., 1 h; (iii) formic acid, room temp., 1 h.

enamide **7** is formed from the bridged compound **6**. Enamide **7** was also formed when **8(4,1,4)** was exposed to 10% TFA (entry 8). In contrast, treatment of the polymer-supported precursor **4(4,1,4)** with formic acid for 1 h followed by sodium hydroxide cleavage from the resin yielded only bridged compound **6**. However, only 17% of the *t*Bu protecting group was cleaved (entry 9). Thus, mildly acidic conditions could not be used for on-resin *t*Bu deprotection and subsequent cyclization.

Based on the observations described herein, we suggest the mechanism presented in Scheme 3 for the formation of the bridged bicycle **6** and its acid-mediated transformation into enamide **7**. The initial formation of the oxonium species **9** was adopted from the mechanism proposed for acetal deprotection under anhydrous conditions.[50]



Scheme 3. Suggested mechanism for the formation and transformation of bridged bicycle **6**.

The study next focused on the acid lability of bicycle **6** as a function of its substitution pattern. To study the stability of the diversely substituted target compound **6** in the acid-based cocktail typically used for its release from acid-labile linkers, we prepared a series of compounds on the Rink amide resin. The substituent R^3 was expected to be the factor determining the ratio **6/7** because this substituent

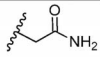
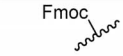
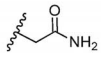
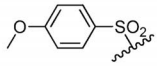
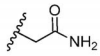
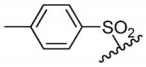
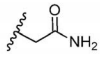
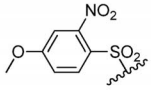
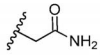
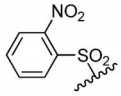
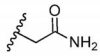
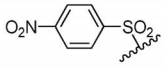
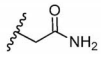
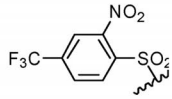
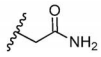
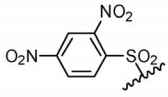
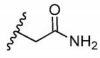
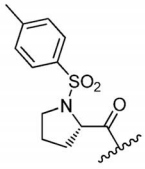
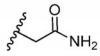
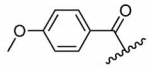
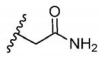
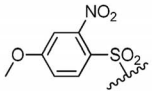
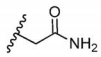
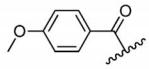
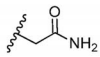
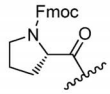
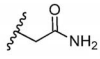
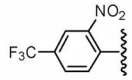
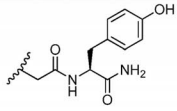
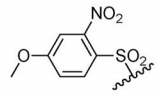
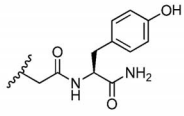
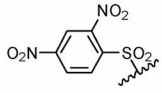
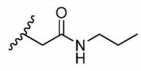
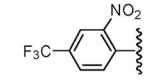
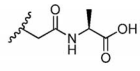
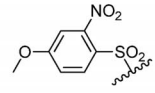
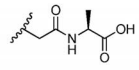
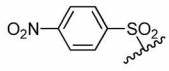
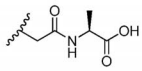
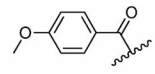
Table 2. Correlation of the ratio of bridged **6** to the Hammett constant σ of the substituents on the aromatic rings of R^3 from the sulfonamides.

Resin	Substituent	σ_{para}[a]	σ_{ortho}[b]	σ_{sum}[c]	Amount of **6**[d] [%]
4(1,1,2)	4-OMe	–0.27	–	–0.27	44
4(1,1,3)	4-Me	–0.17	–	–0.17	62
4(1,1,4)	2-NO_2, 4-OMe	–0.27	0,51	0.24	83
4(1,1,5)	2-NO_2	–	0,51	0.51	90
4(1,1,2)	4-NO_2	0.78	–	0.78	89
4(1,1,7)	2-NO_2, 4-CF_3	0.54	0.51	1.05	95
4(1,1,8)	2,4-diNO_2	0.78	0.51	1.28	99

[a] Values from refs.[51,52] [b] Calculated by using $\sigma_{ortho} = 0.65\sigma_{para}$.[53] [c] Sum of the corresponding *ortho* and *para* constants.[54] [d] Based on the relative amount of product **6**, estimated from the LC traces at 240 nm.

is directly linked to the nitrogen atom involved in the formation of the cyclic iminium. Thus, the first set of compounds were prepared with different R^3 groups and included *N*-arylsulfonyl, *N*-alkyl, *N*-aryl, and *N*-acyl derivatives.

Table 3. Synthesized derivatives of (*S*)-3-(hydroxymethyl)-3,4-dihydropyrazin-2(1*H*)-one **7** and (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octane **6**.

Resin	R^1	R^2	R^3	Cleavage	Ratio[a] **6**:**7** Yield[b] **6**/**7**
4(1,1,1)		H		A	39:61 41/46
4(1,1,2)		H		A	44:56 12/30
4(1,1,3)		H		A	62:38 47/39
4(1,1,4)		H		A	83:17 36/24
4(1,1,5)		H		A	90:10 50/11
4(1,1,6)		H		A	89:11 37/10
4(1,1,7)		H		A	95:5 41/NI
4(1,1,8)		H		A	>99:<1 55/NI
4(1,1,9)		H		A	<1:>99 NI/NI
4(1,1,10)		H		A	<1:>99 NI/50
4(1,2,4)		CH_3		A	99:1 69/4
4(1,2,10)		CH_3		A	95:5 71/NI
4(1,2,11)		CH_3		A	86:14 81/NI
4(1,2,12)		CH_3		A	85:15 51/NI
4(2,1,4)		H		A	81:19 27/17
4(2,1,8)		H		A	99:1 17/NI
4(3,1,12)		H		A	<1:>99 NI/44
4(4,1,4)		H		A	84:16 95/NI
4(4,1,6)		H		A	99:1 84/NI
4(4,1,10)		H		C	60:30 43/NI
4(4,1,13)		H		C	99:1 31/NI
4(4,2,4)		CH_3		A	99:1 90/NI
4(4,2,6)		CH_3		A	99:1 74/NI
4(5,1,4)		H		B	82:18 23/NI
4(6,1,4)		H		B	79:21 14/8
4(7,1,3)		H		A	60:40 36/39
4(7,1,7)		H		A	99:1 12/NI

[a] The relative ratios of products **6**/**7** were estimated from the LC traces at 240 nm. [b] Yield [%] after HPLC purification based on initial loading of the resin. NI, not isolated. Cleavage protocol A: 50% TFA in DCM, 1.5 h; B: 5% water in TFA, 1.5 h; C: 0.5 M NaOH in THF/MeOH (1:1) 30 min, isolation, then formic acid, 1 h.

tives. Table 3 summarizes the influence of the R^3 substituent on the ratio of the final products **6** and **7** (as well as the R groups numbering).

The urethane derivative [R^3 = Fmoc; **4(1,1,1)**] formed both products, with enamide **7** being the major component. The sulfonamides afforded various ratios of both products; the relative quantity of bicycle **6** increased with increasing electron-withdrawing nature of the substituents present on the aromatic ring (OMe < Me < OMe + NO_2 < NO_2 ≈ CF_3 + NO_2 ≈ $2NO_2$) and the trend corresponds to the Hammett constants of the substituents (Table 2).

The *N*-acyl derivatives, including *p*Tos-Pro [**4(1,1,9)**], 4-methoxybenzoyl [**4(1,1,10)**] and 4-trifluoromethylbenzoyl [**4(1,1,11)**], completely decomposed to enamide **7** when prepared on the Rink amide resin and cleaved by using 50% TFA in DCM (Table 3). Thus, the acid-labile bridged compound **6** was synthesized on the Wang ester linker followed by cleavage of the protected linear precursor with 0.5 M NaOH in THF/MeOH for 30 min and cyclization by using formic acid in solution. The *N*-acyl derivatives exhibited the same trend in stability as the *N*-sulfonyl derivatives: The 4-methoxy derivative **4(4,1,10)** partially decomposed to the enamide, whereas the 4-trifluoromethylbenzoyl compound **4(4,1,13)** was stable under these conditions. The NMR spectra of the *N*-acyl derivatives indicated the formation of rotamers. The presence of two rotamers is manifested by the existence of two singlet lines in the ^{1}H NMR spectra, corresponding to the Ala methyl protons. We present the NMR spectra of the major rotamers in the Supporting Information. In addition, the ^{1}H NMR spectra of the *N*-acylated target compounds show broad, unresolved peaks for both methines at room temperature. Therefore the spectrum of the derivative **6(4,1,13)** was measured at an elevated temperature (50 °C).

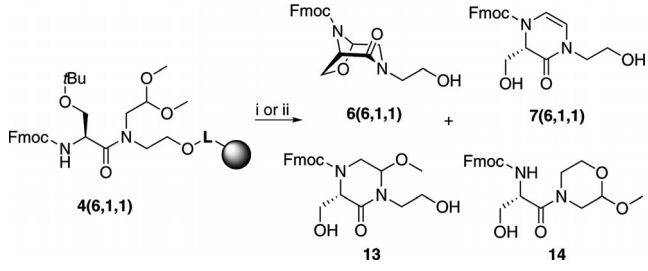
Although two strong electron-withdrawing groups (CF_3 and NO_2) are present on the aromatic ring, the *N*-aryl derivative **4(3,1,12)** yielded only the corresponding enamide **7**; the ^{1}H NMR spectrum revealed the presence of characteristic olefin resonances. The *N*-alkylated precursors decomposed during cleavage from the resin and neither product could be identified.

To obtain target compounds with three points of diversification, we introduced methyl as the R^2 group into the molecule and synthesized **4(R^1,2,R^3)** resins with Fmoc-Thr(*t*Bu)-OH. The presence of the methyl group significantly increased the acid stability of bridged scaffold **6**, which was formed almost exclusively, including the *N*-acyl and *N*-aryl derivatives **6(1,2,10)**, **6(1,2,11)**, and **6(1,2,12)**. The derivative **6(1,2,11)** with N-terminal Pro documents the incorporation of the bridged constraint into a peptide.

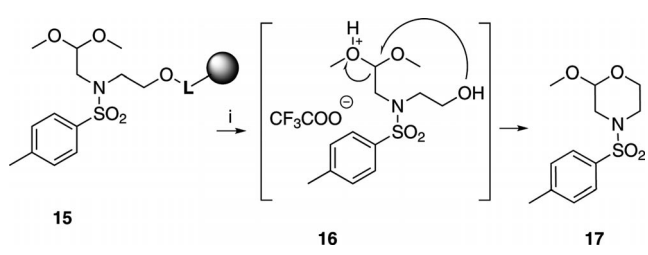
Having addressed the effects of the R^2 and R^3 groups on the outcome of the reaction, we focused on the importance of the R^1 group on the formation of bicycle **6**. We prepared several R^1-derivatized compounds with 4-methoxy-2-nitrophenylsulfonyl because this R^3 group led to the formation of both the enamide **7** and bicycle **6** and allowed the effect of the R^1 substituent on the formation of the bicycle to be assessed. In addition, 4-trifluoromethyl-2-nitrophenylsulfonyl and 2,4-dinitrophenylsulfonyl derivatives were prepared as a result of the high purity of their corresponding bicycles (**6**). To document the compatibility of this method with peptide synthesis, we extended the R^1 chain by one amino acid towards the C terminus and prepared the Gly-Tyr-NH_2 derivative as a terminal amide [**4(2,1,4)**] and the Gly-Ala-OH compound as a terminal carboxylate [**4(4,1,4)**]. To obtain compounds with alcohol and amine terminal groups, *N*-(2-hydroxyethyl) [**4(6,1,4)**] and *N*-(2-aminopropyl) [**4(5,1,4)**] resins were prepared. No compounds exhibited significant variation in their **6**/**7** ratios, thus proving the expected independence of the R^1 group on the acid stability.

The synthesis of the *N*-(2-hydroxyethyl) derivative **4(6,1,4)** deserved further attention because it behaved differently. The LC–MS analysis of the crude Fmoc derivative **4(6,1,1)** revealed the presence of one major product (purity >5%) when using the conventional cleavage cocktail of 50% TFA in DCM. However, the mass spectrum indicated the presence of a species with *m*/*z* = 427, which formally corresponds to the potential methoxy derivative **13** or **14** (Scheme 4). Attempts to purify and characterize the putative methoxy derivatives and determine their structures were unsuccessful because the product was unstable and decomposed. The use of a cleavage cocktail containing 5% water in 95% TFA yielded a product with the expected molecular ion in the mass spectrum (*m*/*z* = 395). Thus, we continued with the synthesis, prepared the sulfonamide **4(6,1,4)**, and cleaved the product by using 5% water in 95% TFA. The product was isolated and fully characterized as the expected bridged compound **6**.

Owing to the instability of the putative *N*-acyl methoxy derivatives **13** and **14**, we prepared the simpler *N*-*p*Tos



Scheme 4. Potential products formed by cleavage of the resin-bound compound **4(6,1,1)**. Reagents and conditions: (i) TES, 50% TFA in DCM, room temp., 30 min; (ii) 50% TFA in DCM, room temp., 30 min.



Scheme 5. Alternate cyclization route. Reagents and conditions: (i) TES, 50% TFA in DCM, room temp., 1 h.

model compound **15**, for which only one mode of cyclization[55] was possible (Scheme 5). The synthesis was carried out on resin **1(6)** [R^1 = *N*-(2-hydroxyethyl)]. Cleavage of the 4-Nos group was followed by reaction with *p*Tos-Cl to yield resin **15**. After cleavage from the resin with 50% TFA in DCM, product **17** was isolated and its structure was confirmed by NMR spectroscopy and HRMS.

Conclusions

We have developed a polymer-supported, stereoselective synthesis of the (1*S*,5*S*)-6-oxa-3,8-diazabicyclo[3.2.1]octane bridged scaffold by tandem iminium ion cyclization/nucleophilic addition reactions. The 7-methyl derivatives prepared by using Thr were acid-stable, whereas the Ser-derived compounds suffered a partial acid-mediated transformation into enamides. Substitution at the iminium-forming nitrogen was critical for the acid stability of these target compounds. The *N*-arylsulfonamide derivatives bearing electron-withdrawing groups were stable, whereas the *N*-acyl derivatives were substantially more acid labile and were prepared by the hydroxide-mediated hydrolysis of their acyclic precursors from the Wang ester resin followed by cyclization with formic acid in solution. The synthesized compounds will serve as scaffolds for the construction of compound libraries and as peptide backbone-constrained peptidomimetics.

Experimental Section

General: The solid-phase syntheses were carried out in plastic reaction vessels (syringes, each equipped with a porous disc). The volume of the wash solvent was 10 mL per 1 g of resin. The resin slurry was washed by shaking with fresh solvent for at least 1 min before changing the solvent. All reactions were carried out at ambient temperature unless stated otherwise. Commercially available Rink resin (100–200 mesh, 0.66 mmol/g) and Wang resin (100–200 mesh, 1.0 mmol/g) were used. Individual synthetic steps for the synthesis of resins **1**–**4** have been described in our recent publications.[5,46] CCDC-932765 [for **6(1,1,6)**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acid-Mediated Cleavage, Cyclization, and Isolation (6, 7, and 17): Resin **4** (250 mg) was treated with 50% TFA in DCM (3 mL, v/v; Route I) or with 95% TFA in water (3 mL, v/v; Route II) for 90 min. The TFA solution was collected, the resin was washed three times with 50% TFA in DCM (3 mL), and the combined extracts were evaporated in a stream of nitrogen. The residual material was analyzed by LC–MS. The products were purified by semi-preparative reversed-phase HPLC. All products were characterized by LC–MS, HRMS, and ^{1}H and ^{13}C NMR spectroscopy.

Hydrolysis from the Wang Resin, Cyclization, and Isolation [8(4,R^2,R^3)]: The resin **4(4,R^2,R^3)** (250 mg) was washed three times with THF and treated with 0.5 M NaOH in MeOH/THF (1:1, v/v; 3 mL) for 30 min. The solution was collected and the resin was washed three times with MeOH (3 mL). The combined solutions were neutralized with AcOH and the products isolated by HPLC. The protected intermediates were treated with formic acid (1 mL) for 1 h. The solution was then diluted with water (1 mL) and purified by semi-preparative reversed-phase HPLC. All products were characterized by LC–MS, HRMS, and ^{1}H and ^{13}C NMR spectroscopy.

Supporting Information (see footnote on the first page of this article): Materials and methods, product characterization data, ^{1}H and ^{13}C NMR spectra, and crystallographic data.

Acknowledgments

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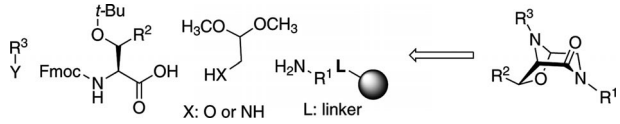

The title compounds were prepared by tandem iminium ion cyclization/nucleophilic addition reactions. The scope and limitations of the chemical route leading to the bridged scaffold were evaluated. The Thr-derived bridged scaffold is substantially more stable in acid than the Ser-derived scaffold, which is partially transformed into dihydropyrazinones.

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Polymer-Supported Stereoselective Synthesis of (1*S*,5*S*)-6-Oxa-3,8-diazabicyclo-[3.2.1]octanes

Keywords: Peptidomimetics / Heterocycles / Nucleophilic addition / Solid-phase synthesis / Bicyclic compounds

