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A new approach to cyclic hydroxamic acids: intramolecular cyclization of *N*-benzyloxy carbamates with carbon nucleophiles

Yuan Liu, Hollie K. Jacobs, Aravamudan S. Gopalan *

Department of Chemistry and Biochemistry, MSC 3C, New Mexico State University, Las Cruces, NM 88003-8001, USA

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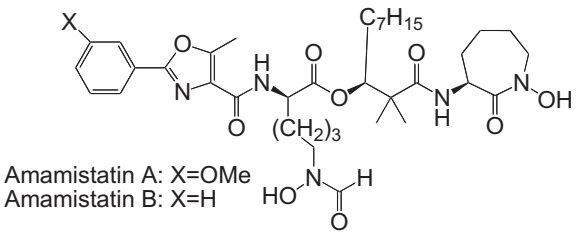
ABSTRACT

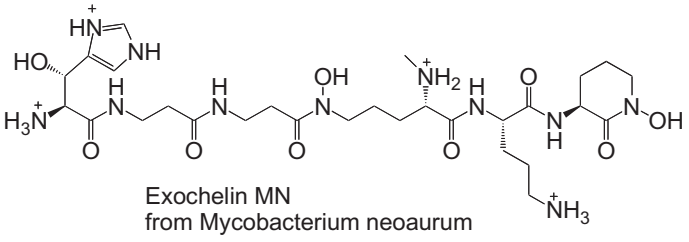
N-Alkyl-*N*-benzyloxy carbamates, **2**, undergo facile intramolecular cyclization with a variety of carbon nucleophiles to give functionalized five- and six-membered protected cyclic hydroxamic acids, **3**, in good to excellent yields. This method can be extended to prepare seven-membered cyclic hydroxamic acids in moderate yields. The sulfone intermediates **3** from this study can be alkylated while the corresponding phosphonates have been shown to undergo HWE reaction. The α,β-unsaturated synthon, **8**, prepared by thermal elimination of sulfoxide **3m**, undergoes Michael addition with secondary amines. The usefulness of this approach to prepare polydentate chelators has been demonstrated by the synthesis of bis cyclic hydroxamic acids **12**, **14**, and **15**.

1. Introduction

Hydroxamic acids are a commonly found ligand in many siderophores and have received much attention due to their diverse biological activity that ranges from matrix metalloproteinase and histone deacetylase inhibition to therapeutic applications in the treatment of iron overload diseases.[1] On the other hand, the corresponding cyclic hydroxamic acids, have not been as widely studied. Although not as ubiquitous, cyclic hydroxamic acids are an interesting class of compounds that are present in a variety of natural products, which exhibit varied biological activity.

Mycobacteria, such as *mycobacterium tuberculosis*, which causes tuberculosis in humans, are the source of numerous infections worldwide.[2] Mycobacteria require iron for their growth and produce several classes of siderophores including mycobactins, exochelins, and carboxymycobactins for iron acquisition.[3,4] A common feature in these siderophores is a seven-membered cyclic hydroxamic acid although a few like exochelin MN[5] have a six-membered hydroxamic acid. Many other natural products that are structurally related to the mycobactins have been isolated, such as the amamistatins, nocardimicins, formobactin, nocobactin, and brasilibactin, all of which also have seven-membered cyclic hydroxamic acids. Nocardimicins have been shown to inhibit the muscarinic M3 receptor.[6] Amamistatins A[7] and B[8] as well as brasilibactin[9] have shown an antiproliferative effect against several human tumor cell lines. Incorporation of a seven-membered cyclic hydroxamic acid into the benzodiazepine core structure has resulted in compounds with anticancer activity.[10] Some cyclic hydroxamic acids have been shown to be inhibitors of matrix metalloproteinases.[11]





Several approaches for the synthesis of cyclic non-conjugated hydroxamic acids, **1**, have been reported. Probably the most commonly used method involves the formation of the amide bond, by reaction of a hydroxylamine with an acid derivative (bond a).

* Corresponding author. E-mail address: agopalan@nmsu.edu (A.S. Gopalan).

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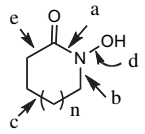
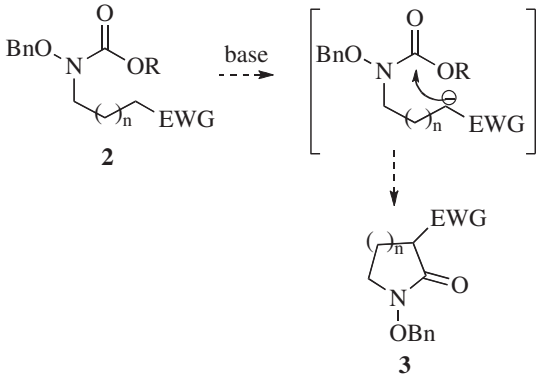
Methods that have been reported include reduction of an oxime in the presence of an activated acid,[12] treatment of a nitrone with hydroxylamine hydrochloride followed by cyclization with EDC and HOAt,[13] reductive cyclization of nitro alkylcarboxylic acids using Zn[14] or hydrogenation of nitrolactones.[15] An on-resin cyclization of a resin-supported hydroxylamine with an activated ester has also been reported.[16] A less commonly used strategy for cyclic hydroxamate ring formation involves *N*-alkylation to form bond 'b'. Alkylation of 4-chlorobutyro-*O*-benzylhydroxamate using sodium hydride followed by hydrogenation was used to prepare the five-membered ring cyclic hydroxamic acid.[17] Formation of bond 'b' has also been accomplished via an intramolecular acylnitroso ene reaction to form spirocyclic hydroxamic acids.[18] The synthesis of seven-membered cyclic hydroxamic acids using Grubbs RCM (bond c) has been recently reported.[19] Oxidation of a lactam to the corresponding cyclic hydroxamic acid (bond d) using a variety of oxidizing agents has been used.[20] Recently, cyclic hydroxamic acids have been prepared by NOH insertion into cyclic ketones.[21] An alternate strategy to synthesize cyclic hydroxamic acids would involve the formation of bond 'e' in the key step. To our knowledge, there have been no reports on the synthesis of cyclic hydroxamic acids via formation of bond 'e'.



1

Some recent discoveries in our laboratory led us to believe that the formation of cyclic hydroxamic acids via intramolecular acylation reactions to form the C–C bond (bond e) may be feasible and provide an attractive alternate method to prepare cyclic hydroxamic acid derivatives. We recently discovered that stabilized carbanions react with *N*-benzyloxy carbamates to give the corresponding protected hydroxamic acids.[22] It is also known that lactams can be prepared by intramolecular cyclization of α-sulfonyl carbanions with carbamates.[23] The question was whether these findings were applicable for the development of a new approach to prepare protected cyclic hydroxamic acids, **3**, via intramolecular acylation of *N*-benzyloxy carbamates, **2** (Scheme 1). The goal was to prepare an array of cyclic hydroxamic acids (ring size 5–7) incorporating different electron withdrawing groups that would allow synthetic options for further manipulation.



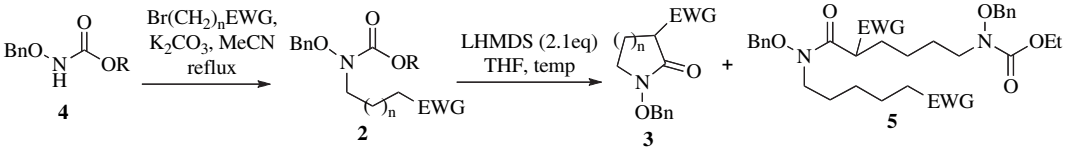
Scheme 1.

2. Results and discussion

The *N*-benzyloxy carbamate derivatives **2** required for this study were prepared in high yields by treating *N*-benzyloxy-carbamic acid ethyl ester **4**[22] with a variety of alkylating reagents in the presence of K_2CO_3 in MeCN at reflux (Table 1). The alkylating reagents were either commercially available or easily prepared from commercially available reagents. The sulfoxide derivatives **2l** and **2m** were prepared by alkylation of **4** with bromopropylphenyl sulfide or bromobutylphenyl sulfide, respectively, followed by oxidation of the sulfide using 1.1 equiv of sodium metaperiodate in MeOH/H_2O (2:3).

With the *N*-benzyloxy carbamate derivatives in hand, it was time to examine their intramolecular cyclization reactions. The *N*-

Table 1
Synthesis and intramolecular cyclization of *N*-benzyloxy carbamate derivatives, **2**



EWG	*n*	Carbamate[a] **2** (yield %)	Temp °C	**3** (yield %)	**5** (yield %)
SO_2Ph	1	**2a** (90)	−78	**3a** (97)	
SO_2Ph	2	**2b** (95)	−78	**3b** (86)	
SO_2Ph	3	**2c** (94)	−78	**3c** (0)	**5c** (44)
SO_2Ph	3	**2c'** (89)[b]	rt	**3c** (35)	
CO_2Et	1	**2d** (94)	−78	**3d** (77)	
CO_2Et	2	**2e** (86)	−78	**3e** (81)	
CO_2Et	3	**2f** (86)	−78	**3f** (32)	**5f** (60)
CN	1	**2g** (93)	−78	**3g** (93)	
CN	2	**2h** (90)	−78	**3h** (92)	
CN	3	**2i** (88)	rt	**3i** (58)	
$PO(OEt)_2$	1	**2j** (94)	0	**3j** (89)	
$PO(OEt)_2$	2	**2k** (89)	0	**3k** (76)	
SOPh	1	**2l** (42)[c]	rt	**3l** (74)[d]	
SOPh	2	**2m** (57)[c]	0	**3m** (89)[e]	

[a] R=Et.
[b] R=tBu.
[c] Two steps: i. alkylation with bromoalkyl phenyl sulfide ii. oxidation with 1.1 equiv $NaIO_4$, MeOH/H_2O (2:3).
[d] Diastereomeric mixture in 2:1 ratio according to ^1H NMR.
[e] Diastereomeric mixture in 1:1 ratio according to ^1H NMR.

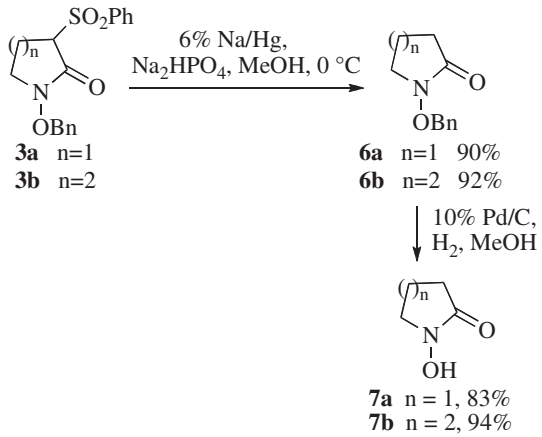
benzyloxy carbamate **2a** was treated with 2.1 equiv of LHMDS at −78 °C in THF and the reaction progress monitored by TLC. After 5 h, the reaction was quenched with 10% acetic acid. Chromatographic purification gave the benzyl protected five-membered cyclic hydroxamic acid **3a** in 97% yield.

Our study showed that this intramolecular cyclization methodology could be readily extended to the formation of other five- and six-membered cyclic hydroxamic acids with a variety of electron withdrawing groups in the α position of the carbonyl group (Table 1). In the case of sulfoxide stabilized carbamates **2l** and **2m**, the cyclization proceeded better at a slightly higher temperature and gave a diastereomeric mixture of products (**3l** and **3m**) in approximately 2:1 and 1:1 ratio, respectively, as evidenced by ^{1}H NMR spectra.

In contrast to the high yields observed in the formation of the five- and six-membered ring cyclic hydroxamic acids, the results with the corresponding seven-membered ring formation were less satisfactory. When sulfone **2c** was treated with 2.1 equiv of LHMDS in THF at −78 °C, the major isolated product was **5c**, which is the result of intermolecular acylation. Variation of the experimental conditions, including dilution, changing the reaction temperature and using different equivalents of base, did not change the course of this reaction. To suppress the undesired intermolecular coupling reaction, we prepared the corresponding *tert*-butyl carbamate, **2c′**, for investigation. Interestingly, when *tert*-butyl carbamate **2c′** was used in the cyclization and the reaction allowed to warm to rt, the desired cyclized product **3c** was isolated in 35% yield, along with recovered staring material (45%). Presumably, the presence of the bulky *tert*-butyl ester moiety deters the intermolecular reaction and allows the intramolecular cyclization to proceed to some extent.

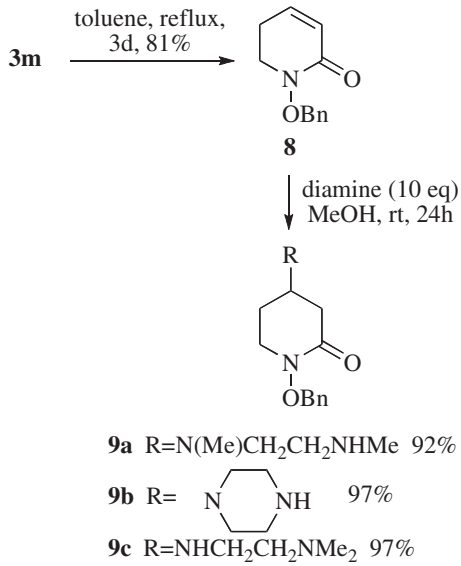
The intramolecular cyclization of ester **2f** gave some of the desired cyclized seven-membered hydroxamate derivative **3f** in 32% yield along with the corresponding dimeric product **5f** (60%). In the case of nitrile **2i**, only the cyclized product, **3i**, was isolated in 58% yield after warming the reaction mixture to rt.

The known 1-hydroxy-2-pyrrolidone and 1-hydroxy-2-piperidone could be readily prepared from the corresponding intermediates **3a** and **3b** by desulfonylation followed by hydrogenolysis to remove the protecting group (Scheme 2). Treatment of **3a** with 6% sodium amalgam in the presence of disodium hydrogen phosphate in MeOH afforded the desulfonylation product **6a** in 90% yield after chromatographic purification. The cleavage of the benzyl group of **6a** was performed using 10% Pd on carbon in MeOH under a hydrogen balloon at rt, to give the five-membered cyclic hydroxamic acid **7a**[20c], in 83% yield. Using a similar synthetic sequence, the six-membered cyclic hydroxamic acid, **7b**[20a,d], was synthesized in 86% overall yield from **3b**. A tris complex of Ga(III) with cyclic hydroxamic acid **7b** has been reported for the treatment of hypercalcemia of malignancy and related disorders of bone metabolism.[24]



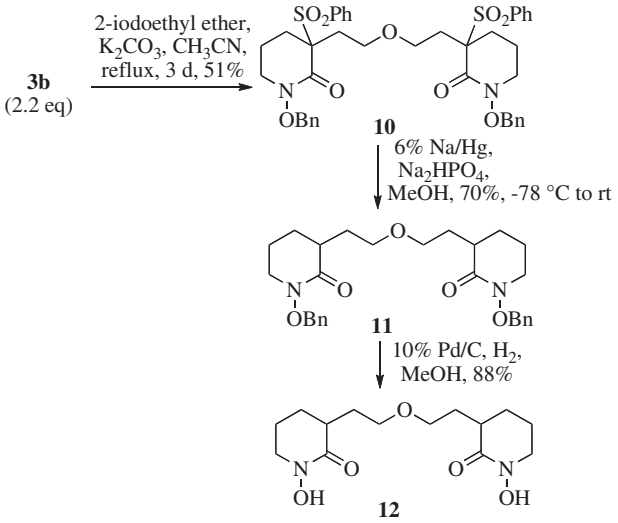
Scheme 2.

The availability of cyclic hydroxamic acid derivatives **3** functionalized with sulfone, sulfoxide and phosphonates in the α position, allows numerous options for further manipulation of the ligand moiety. For example, heating the sulfoxide **3m**, in refluxing toluene gave the unsaturated *N*-benzyloxy lactam **8** in 81% yield (Scheme 3). The conjugate addition reactions of **8** were of interest to us. Treatment of **8** with 1 equiv of *N*,*N′*-dimethyl ethylenediamine in methanol at rt gave only starting materials. However, when **8** was treated with 10 equiv of *N*,*N′*-dimethyl ethylenediamine in methanol at rt, the desired mono-adduct was obtained in 92% yield. Indeed, the Michael addition of **8** with a large excess of readily available diamines proceeded smoothly to give the corresponding mono-adducts in excellent yields. This is a useful result as the secondary amines in **9** provide handles for subsequent coupling of the cyclic hydroxamic unit onto acid chlorides and biomolecules of interest.



Scheme 3.

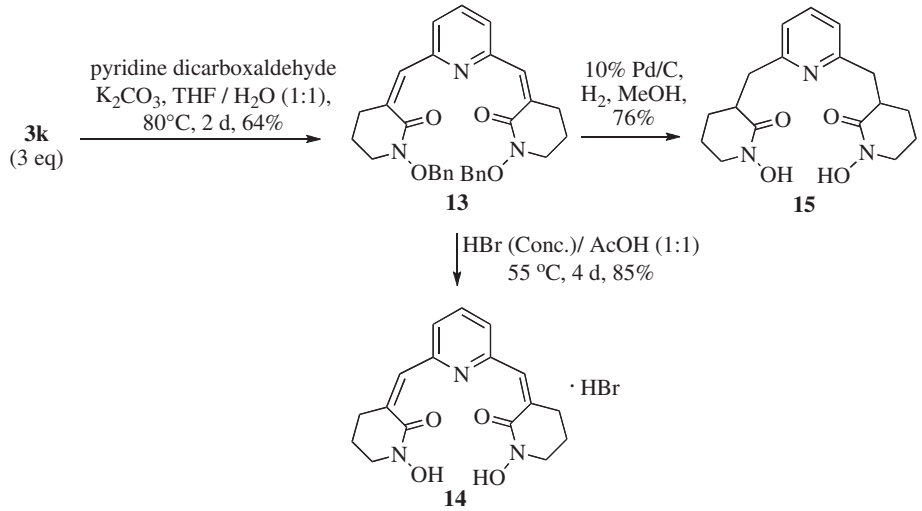
The intermediates **3** are also useful for the preparation of novel polydentate cyclic hydroxamic chelators, a class of ligands whose synthesis, chemistry and biological properties have not been studied. The sulfone derivative **3b** appeared well-suited for alkylation reactions. Alkylation of 2.2 equiv of **3b** with 2-iodoethyl ether in the presence of excess potassium carbonate in refluxing



Scheme 4.

acetonitrile gave the desired dialkylation product **10** in 51% yield (Scheme 4). Desulfonylation using 6% Na/Hg amalgam and disodium hydrogen phosphate in methanol gave **11** in 70% yield after purification. Finally, debenzylation using hydrogenolysis gave the bis cyclic hydroxamic acid **12**.

The phosphonate **3k** is ideally suited for coupling with aldehydes using the well-known Horner–Wittig–Emmons reaction. To demonstrate its synthetic utility, phosphonate **3k** (3 equiv) was heated with 2,6-pyridine dicarboxaldehyde in the presence of potassium carbonate in THF/H_2O (1:1) at 80 °C for two days (Scheme 5).[25] The bisalkene, **13**, with *Z,Z*-configuration, as evidenced by coupling constant analysis of the ^{1}H NMR spectra, was isolated as the major product in 64% yield after chromatographic purification. The benzyl protecting groups of **13** were removed using concentrated HBr/AcOH (1:1) at 55 °C to obtain the pyridine bis cyclic hydroxamic acid ligand **14**. The ligand **14** was isolated as the hydrobromide salt in 85% yield. We also prepared the saturated analog, **15**, for comparison purposes. Concurrent deprotection and reduction of the double bond of the bisalkene **13** were achieved using 10% Pd/C under hydrogen atmosphere to give the saturated pyridine bis cyclic hydroxamic acid **15** in 76% yield as a 1:1 mixture of diastereomers.



Scheme 5.

3. Conclusions

Given the increasing interest in the chemistry and biology of cyclic hydroxamic acids, methods for their preparation and derivatization are important. In this paper, we have shown that stabilized carbanions undergo intramolecular cyclization with internal *N*-benzyloxy carbamates to give functionalized cyclic hydroxamic acids. This provides a new and flexible approach to access this class of molecules. The usefulness of the intermediates obtained from this study has been clearly shown. The unsaturated *N*-benzyloxy lactam **8**, is useful for conjugate addition reactions with amines. Both the sulfone and phosphonate derivatives **3b** and **3k**, permit the tethering of this ligand onto various host molecules. The synthetic value of intermediates **3b** and **3k** has been shown by the preparation of novel classes of bis cyclic hydroxamic acids whose properties remain to be explored.

4. Experimental

4.1. General methods

Melting points were obtained on an Electrothermal® melting point apparatus and are uncorrected. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Varian XL 200. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 MHz Varian NMR. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Unity 400 spectrometer. NMR spectral samples were prepared in $CDCl_3$, CD_3OD, or D_2O as noted. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (TMS) reference for $CDCl_3$ and CD_3OD samples. For ^{1}H spectra obtained in D_2O, the HOD peak was set to 4.72 ppm and used as an internal reference. For ^{13}C spectra obtained in D_2O, 1,4-dioxane (66.5 ppm) was used as an internal reference. Analytical and preparative thin layer chromatography were performed on silica 60/F_{254} plastic plates (EM Science). Column chromatography was performed on silica gel (Merck 60–200 mesh) or basic alumina (Aldrich 150 mesh). Radial chromatography was performed on a Harrison Research, Inc. Chromatotron®. Chromatography solvents were reagent grade and were obtained from either Fisher Scientific or VWR Scientific. Reagents were obtained from Aldrich or Lancaster chemical companies and were used as received. *tert*-Butyl *N*-benzyloxy carbamate was obtained from Sigma–Aldrich. Anhydrous THF was collected from a GlassContour™ solvent purification system. Other dry solvents (CH_3CN, CH_2Cl_2, etc.) were obtained from Acros. Desert Analytics, Tucson, Arizona performed elemental analyses. HRMS analyses were performed by the University of California Riverside Mass Spectrometry Facility.

4.2. Representative procedure for the preparation of carbamates 2

*4.2.1. (3-Benzenesulfonylpropyl)-N-benzyloxy-carbamic acid ethyl ester (**2a**).* Potassium carbonate (0.304 g, 2.2 mmol) was added to a solution of **4**[22] (0.086 g, 0.44 mmol) and 3-bromopropylphenyl sulfone (0.139 g, 0.53 mmol) in MeCN (4 mL) and the mixture was stirred at reflux overnight. The mixture was poured into water (60 mL) and extracted with CH_2Cl_2 (4×15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane=1:2–1:1) to give sulfone **2a** as a colorless oil (0.15 g, 90.4%); IR(neat) 2982, 1699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97–7.77 (m, 2H), 7.72–7.43 (m, 3H), 7.41–7.28 (m, 5H), 4.80 (s, 2H), 4.19 (q, J=7.0 Hz, 2H), 3.53 (t, J=6.6 Hz, 2H), 3.15–3.07 (m, 2H), 2.03–1.95 (m, 2H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.2, 139.0, 135.1, 133.7, 129.4, 129.3, 128.7, 128.5, 128.0, 77.2, 62.3, 53.7, 48.1, 20.9,

14.5. Anal. Calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71. Found: C, 60.68; H, 6.15; N, 3.58.

*4.2.2. (4-Benzenesulfonylbutyl)-N-benzyloxy-carbamic acid ethyl ester (**2b**).* The representative procedure was followed using 3-bromobutylphenyl sulfone as the alkylating reagent to give **2b** as a colorless oil; 94.9% yield; IR (neat) 2938, 1699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98–7.81 (m, 2H), 7.74–7.47 (m, 3H), 7.47–7.30 (m, 5H), 4.81 (s, 2H), 4.19 (q, J=7.0 Hz, 2H), 3.40 (t, J=6.6 Hz 2H), 3.06 (t, J=7.3 Hz, 2H), 1.85–1.49 (m, 4H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.3, 139.2, 135.4, 133.6, 129.3, 129.2, 128.6, 128.4, 128.0, 77.1, 62.1, 55.7, 48.7, 25.7, 20.0, 14.5. Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.20; H, 6.17; N, 3.53.

*4.2.3. (5-Benzenesulfonylpentyl)-N-benzyloxy-carbamic acid ethyl ester (**2c**).* The representative procedure was followed using 3-bromopentylphenyl sulfone as the alkylating reagent to give **2c** as a colorless oil; 94.1% yield; IR (neat) 2941, 1704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00–7.81 (m, 2H), 7.74–7.48 (m, 3H), 7.46–7.29 (m, 5H), 4.82 (s, 2H), 4.19 (q, J=7.0 Hz, 2H), 3.38 (t, J=6.6 Hz, 2H), 3.09–3.01 (m, 2H), 1.84–1.46 (m, 4H), 1.46–1.25 (m, 2H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4, 139.2, 135.5, 133.6, 129.3, 129.2, 128.6, 128.4, 128.0, 77.0, 62.0, 56.1, 49.2, 26.5, 25.4, 22.4, 14.5. Anal. Calcd for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.14; H, 6.73; N, 3.30.

*4.2.4. (5-Benzenesulfonypentyl)-N-benzyloxy-carbamic acid tert-butyl ester (**2c′**).* The representative procedure was followed using *tert*-butyl *N*-benzyloxy carbamate in place of **4** and 5-bromopentylphenyl sulfone as the alkylating reagent to give **2c′** as a colorless oil; 88.7% yield; IR (neat) 2976, 2938, 1699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.02–7.81 (m, 2H), 7.76–7.48 (m, 3H), 7.47–7.30 (m, 5H), 4.79 (s, 2H), 3.35 (t, J=7.0 Hz, 2H), 3.05 (t, J=8.1 Hz, 2H), 1.82–1.60 (m, 2H), 1.49 (s, 9H), 1.44–1.19 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.4, 139.3, 135.7, 133.6, 129.3, 129.2, 128.5, 128.4, 128.0, 81.2, 76.8, 56.1, 49.1, 28.3, 26.5, 25.4, 22.4. Anal. Calcd for $C_{23}H_{31}NO_5S$: C, 63.72; H, 7.21; N, 3.23. Found: C, 63.61; H, 7.22; N, 3.22.

*4.2.5. 4-(N-Benzyloxy-ethoxycarbonyl-amino)-butyric acid ethyl ester (**2d**).* The representative procedure was followed using ethyl 4-bromobutyrate as the alkylating reagent to give **2d** as a colorless oil; 93.7% yield; IR (neat) 2982, 2940, 1733, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5H), 4.86 (s, 2H), 4.22 (q, J=7.3 Hz, 2H), 4.12 (q, J=7.3 Hz, 2H), 3.50 (t, J=7.0 Hz, 2H), 2.33 (t, J=7.3 Hz, 2H), 1.92 (quin, J=7.0 Hz, 2H), 1.31 (t, J=7.3 Hz, 3H), 1.24 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 157.4, 135.4, 129.4, 128.6, 128.5, 77.1, 62.1, 60.4, 48.9, 31.4, 22.5, 14.6, 14.2. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.26; H, 7.39; N, 4.43.

*4.2.6. 5-(N-Benzyloxy-ethoxycarbonyl-amino)-pentanoic acid ethyl ester (**2e**).* The representative procedure was followed using ethyl 5-bromovalerate as the alkylating reagent to give **2e** as a colorless oil: 85.6% yield; IR (neat) 2981, 2939, 1732, 1702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48–7.29 (m, 5H), 4.86 (s, 2H), 4.22 (q, J=7.3 Hz, 2H), 4.11 (q, J=7.0 Hz, 2H), 3.45 (t, J=7.0 Hz, 2H), 2.30 (t, J=7.3 Hz, 2H), 1.66–1.57 (m, 4H), 1.31 (t, J=7.3 Hz, 3H), 1.24 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 157.5, 135.6, 129.3, 128.5, 128.4, 77.1, 62.0, 60.2, 48.3, 33.8, 26.5, 22.1, 14.6, 14.2. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.06; H, 7.69; N, 4.37.

*4.2.7. 6-(N-Benzyloxy-ethoxycarbonyl-amino)-hexanoic acid ethyl ester (**2f**).* The representative procedure was followed using ethyl 6-bromohexanoate as the alkylating reagent to give **2f** as a colorless oil; 86.1% yield; IR (neat) 2981, 2938, 1733, 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47–7.30 (m, 5H), 4.85 (s, 2H), 4.21 (q, J=7.2 Hz, 2H), 4.11 (q, J=7.1 Hz, 2H), 3.43 (t, J=7.0 Hz, 2H), 2.28 (t, J=7.1 Hz, 2H), 1.66–1.55 (m, 6H), 1.31 (t, J=7.0 Hz, 3H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 157.5, 135.6, 129.3, 128.5, 128.4, 77.1, 62.0, 60.1, 49.6, 34.2, 26.7, 26.2, 24.6, 14.6, 14.2. Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.16; H, 7.84; N, 4.20.

*4.2.8. N-Benzyloxy-(3-cyanopropyl)-carbamic acid ethyl ester (**2g**).* The representative procedure was followed using 4-bromobutyronitrile as the alkylating reagent to give **2g** as a colorless oil; 92.7% yield; IR (neat) 2982, 2943, 2247, 1702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51–7.30 (m, 5H), 4.87 (s, 2H), 4.24 (q, J=7.3 Hz, 2H), 3.56 (t, J=6.6 Hz, 2H), 2.34 (t, J=7.0 Hz, 2H), 1.89 (quin, J=7.0 Hz, 2H), 1.34 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.2, 135.2, 129.5, 128.8, 128.6, 119.1, 77.2, 62.4, 48.2, 23.4, 14.8, 14.5. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.88; H, 7.07; N, 10.64.

*4.2.9. N-Benzyloxy-(4-cyanobutyl)-carbamic acid ethyl ester (**2h**).* The representative procedure was followed using 5-chlorovaleronitrile as the alkylating reagent to give **2h** as a colorless oil; 90.0% yield; IR (neat) 2917, 2247, 1699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51–7.29 (m, 5H), 4.86 (s, 2H), 4.23 (q, J=7.3 Hz, 2H), 3.47 (t, J=6.2 Hz, 2H), 2.33 (t, J=7.0 Hz, 2H), 1.72–1.64 (m, 4H), 1.33 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4, 135.4, 129.4, 128.7, 128.5, 119.4, 77.1, 62.2, 48.5, 26.1, 22.6, 16.7, 14.5. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.05; H, 7.34; N, 10.08.

*4.2.10. N-Benzyloxy-(4-cyanopentyl)-carbamic acid ethyl ester (**2i**).* The representative procedure was followed using 6-bromohexanonitrile as the alkylating reagent to give **2i** as a colorless oil; 88.2% yield; IR (neat) 2940, 2245, 1704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51–7.29 (m, 5H), 4.85 (s, 2H), 4.22 (q, J=7.2 Hz, 2H), 3.44 (t, J=6.8 Hz, 2H), 2.32 (t, J=7.0 Hz, 2H), 1.68–1.58 (m, 4H), 1.51–1.39 (m, 2H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4, 135.5, 129.3, 128.6, 128.5, 119.5, 77.1, 62.1, 48.2, 26.2, 25.7, 25.0, 17.0, 14.6. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: 66.21; H, 7.44; N, 9.71.

*4.2.11. [3-(N-Benzyloxy-ethoxycarbonyl-amino)-propyl]-phosphonic acid diethyl ester (**2j**).* The representative procedure was followed using diethyl 3-bromopropyl phosphonate as the alkylating reagent to give **2j** as a colorless oil; 93.5% yield; IR (neat) 2982, 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55–7.30 (m, 5H), 4.86 (s, 2H), 4.22 (q, J=7.0 Hz, 2H), 4.11 (quin, J=6.8 Hz, 4H), 3.52 (t, J=6.6 Hz, 2H), 1.94–1.68 (m, 4H), 1.35–1.27 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4, 135.4, 129.3, 128.6, 128.4, 77.2, 62.2, 61.6 (d, J=6.4 Hz), 50.0 (d, J=18.7 Hz), 23.1 (d, J=141.5 Hz), 20.4 (d, J=4.6 Hz), 16.5 (d, J=5.9 Hz), 14.6. Anal. Calcd for $C_{17}H_{28}NO_6P$: C, 54.68; H, 7.56; N, 3.75. Found: C, 54.60; H, 7.30; N, 3.91.

*4.2.12. [3-(N-Benzyloxy-ethoxycarbonyl-amino)-butyl]-phosphonic acid diethyl ester (**2k**).* The representative procedure was followed using diethyl 4-bromobutyl phosphonate as the alkylating reagent to give **2k** as a colorless oil; 89.4% yield; IR (neat) 2981, 1701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.49–7.30 (m, 5H), 4.85 (s, 2H), 4.21 (q, J=7.1 Hz, 2H), 4.07 (quin, J=7.1 Hz, 4H), 3.44 (t, J=6.4 Hz, 2H), 1.73–1.60 (m, 6H), 1.35–1.25 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4, 135.5, 129.3, 128.6, 128.5, 77.2, 62.1, 61.4 (d, J=6.8 Hz), 49.1, 27.9 (d, J=15.9 Hz), 25.4 (d, J=140.1 Hz), 19.8 (d, J=5.3 Hz), 16.5 (d, J=5.9 Hz), 14.6. Anal. Calcd for $C_{18}H_{30}NO_6P$: C, 55.80; H, 7.81; N, 3.62. Found: C, 56.14; H, 7.66; N, 3.91.

*4.2.13. (3-Benzenesulfinylpropyl)-N-benzyloxy-carbamic acid ethyl ester (**2l**).* The representative procedure was followed using 3-bromopropylphenyl sulfide as the alkylating reagent to give the corresponding sulfide as a colorless oil; 57.4% yield; IR (neat) 2934, 1701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51–7.15 (m, 10H), 4.83 (s, 2H), 4.20 (q, J=7.3 Hz, 2H), 3.57 (t, J=7.0 Hz, 2H), 2.90 (t, J=7.3 Hz, 2H),

1.91 (quintet, J=7.0 Hz, 2H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.4, 136.2, 135.4, 129.5, 129.3, 128.9, 128.6, 128.4, 126.1, 77.1, 62.1, 48.6, 31.1, 26.7, 14.5. A solution of sodium metaperiodate (0.121 g, 0.56 mmol) in H_2O (3 mL) was added to a solution of the sulfide (0.184 g, 0.51 mmol) in MeOH (2 mL) at 0 °C and the mixture stirred at rt for 24 h. The reaction mixture was poured into water (50 mL) and the product extracted into chloroform (3×20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and the solvent removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane=1:2–1:1) to give sulfoxide **2l** (0.140g, 73.3%) as a colorless oil; IR (neat) 2981, 1705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67–7.44 (m, 5H), 7.43–7.30 (m, 5H), 4.82 (s, 2H), 4.20 (q, J=7.0 Hz, 2H), 3.61–3.54 (m, 2H), 2.87–2.74 (m, 2H), 2.23–1.76 (m, 2H), 1.30 (t, J=7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.3, 143.7, 135.2, 130.9, 129.4, 129.2, 128.7, 128.5, 124.0, 77.1, 62.3, 54.4, 48.4, 20.2, 14.5.

*4.2.14. (3-Benzenesulfinylbutyl)-N-benzyloxy-carbamic acid ethyl ester (**2m**).* The representative procedure was followed using 4-bromobutylphenyl sulfide as the alkylating reagent to give the corresponding sulfide as a colorless oil; 77.5% yield; IR (neat) 2935, 1699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.07 (m, 10H), 4.84 (s, 2H), 4.21 (q, J=7.1 Hz, 2H), 3.44 (t, J=6.6 Hz, 2H), 2.90 (t, J=7.0 Hz, 2H), 1.71–1.63 (m, 4H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 136.5, 135.5, 129.3, 129.1, 128.8, 128.6, 128.4, 125.8, 77.1, 62.1, 49.2, 33.2, 26.3, 26.1, 14.6. A solution of sodium metaperiodate (0.786 g, 3.67 mmol) in H_2O (5 mL) was added to a solution of the sulfide (1.20 g, 3.34 mmol) in MeOH (5 mL) at 0 °C and the mixture stirred at rt for 14 h. The reaction mixture was poured into water (50 mL), and the product extracted into chloroform (3×30 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and the solvent removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane=1:2–1:1) to give sulfoxide **2m** (1.13 g, 90.1%) as colorless oil; IR (neat) 2937, 1695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69–7.44 (m, 5H), 7.44–7.29 (m, 5H), 4.82 (s, 2H), 4.20 (q, J=7.1 Hz, 2H), 3.43 (t, J=6.4 Hz, 2H), 2.77 (t, J=7.2 Hz, 2H), 1.73–1.66 (m, 4H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 143.9, 135.5, 130.9, 129.4, 129.2, 128.6, 128.5, 124.0, 77.1, 62.2, 56.7, 49.0, 26.1, 19.4, 14.6. Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 63.79; H, 6.78; N, 3.93.

4.3. Representative procedure for the intramolecular cyclization reactions of *N*-benzyloxy carbamate derivatives 2

*4.3.1. 3-Benzenesulfonyl-1-benzyloxy-pyrrolidin-2-one (**3a**).* Lithium bis(trimethylsilyl) amide (0.92 mL, 0.9 mmol, 1 M solution in THF) was added to a solution of **2a** (0.166 g, 0.44 mmol) in THF (4 mL) under N_2 at −78 °C and the mixture was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C with 10% AcOH aqueous solution (2 mL) and the solvent removed in vacuo. The residue was dissolved in EtOAc (50 mL), washed with brine (3×10 mL), dried over Na_2SO_4, and the solvent removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane=1:3–1:1) to give **3a** as colorless oil in 97.2% yield; IR (neat) 2918, 1721 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09–7.86 (m, 2H), 7.78–7.50 (m, 3H), 7.45–7.30 (m, 5H), 5.00–4.85 (m, 2H), 3.88 (dd, J=10.3, 4.4 Hz, 1H), 3.39 (q, J=8.8 Hz, 1H), 3.23 (ddd, J=8.8, 8.8, 4.0 Hz, 1H), 2.79–2.52 (m, 1H), 2.50–2.20 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.6, 137.5, 134.7, 134.3, 129.5, 129.4, 129.1, 129.0, 128.6, 77.0, 62.8, 44.8, 17.5. Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.50; H, 5.41; N, 4.49.

*4.3.2. 3-Benzenesulfonyl-1-benzyloxy-piperidin-2-one (**3b**).* The representative cyclization procedure was followed using **2b** in place of **2a** to give **3b** as a colorless oil; 85.5% yield; IR (neat) 2920, 1668 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09–7.89 (m, 2H), 7.81–7.54 (m, 3H), 7.54–7.29 (m, 5H), 5.02–4.89 (m, 2H), 4.02 (dd, J=5.5, 4.0 Hz, 1H), 3.47–3.28 (m, 2H), 2.79–2.49 (m, 1H), 2.48–2.21 (m, 1H), 2.21–1.91 (m, 1H), 1.91–1.66 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.4, 139.4, 135.1, 133.9, 129.8, 129.1, 128.9, 128.8, 128.5, 76.1, 66.9, 50.9, 21.8, 20.7 Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.76; H, 5.83; N, 4.33.

*4.3.3. {5-Benzenesulfonyl-5-[(5-benzenesulfonyl-pentyl)-benzyloxy-carbamoyl]-pentyl}-benzyloxy-carbamic acid ethyl ester (**5c**).* The representative cyclization procedure was followed using **2c** in place of **2a** to give dimer **5c** as colorless oil; 44.3% yield; IR (neat) 3065, 3033, 2938, 2871, 1699, 1661 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98–7.75 (m, 4H), 7.72–7.44 (m, 6H), 7.44–7.28 (m, 10H), 5.01 (d, J=10.3 Hz, 1H), 4.83 (d, J=10.6 Hz, 1H), 4.77 (s, 2H), 4.60 (dd, J=10.6, 4.0 Hz, 1H), 4.14 (q, J=7.0 Hz, 2H), 3.76–3.38 (m, 2H), 3.30 (t, J=7.1 Hz, 2H), 3.10–3.02 (m, 2H), 1.93–0.95 (m, 12H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.3, 139.1, 137.0, 135.4, 134.0, 133.8, 133.6, 129.8, 129.3 (two peaks), 129.2, 128.9, 128.7, 128.6, 128.4, 128.0, 77.0, 76.9, 65.5, 62.0, 55.9, 49.0, 45.4, 27.8, 26.6, 26.0, 25.4, 24.0, 22.2, 14.5. Anal. Calcd for $C_{40}H_{48}N_2O_9S_2$: C, 62.81; H, 6.32; N, 3.66. Found: C, 62.79; H, 6.29; N, 3.65.

*4.3.4. 3-Benzenesulfonyl-1-benzyloxy-azepan-2-one (**3c**).* The representative cyclization procedure was followed using **2c′** in place of **2a** and the reaction was allowed to stir at rt for 18 h to give **3c** as a white solid; 34.9% yield (43.8% recovered **2c′**); mp 189–190 °C; IR (KBr) 2896, 2925, 1668 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09–7.89 (m, 2H), 7.81–7.54 (m, 3H), 7.54–7.29 (m, 5H), 4.95–4.81 (m, 2H), 4.03 (dd, J=9.9, 2.9 Hz, 1H), 3.85–3.57 (m, 1H), 3.57–3.29 (m, 1H), 2.52–2.21 (m, 1H), 2.21–1.93 (m, 1H), 1.93–1.67 (m, 1H), 1.67–1.40 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.8, 138.5, 135.3, 133.9, 129.9, 129.7, 128.8, 128.7, 128.6, 76.8, 69.8, 52.5, 26.4, 26.1, 24.3. Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.50; H, 5.61; N, 4.19.

*4.3.5. 1-Benzyloxy-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (**3d**).* The representative cyclization procedure was followed using **2d** in place of **2a** to give **3d** as a colorless oil; 76.5% yield; IR (neat) 2983, 2903, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.36 (m, 5H), 5.00 (d, J=10.8 Hz, 2H), 4.22 (q, J=7.2 Hz, 2H), 3.38–3.27 (m, 3H), 2.29–2.24 (m, 1H), 2.19–2.12 (m, 1H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.0, 135.0, 129.5, 128.9, 128.5, 76.8, 61.7, 45.5, 45.4, 19.9, 14.1. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.58; H, 6.58; N, 5.36.

*4.3.6. 1-Benzyloxy-2-oxo-piperidine-3-carboxylic acid ethyl ester (**3e**).* The representative cyclization procedure was followed using **2e** in place of **2a** to give **3e** as a colorless oil; 80.8% yield; IR (neat) 2949, 2879, 1737, 1667 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56–7.30 (m, 5H), 4.99 (s, 2H), 4.24 (q, J=7.3 Hz, 2H), 3.48 (t, J=6.6 Hz, 1H), 3.38–3.29 (m, 2H), 2.01–1.89 (m, 4H), 1.32 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 163.3, 135.3, 129.7, 128.7, 128.4, 75.8, 61.5, 50.9, 50.1, 24.8, 21.4, 14.1. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.01; H, 7.02; N, 5.05.

*4.3.7. 6-(Benzyloxy-ethoxycarbonyl-amino)-2-[benzyloxy-(5-ethoxycarbonyl-pentyl)-carbamoyl]-hexanoic acid ethyl ester (**3f**) and 1-benzyloxy-2-oxo-azepane-3-carboxylic acid ethyl ester (**5f**).* The representative cyclization procedure was followed using **2f** in place of **2a** and stirring the reaction at 0 °C for 18 h to give cyclized product **3f** (31.9% yield, colorless oil) and dimer **5f** (59.7% yield, colorless oil). Compound **3f**: IR (neat) 2936, 2870, 1743, 1668 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53–7.29 (m, 5H), 5.05–4.91 (m, 2H), 4.25 (q, J=7.0 Hz, 2H), 3.57–3.45 (m, 3H), 2.12–1.69 (m, 3H), 1.66–1.39 (m, 3H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$)

δ 169.7, 168.9, 135.6, 129.7, 128.7, 128.5, 76.4, 61.3, 53.2, 51.9, 27.3, 26.7, 25.8, 14.2. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.00; H, 7.10; N, 5.14. **5f**: IR (neat) 2981, 2938, 2869, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.28 (m, 10H), 4.84 (s, 2H), 4.83 (s, 2H), 4.25–4.11 (m, 6H), 3.46–3.34 (m, 5H), 2.68–2.21 (m, 2H), 1.95–1.71 (m, 2H), 1.70–1.47 (m, 6H), 1.39–1.10 (m, 13H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7, 157.5, 135.6, 129.3, 128.5, 128.4, 77.1, 62.0, 61.3, 59.0, 49.5, 49.4, 41.7, 27.8, 26.8, 24.6, 23.1, 14.6, 14.1. HRMS: calcd for $C_{34}H_{48}N_2O_9Na$ ($M+Na^+$) 651.3252, found 651.3254.

*4.3.8. 1-Benzyloxy-2-oxo-pyrrolidine-3-carbonitrile (**3g**).* The representative cyclization procedure was followed using **2g** in place of **2a** to give **3g** as a pale yellow solid; 92.5% yield; mp: 60–61 °C; IR (KBr) 2895, 2250, 1714 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54–7.31 (m, 5H), 5.03 (s, 2H), 3.44 (t, *J*=9.1 Hz, 1H), 3.31–3.24 (m, 2H), 2.41–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 135.5, 129.5, 129.2, 128.7, 116.7, 77.1, 45.1, 30.7, 21.2. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.61; H, 5.69; N, 13.03.

*4.3.9. 1-Benzyloxy-2-oxo-piperidine-3-carbonitrile (**3h**).* The representative cyclization procedure was followed using **2h** in place of **2a** to give **3h** as a colorless oil; 91.6% yield; IR (neat) 2951, 2886, 2250, 1674 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.57–7.30 (m, 5H), 5.06–4.94 (m, 2H), 3.61 (t, *J*=7.0 Hz, 1H), 3.37–3.32 (m, 2H), 2.21–1.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 134.6, 129.7, 129.1, 128.6, 117.1, 76.0, 50.7, 36.0, 25.6, 21.5. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.45; H, 6.16; N, 12.15.

*4.3.10. 1-Benzyloxy-2-oxo-azepane-3-carbonitrile (**3i**).* The representative cyclization procedure was followed using **2i** in place of **2a** and stirring the reaction at rt for 3 h to give **3i** as a colorless oil; 57.7% yield; IR (neat) 2937, 2252, 1674 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.53–7.31 (m, 5H), 4.97 (s, 2H), 3.84–3.70 (m, 2H), 3.55–3.44 (m, 1H), 2.05–1.98 (m, 4H), 1.62–1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 135.0, 129.8, 129.0, 128.6, 116.3, 76.7, 53.2, 38.7, 27.4, 26.7, 26.3. HRMS: calcd for $C_{14}H_{17}N_2O_2$ ($M+H^+$) 245.1285, found 245.1284.

*4.3.11. (1-Benzyloxy-2-oxo-pyrrolidin-3-yl)-phosphonic acid diethyl ester (**3j**).* The representative cyclization procedure was followed using **2j** in place of **2a** and stirring the reaction at 0 °C for 2 h to give **3j** as a colorless oil; 89.4% yield; IR (neat) 2984, 1714 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.53–7.30 (m, 5H), 5.05–4.92 (m, 2H), 4.28–4.11 (m, 4H), 3.51–3.34 (m, 1H), 3.27–3.23 (m, 1H), 2.90–2.76 (m, 1H), 2.33–2.19 (m, 2H), 1.35 (td, *J*=7.0, 1.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (d, *J*=4.1 Hz), 135.2, 129.5, 128.9, 128.5, 76.9, 62.8 (d, *J*=6.6 Hz), 45.7 (d, *J*=4.5 Hz), 37.9 (d, *J*=143.8 Hz), 18.0 (d, *J*=4.1 Hz), 16.5 (d, *J*=3.8 Hz). Anal. Calcd for $C_{15}H_{22}NO_5P \cdot 0.5H_2O$: C, 53.57; H, 6.89; N, 4.16. Found: C, 53.75; H, 6.56; N, 4.10.

*4.3.12. (1-Benzyloxy-2-oxo-piperidin-3-yl)-phosphonic acid diethyl ester (**3k**).* The representative cyclization procedure was followed using **2k** in place of **2a** and stirring the reaction at 0 °C for 6 h to give **3k** as a colorless oil; 75.8% yield; IR (neat) 2980, 1655 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.57–7.32 (m, 5H), 5.03–4.90 (m, 2H), 4.26–4.15 (m, 4H), 3.35 (t, *J*=5.5 Hz, 2H), 3.04 (dt, *J*=26.0, 6.2 Hz, 1H), 2.31–1.90 (m, 3H), 1.88–1.59 (m, 1H), 1.40–1.33 (t, *J*=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, *J*=5.0 Hz), 135.5, 129.7, 128.7, 128.5, 75.9, 62.7 (d, *J*=6.6 Hz), 50.9, 42.9 (d, *J*=136.0 Hz), 22.8 (d, *J*=4.6 Hz), 21.9 (d, *J*=7.3 Hz), 16.5 (d, *J*=5.9 Hz). Anal. Calcd for $C_{13}H_{14}N_2O_2 \cdot 0.02H_2O$: C, 56.24; H, 7.09; N, 4.10. Found: C, 55.86; H, 6.82; N, 4.49.

*4.3.13. 3-Benzenesulfinyl-1-benzyloxy-pyrrolidin-2-one (**3l**).* The representative cyclization procedure was followed using **2l** in place of **2a** and stirring the reaction at rt for 1 h to give **3l** as a 2:1 diastereomeric mixture in 74.1% yield as a pale yellow solid. IR (KBr) 2937, 1707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81–7.13 (m, 10H), 5.02 (dd, *J*=11.0, 10.6 Hz, 1.4H), 4.73 (dd, *J*=32.0, 11.0 Hz, 0.7H), 4.20–4.00 (dd, *J*=9.5, 3.7 Hz, 0.35H), 3.46 (dd, *J*=9.9, 7.0 Hz, 0.7H), 3.32–3.25 (m, 1.4H), 2.95–2.90 (m, 0.35H), 2.54–2.43 (m, 1.4H), 2.35–2.08 (m, 0.7H), 1.71–1.30 (m, 0.35H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 163.7, 141.7, 138.9, 134.8, 132.0, 131.2, 129.6, 129.3, 129.0, 128.6, 128.5, 125.2, 124.0, 77.3, 63.6, 61.5, 45.8, 45.4, 13.9, 11.9; Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.62; H, 5.58; N, 4.72.

*4.3.14. 3-Benzenesulfinyl-1-benzyloxy-piperidin-2-one (**3m**).* The representative cyclization procedure was followed using **2m** in place of **2a** and stirring the reaction at 0 °C for 0.5 h to give **3m** as a 1:1 mixture of diastereomers in 88.6% yield, colorless oil; IR (neat) 2947, 1652 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.84–7.21 (m, 10H), 5.03 (s, 1H), 4.82 (dd, *J*=35.7, 10.8 Hz, 1H), 4.13 (t, *J*=7.0 Hz, 0.5H), 4.46 (dd, *J*=8.4, 6.6 Hz, 0.5H), 3.38–3.32 (m, 1H), 3.21–3.13 (m, 0.5H), 3.10–2.83 (m, 0.5H), 2.43–1.86 (m, 2H), 1.86–1.54 (m, 1.5H), 1.54–1.34 (m, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 161.4, 142.5, 140.1, 135.1, 131.5, 131.0, 129.8, 129.5, 129.2, 128.9, 128.7, 128.5, 125.9, 124.4, 76.4, 76.2, 67.1, 64.5, 50.8, 50.3, 21.5, 21.3, 18.1, 17.5. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.58; H, 5.85; N, 4.37.

4.4. Representative procedure for desulfonylation

*4.4.1. N-Benzyloxy-pyrrolidin-2-one (**6a**).* Disodium hydrogen phosphate (0.240 g, 1.68 mmol) and 6% Na/Hg amalgam (1.97 g, 5.04 mmol) were added to a solution of **3a** (0.140 g, 0.42 mmol) in MeOH (15 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction mixture was vacuum filtered through a short silica gel column and rinsed with EtOAc (50 mL). The filtrate was washed with saturated $NaHCO_3$ (3×10 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. The product **6a** was obtained as a colorless oil (0.072 g, 90.0%), which was homogeneous by TLC. IR (neat) 2953, 2882, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51–7.30 (m, 5H), 4.99 (s, 2H), 3.26 (t, *J*=7.0 Hz, 2H), 2.32 (t, *J*=8.1 Hz, 2H), 1.91 (quin, *J*=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 135.4, 129.3, 128.8, 128.5, 76.8, 47.0, 27.8, 15.4. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.38; H, 7.20; N, 6.98.

*4.4.2. N-Benzyloxy-piperidin-2-one (**6b**).* The representative desulfonylation procedure was followed using **3b** in place of **3a** to give **6b** as a colorless oil; 92.0% yield; IR (neat) 2948, 2876, 1667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.53–7.31 (m, 5H), 4.97 (s, 2H), 3.34 (t, *J*=6.0 Hz, 2H), 2.32 (t, *J*=6.0 Hz, 2H), 1.87–1.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 135.5, 129.5, 128.7, 128.4, 75.7, 50.8, 33.3, 23.8, 21.0. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.17; H, 7.23; N, 6.88.

4.5. Representative procedure for hydrogenolysis

*4.5.1. N-Hydroxy-pyrrolidin-2-one (**7a**).* Palladium on carbon (10%, 17 mg) was added to a solution of **6a** (35 mg, 0.18 mmol) in MeOH (2 mL) and the mixture was stirred at rt under hydrogen balloon for 18 h. The catalyst was removed by centrifugation followed by filtration. The solvent was removed in vacuo to give the known cyclic hydroxamic acid **7a**[20c] (0.015 g, 83.3%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 10.40 (br s, 1H), 3.67 (t, *J*=7.0 Hz, 2H), 2.41 (t, *J*=7.7 Hz, 2H), 2.06 (quin, *J*=7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 48.5, 28.0, 15.1.

*4.5.2. N-Hydroxy-piperidin-2-one (**7b**).* The representative hydrogenolysis procedure was followed using **6b** in place of **6a** to give the known cyclic hydroxamic acid **7b**[20a,d] as a colorless oil; 94.2% yield,

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 3.63 (t, J=6.0 Hz, 2H), 2.44 (t, J=6.4 Hz, 2H), 1.96–1.88 (m, 2H), 1.82–1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 49.7, 31.2, 23.2, 20.7.

4.6. *N*-Benzyloxy-5,6-dihydro-1*H*-pyridin-2-one (8)

A solution of **3m** (0.437 g, 1.33 mmol) in toluene (10 mL) was stirred at reflux for 3 days. The reaction mixture was diluted with EtOAc (150 mL), washed with saturated $NaHCO_3$ (3×25 mL), brine (25 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane=1:3–1:1) to give **8** (0.212 g, 80.5%) as pale yellow oil; IR (neat) 2940, 2875, 1685, 1618 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54–7.29 (m, 5H), 6.52 (dt, J=9.9, 4.0 Hz, 1H), 5.89 (dt, J=9.9, 1.5 Hz, 1H), 4.99 (s, 2H), 3.41 (t, J=7.0 Hz, 2H), 2.50–2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 140.4, 135.8, 129.6, 128.6, 128.4, 124.8, 77.0, 49.2, 25.8. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.70; H, 6.64; N, 6.59.

4.7. Representative procedure for the Michael addition reactions of 8 with diamines

*4.7.1. 1-Benzyloxy-4-[methyl-(2-methylamino-ethyl)-amino]-piperidin-2-one (**9a**).* *N*,*N*′-Dimethyl ethylenediamine (0.32 mL, 3 mmol) was added to a solution of **8** (60 mg, 0.30 mmol) in MeOH (1 mL) and the mixture was stirred at rt for 2 days. The solvent was removed in vacuo. The crude product was purified by column chromatography on alumina (5% MeOH/DCM) to give **9a** (80 mg, 92.0%) as a yellowish oil; IR (neat) 3317, 2940, 2791, 1667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.31 (m, 5H), 4.99 (d, J=10.5 Hz, 1H), 4.93 (d, J=10.6 Hz, 1H), 3.46–3.14 (m, 2H), 2.85–2.67 (m, 1H), 2.67–2.34 (m, 6H), 2.43 (s, 3H), 2.21 (s, 3H), 2.06–1.85 (m, 1H), 1.84–1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 135.4, 129.5, 128.7, 128.4, 75.8, 57.3, 52.8, 49.3, 48.2, 37.3, 36.5, 35.1, 26.7. HRMS: calcd for $C_{16}H_{26}N_3O_2$ ($M+H^+$) 292.2020, found 292.2022.

*4.7.2. 1-Benzyloxy-4-piperazin-1-yl-piperidin-2-one (**9b**).* The representative procedure for Michael addition was followed using piperazine in place of *N*,*N*′-dimethyl ethylenediamine to give **9b** as a pale yellow solid; mp 131–132 °C; 96.9% yield; IR (KBr) 3436, 2939, 2800, 1651 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.30 (m, 5H), 4.99 (d, J=10.8 Hz, 1H), 4.94 (d, J=10.5 Hz, 1H), 3.47–3.20 (m, 2H), 2.90 (s, 4H), 2.71–2.36 (m, 8H), 2.06–1.89 (m, 1H), 1.85–1.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 135.4, 129.5, 128.7, 128.4, 75.8, 57.8, 50.4, 47.9, 46.2, 35.7, 26.5. HRMS: calcd for $C_{16}H_{24}N_3O_2$ ($M+H^+$) 290.1863, found 290.1869.

*4.7.3. 1-Benzyloxy-4-(2-dimethylamino-ethylamino)-piperidin-2-one (**9c**).* The representative procedure for Michael addition was followed using *N*,*N*-dimethyl ethylenediamine in place of *N*,*N*′-dimethyl ethylenediamine to give **9c** as a pale yellow oil; 96.6% yield; IR (neat) 3301, 2944, 2819, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.28 (m, 5H), 4.98 (d, J=10.6 Hz, 1H), 4.95 (d, J=10.8 Hz, 1H), 3.46–3.36 (m, 1H), 3.36–3.24 (m, 1H), 2.99–2.86 (m, 1H), 2.69–2.59 (m, 2H), 2.43–2.17 (m, 4H), 2.20 (s, 6H), 2.00–1.89 (m, 1H), 1.74–1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 135.5, 129.5, 128.6, 128.4, 75.7, 58.9, 51.3, 47.5, 45.4, 44.4, 39.9, 29.4. HRMS: calcd for $C_{16}H_{26}N_3O_2$ ($M+H^+$) 292.2020, found 292.2025.

4.8. 3-Benzenesulfonyl-1-benzyloxy-3-{2-[2-(3′-benzenesulfonyl-1′-benzyloxy-2′-oxo-piperidin-3′-yl) ethoxy]-ethyl}-piperidin-2-one (10)

Potassium carbonate (304 mg, 2.2 mmol) was added to a solution of **3b** (76 mg, 0.22 mmol) and 2-iodoethyl ether (33 mg, 0.1 mmol) in MeCN (5 mL) and the mixture was stirred at reflux for 3 days. The reaction mixture was cooled, poured into water (50 mL) and the product extracted into CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine (15 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane=1:4–1:1) to give **10** (0.039 g, 51.3%) as a 1:1 mixture of diastereomers; white solid; IR (KBr) 2930, 2876, 1663 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96–7.76 (m, 4H), 7.72–7.29 (m, 16H), 5.07–4.83 (m, 4H), 3.55–3.19 (m, 8H), 2.72–2.48 (m, 2H), 2.48–2.27 (m, 2H), 2.26–1.94 (m, 4H), 1.94–1.66 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.0, 136.3, 135.1, 134.0, 131.0, 129.7, 128.8, 128.7, 128.5, 76.7, 75.9, 72.0, 71.7, 66.4, 66.3, 50.6, 33.9, 25.9, 20.3. Anal. Calcd for $C_{40}H_{44}N_2O_9S_2\cdot H_2O$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.47; H, 5.90; N, 3.31.

4.9. 1-Benzyloxy-3-{2-[2-(1′-benzyloxy-2′-oxo-piperidin-3′-yl) ethoxy]-ethyl}-piperidin-2-one (11)

Disodium hydrogen phosphate (30 mg, 0.21 mmol) and 6% Na/Hg amalgam (200 mg, 0.84 mmol) were added to a solution of **10** (32 mg, 0.042 mmol) in MeOH (1 mL) at −78 °C and the mixture was stirred at −78 °C for 2 h and then at rt for 12 h. The reaction mixture was vacuum filtered through a short column of silica gel and washed with MeOH (30 mL). The solvent was removed in vacuo. The residue was dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2×10 mL), brine (10 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. The product **11** (14 mg, 70.0%) was obtained as colorless oil. IR (neat) 2942, 2870, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.29 (m, 10H), 5.05–4.80 (m, 4H), 3.66–3.45 (m, 4H), 3.45–3.25 (m, 4H), 2.60–2.40 (m, 2H), 2.39–2.13 (m, 2H), 1.98–1.80 (m, 4H), 1.80–1.55 (m, 4H), 1.55–1.39 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2, 135.6, 129.6, 128.6, 128.4, 75.6, 68.8, 68.6, 51.0, 40.1, 40.0, 31.5, 26.8, 26.7, 22.2. Anal. Calcd for $C_{28}H_{36}N_2O_5$: C, 69.98; H, 7.55; N, 5.83. Found: C, 70.29; H, 7.49; N, 5.77.

4.10. 1-Hydroxy-3-{2-[2-(1′-hydroxy-2′-oxo-piperidin-3′-yl) ethoxy]-ethyl}-piperidin-2-one (12)

Palladium on carbon (10%, 8 mg) was added to a solution of **11** (40 mg, 0.08 mmol) in MeOH (1 mL) and the mixture was stirred at rt under a hydrogen balloon for 20 h. The catalyst was removed by centrifugation followed by filtration. The product was lyophilized from deionized water to give bis cyclic hydroxamic acid **12** (22 mg, 88.0%) as pale yellow oil; IR (neat) 3233, 2920, 2861, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58–3.59 (m, 4H), 3.59–3.50 (m, 4H), 3.46–3.38 (m, 2H), 2.64–2.45 (m, 4H), 2.27–2.21 (m, 2H), 2.07–1.81 (m, 6H), 1.75–1.53 (m, 4H); ^{13}C NMR (50 MHz, D_2O) δ 175.5, 72.6, 56.1, 46.3, 43.0, 41.8, 34.9, 29.5, 29.3, 25.2, 24.5. Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.98; H, 8.05; N, 9.33. Found: C, 56.17; H, 8.15; N, 8.91.

4.11. (*Z*,*Z*)-1-Benzyloxy-3-(6-(1′-benzyloxy-2′-oxo-piperidin-3′-ylmethylene)-pyridin-2-ylmethylene)-piperidin-2-one (13)

A solution of potassium carbonate (0.497 g, 3.6 mmol) in H_2O (3 mL) was added to a solution of **3k** (0.612 g, 1.8 mmol) and 2,6-pyridine dicarboxaldehyde (81 mg, 0.6 mmol) in THF (3 mL) and the mixture was stirred at 80 °C for 2 days. The reaction mixture was cooled, poured into water (50 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The crude product was purified by radial chromatography (EtOAc/hexane 33–100%) to give **13** (0.194 g, 63.6%) as a white solid: mp 145–147 °C; IR (KBr) 3049, 2942, 2871, 1660, 1619 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.67 (m, 3H), 7.53–7.33 (m, 10H), 7.29 (s, 2H), 5.28 (s, 4H), 3.50 (t, J=6.0 Hz, 4H), 3.08 (td, J=7.1, 1.9 Hz, 4H),

1.82 (quin, J=6.2 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.7, 154.8, 136.6, 135.5, 134.1, 132.8, 129.7, 128.5, 125.2, 75.9, 50.8, 25.6, 22.7. Anal. Calcd for $C_{31}H_{31}N_3O_4$: C, 73.06; H, 6.13; N, 8.25. Found: C, 72.66; H, 6.05; N, 8.24.

4.12. (*Z*,*Z*)-1-Hydroxy-3-(6-(1′-hydroxy-2′-oxo-piperidin-3′-ylmethylene)-pyridin-2-ylmethylene)-piperidin-2-one hydrobromide (14)

Concentrated HBr (1 mL) and glacial acetic acid (1 mL) was added to **13** (51 mg, 0.1 mmol) and the mixture was stirred at 55 °C for 4 days. The solvent was removed in vacuo. The bis cyclic hydroxamic acid **13** (35 mg, 85.4%) was obtained as brownish solid, which was homogeneous by TLC: mp 121–123 °C; IR (KBr) 3401, 2945, 1710, 1629 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.51 (t, J=8.0 Hz, 1H), 7.89 (d, J=8.2 Hz, 2H), 7.59 (s, 2H), 7.42 (s, 1H), 3.18 (t, J=7.5 Hz, 4H), 2.51 (t, J=7.9 Hz, 4H), 2.01–1.72 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 168.9, 148.2, 142.0, 141.9, 128.8, 126.8, 50.0, 24.8, 22.1. Anal. Calcd for $C_{17}H_{22}N_3O_4S_2Br_3\cdot 2H_2O$: C, 33.58; H, 4.31; N, 6.91. Found: C, 33.87; H, 4.05; N, 6.82.

4.13. 1-Hydroxy-3-(6-(1′-hydroxy-2′-oxo-piperidin-3′-ylmethyl)-pyridin-2-ylmethyl)-piperidin-2-one (15)

Palladium on carbon (10%, 10 mg) was added to a solution of **13** (50 mg, 0.1 mmol) in MeOH (2 mL) and the mixture was stirred at rt under a hydrogen balloon for 2 days. The catalyst was removed by centrifugation followed by filtration. The solvent was removed in vacuo. The residue was purified by washing with CH_2Cl_2 to give **15** (25 mg, 75.8%) as pale yellow solid: mp 95–98 °C; IR (KBr) 3095, 2943, 2864, 1635 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.35 (t, J=7.9 Hz, 1H), 7.75 (d, J=8.2 Hz, 2H), 3.67–3.56 (m, 4H), 3.51–3.38 (m, 2H), 3.30–3.13 (m, 2H), 3.08–2.94 (m, 2H), 2.18–1.76 (m, 6H), 1.76–1.53 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 170.6, 170.2, 160.2, 138.3, 138.1, 122.9, 122.6, 52.6, 50.3, 47.7, 43.0, 42.6, 40.0, 39.8, 26.7, 26.3, 22.7, 22.6. HRMS: calcd for $C_{17}H_{24}N_3O_4$ ($M+H^+$) 334.1761, found 334.1765.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.073.

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