Hydrolysis of Iminium Ethers Derived from the Reaction of Ketones with Hydroxy Azides: Synthesis of Macrocyclic Lactams and Lactones

Jennifer E. Forsee and Jeffrey Aubé*

Department of Medicinal Chemistry University of Kansas Lawrence, Kansas 66045-2506

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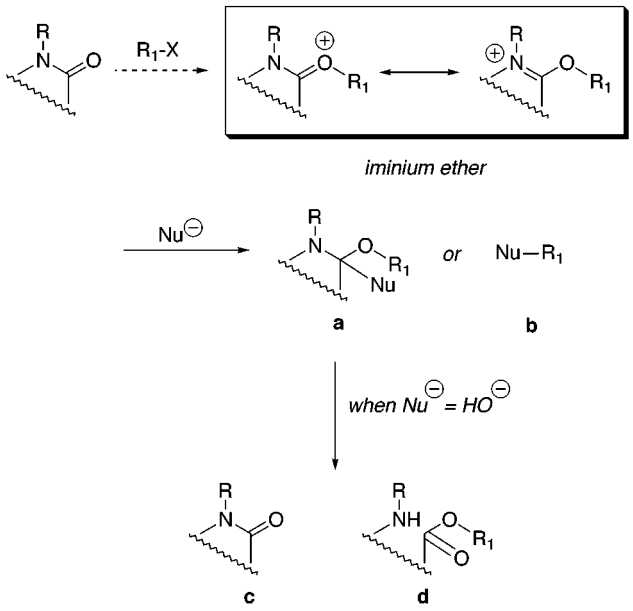
The hydrolysis of iminium ether intermediates formed by a nitrogen insertion sequence involving azido alcohols **1** or **2** and ketones was investigated. Ketones containing 6−12-membered rings were surveyed and shown to provide lactams and lactones in good to excellent overall yield. Reactions employing acetone or 5-nonanone gave similar results, generating analogous amides and esters. The relative amounts of lactone vs lactam produced in a given reaction were found to depend on the structures of the reactants and the pH of the basic media used to hydrolyze the iminium ethers. A mechanism accounting for the formation of each product is discussed in terms of ring strain and the protonation state of ortho ester aminal intermediates.

Iminium ethers, also known as imidate salts, have traditionally been prepared by the alkylation of amides with electrophiles (Scheme 1). The value of this functional group mostly arises from the fact that it is an ambidentate electrophile able to react at the cationic center to afford intermediates, such as **a**, or to alternatively undergo dealkylation to give product **b** (along with the original amide).[1] The choice of pathway is determined by various factors including the nature of the nucleophile; it has been proposed that products such as **a** are the result of kinetic addition to the iminium ether, but that this reaction is readily reversible with suitable stable nucleophiles. In such cases it is possible for the final product to result from irreversible dealkylation (giving **b**).[1a] Further complexity arises from the fact that the amino group in **a** is also a credible leaving group in some circumstances, such as when Nu = OH. For example, breakdown of this tetrahedral intermediate could lead to amides **c** or to esters **d** under appropriate circumstances.

Our own interest in iminium ether chemistry arose from work that showed these intermediates could be conveniently prepared via nitrogen insertion chemistry. Thus, ketals react with simple alkyl azides to afford an adduct which undergoes bond reorganization to give an iminium ether as shown in Scheme 2. Generally, these iminium ethers were dealkylated with NaI in acetone to afford amide and expendable iodomethane as products.[2] A much more general and therefore synthetically useful protocol used ketones and hydroxy azides such as **1** and **2** to afford iminium ethers in good to excellent yield.[3] The tetrafluoroborate counterion (as revealed by elemental analysis, ^{11}B NMR and X-ray crystallography)[3c] presumably results from disproportionation of the Lewis acid.

Scheme 1



For these reactions, subsequent hydrolysis was used to prepare the corresponding neutral amide (via an unknown mechanism, as will be discussed) or various nucleophiles could be added, resulting in substitution in a dealkylative sense (bottom of Scheme 2, where X = Br, I, NHNMe, SPh, and others).[4]

This paper describes the extension of this approach to several acyclic ketones and cyclic ketones containing 7−12 members. In the course of this study, we have found that hydrolysis leads to amides **c** (Scheme 1) or, for the first time, to esters **d** (Scheme 1) for this set of substrates. Furthermore, the selection of product was found to depend on both the structures of the starting materials and on the nature of the iminium ether hydrolysis conditions.

Results and Discussion

In preliminary work, the reaction of cycloheptanone with 2-azidoethanol under $BF_3{\cdot}OEt_2$ promotion was first

(1) For reviews of early work with iminium ethers, see: (a) Hünig, S. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 548−560. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 101−162.

(2) Mossman, C. J.; Aubé, J. *Tetrahedron* **1995**, *52*, 3403−3408.

(3) (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047−8048. (b) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252. (c) Furness, K.; Aubé, J., unpublished results.

(4) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 10−11.

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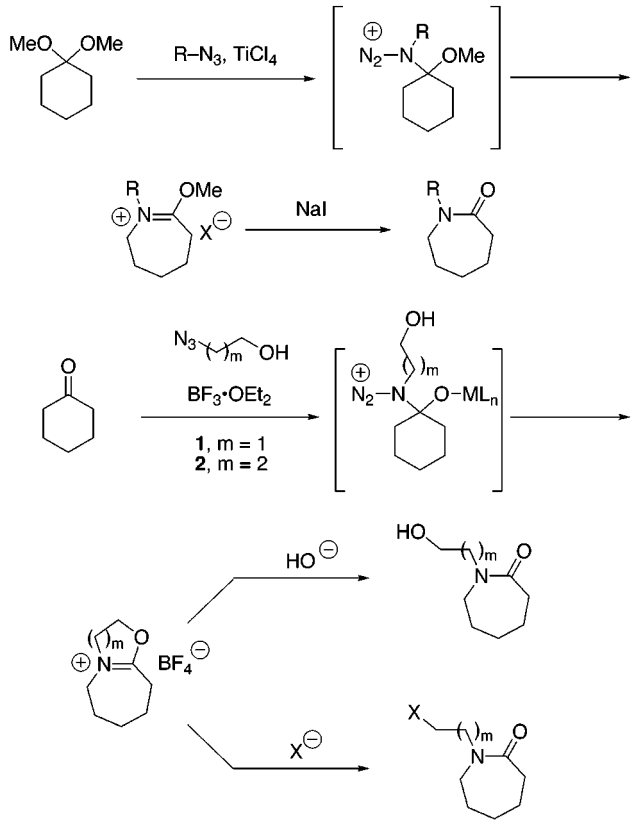
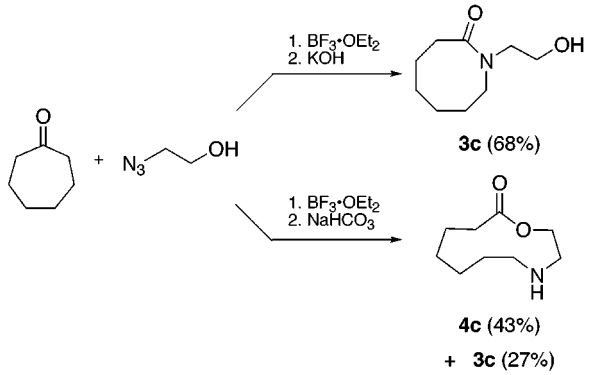
Scheme 2



Scheme 3



carried out as described previously,[3] i.e., in CH_2Cl_2 at room temperature (Scheme 3).[5] Later, it was found that a broader range of substrates could be accommodated by performing this step in refluxing CH_2Cl_2, and the results from these conditions will be reported here. Although initial gas evolution was observed, better yields were obtained when the reaction was allowed to proceed for 2−3 days. The putative iminium ether intermediate (see Scheme 2) was then hydrolyzed with KOH for 12 h to afford the expected eight-membered lactam in 68% isolated yield. In another attempt, the same reaction was carried out using $NaHCO_3$ in the hydrolysis step. Surprisingly, a new product was found to predominate under these conditions. IR spectroscopy indicated that this new product was 11-membered lactone **4c** ($\nu_{N-H} = 3340\ cm^{-1}$; $\nu_{C=O} = 1715\ cm^{-1}$), which was isolated in 43% yield along with a 27% yield of lactam **3c**.

We had not previously observed lactone or ester formation in any of our previously reported examples of this reaction (all of which involved 4-6-membered ketones), even when $NaHCO_3$ was used in the hydrolysis step. As it seemed likely this phenomenon was due to the strain inherent in the formation of a medium-sized (8−10-membered) lactone from such substrates, a survey of carbocyclic ketones ranging from 6 to 12 members, as well as two acyclic cases, was undertaken. One goal of this investigation was to explore the mechanistic details of the breakdown of the iminium salts and their dependence upon ring size and hydrolysis conditions. Furthermore, we wished to exploit the synthetic opportunities of a ring expansion protocol in which 1, 4, or 5 atoms could be inserted into a carbocyclic ring.[6]

Cyclic Ketones. The results of this portion of the study are reported in Table 1. Five ketones containing between 7 and 12 members were treated with 2-azidoethanol **1** and 3-azidopropanol **2**. For each combination of ketone and azido alcohol studied (save cyclooctanone, which gave poor yields), both workup conditions were compared. To permit easy comparison with our earlier results using standard cyclic ketones, the results obtained from using cyclohexanone with all of these permutations are also included in Table 1. The reaction conditions noted in the previous section were used throughout to allow comparison between all of these results. The intermediate iminium ethers were not isolated, although it has proven possible to do so in the past;[3] rather, these crude intermediates were directly subjected to hydrolysis with base. In addition, conditions were not optimized for each example except with respect to the amount of time used for the hydrolysis step, which is noted for each entry. In general, the iminium ethers required relatively long hydrolysis times to drive the reactions to completion. In at least one case, however, a shorter reaction time actually resulted in a superior yield (entry 8). Indeed, the overall yields of combined ring-expansion products were good to excellent, ranging between 62 and 99% for most cases. We attribute the poor yields of the cyclooctanone examples to poor reactivity of the ketone with the hydroxy azides used (entries 10 and 11).

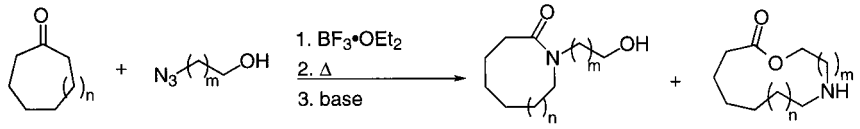
Careful examination of the crude reaction products obtained from cyclohexanone did not reveal lactone under any combination of azido alcohol or workup investigated (entries 1−4), thus confirming our previously reported results with this ketone. In each case, an excellent yield of amide **3a** or **3b** was obtained. In contrast, ester could be isolated from all of the other ketones examined. Three rough trends are apparent from these data. First, the ester/amide ratio was higher when $NaHCO_3$ was used as the hydrolysis medium. Even with KOH workup, the amount of ester obtained generally increases along with ring size of the reacting ketone. Finally, under comparable conditions, more ester is obtained from reactions of 3-azidopropanol **2** relative to 2-azidoethanol **1** (an exception being cyclononanone/ $NaHCO_3$, entries 13 and 15).

The latter two phenomena are likely to be bound up in issues of ring strain that depend on each variation of ketone and azido alcohol. As noted previously, it seems most likely that ester was not observed in the reactions of six-membered ketones or smaller because medium-ring lactones suffer from transannular destabilization.[7] For example, the reactions of cyclohexanone with **1** or **2** would each afford a seven-membered lactam but a 10- or 11-

(5) Forsee, J. E.; Smith, B. T.; Frank, K. E.; Aubé, J. *Synlett* **1998**, 1258−1260.

(6) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991.

Table 1. Reactions of Cyclic Ketones with 1 and 2



entry	ketone	azido alcohol	m	n	base	time (h)[a]	product	yield[b] of **3** (%)	yield[b] of **4** (%)
1	cyclohexanone	1	1	0	KOH	24	a	96	0
2		1	1	0	$NaHCO_3$	24	a	97	0
3		2	2	0	KOH	24	b	95	0
4		2	2	0	$NaHCO_3$	24	b	91	0
5	cycloheptanone	1	1	1	KOH	12	c	68	0
6		1	1	1	$NaHCO_3$	12	c	27	43
7		2	2	1	KOH	12	d	62	0
8		2	2	1	KOH	2	d	99	0
9		2	2	1	$NaHCO_3$	12	d	21	70
10	cyclooctanone	1	1	2	KOH	48	e	29	0
11		2	2	2	KOH	48	f	3	28
12	cyclononanone	1	1	3	KOH	40	g	88	0
13		1	1	3	$NaHCO_3$	40	g	26	64
14		2	2	3	KOH	40	h	23	40
15		2	2	3	$NaHCO_3$	40	h	46	49
16	cyclodecanone	1	1	4	KOH	24	i	51	19
17		1	1	4	$NaHCO_3$	24	i	30	64
18		2	2	4	KOH	30	j	25	54
19		2	2	4	$NaHCO_3$	30	j	29	67
20	cyclododecanone	1	1	6	KOH	30	k	50	30
21		1	1	6	$NaHCO_3$	29	k	8	79
22		2	2	6	KOH	30	l	36	45
23		2	2	6	$NaHCO_3$	30	l	5	93

[a] Duration of base hydrolysis. [b] Isolated yields.

membered lactone, respectively; the latter two compounds are expected to be significantly more strained than the former. On the other hand, the reactions of cycloheptanone with the same two reagents would yield an eight-membered lactam and lactones of either 11 or 12 members; in this case, there is no clear preference with respect to ring strain, and each product can be formed under appropriate conditions.

This brings up the question of whether these reactions are thermodynamically controlled or reflect kinetic preferences at some point in the reaction pathway. Interconversions of macrocyclic lactones and lactams have been reported in both directions and put to synthetic use (albeit usually under acidic conditions).[8] To address this point, the purified products of the reaction between cyclododecanone and azides **1** and **2** were independently resubjected to conditions used for hydrolysis of the intermediate iminium ethers and the products examined by ^{1}H NMR of the crude reaction mixtures. Cyclododecanone was chosen for this study because it provided lactams and lactones in comparable amounts under KOH workup conditions as described above. Lactams **3k** and **3l**, when exposed to either base, remained unchanged, except for the formation of small amounts (≤ 5−12%) of unidentified, but clearly non-ester, byproducts. In contrast, some conversion of ester to amide was observed when lactone **4k** was treated with KOH (yielding a 27:73 ratio of lactam **3k**/lactone **4k**) or $NaHCO_3$ (yielding a 44:56 ratio of lactam **3k**/lactone **4k**). Significantly, none of these experiments resulted in the lactam/lactone ratios obtained in the direct reactions of a given base. Overall, whereas the product ratio obtained in the direct reactions may reflect some amount of lactone→lactam conversion, it appears that true thermodynamic control is not at work. The dependence of product ratio on structure most likely results from the minimization of transannular ring strain in the transition states leading from intermediates **a** (Scheme 1, R_1 = H) to **c** or **d**.

There are two reasonable mechanisms for lactam formation under basic conditions (Scheme 4). Hydrolysis of the iminium ether **A** with KOH can occur by hydroxide attack on the distal carbon (*) to give the lactam product directly. Alternatively, hydroxide addition to the imine carbon reversibly provides ortho ester aminal **B** which may be deprotonated and subsequently collapse to yield the lactam. It is not possible to distinguish between these alternatives by product analysis.

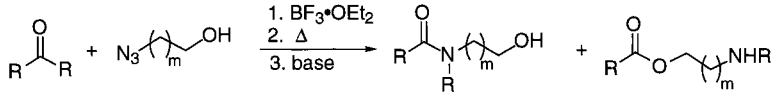
On the other hand, some version of intermediate **B** is *required* for the formation of the ester product (Scheme 5). Furthermore, it is reasonable that **B**, which contains a tertiary nitrogen with pK_a of ca. 11, would exist predominately as a protonated species **BH**$^+$ at a pH of 9 ($NaHCO_3$).[1b] Protonation of the nitrogen in $NaHCO_3$ would drive the reaction to form the lactone product by preferential carbon−nitrogen bond cleavage, as opposed to breaking the carbon−oxygen bond.

Accordingly, the observed tendency for greater amounts of lactone to be isolated from reactions worked up in $NaHCO_3$ medium may depend on controlling the protonation state of **B**. It is important to recognize, however, that this trend is only observed in the context of the ring-

(7) Eliel, E. L.; Wilen, S. H.; Mander, L. N. John Wiley & Sons: New York, 1994; pp 675−678 and references contained therein.

(8) For some recent examples, see: (a) Gribble, G. W.; Silva, R. A. *Tetrahedron Lett.* **1996**, *37*, 2145−2148. (b) Derrer, S.; Feeder, N.; Teat, S. J.; Davies, J. E.; Holmes, A. B. *Tetrahedron Lett.* **1998**, *39*, 9309−9312. (c) Banfi, L.; Guanti, G.; Rasparini, M. *Tetrahedron Lett.* **1998**, *39*, 9539−9542.

Table 2. Reactions of Acyclic Ketones with 1 and 2



1, m = 1
2, m = 2

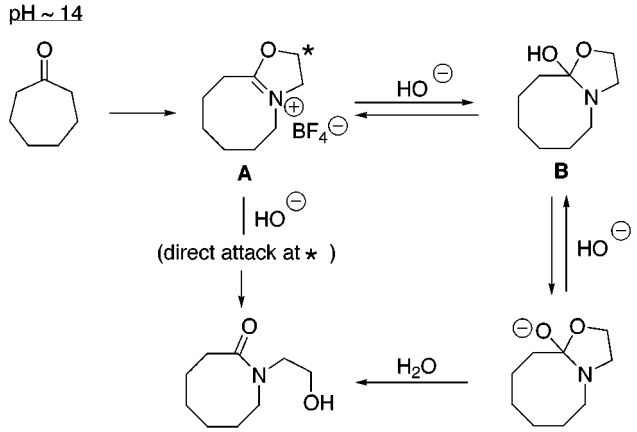
5a, m = 1, R = Me
5b, m = 2, R = Me
5c, m = 1, R = *n*Bu
5d, m = 2, R = *n*Bu

6a, m = 1, R = Me
6b, m = 2, R = Me
6c, m = 1, R = *n*Bu
6d, m = 2, R = *n*Bu

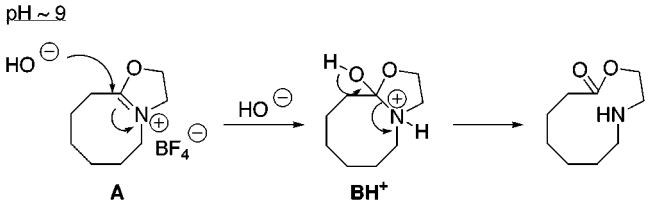
entry	ketone	R	azido alcohol	m	product	base[a]	yield[b] of **5** (%)	yield[b] of **6** (%)
1	acetone	Me	1	1	a	KOH	87	0
2		Me	1	1	a	$NaHCO_3$	0	0
3		Me	2	2	b	KOH	40	19
4		Me	2	2	b	$NaHCO_3$	0	0
5	5-nonanone	*n*-Bu	1	1	c	KOH	55	28
6		*n*-Bu	1	1	c	$NaHCO_3$	6	92
7		*n*-Bu	2	2	d	KOH	18	64
8		*n*-Bu	2	2	d	$NaHCO_3$	0	75

[a] Duration of base hydrolysis for all entries was 24 h. [b] Isolated yields.

Scheme 4



Scheme 5



strain effects noted above. A brief investigation of acyclic ketones was initiated to address this proviso.

Acyclic Ketones. In the event, similar results were obtained in experiments carried out with acetone, 5-nonanone, and **1** or **2** (Table 2). Again, amide products were found to predominate when KOH workup conditions were employed. In $NaHCO_3$, enhanced production of esters **6b**, **6c**, or **6d** was again observed. In addition, higher ester/amide ratios were obtained from reactions involving azido alcohol **2** relative to **1**. However, poor yields of ester, or no ester at all, were observed from the reactions of acetone with **1** or **2**. In fact, we were unable to isolate any product whatsoever from reactions of acetone with either hydroxy azide when $NaHCO_3$ was used, conditions that would be expected to mostly afford ester (by analogy with entries 6 and 8). We hypothesize that prolonged exposure to base effected the hydrolysis of the expected esters resulting only in volatile or water-soluble products that were not isolated in these examples.

Summary

In summary, we have shown that the reaction of azido alcohols with ketones gives lactams or lactones, with the preponderance of one or the other depending on both the substrates and the reaction conditions. These reactions rarely afford only a single product, but the process involves a straightforward two-stage procedure, and the products are readily isolated by column chromatography. Acyclic ketones also gave analogous amide and ester products. Finally, some general guidelines for which product will predominate through this series of compounds have been suggested.

Experimental Section

General methods. General methods have been published,[3] and azido alcohols **1** and **2** were prepared as previously disclosed.[9]

General Experimental Procedure. Azido alcohol **1** *or* **2** (3.0 equiv) and ketone (1.0 equiv) were weighed into a flask and suspended in CH_2Cl_2 (20 mL). The resulting solution was stirred at 0 °C for 20 min, whereupon $BF_3{\cdot}OEt_2$ (5.0 equiv) was added dropwise. After being stirred for 1 h, the solution was heated to reflux for 72 h. After cooling, 15% aqueous KOH (10 mL) *or* saturated aqueous $NaHCO_3$ (10 mL) was added over 5 min, and the resulting mixture was stirred for the specified time shown in Tables 1 and 2. The mixture was then extracted with CH_2Cl_2 (2 × 100 mL) and ether (3 × 100 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. Concentration and silica gel chromatography afforded the amide and ester products using primarily 2% MeOH/CH_2Cl_2, followed by 25% MeOH/EtOAc if additional chromatographic purification was necessary.

***N*-(2′-Hydroxyethyl)-1-azacyclooctan-2-one (3c).** 205 mg of a white solid, 68% yield; mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (m, 4H), 1.68 (m, 2H), 1.81 (m, 2H), 2.54 (t, J = 6.3 Hz, 2H), 3.53 (t, J = 5.3 Hz, 4H), 3.79 (t, 2H), 3.86 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.3, 26.2, 28.6, 29.3, 34.0, 49.1, 50.0, 62.8, 177.4; IR (neat) 3330, 2905, 2820, 1610, 1460, 1355, 1240 cm^{-1}; MS (EI) *m/e* 171 (M^+), 153, 141, 55; HRMS calcd for $C_9H_{18}NO_2$ (M^+ + H), 172.1338; found, 172.1325.

1-Oxa-4-azacycloundecan-11-one (4c). 134 mg of a crystalline solid, 43% yield; mp 81−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42−1.59 (m, 7H), 1.82 (m, 2H), 2.39 (t, 2H), 2.68 (t, J = 4.4 Hz, 2H), 2.94 (t, J = 4.7 Hz, 2H), 4.22 (t, J = 4.8 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.7, 26.6, 29.0, 29.8, 34.4, 49.6, 50.6, 63.3, 177.9; IR (CH_2Cl_2) 3340, 2920, 1715,

(9) Badiang, J. G.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 2484−2487.

1345, 1240 cm^{-1}; MS (CI) *m/e* 172 (M^+ + H). HRMS calcd for $C_9H_{18}NO_2$ (M^+ + H), 172.1337; found, 172.1348.

***N*-(3′-Hydroxypropyl)-1-azacyclooctan-2-one (3d).** 330 mg of a pale yellow oil, 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (m, 4H), 1.68 (m, 4H), 1.81 (m, 2H), 2.54 (m, 2H), 3.45 (t, J = 5.9 Hz, 2H), 3.50 (t, J = 5.8 Hz, 2H), 3.53 (t, J = 5.4 Hz, 2H), 4.15 (t, J = 7.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.1, 25.7, 28.1, 28.8, 29.9, 33.0, 40.8, 46.9, 57.7, 175.7; IR (neat) 3360, 2905, 2820, 1610, 1665, 1455, 1440, 1415, 1355, 1240 cm^{-1}; MS (CI) *m/e* 186 (M^+ + H). HRMS calcd for $C_{10}H_{20}NO_2$ (M^+ + H), 186.1494; found 186.1469. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.99; H, 10.12; N, 7.31.

1-Oxa-5-azacyclododecan-12-one (4d). 233 mg of a pale yellow oil, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (pentet, J = 8.2 Hz, 2H), 1.69 (m, 2H), 1.81 (pentet, J = 6.5 Hz, 2H), 1.97 (pentet, J = 6.0 Hz, 2H), 2.23 (pentet, J = 5.4 Hz, 2H), 2.59 (m, 2H), 3.14 (t, J = 5.9 Hz, 2H), 3.36 (t, J = 5.6 Hz, 2H), 4.40 (t, J = 5.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.8, 23.3, 23.6, 23.9, 24.2, 33.1, 44.5, 46.9, 64.6, 172.7; IR (neat) 3490, 2910, 1725, 1145 cm^{-1}; MS (CI) *m/e* 186 (M^+ + H) HRMS calcd for $C_{10}H_{20}NO_2$ (M^+ + H),186.1494; found 186.1469.

***N*-(2′-Hydroxyethyl)-1-azacyclotridecan-2-one (3k):** 129 mg of an oil, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26−1.45 (m, 15H), 1.69 (m, 2H), 1.76 (m, 2H), 2.36 (t, J = 7.8 Hz, 2H), 3.31 (t, J = 7.8 Hz, 2H), 3.53 (t, J = 4.1 Hz, 2H), 3.77 (t, J = 4.7 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.9, 24.1, 24.6, 25.1, 25.2, 25.6, 25.7, 26.0, 26.2, 32.5, 48.4, 50.6, 63.3, 176.6; IR (neat) 3380, 2910, 2840, 1615, 1500, 1410, 1100 cm^{-1}; MS (CI) *m/e* 242 (M^+ + H), 210. HRMS calcd for $C_{14}H_{28}NO_2$ (M^+ + H), 242.2120; found 242.2129.

1-Oxa-4-azacyclohexadecan-16-one (4k). 78 mg of a pale yellow oil, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (m, 13H), 1.53 (pentet, J = 6.1 Hz, 2H), 1.67 (m, 4H), 2.35 (t, J = 6.9 Hz, 2H), 2.68 (t, J = 6.0 Hz, 2H), 2.88 (t, J = 4.8 Hz, 2H), 4.24 (t, J = 4.8 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.1, 26.2, 26.4, 26.6, 26.9, 27.3, 27.9, 28.5, 34.7, 48.2, 48.4, 64.2, 174.2; IR (neat) 3300, 2900, 2820, 1725, 1450, 1240, 1135 cm^{-1}; MS (CI) *m/e* 242 (M^+ + H), 226, 56. HRMS calcd for $C_{14}H_{28}NO_2$ (M^+ + H), 242.2120; found 242.2108.

***N*-(2′-Hydroxypropyl)-1-azacyclotridecan-2-one (3l).** 102 mg of a colorless oil, 36% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34−1.47 (m, 14H), 1.67−1.82 (m, 6H), 2.37 (t, J = 7.9 Hz, 2H), 3.23 (t, J = 7.8 Hz, 2H), 3.51 (m, 4H), 4.22 (t, J = 7.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.9, 24.1, 24.2, 24.8, 24.9, 25.3, 25.6, 25.9, 26.2, 30.7, 32.4, 41.9, 46.6, 58.3, 175.6; IR (neat) 3400, 2920, 1610, 1455 cm^{-1}; MS (CI) *m/e* 256 (M^+ + H), 88; HRMS calcd for $C_{15}H_{30}NO_2$ (M^+ + H), 256.2276; found 256.2283.

1-Oxa-5-azacycloheptadecan-17-one (4l). 126 mg of a crystalline solid, 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (m, 15H), 1.64 (m, 4H), 2.08 (m, 2H), 2.34 (t, J = 6.6 Hz, 2H), 2.92 (m, 4H), 4.21 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.2, 24.4, 24.5, 26.1, 26.2, 26.26, 26.31, 26.8, 26.9, 27.4, 33.7, 43.5, 46.4, 61.5, 173.5; IR (neat) 3325, 2910, 2840, 1720, 1450, 1235, 1160 cm^{-1}; MS (CI) *m/e* 256 (M^+ + H), 44 HRMS calcd for $C_{15}H_{30}NO_2$, 256.2276; found 256.2287.

***N*-(2′-Hydroxyethyl)-*N*-butylpentamide (5c).** Mixture of amide bond rotamers (ca. 6:1), 155 mg of a colorless oil, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 0.96 (m, 6H), 1.38 (m, 4H), 1.60 (m, 4H), 2.36 (t, J = 7.9 Hz, 2H), 3.30 (t, J = 7.7 Hz, 2H), 3.55 (t, J = 5.0 Hz, 2H), 3.78 (t, J = 4.8 Hz, 2H); ^{1}H NMR (400 MHz, $CDCl_3$, minor isomer, diagnostic peaks only) δ 3.37 (m, 1H), 3.48 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, major isomer) δ 14.2, 14.3, 20.4, 22.9, 27.9, 31.6, 33.2, 49.9, 50.6, 63.4, 176.0; ^{13}C NMR (100.6 MHz, $CDCl_3$, minor isomer, diagnostic peaks only) δ 20.6, 22.9, 33.4, 43.8, 49.8, 60.9; IR (neat) 3400, 2940, 2860, 1615, 1460, 1050 cm^{-1}; MS CI *m/e* 202 (M^+ + H), 86, 74. HRMS calcd for $C_{11}H_{24}NO_2$, 202.1807; found 202.1806. Anal. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.31; H, 11.68; N, 6.83.

2-Butylaminoethylpentanoate (6c). 80 mg of a colorless oil, 28% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (dt, J = 7.3 Hz, J = 7.3 Hz, 6H), 1.34−1.61 (m, 9H), 2.35 (t, J = 7.5 Hz, 2H), 2.65 (t, J = 7.1 Hz, 2H), 2.88 (t, J = 5.5 Hz, 2H), 4.20 (t, J = 5.5 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 14.4, 20.8, 22.7, 27.4, 32.6, 34.4, 48.6, 49.8, 64.2, 174.3; IR (neat) 3325, 2950, 2870, 1730, 1455, 1170 cm^{-1}; MS CI *m/e* 202 (M^+ + H), 154, 86, 74, 57, 44; HRMS calcd for $C_{11}H_{24}NO_2$, 202.1807; found 202.1801.

***N*-(3′-Hydroxypropyl)-*N*-butylpentanamide (5d).** Mixture of amide bond rotamers (ca. 10:1), 55 mg of a colorless oil, 18% yield. ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 0.95 (t, J = 7.3 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.37 (m, 4H), 1.68 (m, 6H), 2.36 (t, J = 7.4 Hz, 2H), 3.22 (t, J = 7.8 Hz, 2H), 3.51 (m, 4H), 4.13 (t, J = 7.1 Hz, 1H); ^{1}H NMR (400 MHz, $CDCl_3$, minor isomer, diagnostic peaks only) δ 3.33 (t, J = 7.7 Hz, 2H), 3.41 (t, J = 7.4 Hz, 2H), 3.71 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$, major isomer only), δ 13.8, 13.9, 20.1, 22.6, 27.8, 30.4, 31.1, 32.7, 41.5, 47.8, 58.1, 174.6; IR (neat) 3400, 2940, 2860, 1615, 1455, 1055 cm^{-1}; MS CI *m/e* 216 (M^+ + H), 86, 44; HRMS calcd for $C_{12}H_{26}NO_2$, 216.1963; found 216.1966.

3-Butylaminopropylpentanoate (6d): 226 mg of a yellow oil, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 6H), 1.34 (sextet, J = 7.6 Hz, 4H), 1.48 (pentet, J = 7.2 Hz, 2 H), 1.61 (pentet, J = 7.6 Hz, 2H), 1.84 (pentet, J = 6.8 Hz, 2H), 2.31 (t, J = 7.6 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 4.14 (t, J = 6.4 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$), δ 13.7, 13.9, 30.5, 22.3, 27.1, 29.2, 32.1, 34.1, 46.6, 49.7, 62.5, 173.9; IR (neat) 2950, 1725 cm^{-1}; MS CI *m/e* 216 (M^+ + H), 172, 44. HRMS calcd for $C_{12}H_{26}NO_2$, 216.1963; found 216.1956.

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Supporting Information Available: Characterization of compounds **3a**-**b**, **3e**-**j**, **4f**-**j**, **5a**-**b**, and **6b**, and copies of ^{1}H- and ^{13}C NMR spectra for compounds **3a**−**l**, **4a**−**l**, **5a**−**d**, and **6a**-**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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