

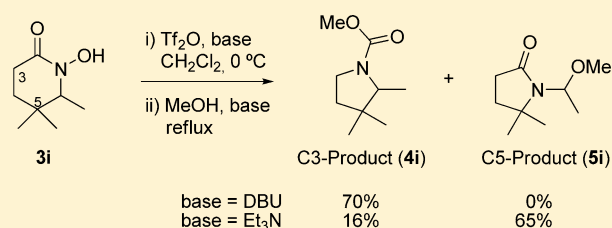
# Photochemical and Thermal Ring-Contraction of Cyclic Hydroxamic Acid Derivatives

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**S** Supporting Information

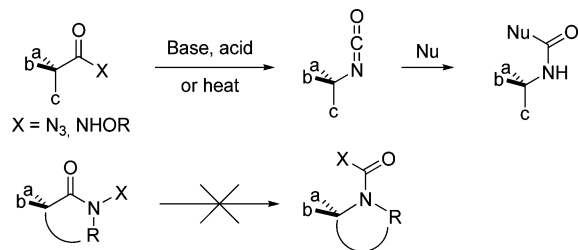
**ABSTRACT:** Cyclic hydroxamic acids can undergo a thermal ring contraction after an in situ triflation. High yields of ring-contraction products are obtained with DBU when the migrating carbon is a methylene, while best results are obtained with Et<sub>3</sub>N for the migration of quaternary carbons. In some cases, the regiochemical outcome of the reaction can be controlled by changing the base. This novel thermal rearrangement complements a similar but photochemical rearrangement of *N*-mesyloxylactams.



## INTRODUCTION

Reactions in which a carbon migrates from a carbonyl to a nitrogen atom, such as the Curtius, Hofmann, Schmidt and Lossen rearrangement, are frequently used methods to make a chiral carbon bearing a nitrogen atom (Scheme 1).<sup>1</sup> There are

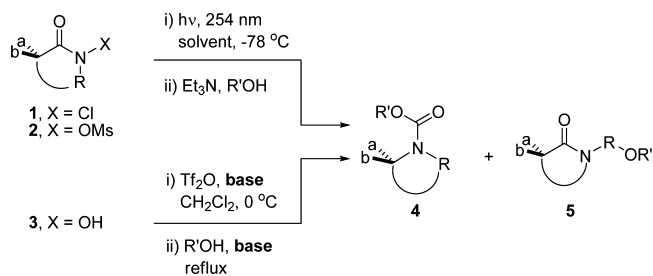
### Scheme 1. Lossen-Type Rearrangements



several advantages to using these rearrangements to make a C–N bond, not the least of which are their stereospecificity and the comparative ease of preparation of carbonyl compounds with an  $\alpha$ -chiral carbon.<sup>2</sup> In particular, quaternary chiral carbons (Scheme 1; a, b, c = carbons) bearing nitrogen are difficult to prepare by other means. However, such rearrangements are only possible on primary amide derivatives: secondary amide or lactam derivatives cannot be converted to the corresponding carbamate.<sup>3</sup> In the context of synthetic strategies, this limits the “amine” component to ammonia or its equivalent.

We have recently reported on the photochemical rearrangement of *N*-chlorolactams<sup>4</sup> and *N*-mesyloxylactams,<sup>5</sup> currently the only methods able to effect such migration on secondary amides.<sup>6</sup> Since these reports, we have developed a thermal rearrangement of cyclic hydroxamic acids (Scheme 2), which not only complements the current photochemical methods but also gives an unprecedented level of control over the regiochemical outcome of the ring-contraction event for certain substrates. We wish to report here a full account of these

### Scheme 2. Rearrangements of *N*-Substituted Lactams



rearrangements, divulging for the first time the thermal ring-contraction and emphasizing the complementarity of the three methods.

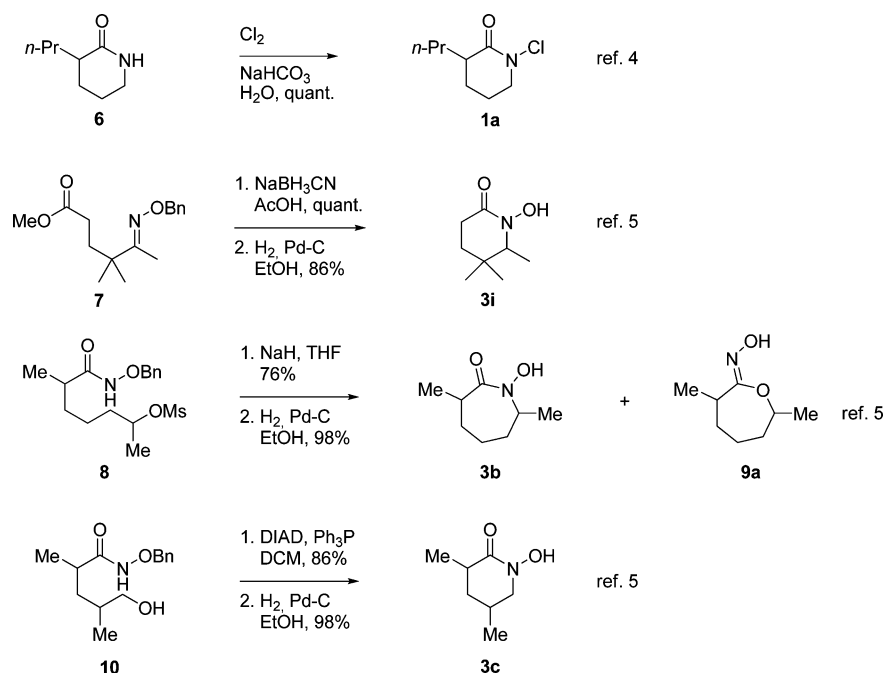
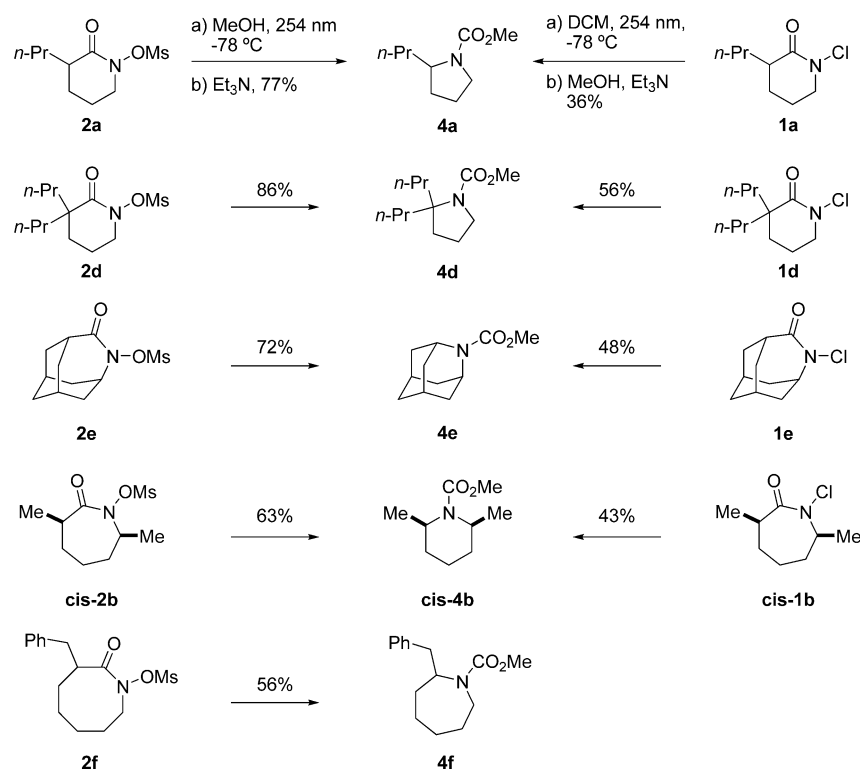
## RESULTS AND DISCUSSION

A priori, there seems to be little difference between the three methods shown in Scheme 2: all of them start with a *N*-activated lactam 1–3 and lead to the regioisomeric products 4 or 5. In reality, the three methods are complementary and display major differences in yields, regiochemistry, or methods of preparation of the *N*-activated lactams.

*N*-Chlorolactams, for example, are best prepared by direct *N*-chlorination of lactams in high yield (Scheme 3, 6 → 1a).<sup>4</sup> So far, we have not been able to develop a general and satisfactory oxidation method to convert lactams to hydroxamic acids.<sup>7</sup> Cyclic hydroxamic acid derivatives 3 can be prepared by amidation (Scheme 3, 7 → 3i), cyclization (8 → 3b) or Mitsunobu reactions (10 → 3c).<sup>5</sup> Such methods are unsuitable to make *N*-chlorolactams. *O*-Alkylation to produce cyclic iminoethers 9 is a potential problem in the latter two reactions, but one can distinguish the two products easily by <sup>13</sup>C NMR (the carbonyl signal is between 175 and 180 ppm for the

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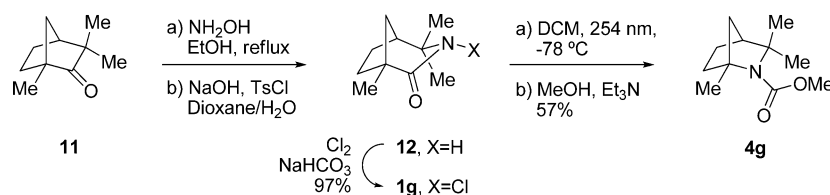
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Scheme 3. Preparation of *N*-Chlorolactams and Cyclic Hydroxamic AcidsScheme 4. Photochemical Ring-Contraction of *N*-Mesyloxylactams and *N*-Chlorolactams<sup>5</sup>

hydroxamic acids **3**, while the iminoether signal is between 150 and 155 ppm in the *O*-alkylation products **9**). Of course, these methods of preparation are shown as useful suggestions and should not be considered as a necessary part of the overall sequence. We have used a number of other ways to prepare these cyclic precursors to the rearrangement products, including metathesis for example.

In earlier work, we have compared the photochemical rearrangement of *N*-mesyloxylactams **2** with that of *N*-

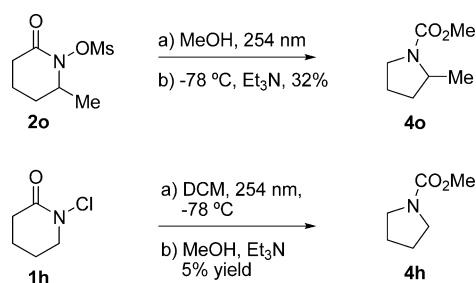
chlorolactams **1**.<sup>5</sup> Invariably, the former leads to higher yields of products than the latter upon irradiation at 254 nm (Scheme 4). The main issue with *N*-chlorolactams was the formation of the parent lactam and byproducts derived from side reactions of the initially formed chlorine radical. Such byproducts were never detected upon irradiation of *N*-mesyloxylactams. The ring-contraction of *N*-mesyloxylactams is synthetically useful starting from 6- to 8-membered rings, so long as the carbon  $\alpha$  to the amide carbonyl bears one or more substituents (Scheme

Scheme 5. Replacement of C=O by N–CO<sub>2</sub>Me in a Cyclic Structure<sup>6</sup>

4, 2a,b,d–f). On the other hand, the direct chloration of lactam allows one to obtain the *N*-chlorolactam in two steps from the corresponding ketone via a Beckmann rearrangement (Scheme 5). The corresponding hydroxamic acid of **1g** would be difficult to obtain. The ring-contraction of rigid bicyclic *N*-chlorolactam **1g** gave a synthetically useful 57% of product **4g** (Scheme 5).<sup>4b</sup>

Conspicuously absent from Scheme 4 are examples of the ring-contraction of 3-unsubstituted lactam derivatives. Unsubstituted *N*-chlorovalerolactam **1h** gave a low 5% yield of rearranged product **4h** upon irradiation, the remainder being mostly the parent  $\delta$ -valerolactam (Scheme 6).<sup>4</sup> The *N*-

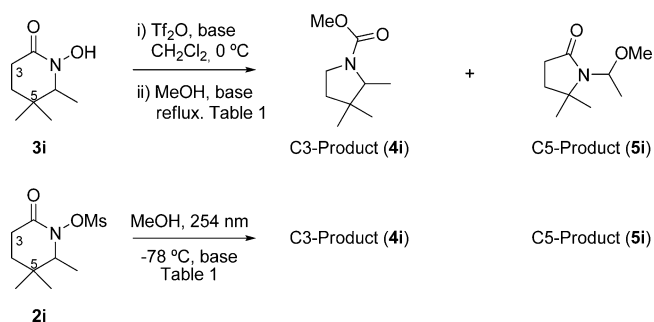
## Scheme 6. Rearrangements of 3-Unsubstituted Valerolactams



mesyloxyvalerolactam **2o** gave 32% of rearranged product **4o**, the remainder being decomposition material. The migrating carbon in these compounds may not be sufficiently electron-rich for the reaction to proceed at a competitive rate.

It was with this particular problem in mind that we decided to explore other leaving groups in the hope of favoring migration over other pathways. We should mention that additives such as silver nitrate did not improve the situation when used in conjunction with *N*-chlorolactams, nor did the use of other Lewis acids increase the yields of products in the case of *N*-chloro or *N*-mesyloxy lactams. However, when we performed the triflation of cyclic hydroxamic acid **3i**, it became apparent that it underwent partial rearrangement before we could submit it to irradiation (Scheme 7). Heating it in refluxing methanol without base gave 33% of pyrrolidine **4i** (Table 1, entry 1). This result was somewhat surprising since *N*-chloro-, *N*-mesyloxy- or *N*-tosyloxy lactams are inert below 190 °C.<sup>8</sup> Above that temperature, they may undergo a thermal rearrangement but usually in low yields.

We believed that the addition of a base during the rearrangement, to remove triflic acid as it forms, could help increase the yield of the rearrangement product. We therefore tested a variety of bases, and the results are reported in Table 1. The addition of NaOMe did not improve the yield of product **4i** (entry 2), but K<sub>2</sub>CO<sub>3</sub> did, albeit slightly (entry 3). A much better result was obtained using DBU (70%, entry 4). This is the first example of a 3-unsubstituted lactam derivative to undergo the rearrangement in high yield. Such a high yield was surprising, but even more surprising was the influence of the

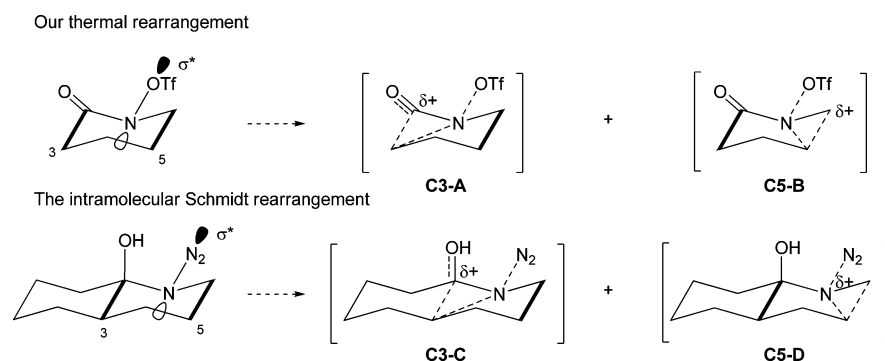
Scheme 7. Thermal Ring-Contraction of Cyclic Hydroxamic Acid **3i** and Photochemical Rearrangement of Its Analogue *N*-Mesyloxy lactam **2i**Table 1. Effect of the Base on the Rearrangement of Hydroxamic Acid **3i** or *N*-Mesyloxy lactam **2i**

entry	starting material	conditions <sup>a</sup>	base	C3 product ( <b>4i</b> ) <sup>b</sup> (%)	C5 product ( <b>5i</b> ) <sup>b</sup> (%)	total (%)
1	<b>13i</b>	A	–	33	–	33
2	<b>13i</b>	A	NaOMe	31	–	31
3	<b>3i</b>	B	K <sub>2</sub> CO <sub>3</sub>	46	–	46
4	<b>3i</b>	B	DBU	70	–	70
5	<b>3i</b>	B	DMAP	17	41	58
6	<b>3i</b>	B	Pyridine	11	50	61
7	<b>3i</b>	B	Et <sub>3</sub> N	16	65	81
8	<b>13i</b>	C	–	22	24	46
9	<b>13i</b>	C	Et <sub>3</sub> N	14	33	47
10	<b>13i</b>	C	DBU	63	–	63
11	<b>2i</b>	C	–	49	12	61
12	<b>2i</b>	C	Et <sub>3</sub> N	43	7 <sup>c</sup>	50
13	<b>2i</b>	C	DBU	33	0	33

<sup>a</sup>Conditions A: MeOH, base, reflux. Conditions B: (i) CH<sub>2</sub>Cl<sub>2</sub>, Tf<sub>2</sub>O; (ii) evaporate, MeOH, base, reflux. Conditions C: MeOH, base, 250 nm, –78 °C. <sup>b</sup>Isolated yield. <sup>c</sup>Not isolated; ratio determined by NMR of crude reaction mixture.

base on the regioselectivity of the reaction. Indeed, when replacing DBU with other nitrogen-based bases such as DMAP, pyridine or Et<sub>3</sub>N, we observed a reversal of the selectivity in favor of the C5 rearrangement product **5i** (Scheme 7 and Table 1, entries 5–7)!

A control experiment was performed by irradiating the triflate derivative **13i** (derived from **3i** and isolated) at 254 nm in methanol. In the absence of base, 22% of **4i** and 24% of **5i** were obtained (Table 1, entry 8). In the presence of Et<sub>3</sub>N, the C5-rearrangement product was again favored, with isolated yields of 14% **4i** and 33% **5i** (entry 9). As we suspected, in the presence of DBU only the C3-rearrangement product **5i** was obtained in 63% isolated yield (entry 10). We photolyzed the *N*-mesyloxy derivative **2i** in the absence of base (entry 11) or the presence of Et<sub>3</sub>N (entry 12) or DBU (entry 13), for



**Figure 1.** Possible competing transition states in the thermal rearrangement of *N*-trifloxylactams.

comparison, and found that the C3 product **4i** is predominant, regardless of the nature of the base used.

In cyclic hydroxamic acid derivatives, two C–C bonds are well aligned with the  $\sigma^*$  orbital of the N–O bond, thus enabling the formation of two rearrangement products: the C3 and the C5 migration products (Figure 1). This nearly locked-in alignment of the migrating bond with the departing group is crucial for the efficiency of the rearrangement, perhaps explaining why acyclic *N*-activated amides do not usually undergo this reaction efficiently.<sup>5a</sup> The carbonyl lone pair should assist the migration of the C3 carbon, much like the intramolecular Schmidt reaction of azidohydrin intermediates where the lone pair of the hydroxyl group dictates the regiochemistry of the rearrangement (Figure 1, bottom).<sup>9</sup> Indeed, the normal preference we observe is for migration of the C3 carbon (via transition state C3-A in Figure 1). The same preference for C3 migration is also observed upon irradiation of *N*-mesyloxylactams or *N*-chlorolactams.<sup>5</sup> However, in substrates such as **3i–l**, this preference is much less pronounced, contrary to the Schmidt reaction just mentioned that never gives the product equivalent to a C5-migration (via transition state C5-D in Figure 1). Moreover, the dependence of the regiochemistry on the nature of the base, in the case of substrates **3i–l**, has no precedent that we are aware of. A more in-depth mechanistic study is required to elucidate the role of the base in the regioselectivity.

We investigated other substrates to test the generality of this new thermal ring-contraction and to determine more fully its regiochemical particularities. The prospect of exercising a control over the regiochemical outcome was indeed appealing. We soon established that in most cases, it is possible and desirable to perform the whole operation in one-pot by simply evaporating the dichloromethane after triflation, adding methanol and the base, and heating.

Several trends can be discerned from the results shown in Table 2. First, the use of DBU gives good yields of the C3-rearrangement product **4** and better yields than the use of Et<sub>3</sub>N when the C3-position is unsubstituted (entries 1–3, 5, 6); second, the use of Et<sub>3</sub>N gives similar or higher yields of product **4** than DBU when the substrate possesses at least one substituent at C3 (entries 7–16); third, and most importantly, while the use of DBU leads exclusively to the C3-rearrangement product **4** in most cases, no matter the substitution (all entries except entries 2 and 4), the use of Et<sub>3</sub>N allows for the regioselective formation of the C5-rearrangement product **5** in some substrates (Table 1, entry 7 and Table 2, entries 1–4). The formation of large amounts of the C5-rearrangement products **5k** and **5m** from **3k** and **3m**, respectively, with both

DBU and Et<sub>3</sub>N can be attributed to the development of ring-strain in the corresponding products, especially in the case of **5m**.

The C5 rearrangement product **5** was obtained only with substrates bearing both an alkyl group at position 6 and at position 5 (Table 1, entry 7, and Table 2, entries 1–4). None of the corresponding product **5** was obtained from the rearrangement of substrate **3n** bearing two methyl groups at position 5 but no substituent at position 6 (entry 5) or of substrate **3o** bearing only a methyl at position 6 (entry 6). Substitution at position 6 is necessary to stabilize the developing positive charge in the product **5** (Figure 1). This stabilization competes with the stabilization provided by the carbonyl's lone pair of electrons during migration of the C3 carbon. The fact that the migration of electron-rich carbons is faster explains the need for substituents at position 5.

The thermal rearrangement of *N*-trifloxylactams under these reaction conditions is tolerant of spectator functional groups. The results shown in entries 14–16 demonstrate that esters, silyl ethers, acetals and epoxides are all compatible with the reaction conditions. By contrast, an acetonide group was hydrolyzed to the corresponding diol in the photochemical rearrangement of a *N*-mesyloxy lactam.<sup>5a</sup> In addition, the rearrangement can be performed in alcohols other than methanol. For example, the *N*-benzylcarbamate (Cbz) **33**, analogue of **4i** (c.f. Scheme 7, MeO = BnO), was obtained in 60% yield by heating the triflate **13i** at 70 °C in benzyl alcohol in the presence of DBU.

In cases where the C5 rearrangement can compete with the C3 rearrangement, we now have the possibility to *control* the regioselectivity of the rearrangement simply by choosing the appropriate base. For example, substrates **3j**, **3k**, **3l** and **3i** led exclusively or mostly to the corresponding C3-rearrangement product **4** when DBU was used but gave predominantly or exclusively the corresponding C5-rearrangement product **5** when Et<sub>3</sub>N was utilized (Table 1, entry 7 and Table 2 entries 1–3).

The underlying reasons for the regioselectivity brought about by a simple change in base with substrates **3j**, **3k**, **3l** and **3i** is not well understood at the moment. We speculate that DBU may favor the addition of methanol to the carbonyl of the amide derivative thereby promoting the C3-rearrangement. Possibly, the weaker bases like Et<sub>3</sub>N or pyridine do not favor this pathway and instead may let the regiochemical outcome of the reaction be decided by the relative migrating abilities of C3 vs. C5 as well as by the degree of substitution at C6. However, the reason why the thermal rearrangement of *N*-trifloxylactams with Et<sub>3</sub>N leads to a different regioisomer as compared to the

Table 2. Thermal Rearrangements of Cyclic Hydroxamic Acids **3a,c,d,j–u** in the Presence of DBU or Et<sub>3</sub>N and Photochemical Rearrangements of the Corresponding *N*-Mesyloxy **2a,c,d,j–u**



























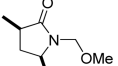


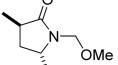


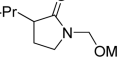


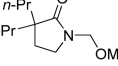


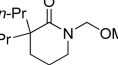


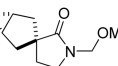


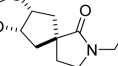


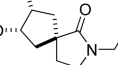
Entry	2 or 3	Conditions	Base	Yield of 4 <sup>a</sup>	Yield of 5 <sup>ab</sup>	Total yield
1	 <b>3j</b> X = OH	Thermal	DBU	 64%	 0%	64%
	<b>2j</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	0% 54%	95% 19%	95% 73%
2	 <b>3k</b> X = OH	Thermal	DBU	 48%	 49%	97%
	<b>2k</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	0% 38%	86% 31%	86% 69%
3	 <b>3l</b> X = OH	Thermal	DBU	 54%	 0%	54%
	<b>2l</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	4% 37%	58% 30%	62% 67%
4	 <b>3m</b> X = OH	Thermal	DBU	 0%	 63%	63%
	<b>2m</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	0% 16%	81% 57%	81% 73%
5	 <b>3n</b> X = OH	Thermal	DBU	 63%	 0%	63%
	<b>2n</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	19% 50%	0% 0%	19% 50%
6	 <b>3o</b> X = OH	Thermal	DBU	 68% <sup>c</sup>	 0%	68%
	<b>2o</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	0% 34%	0% 0%	0% 34%
7	 <b>3p</b> X = OH	Thermal	DBU	 0%	 0%	0%
	<b>2p</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	63% <sup>d</sup> 39%	0% 0%	63% 39%
8	 <b>3q</b> X = OH	Thermal	DBU	 19% <sup>c</sup>	 0%	19%
	<b>2q</b> X = OMs	hv	Et <sub>3</sub> N Et <sub>3</sub> N	52% <sup>c</sup> 47%	0% 13%	52% 60%

Table 2. continued

Entry	2 or 3	Conditions	Base	Yield of 4 <sup>a</sup>	Yield of 5 <sup>ab</sup>	Total yield
9		Thermal	DBU			43%
	<b>cis-3c</b> X = OH			0%		
	<b>cis-2c</b> X = OMs	hv	Et <sub>3</sub> N	47%	0%	47%
10		Thermal	DBU			45%
	<b>trans-3c</b> X = OH			0%		
	<b>trans-2c</b> X = OMs	hv	Et <sub>3</sub> N	47%	0%	47%
11		Thermal	DBU			51%
	<b>3a</b> X = OH			0%		
	<b>2a</b> X = OMs	hv	Et <sub>3</sub> N	39%	0%	39%
12		Thermal	DBU			14%
	<b>3d</b> X = OH			0%		
	<b>2d</b> X = OMs	hv	Et <sub>3</sub> N	82%	0%	82%
13		Thermal	DBU			36%
	<b>3r</b> X = OH			0%		
	<b>2r</b> X = OMs	hv	Et <sub>3</sub> N	80%	0%	80%
14			DBU <sup>f</sup>			58%
				Et <sub>3</sub> N <sup>f</sup>		66%
15			DBU			33%
				Et <sub>3</sub> N		77%
16			DBU <sup>f</sup>			67%
				Et <sub>3</sub> N <sup>f</sup>		67%

<sup>a</sup>Isolated yields. <sup>b</sup>Isolated as a mixture of the usual C5 product **5** and the corresponding enamide **14** (derived from **3j,k**) and enamide **15** (derived from **3l,m**) (Figure 2). <sup>c</sup>Represents the highest yield obtained with **3o** (15–68%). We believe the instability of the triflate intermediate may be at the origin of this nonreproducibility. <sup>d</sup>Combined yield of carbamate **4p** (8%), isocyanate **16** (15%) and acyclic carbamate **17** (40%), all of which are C3-migration products (Figure 2). <sup>e</sup>Compound **18** (Figure 2) was also isolated (21% using DBU and 15% using Et<sub>3</sub>N); see the Supporting Information. <sup>f</sup>Rearrangement performed using the same procedure, but the triflate derivatives **13s** (entry 14) and **13u** (entry 16) were isolated and purified between steps i and ii (c.f. Scheme 7).

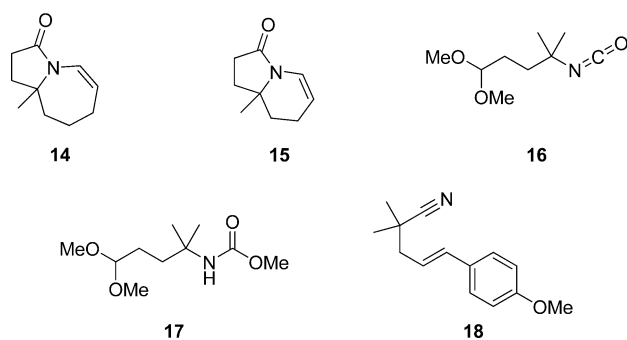


Figure 2. Compounds 14–18.

photochemical rearrangement of the corresponding *N*-mesyloxylactam is puzzling.

In summary, we have presented the first thermal Lossen-type rearrangement of secondary amide derivatives. In addition to improved yields of rearrangement products, this method is complementary to our previously reported photochemical rearrangements of *N*-chloro- and *N*-mesyloxylactams.<sup>4,5</sup> Efforts to uncover the exact reaction mechanism and to explain the base-dependent regiochemistry are currently under way.

## EXPERIMENTAL SECTION

All reactions were performed under an inert atmosphere of argon in glassware that had been flame-dried. Solvents were distilled from potassium/benzophenone ketyl (THF), from calcium hydride (CH<sub>2</sub>Cl<sub>2</sub>, toluene) and from 4 Å molecular sieves (MeOH) prior to use. Triflic anhydride and DBU were distilled prior to use. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on a 300 or 400 MHz spectrometer. NMR samples were dissolved in chloroform-*d* (unless specified otherwise), and chemical shifts are reported in ppm relative to the residual undeuterated solvent. Carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded on a 75.5 or 100.7 MHz spectrometer. NMR samples were dissolved in chloroform-*d* (unless specified otherwise), and chemical shifts are reported in ppm relative to the solvent. LRMS analyses were performed on a GC system spectrometer (30 m length, 25 μ OD, DB-5 ms column) coupled with a mass spectrometer. High-resolution spectrometry was performed by electrospray time-of-flight. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plate UV 254. Silica gel (particle size: 230–400 mesh) was used for flash chromatography. Melting points are uncorrected.

**1-Hydroxy-6-methylpiperidin-2-one (3o).** Methyl 5-oxohexanoate **19** (4.84 g, 33.6 mmol) was dissolved at rt in a 2:1 mixture of H<sub>2</sub>O (63 mL) and methanol (32 mL). Sodium acetate (13.8 g, 168 mmol) and *O*-benzylhydroxylamine hydrochloride (6.43 g, 40.3 mmol) were successively added. The reaction was stirred for 3.5 h at reflux temperature, after which time the methanol was removed under reduced pressure. The residue was diluted with water (200 mL) and extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexanes (10:90) as eluent to give methyl 5-(benzyloxylimino)hexanoate (**20**) as colorless oil (7.00 g, 84%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.37–7.27 (m, 5H), 5.07 (s, 2H), 3.67 (s, 3H), 2.31 (t, 2H, *J* = 7.3 Hz), 2.21 (t, 2H, *J* = 7.3 Hz), 1.87 (s, 3H), 1.84 (quint, 2H, *J* = 7.3 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 173.6 (s), 157.0 (s), 138.3 (s), 128.2 (d), 127.9 (d), 127.5 (d), 75.3 (t), 51.4 (q), 35.1 (t), 33.1 (t), 21.5 (t), 14.2 (q); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3065, 3037, 2953, 2874, 1725, 1453, 1367, 1262, 1159, 1043; LRMS (*m/z*, relative intensity) 272 (MNa<sup>+</sup>, 100), 250 (MH<sup>+</sup>, 12); HRMS calculated for C<sub>14</sub>H<sub>19</sub>NO<sub>3</sub>Na 272.1257, found 272.1260.

To a solution of this oxime (**20**) (7.00 g, 28.1 mmol) in acetic acid (95 mL) was added portionwise sodium cyanoborohydride (3.64 g, 56.2 mmol). The reaction mixture was stirred at rt for 2.25 h and at 80 °C for 30 min before it was added dropwise into a 5 N aqueous NaOH solution (400 mL) at 0 °C. The aqueous layer was extracted with dichloromethane (3 × 100 mL), and the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. 1-Benzyloxy-6-methylpiperidin-2-one (**21**) (5.79 g, 94%) was obtained as colorless oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.49–7.42 (m, 2H), 7.41–7.31 (m, 3H), 5.04 (d, 1H, *J* = 10.0 Hz), 4.90 (d, 1H, *J* = 10.0 Hz), 3.61 (sext, 1H, *J* = 6.3 Hz), 2.46 (t, 2H, *J* = 6.1 Hz), 2.00–1.74 (m, 2H), 1.72–1.54 (m, 2H), 1.29 (d, 3H, *J* = 6.3 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 167.7 (s), 135.5 (s), 129.3 (d), 128.5 (d), 128.4 (d), 76.1 (t), 56.5 (d), 33.5 (t), 31.4 (t), 19.3 (q), 18.5 (t); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3065, 3037, 2978, 2950, 2884, 1657, 1450, 1406, 1381, 1325, 1294, 1159, 1078; LRMS (*m/z*, relative intensity) 242 (MNa<sup>+</sup>, 100), 220 (MH<sup>+</sup>, 7); HRMS calculated for C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>Na 242.1152, found 242.1154.

1-Benzyloxy-6-methylpiperidin-2-one (**21**) (5.79 g, 26.4 mmol) was dissolved in anhydrous ethanol (275 mL) at rt. Then, 5% Pd/C (500 mg) was added, and the solution was degassed by bubbling argon through for 10 min. Argon was replaced by hydrogen, and the latter was bubbled into the solution for several seconds. The solution was stirred under hydrogen for 1 h, and argon was bubbled through the solution for another 10 min. The reaction mixture was filtered over Celite, and the filter cake was washed with anhydrous ethanol. The solvent was removed under reduced pressure to give product **3o** as orange oil (3.28 g, 96%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 3.91–3.79 (m, 1H), 2.45 (t, 2H, *J* = 6.2 Hz), 2.13–1.98 (m, 1H), 1.95–1.81 (m, 1H), 1.79–1.60 (m, 2H), 1.36 (d, 3H, *J* = 6.2 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 165.4 (s), 55.6 (d), 31.4 (t), 30.7 (t), 19.1 (q), 18.0 (t); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3519–3025 (br), 2959, 2871, 1604, 1450, 1391, 1331, 1300, 1162, 1093; LRMS (*m/z*, relative intensity) 152 (MNa<sup>+</sup>, 100), 130 (MH<sup>+</sup>, 11); HRMS calculated for C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub>Na 152.0682, found 152.0679.

**1-Hydroxy-3,3-dipropylazepan-2-one (3r).** To a solution of AlMe<sub>3</sub> (2 M in hexanes, 59.4 mL, 119 mmol) in THF (235 mL) at –10 °C was added *O*-benzylhydroxylamine hydrochloride (19.0 g, 119 mmol) portionwise. The reaction mixture was stirred at –10 °C for 30 min and at rt for 30 min. The solution was cooled back to –10 °C before a solution of 3,3-diallyloxepan-2-one **22** (7.69 g, 39.6 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred 15 min at –10 °C and 2 h at rt before a 1 N aqueous HCl solution was added carefully. When all of the AlMe<sub>3</sub> was quenched, the solution was allowed to warm to rt. The aqueous layer was extracted with dichloromethane (3 × 200 mL), and the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (60:40) as eluent to give the product as a sticky gum (12.5 g, 99%) that was used in the next reaction without purification.

Diisopropylazodicarboxylate (12.2 mL, 58.9 mmol) was added to a solution of triphenylphosphine (15.5 g, 58.9 mmol) in dichloromethane (355 mL). The solution was stirred at rt for 30 min before the addition of the product of the previous step dissolved in dichloromethane (10 mL). The reaction mixture was stirred at rt for 18 h, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (10:90) as eluent to give 3,3-diallyl-1-(benzyloxy)azepan-2-one (**23**) as colorless oil (5.34 g, 45%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.45–7.40 (m, 2H), 7.39–7.31 (m, 3H), 5.80 (dddd, 2H, *J* = 20.7, 9.3, 7.3, 7.3 Hz), 5.14–5.03 (m, 4H), 4.88 (s, 2H), 3.65–3.61 (m, 2H), 2.48 (dd, 2H, *J* = 13.8, 7.3 Hz), 2.30 (dd, 2H, *J* = 13.8, 7.3 Hz), 1.68–1.47 (m, 6H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 174.1 (s), 135.8 (s), 134.1 (d), 129.5 (d), 128.4 (d), 128.2 (d), 118.0 (t), 75.8 (t), 52.8 (t), 47.0 (s), 41.5 (t), 31.6 (t), 26.6 (t), 22.4 (t); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3003, 2981, 2943, 2878, 1641, 1450, 1391, 1359, 1309, 1262, 996, 915; LRMS (*m/z*, relative intensity) 322 (MNa<sup>+</sup>, 100), 300 (MH<sup>+</sup>, 15); HRMS calculated for C<sub>19</sub>H<sub>25</sub>NO<sub>2</sub>Na 322.1778, found 322.1775.

3,3-Diallyl-1-(benzyloxy)azepan-2-one (**23**) (5.34 g, 17.8 mmol) was dissolved in anhydrous ethanol (180 mL) at rt. Then, 10% palladium hydroxide on activated carbon (500 mg) was added, and the solution was degassed by bubbling argon for 10 min. Argon was replaced by hydrogen, and the latter was bubbled in the solution for several minutes. The solution was stirred under hydrogen for 2 h, and argon was bubbled through the solution again for another 10 min. The reaction mixture was filtered over Celite, and the filter cake was washed with anhydrous ethanol. The solvent was removed under reduced pressure to give product **3r** as colorless oil (3.45 g, 91%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 3.80–3.72 (m, 2H), 1.86–1.67 (m, 4H), 1.64–1.45 (m, 6H), 1.35–1.17 (m, 4H), 0.90 (t, 6H,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 172.9 (s), 50.5 (t), 46.0 (s), 38.7 (t), 32.0 (t), 26.8 (t), 22.6 (t), 16.9 (t), 14.5 (q); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3435–3022, 2950, 2874, 1588, 1444, 1378, 1334, 1272, 1162, 993; LRMS ( $m/z$ , relative intensity) 236 ( $\text{MNa}^+$ , 100), 214 ( $\text{MH}^+$ , 10); HRMS calculated for  $\text{C}_{12}\text{H}_{23}\text{NO}_2\text{Na}$  236.1621, found 236.1620.

**1'-Hydroxy-6-oxaspiro[bicyclo[3.1.0]hexane-3,3'-piperidin]-2'-one (3s).** To a solution of 3,3-diallyl-1-(benzyloxy)piperidin-2-one **24** (10.6 g, 37.2 mmol) in toluene (745 mL) was added Grubbs first gen catalyst (922 mg, 1.12 mmol) and titanium(IV) isopropoxide (3.3 mL, 11 mmol). The mixture was stirred for 18 h at rt, after which time the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (20:80 to 30:70) as eluent to give a 7-(benzyloxy)-7-azaspiro[4.5]dec-2-en-6-one (**25**) as waxy solid (8.89 g, 93%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.46–7.43 (m, 2H), 7.40–7.35 (m, 3H), 5.61 (s, 2H), 4.96 (s, 2H), 3.39 (t, 2H,  $J = 6.1$  Hz), 3.02 (d, 2H,  $J = 14.2$  Hz), 2.24 (d, 2H,  $J = 14.2$ ), 1.83–1.75 (m, 2H), 1.70–1.66 (m, 2H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 173.5 (s), 135.5 (s), 129.7 (d), 128.6 (d), 128.3 (d), 128.0 (d), 75.4 (t), 51.1 (t), 49.2 (s), 45.5 (t), 34.7 (t), 20.4 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3059, 2978, 1657; LRMS ( $m/z$ , relative intensity) 280 ( $\text{MNa}^+$ , 45), 257 ( $\text{MH}^+$ , 7); HRMS calculated for  $\text{C}_{16}\text{H}_{19}\text{NO}_2\text{Na}^+$  280.1308, found 280.1301; mp 40–43 °C.

7-(Benzyloxy)-7-azaspiro[4.5]dec-2-en-6-one (**25**) (100 mg, 0.390 mmol), methyltrioxorhenium (Re 71–76%, 0.3 mg, 0.0008 mmol) and pyrazole (2.7 mg, 0.039 mmol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (0.2 mL) at rt. A 30% aqueous  $\text{H}_2\text{O}_2$  solution (0.09 mL, 0.8 mmol) was then added, and the biphasic mixture was stirred vigorously for 4 h. EtOAc (10 mL) was added, and the organic layer was washed sequentially with a 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution (2  $\times$  5 mL), saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and saturated aqueous  $\text{NaHCO}_3$  (5 mL). The organic layer was then dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (40:60 to 100:0) as eluent to give 1'-(benzyloxy)-6-oxaspiro[bicyclo[3.1.0]hexane-3,3'-piperidin]-2'-one (**26**) as colorless oil (83 mg, 78%). The stereochemistry of the product was determined by NOESY (see Supporting Information):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.43–7.34 (m, 5H), 4.93 (s, 2H), 3.59 (s, 2H), 3.35–3.30 (m, 2H), 2.45 (d, 2H,  $J = 14.5$  Hz), 1.94 (d, 2H,  $J = 14.5$  Hz), 1.73–1.71 (m, 4H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 172.0 (s), 135.1 (s), 129.6 (d), 128.7 (d), 128.4 (d), 75.3 (t), 58.5 (d), 50.7 (t), 48.2 (s), 39.0 (t), 36.3 (t), 19.7 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3047, 2978, 1641, 1253; LRMS ( $m/z$ , relative intensity) 296 ( $\text{MNa}^+$ , 100), 274 ( $\text{MH}^+$ , 10); HRMS calculated for  $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{Na}^+$  296.1257, found 296.1258.

1'-(Benzyloxy)-6-oxaspiro[bicyclo[3.1.0]hexane-3,3'-piperidin]-2'-one (**26**) (925 mg, 3.39 mmol) was dissolved in anhydrous EtOH (35 mL). A catalytic amount of 5% palladium hydroxide on activated carbon was added, and the solution was degassed by bubbling argon for 10 min. Argon was replaced by hydrogen, and the latter was bubbled through the solution for several seconds. After being stirred for 3.5 h under hydrogen, argon was bubbled through the solution for another 10 min. The reaction mixture was then filtered on Celite, which was washed with anhydrous EtOH. The solvent was removed under reduced pressure to yield hydroxamic acid **3s** (606 mg, 98%) as a gum:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 3.60 (t, 2H,  $J = 5.8$  Hz), 3.60 (s, 2H), 2.42 (d, 2H,  $J = 14.5$  Hz), 1.98 (d, 2H,  $J = 14.5$  Hz),

1.93–1.82 (m, 4H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 169.3 (s), 58.4 (d), 49.7 (t), 46.6 (s), 38.7 (t), 36.1 (t), 19.1 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3294, 2978, 1607, 1266; LRMS ( $m/z$ , relative intensity) 206 ( $\text{MNa}^+$ , 100); HRMS calculated for  $\text{C}_9\text{H}_{13}\text{NO}_3\text{Na}^+$  206.0788, found 206.0788.

**1'-Hydroxy-2,2-dimethyltetrahydrospiro[cyclopenta[d][1,3]-dioxole-5,3'-piperidin]-2'-one (3t).** To a solution of AD-mix  $\beta$  (10.9 g) in a 1:1 mixture of *t*-BuOH (40 mL) and water (40 mL) cooled to 0 °C was added 7-(benzyloxy)-7-azaspiro[4.5]dec-2-en-6-one (**25**) (2.00 g, 7.77 mmol). The mixture was left to warm up to rt and stirred for 48 h. Sodium sulfite (11.7 g) was then added, and the mixture was stirred for 1 h. Water (100 mL) was then added, and the mixture was extracted with EtOAc (3  $\times$  100 mL). The organic extracts were combined, washed with brine (2  $\times$  100 mL), dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to yield 7-(benzyloxy)-2,3-dihydroxy-7-azaspiro[4.5]decan-6-one (**27**) (2.26 g, 100%) as viscous colorless oil. The stereochemistry of the product was determined by NOESY (see Supporting Information):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.42–7.38 (m, 2H), 7.38–7.33 (m, 3H), 4.90 (s, 2H), 4.33–4.29 (m, 2H), 3.34 (t, 2H,  $J = 6.1$  Hz), 2.86 (s, 2H), 2.34 (dd, 2H,  $J = 13.6$ , 6.5 Hz), 1.84–1.81 (m, 2H), 1.78–1.72 (m, 2H), 1.65 (dd, 2H,  $J = 13.6$ , 5.2 Hz);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 174.0 (s), 135.1 (s), 129.6 (d), 128.8 (d), 128.4 (d), 75.4 (t), 73.8 (d), 50.9 (t), 47.5 (s), 42.8 (t), 36.4 (t), 20.6 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3438 (br), 3059, 2978, 1641, 1043; LRMS ( $m/z$ , relative intensity) 314 ( $\text{MNa}^+$ , 100); HRMS calculated for  $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{Na}^+$  314.1363, found 314.1366.

To a solution of 7-(benzyloxy)-2,3-dihydroxy-7-azaspiro[4.5]decan-6-one (**27**) (1.00 g, 3.43 mmol) and 2,2-dimethoxypropane (9.25 mL, 75.5 mmol) in acetone (35 mL) was added a catalytic amount of *p*-TsOH. The reaction mixture was stirred at rt for 2.5 h, and then were added saturated aqueous  $\text{NaHCO}_3$  (25 mL) and water (50 mL). The mixture was extracted with EtOAc (3  $\times$  75 mL). The organic extracts were combined, dried over anhydrous  $\text{MgSO}_4$ , filtered and then evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (50:50) as eluent to give 1'-(benzyloxy)-2,2-dimethyltetrahydrospiro[cyclopenta[d][1,3]-dioxole-5,3'-piperidin]-2'-one (**28**) as a colorless solid (830 mg, 73%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.43–7.33 (m, 5H), 4.93 (s, 2H), 4.84–4.78 (m, 2H), 3.33 (t, 2H,  $J = 6.1$  Hz), 2.40 (ddd, 2H,  $J = 14.5$ , 4.7, 1.6 Hz), 1.94–1.90 (m, 2H), 1.86 (d, 2H,  $J = 14.5$  Hz), 1.80–1.72 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 171.6 (s), 135.1 (s), 129.5 (d), 128.5 (d), 128.2 (d), 81.2 (d), 77.6 (s), 75.0 (t), 52.0 (s), 50.6 (t), 42.5 (t), 32.9 (t), 26.3 (q), 23.5 (q), 20.4 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3047, 2981, 1641, 1050; LRMS ( $m/z$ , relative intensity) 354 ( $\text{MNa}^+$ , 100); HRMS calculated for  $\text{C}_{19}\text{H}_{25}\text{NO}_4\text{Na}^+$  354.1676, found 354.1679; mp 88–90 °C.

1'-(Benzyloxy)-2,2-dimethyltetrahydrospiro[cyclopenta[d][1,3]-dioxole-5,3'-piperidin]-2'-one (**28**) (830 mg, 2.50 mmol) was dissolved in anhydrous EtOH (25 mL). A catalytic amount of 5% palladium on activated carbon was added, and the solution was degassed with argon for 10 min. Argon was replaced by hydrogen, and the latter was bubbled through the solution for several seconds. After being stirred for 4.5 h under hydrogen, argon was bubbled through the solution for another 10 min. The reaction mixture was then filtered on Celite while being washed with anhydrous EtOH. The solvent was removed under reduced pressure to yield hydroxamic acid **3t** (576 mg, 95%) as a solid:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 4.82–4.78 (m, 2H), 3.63 (t, 2H,  $J = 6.1$  Hz), 2.36 (dd, 2H,  $J = 14.7$ , 6.1 Hz), 2.09–2.05 (m, 2H), 2.00–1.91 (m, 2H), 1.94 (d, 2H,  $J = 14.7$  Hz), 1.49 (s, 3H), 1.30 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 168.4 (s), 81.4 (d), 50.0 (s), 48.6 (t), 42.2 (t), 32.8 (t), 26.2 (q), 24.0 (s), 23.5 (q), 19.7 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3275 (br), 2978, 2940, 1610, 1128; LRMS ( $m/z$ , relative intensity) 264 ( $\text{MNa}^+$ , 100); HRMS calculated for  $\text{C}_{12}\text{H}_{19}\text{NO}_4\text{Na}^+$  264.1206, found 264.1211; mp 146–149 °C.

**3-(tert-Butyldimethylsilyloxy)-7-hydroxy-6-oxo-7-azaspiro[4.5]decan-2-yl acetate (3u).** A solution of 7-(benzyloxy)-2,3-dihydroxy-7-azaspiro[4.5]decan-6-one (**27**) (1.11 g, 3.81 mmol) in



THF (20 mL) was cooled down to 0 °C. Sodium hydride (60% dispersion in mineral oil, 160 mg, 4.00 mmol) was added, and the solution was stirred for 15 min at 0 °C and then 15 min at rt. Then, *t*-butyldimethylsilyl chloride (633 mg, 4.20 mmol) was added, and the reaction mixture was stirred at rt for 18 h. Saturated aqueous ammonium chloride (20 mL) and water (20 mL) were then added. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL); the organic extracts were combined, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (30:70) as eluent to give 7-(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-7-azaspiro[4.5]decan-6-one (**29**) as colorless oil (1.30 g, 84%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.44–7.40 (m, 2H), 7.38–7.35 (m, 3H), 4.96–4.89 (AB quartet, 2H), 4.40 (ddd, 1H, *J* = 7.5, 7.5, 4.2 Hz), 4.13–4.09 (m, 1H), 3.42–3.29 (m, 2H), 2.54 (br s, 1H), 2.32 (ddd, 2H, *J* = 13.8, 7.5, 5.4 Hz), 1.85–1.71 (m, 4H), 1.67 (dd, 1H, *J* = 13.8, 3.3 Hz), 1.56 (dd, 1H, *J* = 13.8, 7.6 Hz), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 173.7 (s), 135.3 (s), 129.6 (d), 128.7 (d), 128.4 (d), 75.3 (t), 75.0 (d), 73.9 (d), 50.9 (t), 47.7 (s), 43.6 (t), 42.4 (t), 36.6 (t), 25.8 (q), 20.6 (t), 18.0 (s), –4.6 (q), –5.0 (q); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3050, 2956, 1641, 1256, 1100; LRMS (*m/z*, relative intensity) 406 (MH<sup>+</sup>, 100), 428 (MNa<sup>+</sup>, 50); HRMS calculated for C<sub>22</sub>H<sub>35</sub>NO<sub>4</sub>SiH<sup>+</sup> 406.2408, found 406.2413.

7-(Benzyloxy)-2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-7-azaspiro[4.5]decan-6-one (**29**) (1.30 g, 3.21 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (16 mL) and cooled down to 0 °C. Triethylamine (1.12 mL, 8.01 mmol), acetic anhydride (0.61 mL, 6.4 mmol), and a catalytic amount of DMAP were then successively added, and the reaction mixture was stirred for 2 h while being left to slowly warm up to rt. Aqueous saturated NH<sub>4</sub>Cl (15 mL) and water (15 mL) were then added, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The organic extracts were combined, washed with aqueous saturated K<sub>2</sub>CO<sub>3</sub> (50 mL), dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to yield 7-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-6-oxo-7-azaspiro[4.5]decan-2-yl acetate (**30**) (1.44 g, 100%) as colorless oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.44–7.40 (m, 2H), 7.38–7.35 (m, 3H), 5.18 (ddd, 1H, *J* = 6.0, 6.0, 4.1 Hz), 4.93 (s, 2H), 4.45 (ddd, 1H, *J* = 6.0, 6.0, 4.1 Hz), 3.42–3.30 (m, 2H), 2.46 (dd, 1H, *J* = 13.6, 6.0 Hz), 2.36 (dd, 1H, *J* = 13.3, 6.0 Hz), 2.05 (s, 3H), 1.85–1.74 (m, 4H), 1.70 (dd, 1H, *J* = 13.6, 6.0 Hz), 1.59 (dd, 1H, *J* = 13.3, 6.0 Hz), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 173.2 (s), 170.1 (s), 135.2 (s), 129.5 (d), 128.6 (d), 128.3 (d), 76.1 (d), 75.2 (t), 73.0 (d), 50.8 (t), 46.7 (s), 43.7 (t), 40.0 (t), 36.4 (t), 25.7 (q), 21.1 (q), 20.5 (t), 18.0 (s), –5.0 (q), –5.1 (q); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3040, 2953, 1726, 1657, 1262, 1125; LRMS (*m/z*, relative intensity) 448 (MH<sup>+</sup>, 100), 470 (MNa<sup>+</sup>, 85); HRMS calculated for C<sub>24</sub>H<sub>37</sub>NO<sub>5</sub>SiH<sup>+</sup> 448.2514, found 448.2518.

7-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-6-oxo-7-azaspiro[4.5]decan-2-yl acetate (**30**) (956 mg, 2.13 mmol) was dissolved in ethanol (21 mL). A catalytic amount of 5% palladium on activated carbon was added, and the solution was degassed by bubbling argon for 10 min. Argon was replaced by hydrogen, and the latter was bubbled through the solution for several seconds. After being stirred for 1 h under hydrogen, argon was bubbled through the solution for another 10 min. The reaction mixture was then filtered on Celite while being washed with EtOH. The solvent was removed under reduced pressure to yield hydroxamic acid **3u** as an oil (713 mg, 93%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 5.17 (ddd, 1H, *J* = 6.3, 6.3, 4.0 Hz), 4.43 (ddd, 1H, *J* = 5.6, 5.6, 4.0 Hz), 3.65–3.58 (m, 2H), 2.43 (dd, 1H, *J* = 13.6, 6.3 Hz), 2.33 (dd, 1H, *J* = 13.4, 5.6 Hz), 2.05 (s, 3H), 1.97–1.91 (m, 4H), 1.76 (dd, 1H, *J* = 13.6, 6.3 Hz), 1.64 (dd, 1H, *J* = 13.4, 5.6 Hz), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 170.9 (s), 170.2 (s), 76.1 (d), 72.9 (d), 49.8 (t), 45.2 (s), 43.5 (t), 39.9 (t), 36.3 (t), 25.7 (q), 21.1 (q), 19.9 (t), 18.0 (s), –5.1 (q), –5.1 (q); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3281 (br), 2978, 1729, 1610, 1256, 1046; LRMS (*m/z*, relative intensity) 380 (MNa<sup>+</sup>, 100); HRMS calculated for C<sub>17</sub>H<sub>31</sub>NO<sub>5</sub>SiNa<sup>+</sup> 380.1864, found 380.1866.

**2,3,3-Trimethyl-6-oxopiperidin-1-yl trifluoromethanesulfonate (13i)**. To a solution of hydroxamic acid **3i** (0.200 g, 1.27 mmol) in dichloromethane (6 mL) at 0 °C was added triethylamine (0.26 mL, 1.9 mmol) and triflic anhydride (0.26 mL, 1.52 mmol). After being stirred 5 min at 0 °C, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using ethyl acetate and hexanes (15:85) as eluent to give **13i** as colorless oil (0.258 g, 70%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 3.72 (q, 1H, *J* = 6.4 Hz), 2.66 (ddd, 1H, *J* = 17.4, 11.0, 7.0 Hz), 2.56 (ddd, 1H, *J* = 17.4, 6.7, 3.8 Hz), 1.84 (ddd, 1H, *J* = 14.1, 11.0, 6.7 Hz), 1.57–1.49 (m, 1H), 1.30 (d, 3H, *J* = 6.4 Hz), 1.27 (s, 3H), 1.06 (s, 3H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 169.4 (s), 118.4 (q, *J* = 32 Hz), 70.8 (d), 36.1 (s), 30.5 (t), 30.1 (t), 25.7 (q), 13.6 (q); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 2978, 1641, 1463, 1291, 1168, 1029. LRMS and HRMS could not be obtained because of the thermal instability of the molecule.

**2,3,3-Trimethyl-6-oxopiperidin-1-yl 4-methylbenzenesulfonate (32)**. To a solution of hydroxamic acid **3i** (0.151 g, 0.960 mmol) in dichloromethane (7 mL) was added triethylamine (0.16 mL, 1.2 mmol), DMAP (35 mg, 0.29 mmol) and tosyl chloride (0.202 g, 1.06 mmol). After being stirred 15 min at rt, water (25 mL) and a 1 M aqueous HCl solution (25 mL) were added. The aqueous phase was extracted with dichloromethane (3 × 50 mL); the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (25:75) as eluent to give 2,3,3-trimethyl-6-oxopiperidin-1-yl 4-methylbenzenesulfonate (**32**) as colorless oil (0.156 g, 52%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.88 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.3 Hz), 3.79 (q, 1H, *J* = 6.4 Hz), 2.44 (s, 3H), 2.29–2.24 (m, 2H), 1.77 (ddd, 1H, *J* = 13.8, 9.1, 9.1 Hz), 1.38 (dt, 1H, *J* = 13.8, 4.8 Hz), 1.25 (d, 3H, *J* = 6.4 Hz), 1.25 (s, 3H), 1.00 (s, 3H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 168.4 (s), 145.9 (s), 131.4 (s), 129.5 (d), 129.3 (d), 69.3 (d), 35.2 (s), 30.2 (t), 29.7 (t), 26.1 (q), 25.9 (q), 21.8 (q), 13.9 (q); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 3047, 2978, 2943, 2874, 1710, 1600, 1463, 1372, 1175, 1090; LRMS (*m/z*, relative intensity) 334 (MNa<sup>+</sup>, 100); HRMS calculated for C<sub>15</sub>H<sub>21</sub>NO<sub>4</sub>SNa 334.1084, found 334.1088.

**2-Methyl-6-oxopiperidin-1-yl methanesulfonate (2o)**. Triethylamine (0.49 mL, 3.5 mmol) and 4-dimethylaminopyridine (86 mg, 0.70 mmol) were added to a solution of hydroxamic acid **3o** (300 mg, 2.32 mmol) in dichloromethane (12 mL). Mesyl chloride (0.22 mL, 2.8 mmol) was added, and the reaction mixture was stirred at rt for 15 min. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexanes (50:50) as eluent to give compound **2o** as colorless oil (376 mg, 78%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 4.17–4.04 (m, 1H), 3.29 (s, 3H), 2.56 (t, 2H, *J* = 6.6 Hz), 2.24–2.09 (m, 1H), 1.99–1.87 (m, 1H), 1.86–1.72 (m, 2H), 1.38 (d, 3H, *J* = 6.4 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 169.0 (s), 60.2 (d), 39.1 (q), 33.7 (t), 31.2 (t), 18.4 (q), 18.0 (t); IR (CHCl<sub>3</sub>) ν (cm<sup>-1</sup>) 2984, 2959, 2884, 1688, 1450, 1366, 1325, 1291, 1172, 968; LRMS (*m/z*, relative intensity) 230 (MNa<sup>+</sup>, 100), 208 (MH<sup>+</sup>, 1); HRMS calculated for C<sub>7</sub>H<sub>13</sub>NO<sub>4</sub>SNa 230.0458, found 230.0474; mp 52–54 °C.

**2-Oxo-3,3-dipropylazepan-1-yl methanesulfonate (2r)**. Triethylamine (0.30 mL, 2.1 mmol) and 4-dimethylaminopyridine (51 mg, 0.42 mmol) were added to a solution of hydroxamic acid **3r** (300 mg, 1.41 mmol) in dichloromethane (9 mL). Mesyl chloride (0.13 mL, 1.7 mmol) was added, and the reaction mixture was stirred at rt for 5 min. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexanes (10:90) as eluent to give compound **2r** as colorless oil (391 mg, 95%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 3.95–3.91 (m, 2H), 3.13 (s, 3H), 1.93–1.80 (m, 2H), 1.78–1.45 (m, 8H), 1.27 (sext, 4H, *J* = 7.2 Hz), 0.92 (t, 6H, *J* = 7.2 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 177.1 (s), 56.0 (t), 47.7 (s), 39.3 (t), 37.7 (q), 32.1 (t), 26.6 (t), 22.3 (t), 17.0 (t), 14.6 (q); IR (neat) ν (cm<sup>-1</sup>) 2965, 2934, 2878, 1691, 1466, 1366, 1322, 1175, 1046, 962, 880; LRMS (*m/z*, relative intensity) 314 (MNa<sup>+</sup>,

100); HRMS calculated for  $C_{13}H_{25}NO_4SiNa$  314.1397, found 314.1400.

**2'-Oxo-6-oxaspiro[bicyclo[3.1.0]hexane-3,3'-piperidine]-1'-yl trifluoromethanesulfonate (13s).** Hydroxamic acid **3s** (300 mg, 1.10 mmol) was dissolved in dichloromethane (9 mL) at 0 °C.  $Et_3N$  (0.23 mL, 1.7 mmol) was added followed by the addition of freshly distilled triflic anhydride (0.22 mL, 1.3 mmol). The solution was stirred 2 min at 0 °C before the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (10:90) as eluent to give 2'-oxo-6-oxaspiro[bicyclo[3.1.0]hexane-3,3'-piperidine]-1'-yl trifluoromethanesulfonate (**13s**) as colorless oil (346 mg, 100%):  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 3.80 (t, 2H,  $J = 6.0$  Hz), 3.60 (s, 2H), 2.44 (d, 2H,  $J = 14.8$  Hz), 2.09–2.04 (m, 2H), 2.07 (d, 2H,  $J = 14.8$  Hz), 1.90–1.86 (m, 2H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  (ppm) 175.2 (s), 118.3 (q,  $J = 322$  Hz), 57.9 (d), 55.9 (t), 50.3 (s), 37.9 (t), 36.2 (t), 20.7 (t); IR ( $CHCl_3$ )  $\nu$  ( $cm^{-1}$ ) 2975, 1604, 1253, 1046. A mass spectrum could not be obtained because of the thermal instability of the compound.

**3-(tert-butyl dimethylsilyloxy)-6-oxo-7-(trifluoromethylsulfonyloxy)-7-azaspiro[4.5]decan-2-yl acetate (13u).** Hydroxamic acid **3u** (200 mg, 0.559 mmol) was dissolved in dichloromethane (6 mL) at 0 °C.  $Et_3N$  (0.12 mL, 0.84 mmol) was added followed by the addition of freshly distilled triflic anhydride (0.11 mL, 0.67 mmol). The solution was stirred 2 min at 0 °C before the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (10:90) as eluent to give 3-(tert-butyl dimethylsilyloxy)-6-oxo-7-(trifluoromethylsulfonyloxy)-7-azaspiro[4.5]decan-2-yl acetate (**13u**) as oil (234 mg, 85%):  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 5.09 (ddd, 1H,  $J = 6.4, 6.4, 4.0$  Hz), 4.33 (ddd, 1H,  $J = 5.6, 5.6, 4.0$  Hz), 3.84 (t, 2H,  $J = 6.0$  Hz), 2.56 (dd, 1H,  $J = 13.8, 6.4$  Hz), 2.38 (dd, 1H,  $J = 13.6, 5.6$  Hz), 2.15–2.07 (m, 2H), 2.05 (s, 3H), 1.99–1.94 (m, 2H), 1.79 (dd, 1H,  $J = 13.8, 6.4$  Hz), 1.71 (dd, 1H,  $J = 13.6, 5.6$  Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  (ppm) 176.3 (s), 170.1 (s), 118.3 (q,  $J = 322$  Hz), 75.2 (d), 72.4 (d), 56.0 (t), 48.7 (s), 43.1 (t), 39.1 (t), 36.5 (t), 25.6 (q), 21.4 (t), 21.0 (q), 17.9 (s), –5.2 (q), –5.2 (q); IR ( $CHCl_3$ )  $\nu$  ( $cm^{-1}$ ) 2978, 1710, 1600, 1250, 1046. A mass spectrum could not be obtained because of the thermal instability of the compound.

**General Procedure for the Thermal Rearrangement.** The cyclic hydroxamic acid (1 equiv) was dissolved in dichloromethane (0.15 M) and cooled to 0 °C. Base (1.5 equiv) was added followed by the addition of freshly distilled triflic anhydride (1.2 equiv). After 5 min (reaction monitored by TLC) the solvent was removed under reduced pressure. Methanol (0.15 M) and base (2.0 equiv) were successively added, and the solution was stirred at reflux temperature for 30 min. The reaction mixture was then allowed to cool to rt before the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

**Methyl 2-methylpyrrolidine-1-carboxylate (4o).** Carbamate **4o** was synthesized according to the general procedure starting from **3o**. The reaction was made on a 0.774 mmol scale, the base used was DBU, the eluent for the flash chromatography was a mixture of ethyl acetate and hexanes (10:90), and the product **4o** was obtained in 68% yield as colorless oil:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 4.01–3.80 (m, 1H), 3.69 (s, 3H), 3.46–3.28 (m, 2H), 2.05–1.73 (m, 3H), 1.65–1.48 (m, 1H), 1.23–1.08 (m, 3H).

**Methyl 2,2-dipropylpiperidine-1-carboxylate (4r).** Carbamate **4r** was synthesized according to the general procedure starting from **3r**. The reaction was made on a 0.47 mmol scale, the base used was triethylamine, the eluent for the flash chromatography was a mixture of ethyl acetate and hexanes (5:95), and the product **4r** was obtained in 74% yield as colorless oil:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 3.63 (s, 3H), 3.47–3.43 (m, 2H), 1.96 (ddd, 2H,  $J = 16.8, 12.0, 4.9$  Hz), 1.63–1.53 (m, 8H), 1.35–1.11 (m, 4H), 0.89 (t, 6H,  $J = 7.2$  Hz);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  (ppm) 156.7 (s), 60.1 (s), 51.7 (q), 41.9 (t), 39.7 (t), 30.5 (t), 23.5 (t), 17.9 (t), 17.1 (t), 14.7 (q); IR ( $CHCl_3$ )  $\nu$  ( $cm^{-1}$ ) 2962, 2874, 1691, 1444, 1381, 1353, 1266, 1153, 1090;

LRMS ( $m/z$ , relative intensity) 250 ( $MNa^+$ , 100), 228 ( $MH^+$ , 3); HRMS calculated for  $C_{13}H_{25}NO_3Na$  250.1778, found 250.1782.

**Methyl 6-oxaspiro[bicyclo[3.1.0]hexane-3,2'-pyrrolidine]-1'-carboxylate (4s).** Triethylamine (0.09 mL, 0.6 mmol) was added to a solution of 2'-oxo-6-oxaspiro[bicyclo[3.1.0]hexane-3,3'-piperidine]-1'-yl trifluoromethanesulfonate (**3s**) (100 mg, 0.317 mmol) in MeOH (3 mL). The solution was stirred at reflux temperature for 30 min and was then allowed to cool to rt before the solvent was removed under reduced pressure. The crude product **4s** was purified by flash chromatography on silica gel using ethyl acetate and hexanes (15:85) as eluent to give product **4s** a colorless solid in 66% yield (58% when using DBU instead of triethylamine):  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) **Rotamer A** 3.64 (s, 3H), 3.52 (s, 2H), 3.32 (t, 2H,  $J = 6.8$  Hz), 2.68 (d, 2H,  $J = 14.1$  Hz), 1.91–1.67 (m, 6H); **Rotamer B** 3.71 (s, 3H), 3.52 (s, 2H), 3.40 (t, 2H,  $J = 6.5$  Hz), 2.43 (d, 2H,  $J = 14.3$  Hz), 1.91–1.67 (m, 6H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  (ppm) **Rotamer A** 154.3 (s), 66.8 (s), 56.6 (d), 51.7 (q), 47.1 (t), 44.7 (t), 37.8 (t), 22.6 (t); **Rotamer B** 154.3 (s), 66.8 (s), 56.6 (d), 52.1 (q), 48.1 (t), 46.0 (t), 39.4 (t), 22.2 (t); IR ( $CHCl_3$ )  $\nu$  ( $cm^{-1}$ ) 2978, 1691, 1247; LRMS ( $m/z$ , relative intensity) 220 ( $MNa^+$ , 80), 198 ( $MH^+$ , 100); HRMS calculated for  $C_{10}H_{16}NO_3^+$  198.1125, found 198.1119; mp 36–40 °C.

**Methyl 2,2-dimethyltetrahydrospiro[cyclopenta[d][1,3]-dioxole-5,2'-pyrrolidine]-1'-carboxylate (4t).** Carbamate **4t** was synthesized according to the general procedure starting from **3t**. The reaction was made on a 0.414 mmol scale, the eluent for the flash chromatography was a mixture of ethyl acetate and hexanes (10:90), and the product **4t** was obtained as a colorless solid in 77% yield when using  $Et_3N$  as base and 33% when using DBU instead of triethylamine:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 4.72 (d, 2H,  $J = 4.8$  Hz), 3.63 (s, 3H), 3.34 (t, 2H,  $J = 6.7$  Hz), 2.82 (dd, 2H,  $J = 14.2, 4.8$  Hz), 2.14 (t, 2H,  $J = 6.7$  Hz), 1.75 (quint, 2H,  $J = 6.7$  Hz), 1.69 (d, 2H,  $J = 14.2$  Hz), 1.49 (s, 3H), 1.29 (s, 3H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  (ppm) 154.1 (s), 108.8 (s), 79.7 (d), 69.7 (s), 51.5 (q), 47.0 (t), 40.7 (t), 40.3 (t), 25.9 (q), 23.4 (q), 22.8 (t); IR ( $CHCl_3$ )  $\nu$  ( $cm^{-1}$ ) 2981, 1691, 1378, 1115; LRMS ( $m/z$ , relative intensity) 278 ( $MNa^+$ , 100), 256 ( $MH^+$ , 30); HRMS calculated for  $C_{13}H_{21}NO_4Na^+$  278.1363, found 278.1366; mp 66–69 °C.

**Methyl 7-acetoxy-8-(tert-butyl dimethylsilyloxy)-1-azaspiro[4.4]nonane-1-carboxylate (4u).** Triethylamine (0.09 mL, 0.6 mmol) was added to a solution of 3-(tert-butyl dimethylsilyloxy)-6-oxo-7-(trifluoromethylsulfonyloxy)-7-azaspiro[4.5]decan-2-yl acetate (**3u**) (100 mg, 0.317 mmol) in MeOH (3 mL). The solution was stirred at reflux temperature for 30 min and was then allowed to cool to rt before the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (15:85) as eluent to give product **4u** as colorless oil in 67% yield (same yield with DBU instead of triethylamine):  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) **Rotamer A** 5.35 (ddd, 1H,  $J = 6.4, 6.4, 4.5$  Hz), 4.56 (ddd, 1H,  $J = 4.5, 4.5, 4.5$  Hz), 3.64 (s, 3H), 3.34 (t, 2H,  $J = 6.7$  Hz), 2.49–1.60 (m, 8H), 2.03 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); **Rotamer B** 5.22–5.16 (m, 1H), 4.42–4.38 (m, 1H), 3.71 (s, 3H), 3.48–3.39 (m, 2H), 2.49–1.60 (m, 8H), 2.03 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  (ppm) **Rotamer A** 170.3 (s), 154.3 (s), 76.8 (d), 73.2 (d), 66.5 (s), 51.7 (q), 47.2 (t), 43.9 (t), 43.5 (t), 39.9 (t), 25.7 (q), 22.9 (t), 21.1 (q), 18.0 (s), –5.0 (q), –5.1 (q); **Rotamer B** 170.3 (s), 154.3 (s), 76.2 (d), 73.2 (d), 66.0 (s), 52.1 (q), 48.2 (t), 45.1 (t), 44.5 (t), 40.8 (t), 25.7 (q), 22.4 (t), 21.1 (q), 18.0 (s), –5.0 (q), –5.1 (q); IR ( $CHCl_3$ )  $\nu$  ( $cm^{-1}$ ) 2956, 1726, 1691, 1269, 1078; LRMS ( $m/z$ , relative intensity) 372 ( $MH^+$ , 50), 394 ( $MNa^+$ , 100); HRMS calculated for  $C_{18}H_{33}NO_5SiNa^+$  394.2020, found 394.2024.

**9-Methyl-7,8,9a-tetrahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (14).** Enamide **14** was synthesized according to the general procedure starting from **3j** or **3k**. The reaction was made on a 1.09 mmol scale, the base used was DBU, the eluent for the flash chromatography was a mixture of ethyl acetate and hexanes (25:75), and the product **14** was obtained in 28% yield as colorless oil:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 6.40 (dd, 1H,  $J = 9.0, 3.1$  Hz), 5.18

(ddd, 1H,  $J = 11.3, 9.0, 3.2$  Hz), 2.59–2.43 (m, 2H), 2.41–2.25 (m, 1H), 2.13–2.01 (m, 1H), 1.99–1.77 (m, 3H), 1.69–1.52 (m, 3H), 1.19 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 174.1 (s), 123.1 (d), 115.6 (d), 63.2 (s), 42.7 (t), 34.3 (t), 29.5 (t), 28.7 (t), 21.5 (q), 20.1 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3014, 2946, 2874, 1678, 1445, 1402, 1359, 957, 906; LRMS ( $m/z$ , relative intensity) 353 ( $2\text{MNa}^+$ , 59), 188 ( $\text{MNa}^+$ , 100); HRMS calculated for  $\text{C}_{10}\text{H}_{15}\text{NONa}$  188.1046, found 188.1049.

**8a-Methyl-1,2,8,8a-tetrahydroindolizin-3(7H)-one (15).** Enamide **15** was synthesized according to the general procedure starting from **3l** or **3m**. The reaction was made on a 0.591 mmol scale, the base used was DBU, the eluent for the flash chromatography was a mixture of ethyl acetate and hexanes (50:50), and the product **15** was obtained in 64% yield as colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 6.74 (dt, 1H,  $J = 8.2, 2.0$  Hz), 5.10–5.05 (m, 1H), 2.60 (ddd, 1H,  $J = 18.8, 12.0, 7.6$  Hz), 2.36 (dd, 1H,  $J = 18.8, 9.2$  Hz), 2.28–2.07 (m, 2H), 2.01 (dd, 1H,  $J = 11.8, 8.0$  Hz), 1.89 (dd, 1H,  $J = 11.8, 4.6$  Hz), 1.78 (ddd, 1H,  $J = 12.0, 9.2$  Hz), 1.53 (ddd, 1H,  $J = 12.0, 7.6$  Hz), 1.16 (s, 3H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 170.8 (s), 120.3 (d), 108.2 (d), 58.3 (s), 34.2 (t), 34.1 (t), 29.6 (t), 21.2 (q), 20.2 (t); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 2975, 2943, 1691, 1460, 1406, 1325, 1299, 1153, 1050; LRMS ( $m/z$ , relative intensity) 174 ( $\text{MNa}^+$ , 100), 152 ( $\text{MH}^+$ , 20); HRMS calculated for  $\text{C}_9\text{H}_{13}\text{NONa}$  174.0889, found 174.0891.

**(E)-5-(4-Methoxyphenyl)-2,2-dimethylpent-4-enenitrile (18).** Nitrile **18** was obtained as a side product starting from **3q** following general procedure. The reaction was made on a 0.20 mmol scale, the base used was triethylamine, the eluent for the flash chromatography was a mixture of ethyl acetate and hexanes (10:90), and the product **18** was obtained in 15% yield as colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.32 (d, 2H,  $J = 8.7$  Hz), 6.86 (d, 2H,  $J = 8.7$  Hz), 6.44 (d, 1H,  $J = 15.4$  Hz), 6.11 (dt, 1H,  $J = 15.4, 7.3$  Hz), 3.81 (s, 3H), 2.41 (dd, 2H,  $J = 7.3, 0.7$  Hz), 1.37 (s, 6H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 159.2 (s), 134.1 (d), 129.5 (s), 127.5 (d), 124.9 (s), 121.2 (d), 114.0 (d), 55.3 (q), 44.3 (t), 32.6 (s), 26.3 (q); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3024, 2982, 2932, 2200, 1609, 1510, 1468, 1305, 1252, 1178, 1036, 969; LRMS ( $m/z$ , relative intensity) 238 ( $\text{MNa}^+$ , 100), 216 ( $\text{MH}^+$ , 15), 207 (100), 173 (75); HRMS calculated for  $\text{C}_{14}\text{H}_{17}\text{NONa}^+$  238.1202, found 238.1203.

**Benzyl 2,3,3-trimethylpyrrolidine-1-carboxylate (31).** DBU (0.10 mL, 0.70 mmol) was added to a solution of triflate **13i** (100 mg, 0.346 mmol) in  $\text{BnOH}$  (3 mL). The solution was stirred at 70 °C for 30 min and was then allowed to cool to rt. The crude product was directly purified by flash chromatography on silica gel using ethyl acetate and hexanes (5:95) as eluent to give benzyl 2,3,3-trimethylpyrrolidine-1-carboxylate (**31**) as colorless oil (52 mg, 60%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.37–7.30 (m, 5H), 5.21–5.08 (m, 2H), 3.57–3.48 (m, 1H), 3.44 (dd, 1H,  $J = 9.2, 5.2$  Hz), 1.76 (ddd, 1H,  $J = 12.4, 9.2, 9.2$  Hz), 1.54 (dt, 1H,  $J = 12.4, 5.2$  Hz), 1.08 (s(br), 3H), 1.01 (s, 3H), 0.98 (s, 3H);  $^{13}\text{C}$  NMR (100.7 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) **Rotamer A** 155.5 (s), 137.4 (s), 128.6 (d), 128.0 (d), 127.9 (d), 66.8 (t), 62.8 (d), 44.7 (t), 41.0 (s), 36.9 (t), 27.7 (q), 23.2 (q), 17.0; **Rotamer B** 155.2 (s), 137.4 (s), 128.6 (d), 128.0 (d), 127.9 (d), 66.6 (t), 62.4 (d), 44.4 (t), 40.2 (s), 35.9 (t), 27.6 (q), 23.0 (q), 16.0 (q); IR ( $\text{CHCl}_3$ )  $\nu$  ( $\text{cm}^{-1}$ ) 3009, 2966, 2893, 1684, 1412, 1358, 1105, 1047; LRMS ( $m/z$ , relative intensity) 270 ( $\text{MNa}^+$ , 100), 248 ( $\text{MH}^+$ , 20); HRMS calculated for  $\text{C}_{15}\text{H}_{21}\text{NO}_2\text{Na}^+$  270.1465, found 270.1467.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) For lead references and reviews, see: (a) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2005**, *35*, 146–156. (b) Kürti, L.; Czako, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, 2005; pp 116–117, pp 210–211, pp 266–267, and pp 396–397. (c) Kyba, P. E. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: Orlando, FL, 1984; p 2. (d) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S. J., Ed.; Wiley & Sons: London, 1971; p 221.
- (2) For reviews on chiral enolates, see: (a) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947 and references cited therein. (b) Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2753–2768. (c) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65–75. (d) Dalgo, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5128–5175. (e) For a review on chiral enolate equivalents, see: Spino, C. *Org. Prep. Proced. Int.* **2003**, *35*, 1–140.
- (3) The Hofmann rearrangement of cyclic imides is possible: Jiang, X.; Wang, J.; Hu, J.; Ge, Z.; Hu, Y.; Hu, H.; Covey, D. F. *Steroids* **2001**, *66*, 655–662. However, it likely proceeds via a base-promoted ring-opening followed by a normal Lossen-like rearrangement.
- (4) (a) Drouin, A.; Lessard, J. *Tetrahedron Lett.* **2006**, *47*, 4285–4288. (b) Winter, D. K.; Drouin, A.; Lessard, J.; Spino, C. *J. Org. Chem.* **2010**, *75*, 2610–2618.
- (5) (a) Drouin, A.; Winter, D. K.; Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. *J. Org. Chem.* **2011**, *76*, 164–169. (b) Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. *Eur. J. Org. Chem.* **2012**, 1328–1335.
- (6) Edwards and co-workers have reported that the photolysis of *N*-mesyloxy-4-aza-cholestan-3-one in methanol at rt gave the undesired ring-contracted carbamate in 35% yield, besides several other products. To the best of our knowledge, no further study of this reaction has been reported since. See: Edwards, O. E.; Grue-Sørensen, G.; Blackwell, B. A. *Can. J. Chem.* **1997**, *75*, 857–872.
- (7) We are aware of only one method to oxidize *N*-silylated lactams to cyclic hydroxamic acids, but this method proved unsatisfactory in our hands: (a) Matlin, S. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1972**, 1222–1223. (b) Matlin, S. A.; Sammes, P. G.; Upton, R. M. *J. Chem. Soc., Perkin Trans 1* **1979**, 2481–2487. For other oxidative methods to obtain cyclic hydroxamic acids, see: (c) Nesset, S. M.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1993**, *47*, 1141–1143. (d) Yamada, K.; Tanaka, S.; Naruchi, K.; Yamamoto, M. *J. Org. Chem.* **1982**, *47*, 5283–5289. (e) Banerjee, R.; King, S. B. *Org. Lett.* **2009**, *11*, 4580–4583.
- (8) Edwards and co-workers had previously reported two examples of bicyclic *N*-mesyloxylactams undergoing rearrangement when heated in MeOH at 190 °C in a sealed tube (see ref 6).
- (9) For a leading reference and a more mechanistic discussion on the Schmidt rearrangement, see: Gutierrez, O.; Aubé, J.; Tantillo, D. J. *J. Org. Chem.* **2012**, *77*, 640–647.