Ceric ammonium nitrate oxidation of *N*-(*p*-methoxybenzyl) lactams: competing formation of *N*-(hydroxymethyl) *δ*-lactams

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DOI: http://dx.doi.org/10.3998/ark.5550190.p008.840

Abstract

The ceric ammonium nitrate mediated oxidative deprotection of *N*-(*p*-methoxybenzyl) *δ*-lactams leads to the formation of an unexpected *N*-(hydroxymethyl) *δ*-lactam along with the N-deprotected *δ*-lactam. In comparison, *N*-(*p*-methoxybenzyl) *γ*-lactams are completely deprotected under the same reaction conditions. Further studies indicated that addition of an aqueous solution of ceric ammonium nitrate to an acetonitrile solution of *N*-(*p*-methoxybenzyl) *δ*-lactams in the presence of 2-amino-2-methyl-1-propanol as an additive promoted N-deprotection. Ceric ammonium nitrate oxidation of *N*-(*α*,*α*-dideuterio-*p*-methoxybenzyl)-6-allyl-*δ*-lactam (**8**), revealed that the methylene unit of the *N*-(hydroxymethyl) group is derived from the benzylic methylene unit of the N-protecting group. A plausible reaction pathway for the formation of the *N*-(hydroxymethyl) *δ*-lactams from an *N*-acyliminium ion intermediate is proposed.

Keywords: Ceric ammonium nitrate, deprotection, *p*-methoxybenzyl group, lactams, *N*-acyliminium ions

Introduction

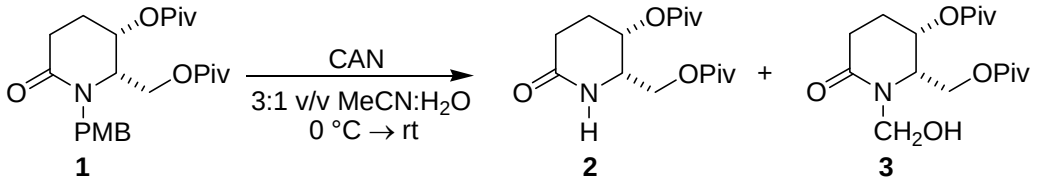
The *p*-methoxybenzyl (PMB) group is often used for the N-protection[1] of amides, lactams and aza-heterocycles in the synthesis of natural[2-12] and non-natural products[13-23] because of its ease of removal. Many methods, such as Lewis[24] and Brönsted acid[18,22,25-27] -mediated hydrolysis, benzylic anion oxidation,[12,28,29] catalytic hydrogenation,[30] and persulfate-mediated oxidative cleavage,[31] have been employed for the removal of the *N*-PMB group. Nevertheless, the most widely used method for deprotection involves the oxidative cleavage of the *N*-PMB moiety using ceric ammonium nitrate (CAN).[2-11,13-17,19-21,23,32,33] Factors such as the mild reaction conditions that are generally tolerant towards many different functional groups, the experimental simplicity, and the relatively low cost of CAN make this a method of choice.

The CAN oxidation of *N*-PMB *γ*- and *δ*-lactams has generally been reported to proceed cleanly to afford the unprotected lactams. In connection with one of our studies related to the synthesis of piperidine alkaloids, we examined the CAN oxidation of the *N*-PMB *δ*-lactam **1** (Scheme 1, vide supra). In addition to the desired deprotected *δ*-lactam **2**, an unexpected product was isolated that was identified as the *N*-(hydroxymethyl) derivative **3**. To the best of our knowledge, the formation of *N*-(hydroxymethyl) lactams during CAN mediated *N*-PMB deprotection has not been documented before. Intrigued by this observation, we conducted a more detailed study of the CAN oxidation of *N*-PMB lactams and we report our findings here. We found that (a) *δ*-lactams have a higher tendency to give the *N*-(hydroxymethyl) derivative whereas *γ*-lactams undergo efficient and complete deprotection, (b) the ratio of the N-deprotected to *N*-(hydroxymethyl) *δ*-lactams is sensitive to the substrate structure and the reaction conditions employed, and (c) the *p*-methoxybenzyl methylene unit is the source of the methylene moiety of the *N*-(hydroxymethyl) group. The findings reported in this study will be helpful where CAN oxidation method is used for the deprotection of *N*-PMB *δ*-lactams.

Results and Discussion

CAN oxidation of *N*-PMB *δ*-lactam 1

As mentioned above, our studies began with the deprotection of *N*-PMB *δ*-lactam **1** (Scheme 1) following literature procedure, which entailed the addition of solid CAN[7,33] (4.1 equiv, final concentration = 0.25 M) to a solution of **1** in 3:1 v/v MeCN/H_2O (conditions A).[34] This resulted in the isolation of a 55:45 ratio of the N-deprotected *δ*-lactam **2** and the unexpected *N*-(hydroxymethyl) derivative **3** in a combined yield of 57%.



Scheme 1. Deprotection of *δ*-lactam **1.**

Compounds **2** (R_f = 0.19, 4:1 v/v EtOAc/pet. ether) and **3** (R_f = 0.33, 4:1 v/v EtOAc/pet. ether) were readily separated by column chromatography on silica gel. The ^{1}H and ^{13}C NMR data for compounds **2** and **3** were in full agreement with their assigned structures. In particular, the ^{1}H and ^{13}C NMR signals for the *N*-(hydroxymethylene) unit in **3** were characteristic and useful for the detection of the presence of *N*-(hydroxymethyl) *δ*-lactams in subsequent studies.[35] Thus, in the ^{1}H NMR of **3**, each of the hydrogens of the methylene moiety resonated as a doublet (*J* 10.3 Hz), one centered at *δ* 4.99 and the other at *δ* 4.73. In the ^{13}C NMR, the methylene carbon was observed at *δ* 71.6.

Compound **3** was readily converted to **2** by treatment with $^{i}Pr_2NEt$ (4.0 equiv) in methanol at reflux which furnished the deprotected *δ*-lactam **2** in an overall yield of 56%. The formation of **2** from **3** also provided confirmation of the assigned structure of **3**.

Next, we tested modified reaction conditions to see whether formation of compound **3** could be minimized or suppressed, which should lead to a greater preference for formation of *δ*-lactam **2**. Thus, an aqueous solution of CAN (4.1 equiv, final concentration = 0.25 M) was added to a solution of **1** in MeCN (final MeCN/H_2O = 3:1; conditions B). This again gave a 50:50 ratio of lactams **2** and **3**, but in an enhanced, combined yield of 76%. The ratio of **2**:**3** was determined based on the integration of the lactam NH signal of **2** at *δ* 5.92-6.03 and one of the doublets of the *N*-CH_2OH unit at *δ* 4.99. In terms of yield, modified conditions using aqueous CAN were superior producing **2** in an overall 75% yield after the deformylation step.

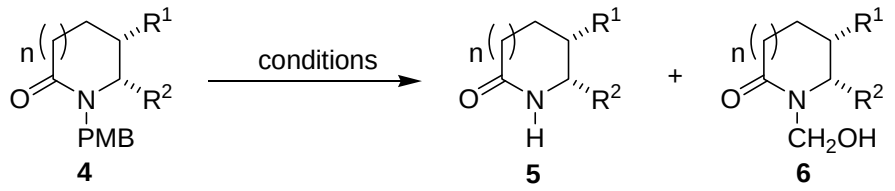
It was hypothesized that the formation of **3** could have potentially arisen from further reaction of the deprotected *δ*-lactam **2** with formaldehyde, which could have been produced through the CAN oxidation of the methoxy unit of the *N*-PMB group in the starting *δ*-lactam **1**. The formation of formaldehyde in similar electron transfer-type oxidation has precedence in the $Mn(OAc)_3$ oxidation of aromatic ethers.[36] Moreover, Ce(III) compounds, which were formed from the reduction of Ce(IV), could act as Lewis acids to facilitate the nucleophilic addition of **2** to formaldehyde. We, therefore, reasoned that by using an additive that is more nucleophilic than the *δ*-lactam **2**, such as 2-amino-2-methyl-1-propanol (AMP), would help to trap formaldehyde thereby suppressing the formation of *N*-(hydroxymethyl) *δ*-lactam **3**. Thus, we investigated the *N*-PMB deprotection of **1** using aqueous CAN in the presence of two mole equivalents of AMP (conditions C). However, under these conditions no products arising from the reaction of AMP with formaldehyde were detected; only *δ*-lactams **2** and **3** were obtained in 66% combined yield. Interestingly, the ratio of **2**:**3** was markedly improved to 75:25 compared to the ratios realized with conditions A and B. It is useful to note that AMP did not decrease nor inhibit the activity of CAN, and it was not oxidized by CAN.

CAN Oxidation of *δ*-lactams 4a–d and *γ*-lactams 4e,f

Structurally varied *δ*-lactams **4a**–**d** and *γ*-lactams **4e**,**f** were then subjected to CAN mediated *N*-PMB deprotection and the results are summarized in Table 1. The results indicated that *δ*-lactams have a tendency to form the *N*-(hydroxymethyl) derivative along with the deprotected product, whereas with the *γ*-lactams complete deprotection was observed under all conditions (B and C) tested. With *δ*-lactams, oxidation under conditions B and C generally favored N-deprotection as reflected in the higher ratio of **5**:**6**. However, the ratio of **5**:**6** was somewhat dependent on the structure of the starting *δ*-lactams **4a**–**d** when reaction conditions B were used (compare entries 2, 4 and 7), and to a lesser extent with reaction conditions C (compare entries 3 and 5). Further, decreasing the concentration of CAN to 0.15 M, as in the reaction of **4c** did not significantly affect the ratio of **5c**:**6c** (compare entries 2, 4 and 6), although a longer reaction time was required for the reaction to complete. As alluded to earlier, *δ*-lactams **6** were efficiently deformylated (4.0 equiv *i*-Pr_2NEt, MeOH, reflux), and in cases where the *δ*-lactams **5** and **6** were

not readily separable, the mixture was subjected to deformylation conditions without loss in overall yield of **5**.

Table 1. CAN oxidation of *δ*- and *γ*-lactams **4a**–**f**



4 **5** **6**

a: n = 1, R^1 = H, R^2 = $CH_2CH{=}CH_2$
b: n = 1, R^1 = OBz, R^2 = H
c: n = 1, R^1 = OPiv, R^2 = $(CH_2)_2OTBDPS$
d: n = 1, R^1 = OPiv, R^2 = $CH_2CH{=}CH_2$
e: n = 0, R^1 = OTBDPS, R^2 = H
f: n = 0, R^1 = OPiv, R^2 = $CH_2CH{=}CH_2$

Entry	Lactam	Conditions[b]	Yield %[d] (ratio **5**:**6**)	% **5**[g]
1	**4a**[a]	A	45 (69:31)[e]	44
2	**4a**[a]	B	58 (88:12)[e]	57
3	**4a**[a]	C	53 (83:17)[e]	52
4	**4b**	B	59 (68:32)[f]	57
5	**4b**	C	67 (85:15)[f]	66
6	**4c**	B[c]	63 (73:27)[f]	62
7	**4d**	B	55 (55:45)[e]	55
8	**4e**	B	65 (100:0)	65
9	**4e**	C	68 (100:0)	68
10	**4f**	C	76 (100:0)	76

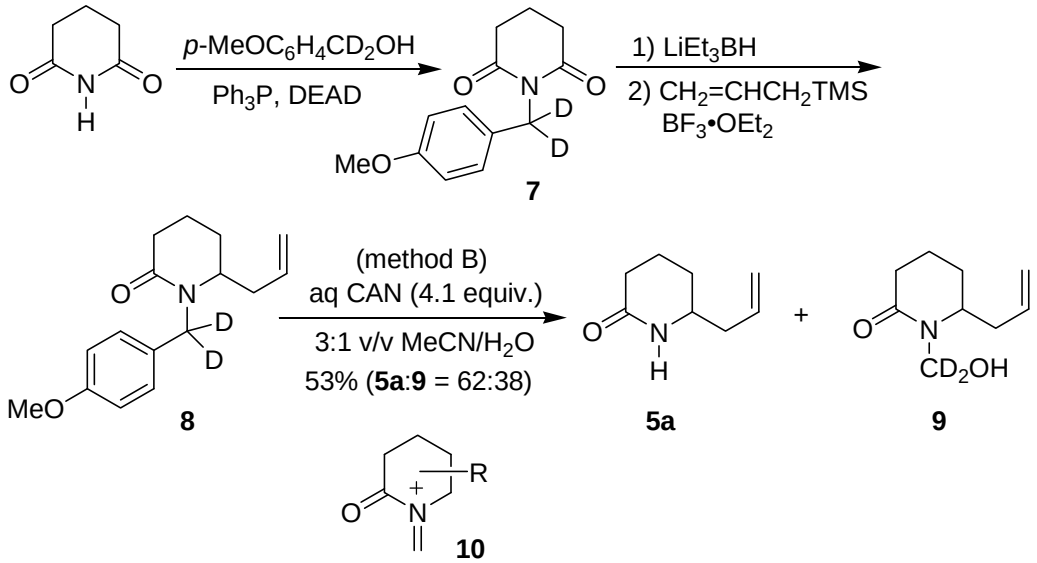
[a] Racemic compound was used. [b] All reactions were conducted at least twice. *Conditions A*: Solid CAN (4.1 equiv), lactam in 3:1 v/v MeCN/H_2O, concentration of CAN = 0.25 M; *Conditions B*: aqueous CAN (4.1 equiv), lactam in MeCN, final ratio MeCN/H_2O = 3:1 v/v, final concentration of CAN = 0.25 M; *Conditions C*: aqueous CAN (4.1 equiv), AMP (2.1 mol equiv), lactam in MeCN, final ratio MeCN/H_2O = 3:1 v/v, final concentration of CAN = 0.25 M. [c] Concentration of CAN was 0.15 M. [d] Combined yield of **5a**–**d**, **6a**–**d**. [e] Ratio was based on isolated yields of **5a**:**6a** or **5d**:**6d**. [f] Ratio was based on the integration of the *δ*-lactam NH and the lower field doublet of *N*-(hydroxymethylene) group: for **5b** [*δ* 6.20–6.45 (NH)]; for **5c** [*δ* 6.36–6.44 (NH);] and **6b** [*δ* 4.94 (d, C*H*HOH)]; **6c** [*δ* 4.94 (d, C*H*HOH)], respectively. [g] Overall yeild of *δ*-lactam **5** after deformylation by treatment of either a mixture of **5b**,**c**/**6b**,**c** or **6a**,**d** with 4 equiv *i*-Pr_2NEt in refluxing methanol.

CAN Oxidation of dideuterated *δ*-lactam 8

Next, our attention was directed at determining how the *N*-(hydroxymethyl) *δ*-lactam is formed and, in particular, the source of the methylene unit in the *N*-(hydroxymethyl) group. The dideuterated *δ*-lactam **8** was prepared using the route shown in Scheme 2. The Mitsunobu reaction of glutarimide[37,38] with *α*,*α*-dideuterio-*p*-methoxybenzyl alcohol yielded the derivative **7** in 70%. Lithium triethylborohydride reduction of **7** followed by reaction with allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ furnished the dideuterated *δ*-lactam **8** in 75%.

Treatment of *δ*-lactam **8** with aqueous CAN under conditions B gave the readily separable N-deprotected *δ*-lactam **5a** and the *N*-[hydroxy(*α*,*α*-dideuteriomethyl)] *δ*-lactam **9** in 53% combined yield, and in a ratio of 62:38. In comparison, the oxidation of **4a** under conditions B (Table 1, entry 2) gave the N-deprotected *δ*-lactam **5a** to the *N*-(hydroxymethyl) *δ*-lactam **6a** in a ratio of 88:12.

The ^{1}H NMR spectrum of **9** is identical to that of **6a** (Table 1) except for the absence of the characteristic AB doublets[35] at *δ* 4.76 and *δ* 4.88, which are ascribed to the *N*CH_2 unit in **6a**. In the ^{13}C NMR spectrum of **9**, the dideuterated methylene carbon was observed as a weak quintet centered at *δ* 71.6.



Scheme 2. Preparation and CAN oxidation of dideuterated *δ*-lactam **8.**

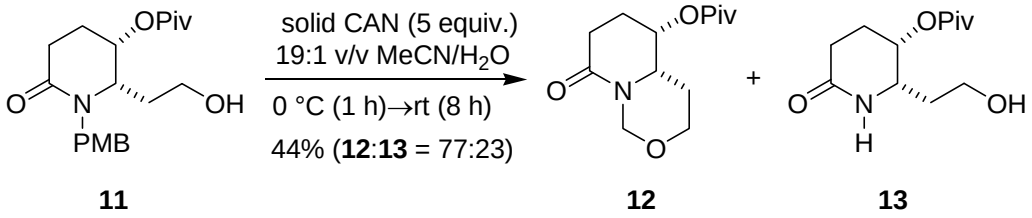
The formation of **9** indicates that the source of the methylene unit of the *N*-(hydroxymethyl) moiety is derived from the benzylic carbon of the *N*-(*p*-methoxybenzyl) protecting group.

In general, the purification of the crude mixtures from the CAN oxidations of the *N*-PMB lactams always resulted in forerun fractions that were yellow-orange in color. Analysis, by t.l.c, of these fractions revealed several non-polar components, one of which was readily identified as anisaldehyde. We also isolated benzoquinone (^{1}H NMR: *δ* 6.78, s; ^{13}C NMR: *δ* 136.5 and 187.2; R_f = 0.38, 4:1 v/v petroleum ether/EtOAc) from the yellow-orange fractions obtained from the

CAN oxidation of the dideuterated *δ*-lactam **8**. The presence of benzoquinone in the CAN oxidation of other *δ*-lactams was confirmed by t.l.c.

Formation of bicycle 12 from CAN oxidation of *δ*-lactam 11

The fact the benzylic methylene unit ends up as the methylene moiety of the *N*-(hydroxymethyl) group suggests that a second, hitherto, unrecognized competitive oxidation pathway is operative during the CAN oxidation of *N*-(*p*-methoxybenzyl) *δ*-lactams. We speculate that for the *N*-(hydroxymethyl) *δ*-lactams to form, a highly reactive *N*-acyliminium ion intermediate of type **10** (Scheme 2) has to be generated, which upon interception by water would form the observed product. To test this hypothesis, we chose to use *δ*-lactam **11** because the hydroxyl group of the C-6 hydoxyethyl side chain could serve as an internal nucleophile to trap the incipient *N*-acyliminium ion once it forms. Thus, the CAN (concentration of CAN = 0.13 M) oxidation of **11** in 19:1 v/v MeCN/H_2O afforded, in 44% combined yield, the bicyclic lactam **12** and the deprotected *δ*-lactam **13** in a ratio of 77:23 (Scheme 3). The formation of the bicycle **12** supports the notion for the involvement of an incipient *N*-acyliminium ion, which undergoes a 6-*endo*-*trig* nucleophilic addition of the hydroxyl group.



11 **12** **13**

Scheme 3. CAN oxidation of *δ*-lactam **11.**

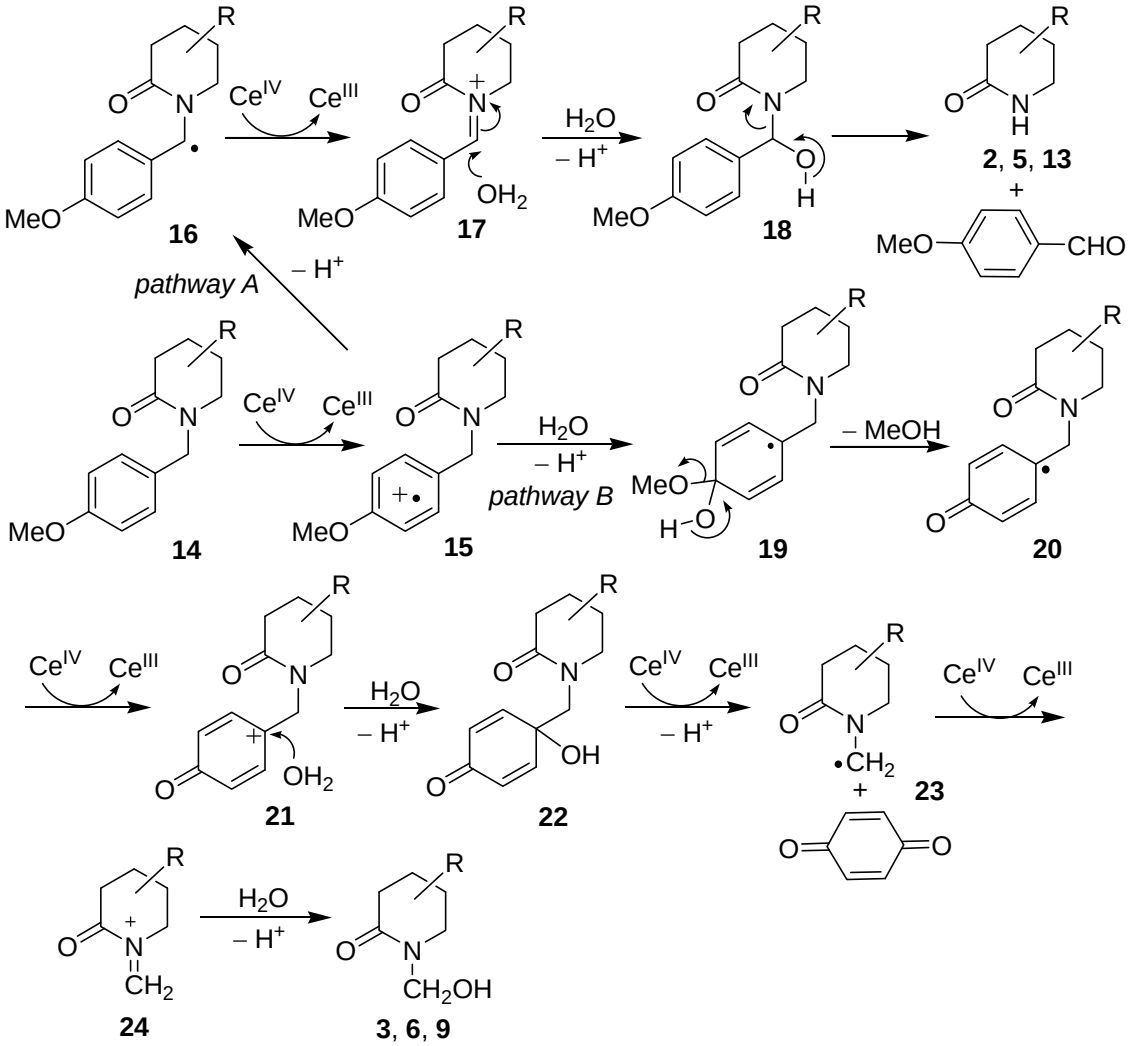
Reaction pathway

On the basis of the composite results from the CAN oxidation of *δ*-lactams **4a**–**d**, the dideuterated *δ*-lactam **8** and the *δ*-lactam **11**, we propose a plausible reaction pathway that may explain the formation of the *N*-(hydroxymethyl) *δ*-lactams **3**, **6** and **9**.

CAN oxidation of the *N*-PMB *δ*-lactam **14** generates the radical cation **15.** The loss of a proton from the benzylic position in **15** leads via pathway A towards **17**, and accounts for the formation of the deprotected lactam **2, 5** and **13.** A second pathway involves the interception of the radical cation **15** by water, which would divert the reaction along pathway B to form the hemiketal **19**. Subsequent loss of methanol gives the free-radical **20**. Free-radicals similar to **20** have been previously invoked as intermediates in the CAN oxidation of *p*-methoxytoluene.[39] Further oxidation of **20** by CAN produces the highly electrophilic carbocation **21** which is expected to be rapidly intercepted by water to form the amido alcohol **22**. The next step involves the CAN oxidation of **22** to initiate mesolytic bond scission to form the free radical intermediate **23** and benzoquinone; **23** upon further oxidation gives the *N*-acyliminium ion **24**. Nucleophilic attack of **24** by water gives the observed *N*-(hydroxymethyl or hydroxydideuteriomethyl) *δ*-lactams **3**, **6** and **9**. The formation of **24** from **22** via **23** is made by analogy to the work[40] of

Fujioka, Kita and co-workers where they found the CAN oxidation of 1,2-amido alcohols led to *N*,*O*-acetal products. The production of the *N*,*O*-acetal product was explained by considering the generation of an amido-stabilized carbon-centered free radical, as is proposed for **23**, which upon CAN oxidation resulted in an *N*-acyliminium ion intermediate. The formation of bicycle **12** in the CAN oxidation of the *δ*-lactam **11** (Scheme 3) lends further support for the involvement of *N*-acyliminium ion intermediates.

As to why the CAN oxidation of the *N*-PMB *γ*-lactams always resulted in the efficient formation of only the deprotected *γ*-lactams and not a mixture of the deprotected and *N*-(hydroxymethyl) *γ*-lactams is not clear presently. Based on the pathway shown in Scheme 4, it is reasonable that a similar radical cation of type **15** will also be formed upon CAN oxidation of *N*-PMB *γ*-lactams. Our results suggest that formation of the *γ*-lactam version of the *N*-acyliminium ion of type **17**, via pathway A, is strongly favored on steric grounds,[41] over formation of the hemiketal of type **19**, which would lead to the preferential formation of N-deprotected *γ*-lactams.



Scheme 4. Plausible reaction pathway for formation of *N*-(hydroxymethyl) *δ*-lactams.

Conclusion

Our studies have revealed that the widely used, CAN oxidation method for the deprotection of *N*-PMB lactams does not necessarily lead directly to the desired N-deprotected lactams. Whereas *N*-PMB *γ*-lactams were deprotected cleanly, the deprotection of *δ*-lactams always led to the formation of a mixture of the N-deprotected and *N*-(hydroxymethyl) *δ*-lactams. The ratio of the deprotected to *N*-(hydroxymethyl) *δ*-lactams was sensitive to the substrate structure and the reaction conditions employed. The formation of the *N*-(hydroxymethyl) *δ*-lactams can be understood by considering the involvement of an *N*-acyliminium ion intermediate of type **24**, which is generated from the initially formed radical cation **15** via a concurrent oxidative pathway B.

Since the CAN deprotection of *N*-PMB lactams is an often encountered synthetic operation in natural and non-natural product synthesis, the findings reported here can help inform as well as serve as a caveat for when deprotection of *N*-PMB *δ*-lactams is practiced. The presence of the *N*-(hyroxymethyl) *δ*-lactams may sometimes be overlooked due to the very similar t.l.c mobilities of the N-deprotected and *N*-(hyroxymethyl) *δ*-lactams. Our results suggest that the *N*-PMB group could potentially serve as a latent *N*-acyliminium precursor, and studies to develop a method that predominately leads to the generation of *N*-acycliminium intermediates of type **10**, and their trapping with various nucleophiles to form synthetically useful C-X (X = O, N, and C) bonds are in progress.

Experimental section

General. Reported melting points are uncorrected. Infrared spectra were recorded either as neat oil or film (CH_2Cl_2) on NaCl plates and only the diagnostic signals were reported. ^1H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$) at 300 MHz and 75 MHz, respectively. The chemical shifts were recorded in parts per million (*δ*) relative to the appropriate reference signal: δ_H 7.26 and δ_C 77.0. High-resolution mass spectral analyses were obtained using either electron impact (70 eV) or electrospray ionization mode. Reaction progress was monitored by thin-layer chromatography on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminium-backed sheets. Air- and moisture-sensitive reactions were conducted under a static pressure of argon. Purification implies flash column chromatography which was performed on SiliaFlash® F60 (230-400 mesh). Acetonitrile and dichloromethane were distilled from calcium hydride. THF was dried by distillation from sodium using sodium benzophenone ketyl as indicator.

CAN oxidation procedure (conditions A). To the N-PMB lactam (**1** and **4a**) (0.1 mmol) in a mixture of acetonitrile and water (3:1 v/v, 1.64 mL), at 0 °C was added solid CAN (225 mg, 0.41 mmol) in one portion and the resulting orange solution was stirred at 0 °C for 30 min. The reaction mixture was diluted with EtOAc and saturated $NaHCO_3$ was added. The resulting

suspension was stirred for 30 min at rt, and then was vacuum filtered through a pad of celite. After the two layers were separated, the organic layer was washed once with brine. The combined aqueous layers were saturated with solid NaCl and back-extracted into EtOAc. The organic layers were combined and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude residue was purified by chromatography.

CAN oxidation procedure (conditions B). An aqueous solution of the CAN (1.0 M) was prepared by dissolving CAN (225 mg, 0.41 mmol) in distilled water (0.41 mL). To the *N*-PMB lactam (**1**, **4a-e** and **8**) (0.1 mmol) in acetonitrile (1.23 mL) at 0 °C was added the above aqueous CAN solution dropwise (final $MeCN/H_2O$ = 3:1 v/v). The resulting orange solution was stirred at 0 °C for 30 min, and then at rt for 1 h. A similar workup procedure described under conditions A was followed for the isolation of products.

CAN oxidation procedure (conditions C). A 0.5 M stock solution of the 2-amino-2-methyl-1-propanol (AMP) in MeCN was prepared by dissolving AMP (0.2 mL, 2.1 mmol) in MeCN (4.0 mL). To a solution of the *N*-PMB lactam (**1** and **4a**,**b**,**e**,**f)** (0.1 mmol) in acetonitrile (0.83 mL) was added AMP in acetonitrile (0.4 mL, 0.5 M) and the mixture was cooled to 0 °C. An aqueous solution of the CAN (0.41 mL, 1 M) was added dropwise to the above reaction mixture (final $MeCN/H_2O$ = 3:1 v/v). The resulting orange solution was stirred at 0 °C for 30 min and at rt for 1 h. A similar workup procedure described under conditions A was followed for the isolation of products.

Procedure for deformylation of *N*-(hydroxymethyl) *δ*-lactams. To the *N*-(hydroxymethyl) *δ*-lactam (**3**,**6a** and **6d**) (0.1 mmol) in dry MeOH (2 mL) was added $^{i}Pr_2NEt$ (70 μL, 0.4 mmol) and the resulting solution was stirred at 55 °C (oil bath) for 1 h. The solvent was evaporated under reduced pressure, and the crude product was purified by chromatography.

In cases where the *N*-(hydroxymethyl) derivative and the deprotected lactam were not separable (**5b,c**/**6b,c**), deformylation was carried on the mixture following a similar procedure.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-pivaloyloxy-6-(pivaloyloxymethyl)piperidin-2-one (1). Colorless oil; IR (CH_2Cl_2) 1734, 1654, 1648 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.12–7.19 (m, 2H, Ar-*H*), 6.81–6.87 (m, 2H, Ar-*H*), 5.18 (d, *J* 15.0 Hz, 1H, NC*H*HAr), 5.05 (ddd, *J* 9.2, 4.6, and 4.6 Hz, 1H, H-5), 4.30 (dd, *J* 11.7 and 5.3 Hz, 1H, C*H*HOPiv), 4.19 (dd, *J* 11.7 and 3.9 Hz, 1H, CH*H*OPiv), 4.06 (d, *J* 15.0 Hz, 1H, NCH*H*Ar), 3.78 (s, 3H, Ar-OCH_3), 3.64–3.72 (m, 1H, H-6), 2.50–2.72 (m, 2H, 2 × H-3), 1.90–2.18 (m, 2H, 2 × H-4), 1.18 (s, 9H, OC(O)C(CH_3)$_3$), 1.17 (s, 9H, OC(O)C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.9, 177.0, 169.3, 159.0, 128.9, 128.7, 114.2, 67.3, 60.9, 55.7, 55.2, 47.4, 38.8, 38.7, 28.7, 27.1, 27.0, 23.6; HRMS-EI calcd for $C_{24}H_{35}NO_6$ $[M]^+$ 433.2464, found 433.2464.

Lactams (2) and (3) from CAN oxidation of *N*-PMB *δ*-lactam (1). Purification of the crude reaction mixture from the CAN oxidation of **1** (1:1 petroleum ether/EtOAc, 1:3 petroleum ether/EtOAc, then 1:4 petroleum ether/EtOAc) afforded the deprotected δ-lactam **2** and *N*-(hydroxylmethyl) δ-lactam **3**.

(5*S*,6*S*)-5-Pivaloyloxy-6-(pivaloyloxymethyl)piperidin-2-one (2). Colorless oil; IR (CH_2Cl_2) 3211, 1734, 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 5.92–6.03 (br s, 1H, NH), 5.20–5.27 (m,

1H, H-5), 4.23 (dd, *J* 10.9 and 4.1 Hz, 1H, C*H*HOPiv), 3.82–3.98 (m, 2H, CHHOPiv & H-6), 2.39–2.49 (m, 2H, 2 × H-3), 2.12–2.25 (m, 1H, H-4), 1.86–2.00 (m, 1H, H-4), 1.21 (s, 9H, OC(O)(CH_3)$_3$), 1.19 (s, 9H, OC(O)(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.8, 177.2, 170.3, 64.8, 63.9, 54.5, 39.1, 38.8, 27.1, 27.0, 26.3, 24.6; HRMS-CI calcd for $C_{16}H_{28}NO_5$ $[M+1]^+$ 314.1967, found 314.1967.

(5*S*,6*S*)-1-(Hydroxymethyl)-5-pivaloloxy-6-(pivaloyloxymethyl)piperidin-2-one (3). Colorless oil; IR (CH_2Cl_2) 3507–3201, 1734, 1654 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 5.22 (ddd, *J* 9.5, 4.7, and 4.7 Hz, 1H, H-5), 4.99 (d, *J* 10.3 Hz, 1H, NCHHOH), 4.73 (d, *J* 10.3 Hz, 1H, NCHHOH), 4.38 (dd, *J* 12.1 and 5.2 Hz, 1H, CHHOPiv), 4.27 (dd, *J* 12.1 and 5.2 Hz, 1H, CHHOPiv), 3.89–3.98 (m, 1H, H-6), 2.42–2.66 (m, 2H, 2 × H-3), 1.89–2.19 (m, 2H, 2 × H-4), 1.47–1.85 (br s, 1H, OH), 1.22 (s, 9H, OC(O)(CH_3)$_3$), 1.20 (s, 9H, OC(O)(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 Hz): δ_C 177.9, 177.1, 171.2, 71.6, 66.9, 62.3, 57.2, 38.9, 38.7, 28.4, 27.0, 27.0, 23.3.

6-Allyl-1-(*p*-methoxybenzyl)piperidin-2-one (4a). Colorless oil; IR (neat) 2951, 1626, 1513, 1454 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.10–7.17 (m, 2H, Ar-*H*), 6.78–6.85 (m, 2H, Ar-*H*), 5.61 (dddd, *J* 17.5, 9.7, 7.8 and 6.4 Hz, 1H, C*H*=CH_2), 5.32 (d, *J* 14.9 Hz, 1H, NC*H*HAr), 5.00–5.10 (m, 2H, CH=CH_2), 3.87 (d, *J* 14.9 Hz, 1H, NC*H*HAr), 3.75 (s, 3H, Ar-OCH_3), 3.31 (ddd, *J* 8.9, 8.9, and 4.4 Hz, 1H, H-6), 2.36–2.47 (m, 3H, 2 × H-3 & C*H*HCH=CH_2), 2.16–2.29 (m, 1H, C*H*HCH=CH_2), 1.56–1.93 (m, 4H, 2 × H-4 and 2 × H-5). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 170.1, 158.7, 134.0, 129.5, 129.0, 117.9, 113.8, 55.1, 54.4, 46.6, 36.6, 31.9, 26.1, 17.0; HRMS-EI calcd for $C_{16}H_{21}NO_2$ $[M]^+$ 259.1572, found 259.1568.

(*S*)-5-Benzoyloxy-1-(*p*-methoxybenzyl)piperidin-2-one (4b). Colorless oil; IR (CH_2Cl_2) 3063, 2957, 2934, 2837, 1716, 1643, 1513 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.90–7.97 (m, 2H, Ar-*H*), 7.58 (tt, *J* 7.5 and 1.2 Hz, 1H, Ar-*H*), 7.38–7.47 (m, 2H, Ar-*H*), 7.13–7.20 (m, 2H, Ar-*H*), 6.70–6.77 (m, 2H, Ar-*H*), 5.37 (ddd, *J* 8.3, 3.3 and 3.3 Hz, 1H, H-5), 4.77 (d, *J* 15.0 Hz, 1H, NC*H*HAr), 4.35 (d, *J* 15.0 Hz, 1H, NC*H*HAr), 3.53 (dd, *J* 13.1 and 3.4 Hz, 1H, H-6), 3.36–3.45 (m, 1H, H-6), 2.75 (ddd, *J* 17.8, 9.4 and 5.6 Hz, 1H, H-3), 2.57 (ddd, *J* 17.8, 7.5 and 4.7 Hz, 1H, H-3), 2.05–2.28 (m, 2H, 2 × H-4). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 168.5, 165.3, 158.8, 133.1, 129.5, 129.4, 129.1, 128.4, 128.2, 113.7, 66.5, 54.9, 50.1, 48.9, 27.70, 25.4; HRMS-ESI calcd for $C_{20}H_{21}NO_4$ $[M]^+$ 339.1471, found 339.1472.

(5*S*,6*S*)-6-(2-*tert*-Butyldiphenylsilyloxyethyl)-1-(*p*-methoxybenzyl)-5-pivaloyloxypiperidin-2-one (4c). Colorless oil; IR (CH_2Cl_2) 1726, 1654, 1643, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.56–7.65 (m, 4H, Ar-*H*), 7.31–7.48 (m, 6H, Ar-*H*), 7.06–7.15 (m, 2H, Ar-*H*), 6.76–6.84 (m, 2H, Ar-*H*), 5.16 (d, *J* 14.9 Hz, 1H, NC*H*HAr), 4.93–5.02 (m, 1H, H-5), 3.98 (d, *J* 14.9 Hz, 1H, NC*H*HAr), 3.77 (s, 3H, Ar-OCH_3), 3.58–3.81 (m, 3H, H-6 & CH_2OTBDPS), 2.48–2.59 (m, 2H, 2 × H-3), 1.84–2.00 (m, 4H, 2 × H-4 & CH_2CH$_2$OTBDPS), 1.11 (s, 9H, OC(O)(CH_3)$_3$), 1.03 (s, 9H, OC(O)(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.2, 169.3, 158.8, 135.4, 133.3, 129.8, 129.3, 128.8, 127.7, 114.0, 68.3, 60.5, 55.1, 54.5, 47.7, 38.7, 32.6, 28.2, 27.0, 26.8, 22.7, 19.1; HRMS-EI calcd for $C_{36}H_{47}NO_5Si$ $[M]^+$ 601.3224 found 601.3232.

(5*S*,6*S*)-6-Allyl-1-(*p*-methoxybenzyl)-5-pivaloyloxypiperidin-2-one (4d). Colorless solid, mp 74–76 °C; IR (CH_2Cl_2) 1727, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.10–7.18 (m, 2 H,

Ar-*H*), 6.80–6.88 (m, 2H, Ar-*H*), 5.60–5.76 (m, 1H, C*H*=CH_2), 5.24 (d, *J* 15.1 Hz, 1H, NC*H*HAr), 4.95–5.11 (m, 3H, H-5 & CH=CH_2), 4.04 (d, *J* 15.1 Hz, 1H, NC*H*HAr), 3.78 (s, 3H, Ar-OCH_3), 3.48–3.56 (m, 1H, H-6), 2.34–2.68 (m, 4H, 2 × H-3 and CH_2CH=CH_2), 2.00–2.14 (m, 1H, H-4), 1.84–1.97 (m, 1H, H-4), 1.19 (s, 9H, OC(O)C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.3, 169.4, 158.9, 134.0, 129.1, 128.9, 118.3, 114.1, 68.1, 57.5, 55.2, 47.1, 38.9, 34.0, 28.2, 27.1, 23.1; HRMS-EI calcd for $C_{21}H_{29}NO_4$ $[M]^+$ 359.2097, found 359.2090.

(*S*)-4-(*tert*-Butyldiphenylsilyloxy)-1-(*p*-methoxybenzyl)-pyrrolidin-2-one (4e). Colorless solid, mp 102–103 °C; IR (CH_2Cl_2) 3051, 2957, 2933, 2859, 1692, 1514 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.58–7.64 (m, 2H, Ar-H), 7.52–7.58 (m, 2H, Ar-H), 7.30–7.48 (m, 6H, Ar-H), 7.12–7.19 (m, 2H, Ar-H), 6.81–6.88 (m, 2H, Ar-H), 4.55 (d, *J* 14.7 Hz, 1H, NCHHAr), 4.36–4.44 (m, 1H, H-4), 4.23 (d, *J* 14.7 Hz, 1H, NCHHAr), 3.79 (s, 3H, Ar-OCH_3), 3.26 (dd, *J* 9.8, 5.4 Hz, 1H, H-5), 3.16 (dd, *J* 9.8 and 2.7 Hz, 1H, H-5), 2.40–2.57 (m, 2H, 2 × H-3), 1.03 (s, 9H, SiC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 172.4, 159.0, 135.6, 135.5, 133.3, 133.1, 129.9, 129.8, 129.2, 128.3, 127.8, 127.7, 114.0, 66.1, 55.2(5), 55.2(2), 45.4, 41.3, 26.7, 18.9; HRMS-EI calcd for $C_{28}H_{33}NO_3Si$ $[M]^+$ 459.2230, found 459.2225.

(4*S*,5*S*)-5-Allyl-1-(*p*-methoxybenzyl)-4-pivaloyloxypyrrolidin-2-one (4f). Colorless oil; IR (CH_2Cl_2) 2976, 2936, 1731, 1698, 1613, 1514 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.11–7.20 (m, 2H, Ar-*H*), 6.80–6.89 (m, 2H, Ar-*H*), 5.56–5.74 (m, 1H, C*H*=CH_2), 5.21–5.32 (m, 1H, H-4), 5.02–5.15 (m, 2H, CH=CH_2), 4.94 (d, *J* 15.0 Hz, 1H, NC*H*HAr), 4.01 (d, *J* 15.0 Hz, 1H, NC*H*HAr), 3.79 (s, 3H, Ar-OCH_3), 3.70 (dd, *J* 12.0, 6.5 Hz, 1H, H-5), 2.74 (dd, *J* 17.4, 7.0 Hz, 1H, H-3), 2.31–2.50 (m, 3H, H-3 and CH_2CH=CH_2), 1.20 (s, 9H, OC(O)C(CH_3)$_3$); HRMS-EI calcd for $C_{20}H_{27}NO_4$ $[M]^+$ 345.1940, found 345.1939.

Lactams (5a) and (6a) from CAN oxidation of *δ*-lactam (4a). Purification of the crude reaction mixture from the CAN oxidation of **4a** (1:4 petroleum ether/ EtOAc then 20:1 EtOAc/MeOH) afforded deprotected *δ*-lactam **5a** and *N*-(hydroxylmethyl) *δ*-lactam **6a** (see Table 1).

6-Allylpiperidin-2-one (5a). Colorless solid, mp 83–85 °C; IR (CH_2Cl_2) 3357–3128 (br), 2952, 1661, 1466 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 5.89–6.10 (br s, 1H, NH), 5.71 (dddd, *J* 16.6, 10.6, 8.2 and 6.0 Hz, 1H, C*H*=CH_2), 5.09–5.21 (m, 2H, CH=CH_2), 3.32–3.45 (m, 1H, H-6), 2.19–2.45 (m, 3H, 2 × H-3 and C*H*HCH=CH_2), 2.04–2.18 (m, 1H, C*H*HCH=CH_2), 1.83–1.97 (m, 2H, 2 × H-4), 1.59–1.77 (m, 1H, H-5), 1.28–1.45 (m, 1H, H-5). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 172.1, 133.3, 119.1, 52.1, 41.3, 31.3, 28.5, 19.8.

6-Allyl-1-(hydroxymethyl)piperidin-2-one (6a). Colorless oil; IR (CH_2Cl_2) 3544–3117, 3055, 2955, 1629, 1477 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 5.65–5.81 (m, 1H, C*H*=CH_2), 5.07–5.18 (m, 2H, CH=CH_2), 4.88 (dd, *J* 10.3 and 7.8 Hz, 1H, NC*H*HOH), 4.76 (dd, *J* 10.3 and 7.8 Hz, 1H, NC*H*HOH), 3.74 (t, *J* 7.8 Hz, 1H, OH), 3.57 (ddd, *J* 8.9, 8.9, and 4.4 Hz, 1H, H-6), 2.25–2.58 (m, 4H, 2 × H-3 and CH_2CH=CH_2), 1.65–1.94 (m, 4H, 2 × H-4 and 2 × H-5). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_H 172.6, 133.9, 118.3, 72.2, 56.9, 38.4, 32.0, 26.1, 16.8; HRMS-EI calcd for $C_9H_{15}NO_2$ $[M]^+$ 169.1103, found 169.1103.

The coupling of the methylene protons with the hydroxyl proton was confirmed by D_2O exchange experiments. The ^{1}H NMR spectrum showed the disappearance of hydroxyl proton signal at δ 3.74 and the simplification of the methylene protons at δ 4.88 and 4.76 from doublet of doublets to doublets.

Lactams (5b) and (6b) from CAN oxidation of *δ*-lactam (4b). Purification of the crude reaction mixture from the CAN oxidation of **4b** (1:4 petroleum ether/EtOAc, then 10:1 EtOAc/MeOH) afforded a mixture of the deprotected *δ*-lactam **5b** and the *N*-(hydroxymethyl) *δ*-lactam **6b** as a colorless oil. The ratio of **5b**:**6b** was determined based on the integration of the *δ*-lactam NH at δ 6.20–6.45 and the low field doublet of the *N*-CH_2OH group at δ 4.94 (see Table 1).

(*S*)-5-Benzoyloxypiperidin-2-one (5b). Colorless solid, mp 137–138 °C; IR (CH_2Cl_2) 3280–3146, 3055, 1717, 1669 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.53–7.61 (m, 1H, Ar-*H*), 7.39–7.48 (m, 2H, Ar-*H*), 6.56–6.73 (br s, 1H, NH), 5.38–5.47 (m, 1H, H-5), 3.66 (dd, *J* 13.2 and 3.6 Hz, 1H, H-6), 3.51–3.61 (m, 1H, H-6), 2.65 (ddd, *J* 17.8, 10.6, and 6.6 Hz, 1H, H-3), 2.47 (ddd, *J* 17.8, 5.8, and 4.8 Hz, 1H, H-3), 2.03–2.30 (m, 2H, 2 × H-4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 165.7, 133.3, 129.7, 129.6, 128.4, 65.8, 46.1, 27.2, 25.2; HRMS-ESI calcd for $C_{12}H_{13}NO_3Na$ $[M+23]^+$ 242.0793, found 242.0799.

Lactams (5c) and (6c) from CAN oxidation of *δ*-lactam (4c). The CAN oxidation of **4c** (3:1 petroleum ether/EtOAc, then 2:1 petroleum ether/EtOAc) afforded a mixture of the deprotected *δ*-lactam **5c** and the *N*-(hydroxylmethyl) *δ*-lactam **6c** as a colorless oil. The ratio of **5c**:**6c** was determined based on the integration of the *δ*-lactam NH at δ 6.36–6.44 and the upper field doublet of the *N*-CH_2OH at δ 4.74 (see Table 1). Compound **6c** was characterized as the corresponding NCH_2OBoc derivative.

(5*S*,6*S*)-6-(2-*tert*-Butyldiphenylsilyloxyethyl)-5-pivaloyloxypiperidin-2-one (5c). Colorless oil; IR (CH_2Cl_2) 3374, 3214, 1724, 1654 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.61–7.68 (m, 4H, Ar-*H*), 7.35–7.48 (m, 6H, Ar-*H*), 6.41–6.50 (br m, 1H, NH), 5.04–5.11 (m, 1H, H-5), 3.70–3.84 (m, 3H, H-6 and C*H*$_2$OTBDPS), 2.44 (ddd, *J* 18.0, 11.6, and 6.0 Hz, 1H, H-3), 2.37 (ddd, *J* 18.0, 7.4 and 2.9 Hz, 1H, H-3), 2.06–2.17 (m, 1H), 1.85–1.99 (m, 1H), 1.58–1.80 (m, 2H), 1.20 (s, 9H, OC(O)C(C*H*$_3$)$_3$), 1.08 (s, 9H, OSiC(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.6, 170.5, 135.5, 132.8, 132.8, 129.9, 129.9, 127.8, 67.2, 61.7, 54.8, 39.1, 34.1, 27.1, 26.8, 26.2, 24.9, 19.0; HRMS-ESI calcd for $C_{28}H_{39}NO_4SiNa$ $[M+23]^+$ 504.2546, found 504.2533.

(5*S*,6*S*)-1-(*tert*-Butyloxycarbonyloxymethyl)-6-(*tert*-butyldiphenylsilyloxyethyl)-5-pivaloyloxy-piperidin-2-one (6c-OBoc derivative). Colorless oil; IR (CH_2Cl_2) 1734, 1706, 1684, 1670, 1654, 1648 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.61–7.68 (m, 4H, Ar-*H*), 7.34–7.47 (m, 6H, Ar-*H*), 5.74 (d, *J* 9.8 Hz, 1H, NC*H*HOBoc), 5.17 (d, *J* 9.8 Hz, 1H, NC*H*HOBoc), 5.10–5.18 (m, 1H, H-5), 4.07 (ddd, *J* 6.6, 6.6, and 4.7 Hz, 1H, H-6), 3.64–3.80 (m, 2H, C*H*$_2$OTBDPS), 2.51 (t, *J* 7.2 Hz, 2H, 2 × H-3), 1.81–2.06 (m, 4H, 2 × H-4 and C*H*$_2$CH$_2$OTBDPS), 1.47 (s, 9H, OC(O)O(C*H*$_3$)$_3$), 1.13 (s, 9H, OC(O)C(C*H*$_3$)$_3$), 1.05 (s, 9H, SiC(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 177.1, 170.5, 152.5, 135.5, 133.2, 129.8, 129.8,

127.8, 82.5, 71.7, 67.8, 60.1, 55.3, 38.8, 32.6, 28.2, 27.7, 26.8, 22.6, 19.1; HRMS-ESI calcd for $C_{34}H_{49}NO_7SiNa$ $[M+23]^+$ 634.3176, found 634.3158.

Lactams (5d) and (6d) from CAN oxidation of *δ*-lactam (4d). Purification of the crude reaction mixture from the CAN oxidation of **4d** (1:1 petroleum ether/ EtOAc then 1:4 petroleum ether/EtOAc) afforded the deprotected *δ*-lactam **5d** and *N*-(hydroxylmethyl) *δ*-lactam **6d** (see Table 1).

(5*S*,6*S*)-6-Allyl-5-pivaloyloxypiperidin-2-one (5d). Colorless solid, mp 139–141 °C; IR (CH_2Cl_2) 3271–3142, 2967, 1727, 1659 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) *δ* 5.60–5.78 (m, 1H, C*H*=CH_2), 5.11–5.25 (m, 3H, H-5 and CH=CH_2), 3.59 (ddd, *J* 8.3, 4.9, and 3.0 Hz, 1H, H-6), 2.31–2.48 (m, 3H, 2 × H-3 & C*H*HCH=CH_2), 2.06–2.23 (m, 2H, C*H*HCH=CH_2 & H-4), 1.84–1.99 (m, 1H, H-4), 1.24 (s, 9H, OC(O)C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.5, 170.8, 132.5, 120.0, 66.5, 54.8, 39.2, 36.5, 27.2, 26.3, 25.0; HRMS-ESI calcd for $C_{13}H_{21}NO_3Na$ $[M+23]^+$ calcd 262.1419, found 262.1423.

(5*S*,6*S*)-6-Allyl-1-(hydroxymethyl)-5-pivaloyloxypiperidin-2-one (6d). Colorless oil; IR (CH_2Cl_2) 3557–3133, 3056, 2976, 2936, 2875, 1729, 1643 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 5.74 (dddd, *J* 17.3, 10.2, 7.2, and 7.2 Hz, 1H, C*H*=CH_2), 5.03–5.14 (m, 3H, H-5 & CH=CH_2), 4.82 (dd, *J* 10.6 and 7.8 Hz, 1H, NC*H*HOH), 4.73 (dd, *J* 10.6 and 8.2 Hz, 1H, NC*H*HOH), 3.68 (dd, *J* 6.5, 6.5 and 4.9 Hz, 1H, H-6), 3.41 (dd, *J* 8.2 and 7.8 Hz, 1H, OH), 2.33–2.55 (m, 4H, 2 × H-3 and CH_2CH=CH_2), 1.95–2.09 (m, 1H, H-4), 1.79–1.92 (m, 1H, H-4), 1.16 (s, 9H, OC(O)C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.3, 171.4, 133.7, 118.7, 71.7, 67.9, 59.2, 39.0, 34.8, 28.2, 27.1, 22.8.

Lactams (5e) from CAN oxidation of *γ*-lactam (4e). Purification of the crude reaction mixture from the CAN oxidation of **4e** (1:1 petroleum ether/ EtOAc then 1:4 petroleum ether/EtOAc) afforded the deprotected γ-lactam **5e** (see Table 1).

(*S*)-4-(*tert*-Butyldiphenylsilyloxy)pyrrolidin-2-one (5e). Colorless solid, mp 79–81 °C; IR (CH_2Cl_2) 3385–3152, 2961, 2932, 2859, 1703, 1472 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.60–7.67 (m, 2H, Ar-*H*), 7.34–7.49 (m, 3H, Ar-*H*), 5.80–5.96 (br s, 1H, NH), 4.49–4.58 (m, 1H, H-4), 3.37 (dd, *J* 10.1 and 6.0 Hz, 1H, H-5), 3.28 (dd, *J* 10.1 and 3.7 Hz, 1H, H-5), 2.29–2.48 (m, 2H, 2 × H-3), 1.06 (s, 9H, OSiC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 176.0, 135.6, 135.5, 133.4, 133.1, 129.9(9), 129.9(6), 127.8(4), 127.8(2), 68.8, 51.1, 40.0, 26.8, 20.0; HRMS-ESI calcd for $C_{20}H_{25}NO_2SiNa$ $[M+23]^+$ 362.1552, found 362.1546.

Lactam (5f) from CAN oxidation of *γ*-lactam (4f). Purification of the crude reaction mixture from the CAN oxidation of **4f** (1:1 petroleum ether/ EtOAc then 1:2 petroleum ether/EtOAc) afforded the deprotected γ-lactam **5f** (see Table 1).

(4*S*,5*S*)-5-Allyl-4-pivaloyloxypyrrolidin-2-one (5f). Colorless solid, mp 66–68 °C; IR (CH_2Cl_2) 3359–3133, 2976, 2933, 1725, 1704, 1479 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 6.06–6.22 (br s, 1H, NH), 5.67–5.82 (m, 1H, C*H*=CH_2), 5.41 (ddd, *J* 6.1, 6.1, and 2.8 Hz, 1H, H-4), 5.11–5.23 (m, 2H, CH=CH_2), 3.90 (ddd, *J* 10.2, 5.2, and 5.2 Hz, 1H, H-5), 2.74 (dd, *J* 17.7 and 6.7 Hz, 1H, H-3), 2.17–2.42 (m, 3H, H-3 and CH_2CH=CH_2), 1.21 (s, 9H, OC(O)C(CH_3)$_3$). ^{13}C NMR

($CDCl_3$, 75 MHz): δ_C 177.7, 174.4, 133.4, 118.9, 67.0, 57.0, 38.9, 38.0, 34.0, 27.1; HRMS-ESI calcd for $C_{12}H_{19}NO_3Na$ $[M+23]^+$ 248.1263, found 248.1258.

6-Allyl-1-(α,α-dideuterio-*p*-methoxybenzyl)piperidin-2-one (8). To the α,α-dideuterio-*p*-methoxybenzyl glutarimide (212 mg, 0.9 mmol) in dry THF (10 mL) at −78 °C under Ar, was added $LiEt_3BH$ in THF (1.35 mL, 1 M) and the solution was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated $NaHCO_3$ and was warmed to 0 °C. Aqueous H_2O_2 (1 mL, 30%) was added dropwise and the resulting solution was stirred at the same temperature for 30 min before allowing to rt. The solvent was evaporated and the crude residue was diluted with CH_2Cl_2. The two layers were separated, and the aqueous layer was back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude lactam alcohol (235 mg), without further purification, was subjected to allylation in the next step.

To the above crude alcohol (235 mg) in dry CH_2Cl_2 (8 mL) under Ar, was added allyltrimethylsilane (0.28 mL, 1.8 mmol) and the solution was cooled to −78 °C. $BF_3.Et_2O$ (0.23 mL, 1.8 mmol) was added dropwise to the above mixture, and the resulting solution was stirred at the same temperature for 30 min before allowing to rt, overnight. The reaction mixture was cooled to 0 °C and saturated $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by chromatography (1:4 pet.ether/Et_2O) afforded **8** (176 mg, 75% over 2-steps) as a colorless oil: IR (neat) 2951, 1626, 1513, 1454 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.10–7.18 (m, 2H, Ar-*H*), 6.77–6.85 (m, 2H, Ar-*H*), 5.53–5.69 (m, 1H, C*H*=CH_2), 5.00–5.10 (m, 2H, CH=C*H*$_2$), 3.74 (s, 3H, Ar-OC*H*$_3$), 3.30 (ddd, *J* 8.9, 8.9, and 4.3 Hz, 1H, H-6), 2.36–2.47 (m, 3H, H-3 and C*H*HCH=CH_2), 2.15–2.29 (m, 1H, C*H*HCH=CH_2), 1.55–1.93 (m, 4H, 2 × H-4 and 2 × H-5). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 170.1, 158.7, 133.9, 129.4, 129.0, 117.9, 113.8, 55.0, 54.3, 46.0 (weak quint), 36.6, 31.8, 26.0, 17.0; HRMS-ESI calcd for $C_{16}H_{19}D_2NO_2Na$ $[M+23]^+$ 284.1596, found 284.1582.

CAN oxidation of dideuterated *δ*-lactam (8). Purification of the crude reaction mixture from the CAN oxidation of **8** (1:4 petroleum ether/ EtOAc then 20:1 EtOAc/MeOH) afforded the deprotected *δ*-lactam **5a** and *N*-[hydroxy(*α*,*α*-dideuteriomethyl)] *δ*-lactam **9**.

6-Allyl-1-[(hydroxy(*α*,*α*-dideuteriomethyl)]piperidin-2-one (9). Colorless oil; IR (CH_2Cl_2) 3544–3117, 3055, 2955, 1629, 1477 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 5.65–5.81 (m, 1H, C*H*=CH_2), 5.07–5.18 (m, 2H, CH=C*H*$_2$), 3.70 (br s, 1H, OH), 3.57 (ddd, *J* 8.9, 8.9, and 4.4 Hz, 1H, H-6), 2.25–2.58 (m, 4H, 2 × H-3 & C*H*$_2$CH=CH_2), 1.65–1.94 (m, 4H, 2 × H-4 and 2 × H-5). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 172.6, 133.9, 118.3, 71.6 (weak quint), 56.8, 38.5, 32.0, 26.1, 16.9; HRMS-ESI calcd for $C_9H_{13}D_2NO_2Na$ $[M+23]^+$ 194.1126, found 194.1115.

(5*S*,6*S*)-6-(2-Hydroxyethyl)-1-(*p*-methoxybenzyl)-5-pivaloyloxypiperidin-2-one (11). Colorless solid, mp 95–97 °C; IR (CH_2Cl_2) 3566–3142, 1726, 1636 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.09–7.19 (m, 2H, Ar-*H*), 6.75–6.84 (m, 2H, Ar-*H*), 5.10 (d, *J* 14.9 Hz, 1H, NC*H*HAr), 4.93–5.03 (m, 1H, H-5), 4.06 (d, *J* 14.9 Hz, 1H, NC*H*HAr), 3.51–3.77 (m, 6H, H-6, C*H*$_2$OH and Ar-OC*H*$_3$), 2.42–2.63 (m, 2H, 2 × H-3), 1.77–2.05 (m, 2H, 2 × H-4), 1.14 (s, 9H,

OC(O)C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.3, 169.4, 158.8, 129.2, 128.8, 113.9, 68.2, 59.2, 55.1, 54.6, 47.6, 38.8, 32.5, 28.2, 27.0, 22.6; HRMS-EI calcd for $C_{20}H_{29}NO_5$ $[M]^+$ 363.2046 found 363.2042.

Formation of bicycle (12) from (11). To the *N*-PMB lactam **11** (0.044 mmol) in a mixture of acetonitrile and water (19:1 v/v, 1.68 mL), at 0 °C was added solid CAN (121 mg, 0.22 mmol) in one portion. The resulting orange solution was stirred at the same temperature for 1 h, followed by 8 h at rt. The reaction mixture was worked up according to the general procedure described for conditions A. Purification by chromatography (1:4 petroleum ether/EtOAc, EtOAc then 10:1 EtOAc/MeOH) afforded the bicycle **12** (3.8 mg, 34%) and the deprotected *δ*-lactam **13** (1.1 mg, 10%).

(4a*S*,5*S*)-Octahydro-8-oxo-5-pivaloyloxypyrido[1,2-c][1,3]oxazine (12). Colorless solid, mp 102–103 °C; IR (CH_2Cl_2) 3056, 2974, 2934, 2858, 1728, 1653, 1477 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 6.09 (d, *J* 10.0 Hz, 1H, H-1), 5.19 (ddd, *J* 7.2, 2.4, and 2.4 Hz, 1H, H-5), 4.14 (dd, *J* 11.5 and 4.8 Hz, 1H, H-3), 4.05 (d, *J* 10.0 Hz, 1H, H-1), 3.78 (ddd, *J* 11.8, 3.6, and 3.6 Hz, 1H, H-4a), 3.63 (ddd, *J* 12.2, 12.2, and 2.3 Hz, 1H, H-3), 2.56 (ddd, *J* 17.4, 11.5, and 5.7 Hz, 1H, H-7), 2.41 (ddd, *J* 17.4, 4.9, and 4.9 Hz, 1H, H-7), 2.03–2.15 (m, 1H, H-6), 1.83–2.01 (m, 2H, H-4 and H-6), 1.42–1.52 (m, 1H, H-4), 1.24 (s, 9H, OC(O)C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.6, 167.7, 74.1, 67.2, 66.9, 57.4, 39.1, 27.7, 27.2 (× 2), 24.2; HRMS-EI calcd for $C_{13}H_{21}NO_4$ $[M]^+$ 255.1471, found 255.1464.

(5*S*,6*S*)-6-(2-Hydroxyethyl)- 5-pivaloyloxypiperidin-2-one (13). Colorless oil; IR (CH_2Cl_2) 3483–3119, 1724, 1654, 1647 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.27–7.38 (br s, 1H, NH), 5.08–5.18 (m, 1H, H-5), 3.94 (ddd, *J* 10.5, 4.3, and 4.3 Hz, 1H, H-6), 3.68–3.88 (m, 3H, CH_2O*H*), 2.31–2.52 (m, 2H, 2 × H-3), 2.07–2.19 (m, 1H), 1.74–2.01 (m, 2H), 1.60–1.72 (m, 1H), 1.23 (s, 9H, OC(O)C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 177.7, 171.4, 67.3, 61.0, 56.5, 39.2, 33.2, 27.1, 25.9, 24.8; HRMS-ESI calcd for $C_{12}H_{21}NO_4Na$ $[M+23]^+$ 266.1368, found 266.1374.

Acknowledgements

We thank NSERC, Canada and the University of Regina for financial support.

Supplementary Materials

^{1}H and ^{13}C NMR spectra for compounds: **1**, **2**, **3**, **4a**, **5a**, **5b**, **5b**+**6b**, **6a**, **6c**-OBoc, **7**, **8**, **9**, **11**, and **12**.

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34. Increasing the amount of CAN to 5.0 equiv (final concentration = 0.13 M) and using 19:1 v/v MeCN:H_2O resulted in a 3:1 ratio of **2** (35%) to **3** (11%), but the reaction was incomplete even after 2 h and 13% of starting **1** was recovered.

35. NCH_2OH: ^{1}H NMR of the methylene protons observed typically in the range δ 4.73–4.80 and δ 4.88–4.99 either as doublets (^2J = 10.3–10.6 Hz) or doublet of doublets (^2J = 10.3–10.6 Hz and ^3J = 7.8–8.2 Hz) due to coupling with the hydroxyl proton; addition of D_2O caused the collapse of the $N$$CH_2$ methylene doublet of doublets to doublets (see experimental for **6a**). ^{13}C NMR of the methylene carbon: δ 71.6–72.2.
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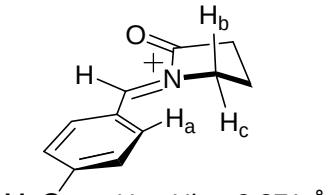
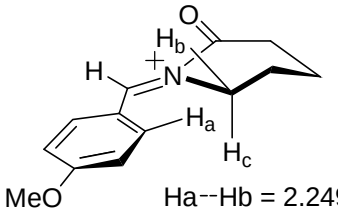
41. Geometry optimizations of the simple γ-lactam- and δ-lactam-derived *N*-acyliminium ions were conducted using Gaussian09[42] program suite at the RB3LYP/6-31G(d) level of theory. The optimized *N*-acyliminium ions (**i**) and (**ii**) showed that the *N*-acyliminium moieties and the *p*-methoxyphenyl ring to be coplanar, and the *N*-acyliminium methine hydrogens are positioned syn-coplanar to the lactam carbonyl function in (**i**) and (**ii**). It is evident from the optimized structure that the H_a/H_b and H_a/H_c bond distances in (**i**) are slightly longer than those in (**ii**). We reasoned that steric interactions between Ha/Hb and Ha/Hc are greater in (**ii**), which may contribute to the destabilization of *N*-acyliminium ion (**ii**). This may result in pathway A to be less preferred in the oxidation of *N*-PMB δ-lactams and allowing pathway B to be competitive.



Ha--Hb = 2.371 Å
Ha--Hc = 2.158 Å
(**i**)



Ha--Hb = 2.249 Å
Ha--Hc = 2.077 Å
(**ii**)

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