Ceric ammonium nitrate oxidation of \(N-(p\text{-methoxybenzyl})\) lactams: competing formation of \(N\)-(hydroxymethyl) \(\delta\)-lactams

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Abstract
The ceric ammonium nitrate mediated oxidative deprotection of \(N-(p\text{-methoxybenzyl})\) \(\delta\)-lactams leads to the formation of an unexpected \(N\)-(hydroxymethyl) \(\delta\)-lactam along with the \(N\)-deprotected \(\delta\)-lactam. In comparison, \(N-(p\text{-methoxybenzyl})\) \(\gamma\)-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 \(N-(p\text{-methoxybenzyl})\) \(\delta\)-lactams in the presence of 2-amino-2-methyl-1-propanol as an additive promoted \(N\)-deprotection. Ceric ammonium nitrate oxidation of \(N-(\alpha,\alpha\text{-dideuterio-}p\text{-methoxybenzyl})\)-6-allyl-\(\delta\)-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) \(\delta\)-lactams from an \(N\)-acyliminium ion intermediate is proposed.

Keywords: Ceric ammonium nitrate, deprotection, \(p\text{-methoxybenzyl} \) group, lactams, \(N\)-acyliminium ions

Introduction

The \(p\text{-methoxybenzyl} \) (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\(^7,3^3\) (4.1 equiv, final concentration = 0.25 M) to a solution of 1 in 3:1 v/v MeCN/H\(_2\)O (conditions A).\(^3^4\) 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.](image)

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.\(^3^5\) 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-Pr₂NEt (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/H₂O = 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-CH₂OH 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. 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-Pr₂NEt, 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactam</th>
<th>Conditions</th>
<th>Yield %d (ratio 5:6)</th>
<th>% 5g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
<td>45 (69:31)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>4a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B</td>
<td>58 (88:12)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>4a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C</td>
<td>53 (83:17)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>4b</td>
<td>B</td>
<td>59 (68:32)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>4b</td>
<td>C</td>
<td>67 (85:15)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>4c</td>
<td>B&lt;sup&gt;c&lt;/sup&gt;</td>
<td>63 (73:27)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>4d</td>
<td>B</td>
<td>55 (55:45)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>4e</td>
<td>B</td>
<td>65 (100:0)</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>4e</td>
<td>C</td>
<td>68 (100:0)</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>4f</td>
<td>C</td>
<td>76 (100:0)</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup> Racemic compound was used. <sup>b</sup> All reactions were conducted at least twice. Conditions A: Solid CAN (4.1 equiv), lactam in 3:1 v/v MeCN/H₂O, concentration of CAN = 0.25 M; Conditions B: aqueous CAN (4.1 equiv), lactam in MeCN, final ratio MeCN/H₂O = 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/H₂O = 3:1 v/v, final concentration of CAN = 0.25 M. <sup>c</sup> Concentration of CAN was 0.15 M. <sup>d</sup> Combined yield of 5a–d, 6a–d. <sup>e</sup> Ratio was based on isolated yields of 5a:6a or 5d:6d. <sup>f</sup> 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, CHHOH)]; 6c [δ 4.94 (d, CHHOH)], respectively. <sup>g</sup> Overall yield of δ-lactam 5 after deformylation by treatment of either a mixture of 5b,c/6b,c or 6a,d with 4 equiv i-Pr₂NEt 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 glutarimide37,38 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 BF₃·OEt₂ 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 ¹H NMR spectrum of 9 is identical to that of 6a (Table 1) except for the absence of the characteristic AB doublets35 at δ 4.76 and δ 4.88, which are ascribed to the NCH₂ unit in 6a. In the ¹³C NMR spectrum of 9, the dideuterated methylene carbon was observed as a weak quintet centered at δ 71.6.

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 (¹H NMR: δ 6.78, s; ¹³C 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 $\delta$-lactam 8. The presence of benzoquinone in the CAN oxidation of other $\delta$-lactams was confirmed by t.l.c.

**Formation of bicycle 12 from CAN oxidation of $\delta$-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) $\delta$-lactams. We speculate that for the $N$-(hydroxymethyl) $\delta$-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 $\delta$-lactam 11 because the hydroxyl group of the C-6 hydroxyethyl 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$_2$O afforded, in 44% combined yield, the bicyclic lactam 12 and the deprotected $\delta$-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.

![Scheme 3. CAN oxidation of $\delta$-lactam 11.](image)

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

CAN oxidation of the $N$-PMB $\delta$-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. 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) $\delta$-lactams 3, 6 and 9. The formation of 24 from 22 via 23 is made by analogy to the work 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, 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-(hydroxymethyl) δ-lactams may sometimes be overlooked due to the very similar t.l.c mobilities of the N-deprotected and N-(hydroxymethyl) 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-acyliminium 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$_2$Cl$_2$) on NaCl plates and only the diagnostic signals were reported. $^1$H 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 60F$_{254}$ 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. The combined aqueous layers were saturated with solid NaCl and back-extracted into EtOAc. The organic layers were combined and dried over Na₂SO₄. 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/H₂O = 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/H₂O = 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 iPr₂NEt (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 out on the mixture following a similar procedure.

**(5S,6S)-1-(p-Methoxybenzyl)-5-pivaloyloxy-6-(pivaloyloxymethyl)piperidin-2-one (1).** Colorless oil; IR (CH₂Cl₂) 3211, 1734, 1670 cm⁻¹. ¹H NMR (CDCl₃, 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, NCHHAr), 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, CHHOPiv), 4.19 (dd, J 11.7 and 3.9 Hz, 1H, CHHOPiv), 4.06 (d, J 15.0 Hz, 1H, NCHHAr), 3.78 (s, 3H, Ar-OCH₃), 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(CH₃)₃), 1.17 (s, 9H, OC(O)C(CH₃)₃). ¹³C NMR (CDCl₃, 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 C₂₄H₃₅NO₆ [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-(hydroxymethyl) δ-lactam 3.

**(5S,6S)-5-Pivaloyloxy-6-(pivaloyloxymethyl)piperidin-2-one (2).** Colorless oil; IR (CH₂Cl₂) 3211, 1734, 1670 cm⁻¹. ¹H NMR (CDCl₃, 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, CHHOPiv), 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)(CH3)3), 1.19 (s, 9H, OC(O)(CH3)3). 13C NMR (CDCl3, 75 MHz): δ 177.8, 177.2, 170.3, 64.8, 63.9, 54.5, 59.1, 38.8, 27.1, 27.0, 26.3, 24.6; HRMS-CI calcd for C16H28NO5 [M+1]+ 314.167, found 314.167.

(5S,6S)-1-(Hydroxymethyl)-5-pivaloloxo-6-(pivaloyloxymethyl)piperidin-2-one (3). Colorless oil; IR (CH2Cl2) 3507–3201, 1734, 1654 cm−1. 1H NMR (CDCl3, 300 MHz): δH 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, CHAr), 1.22 (s, 9H, OC(O)(CH3)3), 1.20 (s, 9H, OC(O)(CH3)3). 13C NMR (CDCl3, 75 Hz): δC 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. 1H NMR (CDCl3, 300 MHz): δH 7.10–7.17 (m, 2H, Ar-H), 6.78–6.85 (m, 2H, Ar-H), 5.61 (ddd, J 17.5, 9.7, 7.8 and 6.4 Hz, 1H, CH=CH2), 5.32 (d, J 14.9 Hz, 1H, NCHHAr), 5.00–5.10 (m, 2H, CH=CH2), 3.87 (d, J 14.9 Hz, 1H, NCHHAr), 3.75 (s, 3H, Ar-OC(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 & CHHCH=CH2), 2.16–2.29 (m, 1H, CHHCH=CH2), 1.56–1.93 (m, 4H, 2 × H-4 and 2 × H-5). 13C NMR (CDCl3, 75 MHz): δC 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-El calcd for C16H21NO2 [M]+ 259.157, found 259.1568.

(5S)-5-Benzoyloxy-1-(p-methoxybenzyl)piperidin-2-one (4b). Colorless oil; IR (CH2Cl2) 3063, 2957, 2934, 2837, 1716, 1643, 1513 cm−1. 1H NMR (CDCl3, 300 MHz): δH 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, NCHHAr), 4.35 (d, J 15.0 Hz, 1H, NCHHAr), 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). 13C NMR (CDCl3, 75 MHz): δC 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 C20H21NO4 [M]+ 339.1471, found 339.1472.

(5S,6S)-6-(2-tert-Butyldiphenysilyloxyethyl)-1-(p-methoxybenzyl)-5-pivaloyloxypiperidin-2-one (4c). Colorless oil; IR (CH2Cl2) 1726, 1654, 1643, 1637 cm−1. 1H NMR (CDCl3, 300 MHz): δH 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, NCHHAr), 4.93–5.02 (m, 1H, H-5), 3.98 (d, J 14.9 Hz, 1H, NCHHAr), 3.77 (s, 3H, Ar-OC(3)), 3.58–3.81 (m, 3H, H-6 & CH2OTBDPS), 2.48–2.59 (m, 2H, 2 × H-3), 1.84–2.00 (m, 4H, 2 × H-4 & CH2CH2OTBDPS), 1.11 (s, 9H, OC(O)(CH3)3), 1.03 (s, 9H, OC(O)(CH3)3). 13C NMR (CDCl3, 75 MHz): δC 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-El calcd for C36H47NO5Si [M]+ 601.3224 found 601.3232.

(5S,6S)-6-Allyl-1-(p-methoxybenzyl)-5-pivaloyloxypiperidin-2-one (4d). Colorless solid, mp 74–76 °C; IR (CH2Cl2) 1727, 1637 cm−1. 1H NMR (CDCl3, 300 MHz): δH 7.10–7.18 (m, 2 H,
(S)-4-((tert-Butyldiphenylsilyloxy)-1-(p-methoxybenzyl)-pyrrolidin-2-one (4e). Colorless solid, mp 102–103 °C; IR (CH2Cl2) 3051, 2957, 2933, 2859, 1692, 1514 cm−1. 1H NMR (CDCl3, 300 MHz): δH 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-OCH3), 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(CH3)3); HRMS-EI calcd for C28H33NO3Si [M]+ 459.2230, found 459.2225.

(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-(hydroxymethyl) δ-lactam 6a (see Table 1).

6-Allylpiperidin-2-one (5a). Colorless solid, mp 83–85 °C; IR (CH2Cl2) 3357–3128 (br), 2952, 1661, 1466 cm−1. 1H NMR (CDCl3, 300 MHz): δH 5.89–6.10 (br s, 1H, NH), 5.71 (dddd, J 16.6, 10.6, 8.2 and 6.0 Hz, 1H, CH=CH2), 5.09–5.21 (m, 2H, CH=CH2), 3.23–3.45 (m, 1H, H-4), 2.19–2.45 (m, 3H, 2 × H-3 and CHHCH=CH2), 2.04–2.18 (m, 1H, CHHCH=CH2), 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). 13C NMR (CDCl3, 75 MHz): δC 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 (CH2Cl2) 3544–3117, 3055, 2955, 1629, 1477 cm−1. 1H NMR (CDCl3, 300 MHz): δH 5.65–5.81 (m, 1H, CH=CH2), 5.07–5.18 (m, 2H, CH=CH2), 4.88 (dd, J 10.3 and 7.8 Hz, 1H, NCHHOH), 4.76 (dd, J 10.3 and 7.8 Hz, 1H, NCHHOH), 3.74 (t, J 7.8 Hz, 1H, OH), 3.57 (dddd, J 8.9, 8.9, and 4.4 Hz, 1H, H-6), 2.25–2.58 (m, 4H, 2 × H-3 and CH2CH=CH2), 1.65–1.94 (m, 4H, 2 × H-4 and 2 × H-5). 13C NMR (CDCl3, 75 MHz): δC 172.6, 133.9, 118.3, 72.2, 56.9, 38.4, 32.0, 26.1, 16.8; HRMS-EI calcd for C9H15NO2 [M]+ 169.1103, found 169.1103.
The coupling of the methylene protons with the hydroxyl proton was confirmed by D$_2$O exchange experiments. The $^1$H NMR spectrum showed the disappearance of hydroxyl proton signal at $\delta$ 3.74 and the simplification of the methylene protons at $\delta$ 4.88 and 4.76 from doublet of doublets to doublets.

**Lactams (5b) and (6b) from CAN oxidation of $\delta$-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 $\delta$-lactam 5b and the N-(hydroxymethyl) $\delta$-lactam 6b as a colorless oil. The ratio of 5b:6b was determined based on the integration of the $\delta$-lactam NH at $\delta$ 6.20–6.45 and the low field doublet of the N-CH$_2$OH group at $\delta$ 4.94 (see Table 1).

**(S)-5-Benzoyloxypiperidin-2-one (5b).** Colorless solid, mp 137–138 °C; IR (CH$_2$Cl$_2$) 3280–3146, 3055, 1717, 1669 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$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); 13C NMR (CDCl$_3$, 75 MHz) $\delta$C 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$_3$Na [M+23]$^+$ 242.0793, found 242.0799.

**Lactams (5c) and (6c) from CAN oxidation of $\delta$-lactam (4c).** The CAN oxidation of 4c (3:1 petroleum ether/EtOAc, then 2:1 petroleum ether/EtOAc) afforded a mixture of the deprotected $\delta$-lactam 5c and the N-(hydroxylmethyl) $\delta$-lactam 6c as a colorless oil. The ratio of 5c:6c was determined based on the integration of the $\delta$-lactam NH at $\delta$ 6.36–6.44 and the upper field doublet of the N-CH$_2$OH group at $\delta$ 4.74 (see Table 1). Compound 6c was characterized as the corresponding NCH$_2$OBoc derivative.

**(5S,6S)-6-(2-tert-Butyldiphenylsilyloxyethyl)-5-pivaloyloxy-piperidin-2-one (5c).** Colorless oil; IR (CH$_2$Cl$_2$) 3374, 3214, 1724, 1654 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$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$_2$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$_6$H$_3$)$_3$), 1.08 (s, 9H, OSiC(C$_6$H$_3$)$_3$). 13C NMR (CDCl$_3$, 75 MHz): $\delta$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$_4$SiNa [M+23]$^+$ 504.2546, found 504.2533.

**(5S,6S)-1-(tert-Butyloxycarbonyloxymethyl)-6-(tert-butyldiphenylsilyloxyethyl)-5-pivaloyloxy-piperidin-2-one (6c-OBoc derivative).** Colorless oil; IR (CH$_2$Cl$_2$) 1734, 1706, 1684, 1670, 1654, 1648 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$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, NCH$_2$OBoc), 5.17 (d, $J$ 9.8 Hz, 1H, NCH$_2$OBoc), 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, CH$_2$OTBDPS), 2.51 (t, $J$ 7.2 Hz, 2H, 2 × H-3), 1.81–2.06 (m, 4H, 2 × H-4 and CH$_2$CH$_2$OTBDPS), 1.47 (s, 9H, OC(O)O(CH$_3$)$_3$), 1.13 (s, 9H, OC(O)C(CH$_3$)$_3$), 1.05 (s, 9H, SiC(CH$_3$)$_3$). 13C NMR (CDCl$_3$, 75 MHz) $\delta$C 177.1, 170.5, 152.5, 135.5, 133.2, 129.8, 129.8,
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-(hydroxymethyl) δ-lactam 6d (see Table 1).

(5S,6S)-6-Allyl-5-pivaloyloxypiperidin-2-one (5d). Colorless solid, mp 139–141 °C; IR (CH2Cl2) 3271–3142, 2967, 2936, 2875, 1725, 1659 cm−1. 1H NMR (CDCl3, 300 MHz) δ 5.60–5.78 (m, 1H, CH=CH2), 5.11–5.25 (m, 3H, H-5 and CH=CH2), 3.59 (ddd, J 8.3, 4.9, and 3.0 Hz, 1H, H-6), 2.31–2.48 (m, 3H, 2 × H-3 & CH2CH=CH2), 2.06–2.23 (m, 2H, CH2CH=CH2 & H-4), 1.84–1.99 (m, 1H, H-4), 1.24 (s, 9H, OC(O)C(CH3)3). 13C NMR (CDCl3, 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 C13H21NO3Na [M+23]+ calcd 262.1419, found 262.1423.

(5S,6S)-6-Allyl-1-(hydroxymethyl)-5-pivaloyloxypiperidin-2-one (6d). Colorless oil; IR (CH2Cl2) 3557–3133, 3056, 2976, 2936, 2875, 1729, 1643 cm−1. 1H NMR (CDCl3, 300 MHz): δ H 5.74 (dddd, J 17.3, 10.2, 7.2, and 7.2 Hz, 1H, CH=CH2), 5.03–5.14 (m, 3H, H-5 & CH=CH2), 4.82 (dd, J 10.6 and 7.8 Hz, 1H, NCCHHOH), 4.73 (dd, J 10.6 and 8.2 Hz, 1H, NCCHHOH), 3.68 (dd, J 6.5, 6.5 and 4.9 Hz, 1H, OH), 3.41 (dd, J 8.2 and 7.8 Hz, 1H, NCCHHOH), 2.33–2.55 (m, 4H, 2 × H-3 and CH2CH=CH2), 1.95–2.09 (m, 1H, H-4), 1.79–1.92 (m, 1H, H-4), 1.16 (s, 9H, OC(O)C(CH3)3). 13C NMR (CDCl3, 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).

(5S,6S)-4-(tert-Butyldiphenylsilyloxy)pyrrolidin-2-one (5e). Colorless solid, mp 79–81 °C; IR (CH2Cl2) 3385–3152, 2961, 2932, 2859, 1703, 1472 cm−1. 1H NMR (CDCl3, 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(CH3)3). 13C NMR (CDCl3, 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 C20H25NO2SiNa [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).

(4S,5S)-5-Allyl-4-pivaloyloxypyrrolidin-2-one (5f). Colorless solid, mp 66–68 °C; IR (CH2Cl2) 3359–3133, 2976, 2933, 1725, 1704, 1479 cm−1. 1H NMR (CDCl3, 300 MHz): δ H 6.06–6.22 (br s, 1H, NH), 5.67–5.82 (m, 1H, CH=CH2), 5.41 (dd, J 6.1, 6.1, and 2.8 Hz, 1H, H-4), 5.11–5.23 (m, 2H, CH=CH2), 3.90 (dd, 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 CH2CH=CH2), 1.21 (s, 9H, OC(O)C(CH3)3). 13C NMR
(CDCl₃, 75 MHz): δC 177.7, 174.4, 133.4, 118.9, 67.0, 57.0, 38.9, 38.0, 34.0, 27.1; HRMS-ESI calcd for C₁₂H₁₉NO₃Na [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 LiEt₃BH 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 NaHCO₃ and was warmed to 0 °C. Aqueous H₂O₂ (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 CH₂Cl₂. The two layers were separated, and the aqueous layer was back-extracted into CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, 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 CH₂Cl₂ (8 mL) under Ar, was added allyltrimethylsilane (0.28 mL, 1.8 mmol) and the solution was cooled to −78 °C. BF₃·Et₂O (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 NaHCO₃ was added. The organic layer was separated, and the aqueous layer was back-extracted into CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by chromatography (1:4 pet.ether/Et₂O) afforded 8 (176 mg, 75% over 2-steps) as a colorless oil: IR (neat) 2951, 1626, 1513, 1454 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δH 7.10 – 7.18 (m, 2H, Ar-H), 6.77 – 6.85 (m, 2H, Ar-H), 5.53 – 5.69 (m, 1H, C=H=CH₂), 5.00 – 5.10 (m, 2H, CH=CH₂), 3.74 (s, 3H, Ar-OC₃H₃), 3.30 (ddd, J 8.9, 8.9, and 4.3 Hz, 1H, H-6), 2.36 – 2.47 (m, 3H, H-3 and C₃H₂CH=CH₂), 2.15 – 2.29 (m, 1H, CHHCH=CH₂), 1.55 – 1.93 (m, 4H, 2 × H-4 and 2 × H-5). ¹³C NMR (CDCl₃, 75 MHz): δC 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 C₁₆H₁₉D₂NO₂Na [M+23]+ 284.1596, found 284.1582.

6-Allyl-1-(hydroxy(α,α-dideuteriomethyl)piperidin-2-one (9). Colorless oil; IR (CH₂Cl₂) 3544–3117, 3055, 2955, 1629, 1477 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δH 7.09–7.19 (m, 2H, Ar-H), 6.75–6.84 (m, 2H, Ar-H), 5.10 (d, J 14.9 Hz, 1H, NCHHAr), 4.93–5.03 (m, 1H, H-5), 4.06 (d, J 14.9 Hz, 1H, NCHHAr), 3.51–3.77 (m, 6H, H-6, CH₂OH and Ar-OCH₃), 2.42–2.63 (m, 2H, 2 × H-3), 1.77–2.05 (m, 2H, 2 × H-4), 1.14 (s, 9H, 16.9; HRMS-ESI calcd for C₉H₁₃D₂NO₂Na [M+23]+ 194.1126, found 194.1115.
OC(O)C(CH₃)₃). ¹³C NMR (CDCl₃, 75 MHz): δC 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 C₂₀H₂₉NO₅ [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%).

(4αS,5S)-Octahydro-8-oxo-5-pivaloyloxypyrido[1,2-c][1,3]oxazine (12). Colorless solid, mp 102–103 °C; IR (CH₂Cl₂) 3056, 2974, 2934, 2858, 1728, 1653, 1477 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δH 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-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-5 and H-6), 1.42–1.52 (m, 1H, H-6), 2.31–2.52 (m, 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(CH₃)₃). ¹³C NMR (CDCl₃, 75 MHz): δC 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 C₁₃H₂₁NO₄ [M⁺] 255.1471, found 255.1464.

(5S,6S)-6-(2-Hydroxyethyl)- 5-pivaloyloxypiperidin-2-one (13). Colorless oil; IR (CH₂Cl₂) 3483–3119, 1724, 1654, 1647 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δH 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, CH₂OH), 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(CH₃)₃). ¹³C NMR (CDCl₃, 75 MHz): δC 177.7, 171.4, 67.3, 61.0, 56.5, 39.2, 33.2, 27.1, 25.9, 24.8; HRMS-ESI calcd for C₁₂H₂₁NO₄Na [M+23]⁺ 266.1368, found 266.1374.

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Supplementary Materials

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

References and Notes

   http://dx.doi.org/10.1021/jo201453x
   http://dx.doi.org/10.1055/s-2008-1072737
   http://dx.doi.org/10.1021/ja071501o
   http://dx.doi.org/10.1016/j.tet.2005.09.112
   http://dx.doi.org/10.1021/jo049166z
   http://dx.doi.org/10.1021/ja0522783
   http://dx.doi.org/10.1021/ja0522783
    http://dx.doi.org/10.1002/anie.200500390
    http://dx.doi.org/10.1021/ja048613p
    http://dx.doi.org/10.1021/ja000930i
    http://dx.doi.org/10.1021/ol401705a
    http://dx.doi.org/10.1073/pnas.1015261108
    http://dx.doi.org/10.1039/C2CC35222B
    http://dx.doi.org/10.1002/ejoc.201201565
    http://dx.doi.org/10.1016/j.tetasy.2010.06.028
    http://dx.doi.org/10.3987/COM-04-10190


34. Increasing the amount of CAN to 5.0 equiv (final concentration = 0.13 M) and using 19:1 v/v MeCN:H₂O 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. NCH₂OH: $^1$H NMR of the methylene protons observed typically in the range $\delta$ 4.73–4.80 and $\delta$ 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 D₂O caused the collapse of the NCH₂ methylene doublet of doublets to doublets (see experimental for 6a). $^{13}$C NMR of the methylene carbon: $\delta$ 71.6–72.2.

[http://dx.doi.org/10.1021/ja00975a021](http://dx.doi.org/10.1021/ja00975a021)

[http://dx.doi.org/10.1002/0471264180.or042.02](http://dx.doi.org/10.1002/0471264180.or042.02)

[http://dx.doi.org/10.1021/jo00347a036](http://dx.doi.org/10.1021/jo00347a036)

[http://dx.doi.org/10.1021/jo00348a007](http://dx.doi.org/10.1021/jo00348a007)

[http://dx.doi.org/10.1016/j.tet.2006.11.004](http://dx.doi.org/10.1016/j.tet.2006.11.004)

41. Geometry optimizations of the simple $\gamma$-lactam- and $\delta$-lactam-derived N-acyliminium ions were conducted using Gaussian09 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 Hₐ/Hₕ and Hₐ/Hₖ 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 $\delta$-lactams and allowing pathway B to be competitive.