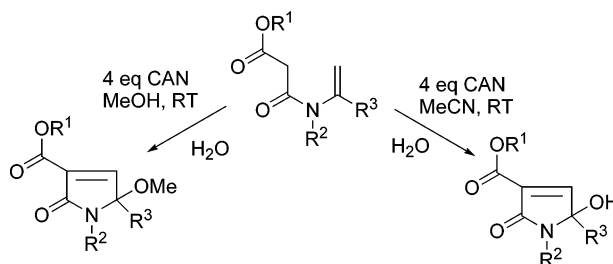


Oxidative 5-*Endo* Cyclization of
Enamides Mediated by Ceric Ammonium
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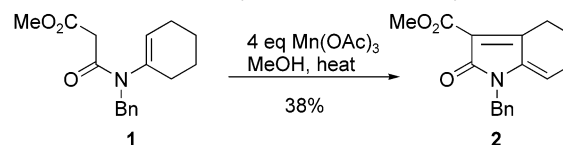
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ABSTRACT



Ceric ammonium nitrate mediates the oxidative 5-*endo* radical–polar crossover reactions of β -enamide esters to give 5,5-*C,O*-disubstituted- γ -lactams. Trapping of the intermediate cations leads to 5-hydroxy- or 5-alkoxy- γ -lactams depending upon the reaction conditions. The methodology was used to synthesize the basic heterocyclic ring fragments of the natural products L-755,807, Quinolactacin C, and PI-091.

The use of radical cyclization protocols to prepare heterocyclic compounds continues to be widespread.¹ By far the most popular methods for conducting such cyclizations involve the use of Bu_3SnH as a mediator. One distinct disadvantage of this approach is that the cyclizations are reductive in nature. We and others have recently reported the use of Cu(I) halide complexes,² nickel metal,³ or Mn(OAc)_3 reagents⁴ in unusual oxidative 5-*endo* cyclization reactions. In these reactions functionality is retained during cyclization via an oxidative radical–polar crossover reaction (e.g. Scheme 1). Cerium(IV) compounds represent some of the most notable oxidants among lanthanide reagents. As

Scheme 1. 5-*Endo* Cyclization Mediated by Mn(OAc)_3 

might be expected for very powerful one-electron oxidants, the chemistry of Ce(IV) oxidations of organic molecules is dominated by radical and radical cation chemistry.⁵

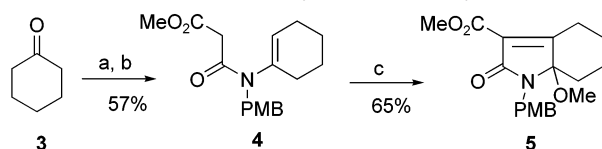
Nair and co-workers⁶ have carried out a number of studies to compare the reactivity of Mn(OAc)_3 with CAN in the oxidative addition of 1,3-dicarbonyl radicals to unactivated

[§] Chemistry Department University of Warwick.[†] Lilly Research Centre Ltd.(1) Bowman, W. R.; Fletcher, A. J.; Potts, E. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747.(2) Clark, A. J. *Chem. Soc. Rev.* **2002**, 1.(3) Cassayre, J.; Quiclet-Sirre, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, 54, 1029.(4) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, 56, 3941.(5) Molander, G. A. *Chem. Rev.* **1992**, 92, 29.(6) (a) Nair, V.; Matthew, J.; Radhakrishnan, K. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1487. (b) Nair, V.; Matthew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187.

alkenes, and discovered that CAN was often superior to $\text{Mn}(\text{OAc})_3$. More recently, CAN-mediated intermolecular radical reactions in ionic liquids have been reported.⁷ Consequently, we decided to investigate whether CAN could be used to mediate 5-*endo-trig* cyclizations of β -enamide esters to give γ -lactams of importance for natural product synthesis.

Our initial experiments examined the cyclization of the β -amido ester precursor **4** (analogous to compound **1** from Scheme 1). Compound **4** was prepared by *N*-acylation of the imine derived from cyclohexanone **3** and *p*-methoxybenzylamine (PMB), with methyl malonyl chloride.⁴ Initial reactions of **4** with 2 equiv of CAN in methanol at room temperature gave the bicyclic lactam **5** in only 28% yield. However, the yield of this reaction was found to improve from 28% to 65% when 4 equiv of CAN was employed for 20 min. Addition of greater than 4 equiv was found to have a detrimental effect on the product yield, Scheme 2. Under

Scheme 2. 5-*Endo* Cyclization of **4** by CAN^a



^a Reagents and conditions: (a) PMBNH_2 , Dean–Stark, toluene, reflux; (b) $\text{MeO}_2\text{CCH}_2\text{COCl}$, toluene, 0 °C; (c) 4 equiv of CAN, MeOH, rt.

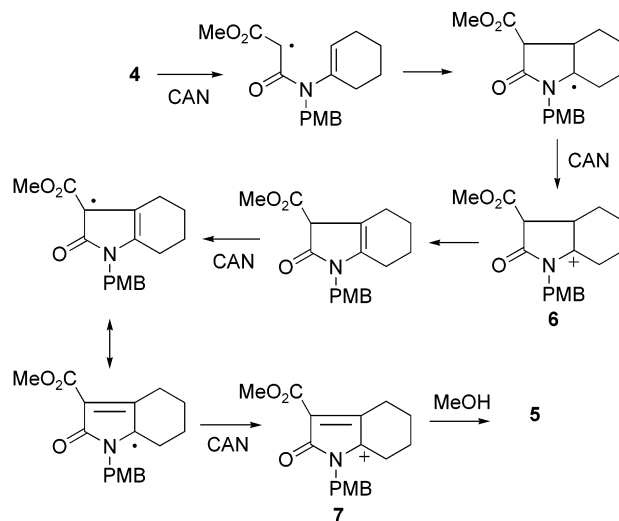
these conditions no deprotection of the PMB group was observed. Interestingly, while the $\text{Mn}(\text{OAc})_3$ -mediated cyclization of **1** leads to the diene **2**, the analogous CAN-mediated cyclization of **4** furnishes the alkoxy trapped product **5**. Thus, the CAN and $\text{Mn}(\text{OAc})_3$ procedures are complementary giving rise to different products.

Mechanistically **5** may be formed by initial radical generation from **4** followed by a 5-*endo* cyclization and oxidation to the acyl iminium ion **6** by a second equivalent of CAN. Elimination, followed by a second radical generation and oxidation sequence furnishes the iminium ion **7**, which upon trapping with the solvent furnishes the observed product **5**. This is in keeping with the fact that 4 equiv of CAN was required for efficient reaction. Cyclization of **4** did not proceed in other solvents (such as dichloromethane, 1,2-dichloroethane, benzene, or toluene) at room temperature or at reflux.

The scope and limitation of the procedure was then examined. Cyclization of **8** with use of the standard conditions gave the expected 5-*endo* cyclization product **9** as an inseparable 10:1 mixture of diastereomers (stereochemistry of the major isomer unconfirmed) as well as an unknown minor component (less than 3–4%) in 78% combined yield.

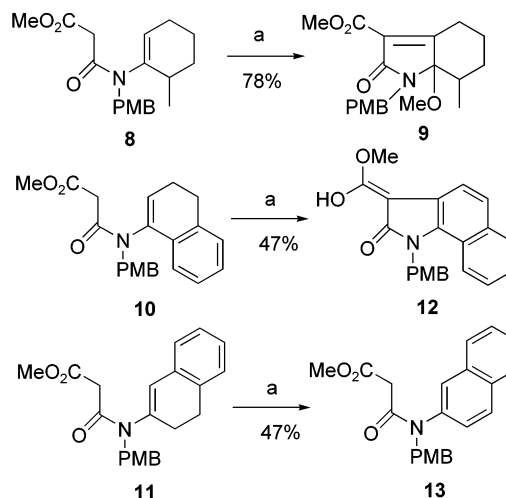
Reaction of the tetralone-derived enamides **10** and **11** proceeded in a slightly different manner. No solvent-trapped products were isolated in either reaction. Instead the fully

Scheme 3. Proposed Mechanism of 5-*Endo* Cyclization of **4** Mediated by CAN



aromatized structures **12** and **13** were isolated in poor yield (compound **13** was contaminated with less than 5% of an unknown inseparable impurity). Thus for **10** CAN-mediated aromatization occurs after cyclization whereas for **11** cyclization is not observed at all.

Scheme 4^a



^a Reagents and conditions: (a) 4 equiv of CAN, MeOH, rt, 20 min.

As part of a programme toward the synthesis of natural products containing the highly functional 5,5-*C,O*-disubstituted- γ -lactam skeleton, such as **14–16**,⁸ we next investi-

(8) Isolation: (a) L-755, 807: Lam, T. Y. K.; Hensens, D. D.; Ransom, R.; Gaicobbe, R. A.; Polishool, J.; Zinc, D. *Tetrahedron* **1996**, 52, 1481. (b) PI-091: Kawashima, A.; Yosohimura, Y.; Sakai, N.; Kamigoori, K.; Mizutani, T.; Omura, S. Jpn. Kokai Tokkyo Koho JP 02 62,859; *Chem Abstr.* **1990**, 113, 113856d. (c) Quinolactacin, C.; Tatsuta, K.; Misawa, H.; Chikauchi, K. *J. Antibiot.* **2001**, 54, 109.

(7) Bar, G.; Bin, F.; Parsons, A. F. *Synth. Commun.* **2003**, 213.

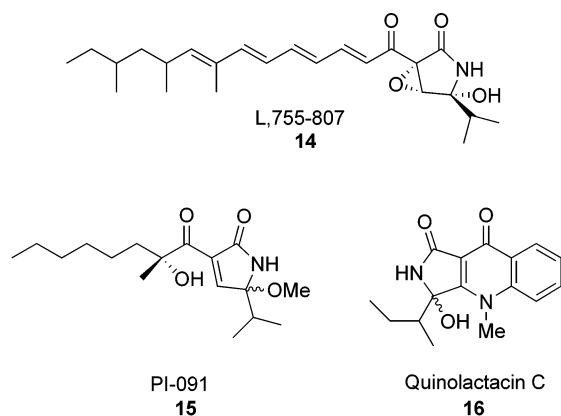
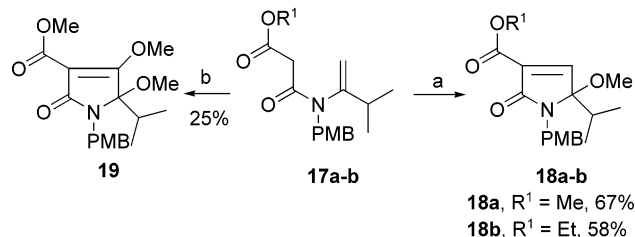


Figure 1. Structures of natural products **14**–**16**.

gated the cyclization of enamides that contained no substitution at the terminal carbon. Hence, cyclization of either the methyl **17a** or ethyl **17b** esters with CAN in MeOH at room temperature for 20 min furnished the desired 5-*endo* products **18a,b** in moderate yield (58–67%). We were delighted that the reaction was successful and allowed access to the desired heterocyclic core of the platelet inhibitor PI-091, Scheme 5.

Scheme 5. CAN-Promoted 5-*Endo* Cyclization to the Heterocyclic Core of PI-091 **15**^a

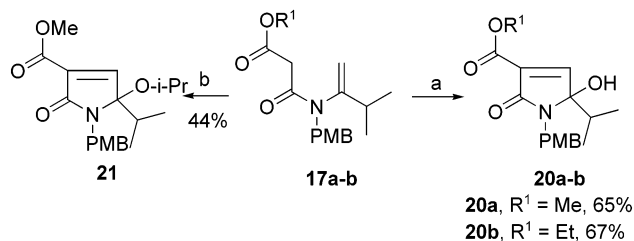


^a Reagents and conditions: (a) 4 equiv of CAN, MeOH, rt, 20 min; (b) 4 equiv of CAN, MeOH, reflux.

To maximize the yield in the synthesis of **18a** the temperature was increased and **17a** was heated with CAN in MeOH for 2 h at reflux. Under these conditions a 1:1 mixture of **18a** and **19** was isolated in 50% yield. Presumably **19** arises from a Michael addition of MeOH to the unsaturated heterocycle **18a** followed by further CAN-mediated oxidation.

We have recently published a route to the side-chain tetraene fragment of L-755,807, **14**.⁹ Consequently, we wished to test our methodology to see if it was applicable for the formation of γ -hydroxylated heterocycles as well as γ -methoxylated heterocycles. In other words, could we mediate the cyclization in the presence of other nucleophiles (e.g. H₂O instead of MeOH). Reaction of both **17a** and **17b**

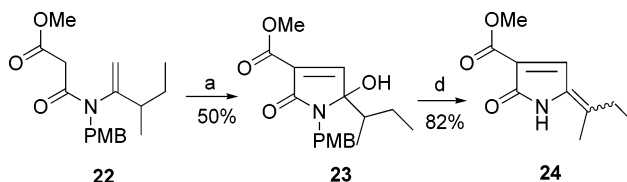
Scheme 6. CAN-Promoted 5-*Endo* Cyclization to the Heterocyclic Core of L,755,807 **14**^a



^a Reagents and conditions: (a) 4 equiv of CAN, MeCN, rt, 20 min; (b) 4 equiv of CAN, i-PrOH, rt, 20 min.

with 4 equiv of CAN in acetonitrile as solvent, followed by aqueous workup furnished the desired hydroxy lactams **20a,b**. In a similar manner changing the solvent from MeOH to i-PrOH led to the isopropoxy-trapped lactam **21**. Attempts

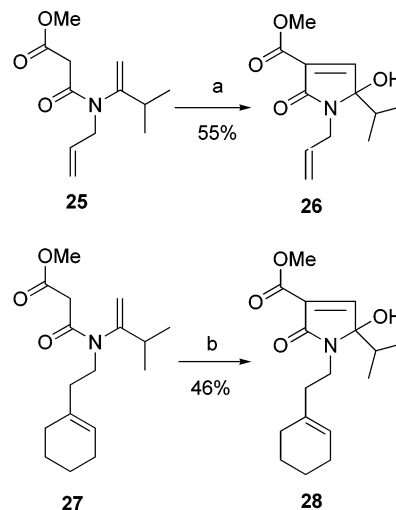
Scheme 7. CAN-Promoted 5-*Endo* Cyclization to the Heterocyclic Core of Quinolactacin C **16**^a



^a Reagents and conditions: (a) 4 equiv of CAN, MeCN, rt, 20 min, H₂O; (b) TFA, heat.

to mediate the reactions by using other Ce(IV) salts such as CeO₂ or Ce(OH)₄ in MeCN led to unreacted starting material.

Scheme 8. 5-*Endo* CAN-Promoted Cyclization of **25** and **27**^a



^a Reagents and conditions: (a) 4 equiv of CAN, MeCN, rt, 20 min; (b) 4 equiv of CAN, MeCN, rt, 20 min, H₂O.

(9) Clark, A. J.; Ellard, J. M. *Tetrahedron Lett.* **1998**, 39, 6033.

Utilizing our approach it was possible to prepare the analogue **23** of the Quinolactacin C skeleton. Thus treatment of **22** with 4 equiv of CAN in acetonitrile led to the desired hydroxy lactams after aqueous workup (albeit as a 2:1 mixture of diastereomers). Attempts to deprotect the *p*-methoxybenzyl group by using more CAN or TFA furnished the eliminated lactam **24** as a 1.3:1 *E:Z* mixture, Scheme 7.

We further tested the scope and limitation of the CAN-mediated 5-*endo* procedure by examining the reaction of the precursor **25**. Cyclization of **25** could in theory proceed either via a 5-*endo* cyclization onto the enamide alkene or by a 5-*exo* cyclization onto the allyl group. Reaction with CAN in MeCN gave rise exclusively to the 5-*endo* product **26**, and no 5-*exo* product was detected, Scheme 8.

In the same way substrate **27** underwent exclusive 5-*endo* cyclization to give **28** in 46% yield. No competing 6-*exo* cyclization or tandem cyclization of the postulated intermediate acyl iminium ion onto the cyclohexenyl group was observed.

In summary, we have demonstrated that efficient 5-*endo* radical–polar crossover reactions can be mediated by CAN in various solvents. The reactions differ from those mediated by Mn(OAc)₃ in that products arise from trapping of

intermediates by solvent instead of dienes. This may be due to the milder reaction temperatures involved for the CAN-mediated reactions (rt) compared to the Mn(OAc)₃ reactions (>70 °C), as the intermediate 5-hydroxylated or 5-alkoxylated products undergo facile elimination of H₂O or ROH upon prolonged heating,¹⁰ or treatment with acid at room temperature. The application of this methodology to the synthesis of the heterocyclic cores of a range of 5,5-*C,O*-disubstituted- γ -lactam natural products has been demonstrated.

Acknowledgment. We acknowledge Lilly Research Ltd for a studentship (J.P.M.).

Supporting Information Available: Selected experimental procedures and characterization data for compounds **4**, **8**, **10**, **11**, **17a**, **17b**, **22**, and **27** and representative ¹H and ¹³C NMR spectra for **9**, **13**, **23**, **24**, and **28**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) Compound **4** was observed to eliminate MeOH when heated or treated with *p*-TSA in toluene at reflux.