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SUBSTITUENT-DIRECTED OXIDATION: HIGHLY REGIOSELECTIVE AND STEREOSELECTIVE OXIDATIVE CYCLIZATION OF CYCLOALKENOLS WITH CERIC AMMONIUM NITRATE.

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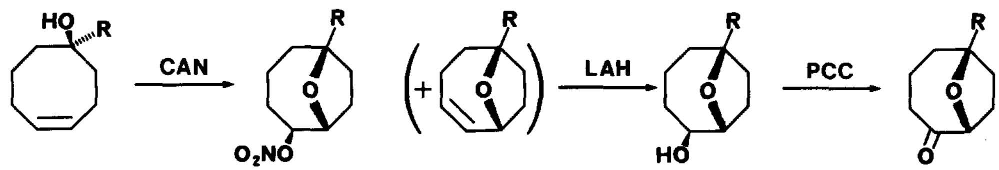
SUMMARY: *A highly regioselective and stereoselective oxidative cyclization of cyclooctenols with ceric ammonium nitrate is described, giving a formal syn oxidative addition to the alkene.*

The substituent-directed oxidative cyclization of cycloalkenols is an innovative synthetic method and a subtle mechanistic probe. Our studies in the area of transannular oxidation have shown that intramolecular participation by the substituent results in a powerful guiding and accelerating effect on the reaction.[1] We now report the highly regio- and stereoselective oxidative cyclization of the cyclooctenols **1a,b** with ceric ammonium nitrate (CAN).[2] This formal syn oxyetherification is a useful transformation not easily achieved by other means.

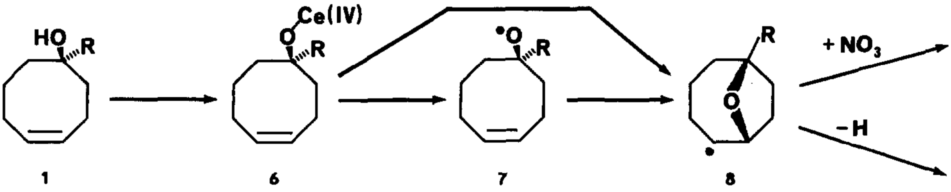
Substrates **1a,b**[1] react with CAN (CH_3CN/H_2O; room temp.) affording modest yields of adducts identified as the nitrates **2a,b** (Equation 1).[3,4] From **1b** a 1:1 inseparable mixture of the unsaturated bicyclic ether **3** and **1b** is also isolated in 20% yield. Alkyl nitrates[4a] and alkenes[4] have been obtained previously in cerate-promoted fragmentations. Reductive cleavage of **2a,b** ($LiAlH_4/Et_2O$) gives the exo-β-hydroxy cyclic ethers **4a,b**.[3] These products were compared with the related endo isomers, prepared by oxidative cyclization with hypervalent iodine reagents.[1c] Analysis of the spectral data gives exo/endo ratios of greater than 95:5 for the present alcohols.[5] Standard PCC oxidation of **4a,b** provides ketones **5a,b**, identical in all respects with the products isolated previously.[1b,c] A single regioisomeric ketone **5b** is obtained from **1b**, and ketone **5a** is a 95:5 mixture of regioisomers ([4.2.1] vs. [3.3.1]).[5]



EQN. 1

	1a,b	2a,b	3	4a,b	5a,b
a: R = H		34%	-	56%	68%
b: R = CH_3		26%	10%	41%	91%

The first step in this reaction is likely the formation of the cerium alkoxide **6** (Equation 2).[2] Intramolecular attack by the alkene on the electrophilic oxygen could occur concomitantly with cleavage of the metal-oxygen bond to give the 9-oxabicyclononan-2-yl radical **8**. Alternatively, the cerium alkoxide could first fragment to the alkoxyl radical **7**, from which the well known[6] cyclization of γ-oxyalkene radicals to five-membered rings would also lead to **8**. Interception of this radical by nitrate from the convex face yields **2**, and hydrogen atom abstraction gives **3**. Further studies of this transformation are in progress.



EQN. 2

<u>Typical procedure</u>: *A solution of 495 mg (3.92 mmol) of* ***1a*** *in 20 mL of acetonitrile/water (9:1) was charged with 4.301 g (7.85 mmol) of CAN, and stirred at room temperature for one day. A further 2.15 g (3.93 mmol) of CAN was charged to the reaction mixture, which was stirred for one more day. The reaction mixture was diluted with 50 mL of water, and extracted twice with 25 mL of methylene chloride. The combined organic portions were dried* ($MgSO_4$) *and concentrated. Chromatography of the residue yielded 245 mg (34%) of* ***2a*** *as a yellow oil.*

A solution of 245 mg (1.32 mmol) of ***2a*** *in 15 mL of ether was charged with 150 mg (3.95 mmol) of* $LiAlH_4$*, and the mixture was heated to reflux for one day. A further 180 mg (4.74 mmol) of* $LiAlH_4$ *was added and reflux continued for two more days. The cooled reaction mixture was treated dropwise with 1 mL of satd. aq.* Na_2SO_4*, dried* ($MgSO_4$)*, and filtered through Celite. The residue after concentration (200 mg) was purified by chromatography to give 104 mg (57%) of* ***4a*** *as a pale yellow oil.*

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1. (a) M. F. Schlecht, H.-j. Kim, <u>Tet. Lett.</u> **26** 127 (1985). (b) M. F. Schlecht, H.-j. Kim, <u>Tet. Lett.</u> **27** 4889 (1986). (c) H.-j. Kim, M. F. Schlecht, <u>Tet. Lett.</u> **28** 5229 (1987). (d) M. F. Schlecht, H.-j. Kim, *manuscript submitted, 1988.*
2. For a review on the organic chemistry of cerium(IV), see: T. L. Ho, <u>Synth.</u> 347 (1973).
3. Spectral data. For **2a**: IR (thin film) 2920 (s), 2870 (m), 1620 (s), 1470 (m), 1450 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.10-2.52 (m, 10H); 4.57 (m, 2H); 4.98 (br t, 1H, J = 7.5 Hz). For **2b**: IR (thin film) 2960 (m), 2920 (m), 1620 (s), 1475 (w), 1450 (w) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.33 (s, 3H); 1.5-2.6 (m, 10H); 4.53 (dd, 1H, J = 3, 11 Hz); 4.97 (dd, 1H, J = 5, 9 Hz). ^{13}C-NMR (C_6D_6) δ 19.9, 28.0, 29.2, 31.4, 35.3, 42.5, 80.1, 84.6, 89.5. For **4a**: IR (thin film) 3400 (br m), 2920 (s), 2860 (m), 1470 (m), 1450 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.02-2.67 (m, 10H); 3.24 (br s, 1H); 3.68 (m, 1H); 4.50 (m, 2H). ^{13}C-NMR (C_6D_6) δ 19.0, 29.3, 31.0, 33.7, 36.7, 75.8, 77.7, 85.2. For **4b**: IR (thin film) 3300 (br s), 2950 (s), 2920 (s), 2860 (s), 1475 (m), 1450 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.30 (s, 3H); 1.08-2.39 (m, 5H); 2.70 (br s, 1H); 3.64 (br t, 1H, J = 6 Hz); 4.40 (dd, 1H, J = 4, 11 Hz). ^{13}C-NMR (C_6D_6) δ 19.8, 29.6, 30.2, 33.5, 37.5, 43.2, 76.0, 83.4, 85.1.
4. (a) K. Meyer, J. Rocek, <u>J. Am. Chem. Soc.</u> **94** 1209 (1972). (b) S. R. Wilson, P. A. Zucker, C. W. Kim, C. A. Villa, <u>Tet. Lett.</u> **26** 1969 (1985).
5. This value represents the lower limit of detection by ^{1}H-NMR for these two isomers.
6. For reviews in this area, see: J.-M. Surzur, <u>Chem. Het. Compds. (Eng. Transl.)</u> **11** 507 (1975) [<u>Chem. Abstr.</u> **83** 97070x (1975)]. A. L. J. Beckwith, <u>Tet.</u> **37** 3073 (1981).

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