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Baeyer–Villiger Oxidation Promoted by Reaction of Peracids with Cyclic Oxocarbenium Ions Generated in Situ from Internal Hemiketals

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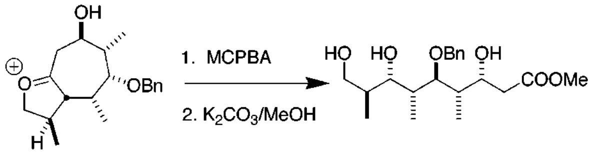
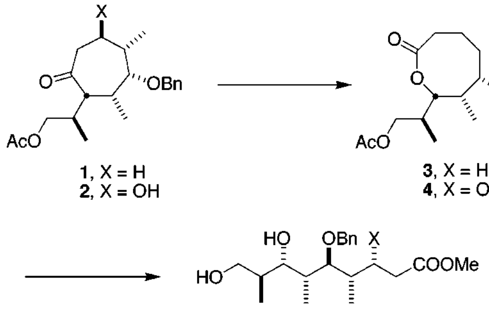
ABSTRACT



Reactive cyclic oxocarbenium ions, generated in situ from internal hemiketals, undergo Baeyer–Villiger oxidation upon exposure to *m*-chloroperbenzoic acid leading, after hydrolysis of the resultant lactones, to acyclic fragments for use in natural product synthesis.

The Baeyer−Villiger oxidation is generally a reliable process for the conversion of cyclic and acyclic ketones into lactones and esters, respectively.[1] The reaction proceeds with rigorous retention of stereochemistry, thereby lending itself readily to the synthesis of complex stereochemical motifs. In conjunction with synthetic studies underway in our laboratory wherein the C_9 fragments **5** and **6** were required for macrolide construction, we set out to employ the Baeyer−Villiger oxygen insertion reaction for the transformation of ketones **1** and **2** into lactones **3** and **4**, respectively.



1, X = H
2, X = OH

3, X = H
4, X = OH

5, X = H
6, X = OH

Attempts to subject either **1** or **2** to the Baeyer−Villiger reaction employing a variety of peracids[2] and other active oxygen sources[3] led, unfortunately, to recovered starting material, loss of stereochemistry adjacent to the carbonyl, β-elimination, and other undesired products.[4] Dreiding models clearly reveal that the carbonyl group in both **1** and **2** is severely encumbered, thereby hindering attack by the

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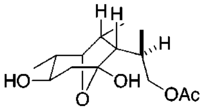
(1) Krow, G. R. *Org. React.* **1993**, *43*, 251. Hassall, C. H. *Org. React.* **1957**, *9*, 73. Bolm, C. In *Advances in Catalytic Processes, Vol. 2*; Doyle, M. P., Ed.; JAI Press: Greenwich, 1997; p 43. Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737. Strukul, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1198.

(2) Monopermaleic, monoperpthalic, monopersulfuric, *m*-chloroperbenzoic, trifluoroperacetic, peracetic, and benzeneperoxyseleninic acids were employed with and without the addition of Lewis acids.

(3) Lapalme, R.; Borschberg, H. J.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1979**, *57*, 3272. Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902. Yamada, T.; Takahashi, K.; Kato, K. *Chem. Lett.* **1991**, 641.

(4) Upon exposure of **2** to trifluoroperacetic acid or *m*-chloroperbenzoic acid in the presence of boron trifluoride etherate at ambient temperature, **2** undergoes debenzylation leading to the formation of hemiketal **i** in ca. 40% yield.

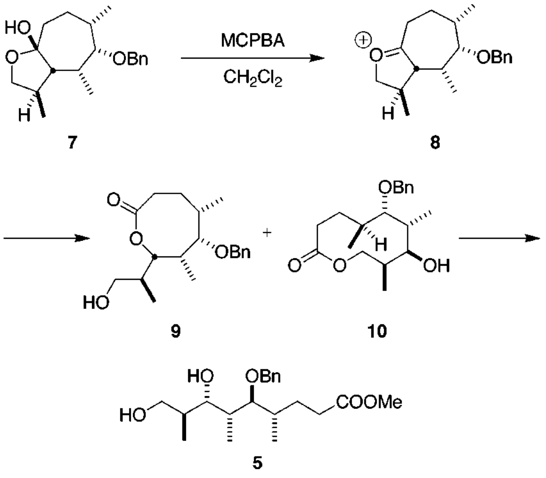


i

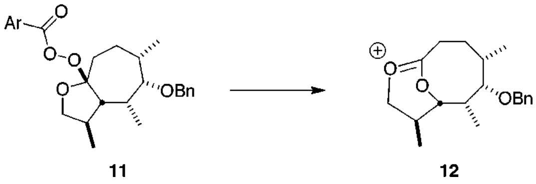
10.1021/ol000068j CCC: $19.00

peracid. That ketones **1** and **2** are indeed sterically congested was further confirmed by our inability to prepare their respective dimethyl or ethylene ketals. We detail below a solution to the problems encountered above in the attempted Baeyer–Villiger oxidations of **1** and **2** which utilizes neighboring hydroxyl groups to generate internal hemiketals (cf. **7**) which upon exposure to MCPBA lead to the formation of reactive cyclic oxocarbenium ions (cf. **8**) and subsequent Baeyer–Villiger oxidation.[5]

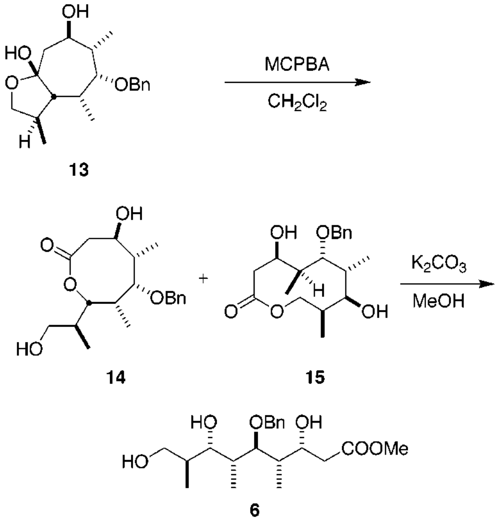
In a preliminary experiment, hemiketal **7**[8a] was treated with 1.4 equiv of MCPBA in methylene chloride. After 4 h at ambient temperature, a 4:1 mixture of lactones **9** and **10**, respectively, was obtained in 70% isolated yield. Exposure of the mixture of **9** and **10** to potassium carbonate in methanol afforded the C_9 fragment **5** in near quantitative yield.



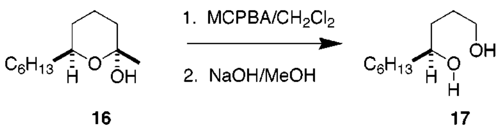
The formation of **9** and **10** undoubtedly arises from reaction of oxocarbenium ion **8** with MCPBA, providing peroxy ketal **11**.[9] Migration of the secondary carbon atom gives rise to **12**, or its equivalent, which upon aqueous workup partitions to the eight- and ten-membered lactones **9** and **10**.



Similar treatment of hemiketal **13**[8b] [1.4 equiv of MCPBA, CH_2Cl_2, rt, 4 h] affords the eight-membered ring lactone **14** along with a trace of **15**. Brief exposure to potassium carbonate in methanol gave rise to **6** in 65% overall yield from **13**.



The utility of the above protocol[10] for effecting the Baeyer–Villiger reaction on unreactive ketones[11] possessing a neighboring hydroxyl group capable of setting up an equilibrium between the parent hydroxy ketone and the corresponding closed hemiketal has been applied to a number of substrates. Thus, treatment of hemiketal **16**[12] with MCPBA (1.4 equiv) in methylene chloride at ambient temperature for 24 h followed by saponification with methanolic sodium hydroxide afforded 1,4-diol **17** in 77% overall yield.



In the case of hydroxy ketone **18**, similar treatment with MCPBA (1.4 equiv) in methylene chloride led to the rapid

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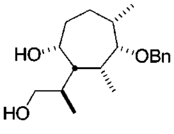
[5] We[6] and others[7] have shown that oxocarbenium ions generated from mixed acetals or ketals react with *m*-chloroperbenzoic acid, giving rise to lactones and orthocarbonates, respectively.

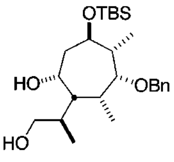
[6] Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, 419.

[7] Bailey, W. F.; Shih, M.-J. *J. Am. Chem. Soc.* **1982**, *104*, 1769. Also see: Gaoni, Y. *J. Chem. Soc. C* **1968**, 2925.

[8] (a) Substrate **7** was prepared in 90% overall yield from diol **ii** via a three-step protocol [(1) TESCl, 2,4,6-collidine, CH_2Cl_2, −78 °C, 6 h; (2) TPAP (5 mol %), NMO (2.0 equiv), 4 Å m.s., 7 h; (3) TBAF, HOAc, THF, 0 °C → rt, 14 h]. (b) Prepared from diol **iii** employing the sequence outlined in ref 8a.



ii



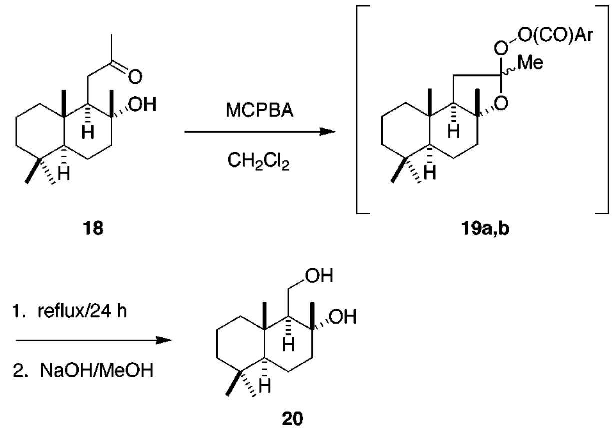
iii

[9] Acylation of hydroperoxy ketals followed by Criegee rearrangement of the resultant acyl peroxide has been reported: Criegee, R. *Chem. Ber.* **1944**, *77*, 772. Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127. Hedaya, E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1661. Schreiber, S. L.; Liew, W. F. *Tetrahedron Lett.* **1983**, *24*, 2363. Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1984**, *25*, 617.

[10] In a typical procedure, the hemiketal **13** (238 mg, 0.743 mmol) in dry methylene chloride (7 mL) was treated with recrystallized MCPBA (180 mg, 1.4 equiv) at ambient temperature. After 4 h, the reaction was diluted with ethyl acetate. The reaction mixture was washed with a 10% aqueous Na_2SO_3 solution and a saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture of lactones was dissolved in dry methanol (7 mL) and was treated with K_2CO_3 (103 mg, l equiv) at ambient temperature for 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The product was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo. Purification on silica gel provided compound **6** (178 mg, 0.483 mmol) in 65% overall yield.

[11] Methyl ketones are often inert to MCPBA.

formation of two less polar, UV active compounds, presumably peroxy ketals **19a** and **19b**, which underwent fragmentation when the reaction mixture was heated at reflux. Saponification gave rise to diol **20** in 70% overall yield. Peroxy ketals **19a** and **19b** could be isolated by purification on neutral silica gel (Davisil Grade 643) and characterized by ^{1}H and ^{13}C NMR.

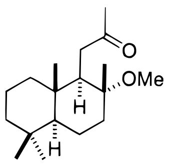


18

19a,b

20

It is of interest to note that when the hydroxyl group in **18** was protected as a methyl ether (cf. **21**) and exposed to MCPBA in methylene chloride followed by reflux, only unreacted starting material (**21**) was recovered, suggesting that internal hemiketal formation followed by generation of the corresponding oxocarbenium ion is required for the Baeyer–Villiger reaction to proceed.



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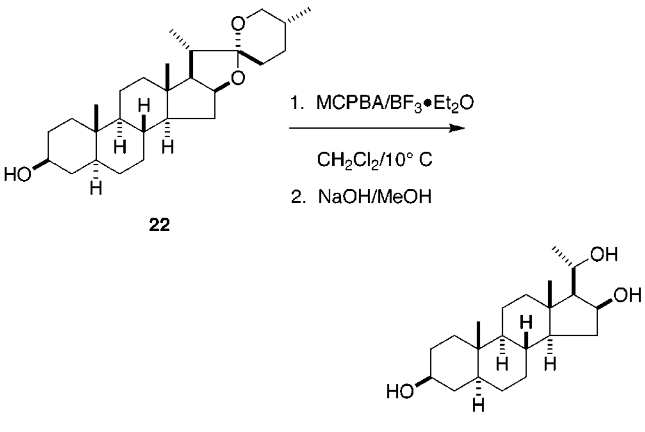
A modification of the above protocol has been applied to the degradation of naturally occurring steroidal cyclic ketals. For example, exposure (2 h) of ticogenin (**22**) to MCPBA (5.0 equiv) and $BF_3 \cdot Et_2O$ (4.0 equiv) in methylene chloride cooled to 10 °C, followed by saponification (NaOH/MeOH), provided triol **23** in 85% isolated yield.[13]



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23

In summary, the reaction of peracids with cyclic oxocarbenium ions generated in situ from internal hemiketals represents an operationally simple protocol which permits the Baeyer–Villiger oxidation of substrate ketones normally inert to oxidation either due to steric congestion or electronic factors.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant from the National Cancer Institute (CA 28865).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **5**, **6**, **17**, **19**, **20**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Compound **16** exists as a 1:1 equilibrium mixture of hemiketal and hydroxyketone in deuteriochloroform.

(13) This transformation has been previously realized in modest yields (<40%) by employing monopersulfuric acid [Marker, R. E.; Turner D. L.; Wagner, R. B.; Ulshafer, P. R. *J. Am. Chem. Soc.* **1941**, *63*, 772].