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NOVEL REARRANGEMENTS OF 7-OXANORBORNENE SYSTEMS

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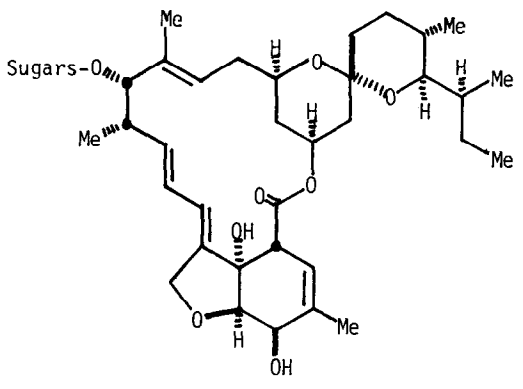
Summary: Treatment of the tricyclic 7-oxanorbornene systems with electrophiles (I^+, Br^+) leads to skeletal rearrangement.

We have recently described[1] our preliminary work on an approach to the broad spectrum antiparasitic compound ivermectin **1**, a member of the avermectin-milbemycin class of pentacyclic lactones having potent biological activity.[2] In our approach to **1**, we have utilized an intramolecular Diels-Alder reaction of an N-furfurylacrylamide such as **2** to generate in high yield the tricylic cycloadduct **3**. One potential method of forming the correct four contiguous asymmetric centers of the bottom half of ivermectin, e.g., compound **5**, would be to oxidize the double bond of a cycloadduct such as **3** from the endo face to generate **4**. We have already shown that the reductive elimination of a chloro ether analogous to **4** proceeds readily to give an olefinic triol similar to **5**. We now wish to report the results of our attempts at cis-oxygenation of **3** from the endo face.



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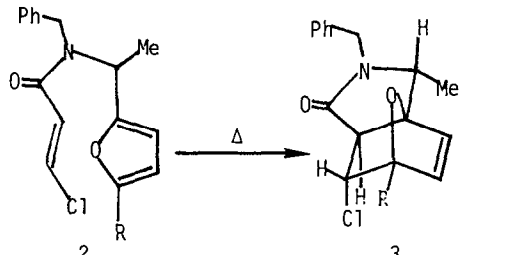
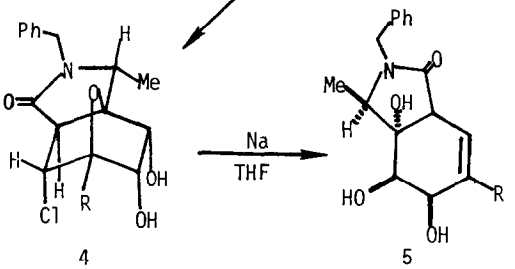


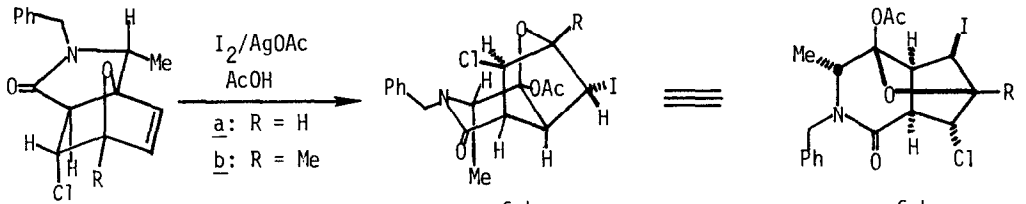
2 3



4 5

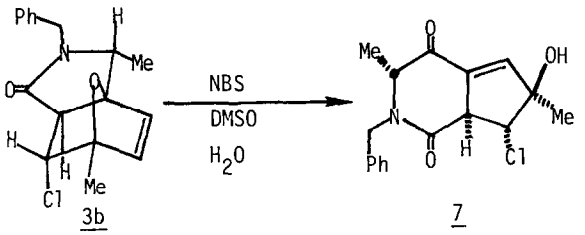
a R = H b R = Me

The endo face of the 7-oxanorbornene system is more sterically hindered than the exo face so that the usual methods for cis-hydroxylation, e.g., OsO_4, give the exo, exo-diol, e.g., treatment of **3b** with OsO_4 affords the exo, exo-diol in 97% yield.[1] We therefore decided to use the Woodward method for cis-hydroxylation from the more sterically hindered direction.[3] Treatment of the cycloadducts **3ab** under Woodward's conditions (AgOAc, I_2, aq. AcOH) for 20h at 25°C afforded, after silica gel chromatography, the rearranged iodo acetates **6ab** in 61% yield. The structure of **6** was inferred from its spectral data (Table), in particular its mass spectrum and quite detailed proton NMR spectrum. Since this direct method for cis-hydroxylation did not



3ab 6ab 6ab

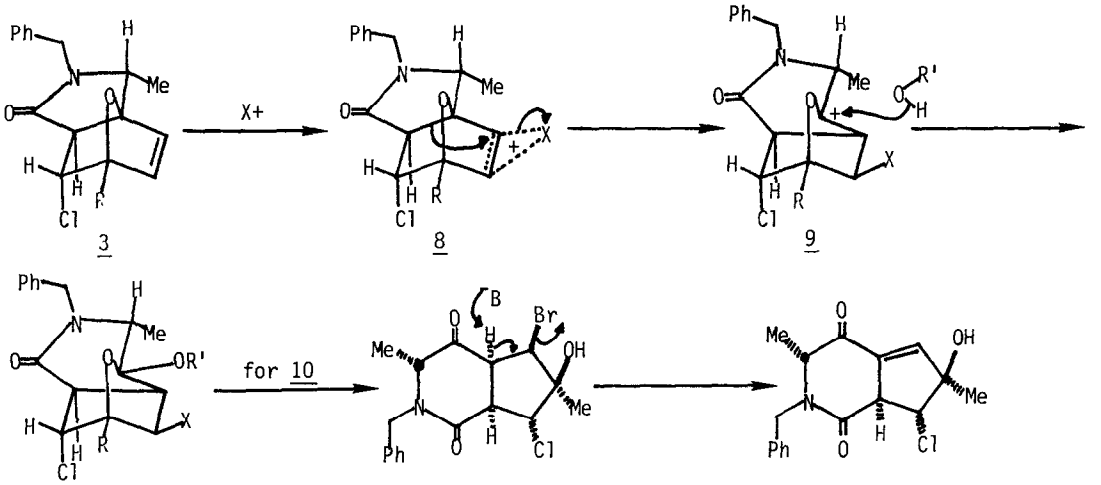
proceed as desired, we attempted to form the bromohydrin (exo Br, endo OH) in the usual manner and then try to displace the bromine with oxygen from the endo face to give the desired diol (e.g., via solvolysis of the derived bromo acetate). However, again in this case a skeletal rearrangement proved to be the favored pathway. Thus treatment of **3b** with NBS in aq. DMSO at 25°C for 3h gave, after silica gel chromatography, the enone amide **7** in 60% yield. The structure of **7** was again inferred from its spectral data (Table).



3b 7

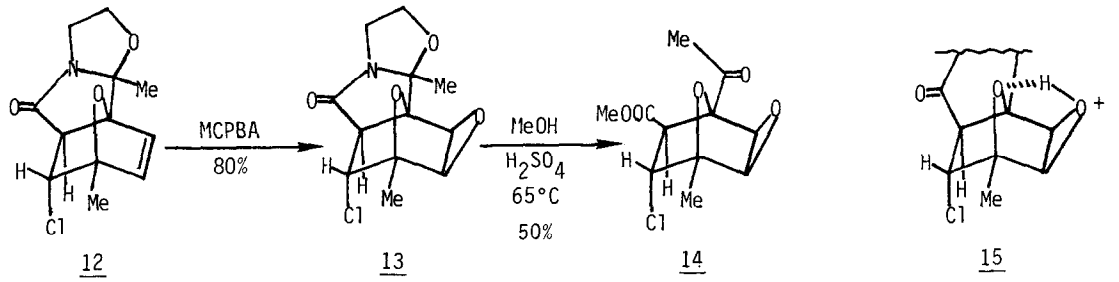
Both of these rearrangements can be explained in terms of the following proposed mechanism. Attack of the carbon-carbon double bond of **3** on the positive halogen species (I^+ or Br^+) from the less-hindered exo face would produce the halonium ion **8**, which could rearrange via migration of the antiperiplanar carbon-carbon bond (perhaps with assistance from the anti lone pair on oxygen) to give the carbonium ion α to oxygen **9**. Attack by acetic acid or water on the carbocation followed by proton loss would produce the iodoacetate **6** or the bromo hemiketal **10**. Opening of the hemiketal to the ketone **11** followed by elimination of HBr would yield **7**.

There is one further intriguing observation to report. Acidic methanolysis of the corresponding exo epoxide **13**, prepared in 80% yield by peracid epoxidation of the olefin **12**,[1] under very vigorous conditions (1N H_2SO_4, MeOH, 65°C, 14h) afforded the epoxy keto ester **14** in 50% yield. It is somewhat surprising that the strongly acidic conditions do not cause skeletal rearrangement of the epoxide similar to that seen above. The reasons for this difference in reactivity are not completely clear but one possibility is that protonation of the epoxide oxygen



6 R'=Ac X=I R=H,Me
10 R'=H X=Br R=Me

occurs syn to the bridging oxygen so that a strong internal hydrogen bond can occur, e.g., **15**. This species would be much less prone to skeletal rearrangement since migration of the C-C bond is made somewhat unfavorable due to both resonance and inductive effects.[4] We are currently attempting to devise synthetic routes to the bottom half of ivermectin from **14** and its derivatives.



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References and Notes

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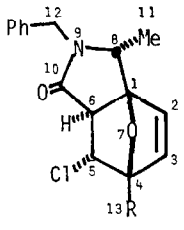
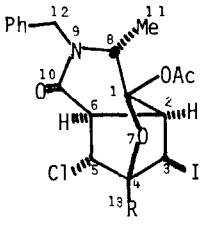
4. Hydrogen bonding of the proton to the bridging oxygen greatly increases the inductive electron withdrawing effects of this oxygen on the adjacent carbon which makes it more difficult to place a positive charge at that center (e.g., via C-C bond migration). Likewise the H-bond ties up the lone pair of electrons on the bridging oxygen so that it can not be used to stabilize the positive charge on the adjacent carbon through resonance (the resonance structure would involve a formal violation of Bredt's rule, since it would have a C-O double bond at the bridgehead of a small bicyclic system).

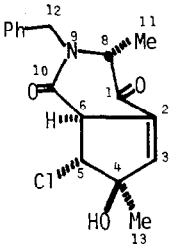
Table: Spectral Data for 7-Oxanorbornenes and Their Rearrangement Products



3ab



6ab



7

200 MHz

^{1}H NMR	**3a** (R=H)	**6a** (R=H)	**6b** (R=Me)	**3b** (R=CH_3)	**7**
H_2	6.60 d J=6Hz	2.91 dd J=2,3Hz	3.09 dd J=4.6,2.4Hz	6.60 d J=6Hz	-------
H_3	6.52 dd J=6,2Hz	3.30 m	3.20 d J=4.6,1Hz	6.32 d J=6Hz	6.80 d J=1.5Hz
H_5	4.48 dd J=4,2Hz	4.46 dd J=4,1Hz	4.5 d J=1Hz	4.18 d J=2Hz	4.64 d J=8Hz
H_6	2.60 d J=2Hz	3.71 m	3.66 d J=2.4Hz	2.76 d J=2Hz	3.72 dd J=8,1.5Hz
H_8	3.61 q J=7Hz	4.45 q J=7Hz	4.61 q J=6.6Hz	3.60 q J=7Hz	3.86 q J=7.3Hz
H_{11}	1.25 d J=7Hz	1.20 d J=7Hz	1.18 d J=6.6Hz	1.21 d J=7Hz	1.31 d J=7.3Hz
$H_{12'}$	4.82 d J=16Hz	5.18 d J=15Hz	5.09 d J=14.6Hz	4.82 d J=16Hz	4.99 d J=14.2Hz
$H_{12''}$	4.00 d J=16Hz	3.84 d J=15Hz	4.01 d J=14.6Hz	4.12 d J=16Hz	4.28 d J=14.2Hz
H_{13}	5.10 dd J=4,2Hz	4.46 dd J=4,1Hz	1.56 s	1.65 s	1.48 s
Ph	7.25 s	7.25 s	7.29 s	7.25 s	7.28 s
Ac	-----	2.02 s	2.10 s	-------	-------
IR	1680, 1420, 940, 860, 730	1770, 1675, 1485 1250, 1040	1770, 1675, 1485, 1250, 1040	1680, 1420, 720	3400, 1720, 1680, 1650, 1470, 1290
MS	291, 299(M^+), 91(base)	477, 476, 475(M^+), 167, 165, 91(base)	491, 490, 489(M^+), 449, 447, 91(base)	305, 303(M^+), 212(base), 124	321, 319(M^+), 301, 266, 91(base)

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