Tetrahedron Letters, Vol.31, No.11, pp 1629-1632, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

TRICYCLIC OXONIUM-DIRECTED ADDITION: REGIOCHEMISTRY AND STEREOCHEMISTRY OF THE IODINATION REACTIONS IN 2,3-EPOXY CYCLOOCT-5-EN-1-OLS AND 2,3-EPOXY-5-EN-1-ONE.

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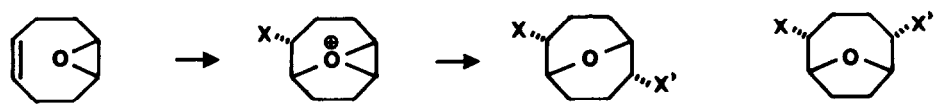
SUMMARY: The transannular O-heterocyclization of 9-oxabicyclo[6.1.0] non-4-en-2-ols and 9-oxabicyclo[6.1.0]non-4-en-2-one by iodine-assisted oxirane ring expansion was studied. The stereo- and regioselectivity for the[4.2.1] vs[3.3.1] 10-oxabicyclo nonane skeletons are studied in terms of a tricyclic oxonium ion intermediate and rationalized by means of MNDO calculations.

The transannular participation of the epoxide oxygen via an oxonium intermediate has been reported[1] in the stereoselective reactions of 9-oxabicyclo[6.1.0] non-4-ene 1 with bromine or iodine, in carbon tetrachloride or acetonitrile, to give a mixture of brominated and iodinated 9-oxacyclononanes 3 (X=X'=Br, I) and 4 (X=X'=Br, I), and more recently[2] in the halofluorination of 1 with one equivalent of N-chloro, N-bromo or N-iodosuccinimide in the presence of an excess of $Et_3N/3HF$ in CH_2Cl_2, to give a mixture of dihalo-9-oxabicyclononanes 3 (X=Cl, Br, I; X'=F) and 4 (X=Cl, Br, I; X'=F), in a 3 to 4 ratio mostly dependent on the difference in thermodynamic stability of the halogenated systems. As a part of an ongoing program aimed at the development of general methods for the construction of medium-sized oxygen-containing heterocycles, we have been investigating[3] the transannular O-heterocyclization by iodination of asymmetri-



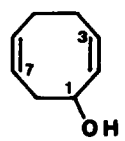
1 2 3 4

cally substituted 10-oxabicyclo[7.1.0]dec-4-enes and 11-oxabicyclo[8.1.0]undec-5-enes to give, respectively, diiodo-10-oxabicyclodecane and diiodo-11-oxabicycloundecane mixtures, in an isomeric ratio strongly dependent on substituents. Unique tricyclic oxonium ions were proposed as intermediates since they provide a ready explanation for both the product stereochemistry and the effects of subtituents.[3]

The source of regioselection is still not completely understood. It is believed, however, that a combination of steric and electronic effects is

involved which influences the possible oxonium ion intermediates such that only one appears to be greatly favoured. It appeared of interest to investigate the transannular O-heterocyclization in a system which due to participation of two oxonium ion intermediates might afford well-defined products providing direct information about the mechanism involved. Our choice fell on 9-oxabicyclo[6.1.0]non-4-en-2-ols, 6 and 8, and 9-oxabicyclo[6.1.0]non-4-en-2-one, 10. The results of these studies are now reported.

The synthesis of 2,6-cyclooctadien-1-ol 5 was carried out from the readily available 1,5-cyclooctadiene according to a literature procedure.[4] Epoxidation of 5 was examined with the following three reagents: i) MCPBA/CH_2Cl_2/0°C,[5] to give 6 (9%) and 8 (91%), combined yield, 78%; ii) t-BuOOH/VO(acac)$_2$ cat/40°C,[5]



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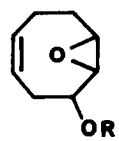
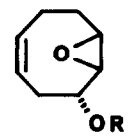
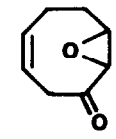


6, R=H
7, R=Ac



8, R=H
9, R=Ac



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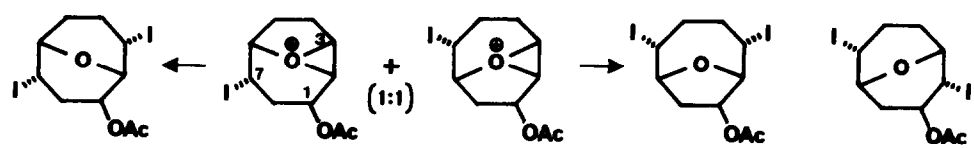
to give 6 (97%) and 8 (3%), 82% overall yield; iii) t-BuOOH/Ti(iPrO)$_4$ / (±)DET/ CH_2Cl_2/-20°C,[6] to give 6 (90%) and 8 (10%), overall yield 72%. Treatment of cis-2,3-epoxy acetate 7 with I_2/CH_2Cl_2/r.t./12 h, gave rise to a mixture of 13 (50%), 14 (37%) and 15 (13%), in a combined yield of 74% (Scheme 1). This result is consistent with a 1:1 participation of the oxonium ion species 11 and 12, which uniformly exhibited an excellent C-3 regioselectivity of the epoxide opening as well as the rigorous stereospecificity of the contiguous centres (Scheme 1).

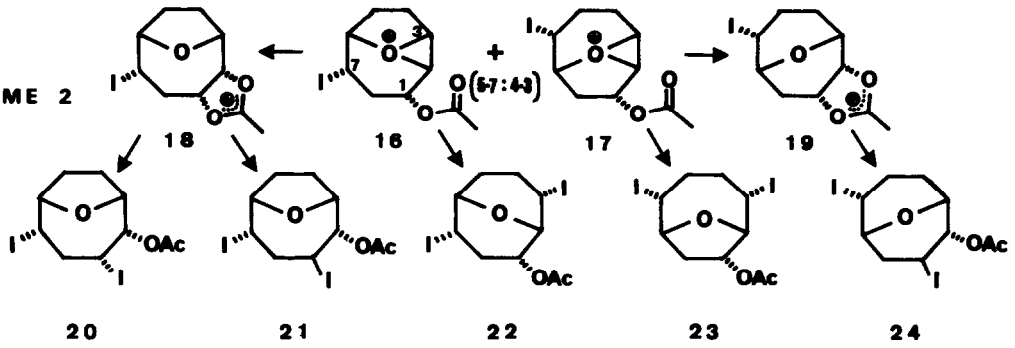
SCHEME 1



13 11 12 14 15

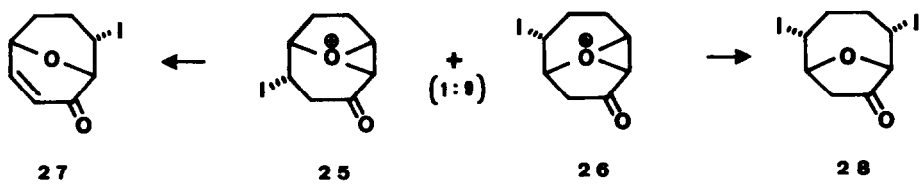
The trans 2,3-epoxy acetate 9 was far more reactive (I_2/CH_2Cl_2 /r.t./4 h, overall yield 61%, in accord with its ability to bring to bear a special driving force (the neighbouring acetoxy participation) which the cis isomer could not do. The results were easily accounted for by invoking iodine attack at the 1,2-dioxolan-2-ylium ion intermediates 18 and 19, the ring of which subsequently opened at the least hindered C-1 position to give 20 (21%) and 21 (11%), and 24 (35%), respectively. Iodine-induced oxonium opening gave 22 (25%) and 23 (8%) with regioselectivity at C-3 (Scheme 2).

SCHEME 2



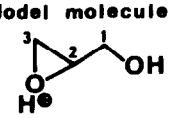
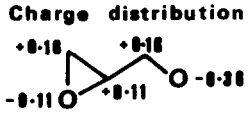
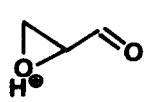
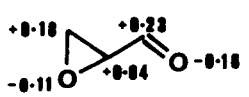
Iodine induced ring expansion of the 2,3-epoxy ketone 10 (I_2/CH_2Cl_2/r.t./12h) gave a mixture of 27 (10%) and 28 (90%) in a combined yield of 85% (Scheme 3). Here again, nucleophilic attack took place preferentially at the C-3 position although the tricyclic oxonium ion intermediates 25 and 26 are formed in a 1:9 ratio, probably due to a lower energy conformation preference of 26.

SCHEME 3



We found it convenient to interpret the results by MNDO calculations on more simple model compounds. In order to simulate the oxonium ion in the simplest possible way, the approach of a proton to the oxirane oxygen in 2,3-epoxy alcohol and 2,3-epoxy ketone models was simulated with the MOPAC package of programs.[7] Full geometry minimizations on these intermediates were carried out giving the results described in Table I. According to the charge distribution, nucleophilic attack in the 2,3-epoxy alcohol occurred preferentially at the C-3 position and in the 2,3-epoxy ketone exclusively at the C-3 site, yielding the products observed experimentally.

TABLE 1

Model molecule	Charge distribution
	
	

All new compounds gave spectroscopic[8] and analytical data entirely in accord with the structures shown.

ACKNOWLEDGEMENTS: Support of this work by DGICT through grant PB-0608 is gratefully acknowledged. E.A. thanks the Spanish M.E.C. for a post-doctoral fellowship.

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7. IBM/CMS version QCPE 486 : S. Olivella, QCPE Bull., 4, 10 (1984).
8. ^{1}H- and ^{13}C NMR spectra of selected compounds follow: 13:^{1}H NMR ($CDCl_3$)δ5.53 (C_1H, dd, J=2.1, 2.0 Hz), 4.73(C_7H, ddd, J=13.3, 6.7, 5.5 Hz), 4.51 (C_3H, ddd, J=12.5, 6.0, 6.0 Hz), 4.07 (C_6H, t, J=5.5 Hz), 3.99 (C_2H, d, J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 70.4 (C1), 72.9(C2), 22.8(C3), 31.7 (C4), 28.6 (C5), 69.9 (C6), 24.1 (C7), 38.3 (C8). 14: ^{1}H NMR ($CDCl_3$) δ 5.72 (C_1H, ddd, J=7.4, 3.0, 1.3 Hz), 4.80 (C_7H, ddd, J=7.0, 5.5, 3.7 Hz), 4.53 (C_2H, brd, J=6.3 Hz), 4.40 (C_3H, C_6H, m), 2.93 (C_8H, ddd, J=15.5, 7.4, 3.7 Hz); ^{13}C NMR ($CDCl_3$) 79.9 (C1), 87.5 (C2), 29.3 (C3), 35.6 (C4), 35.8 (C5), 32.0 (C6), 83.5(C7), 38.8 (C8). 15: ^{1}H NMR ($CDCl_3$) δ 5.72 (C_1H, ddd, J=11.0, 11.0, 6.5 Hz), 4.08 (C_2H, dd, J=11.0, 5.2 Hz), 3.96 (C_7H, ddd, J=11.8, 6.0, 5.0 Hz), 3.84 (C_3H, C_7H, brt, J=5.0 - 6.5 Hz), 2.92 (C_8H, dd, J=13.7, 6.5 Hz); ^{13}C NMR ($CDCl_3$) 71.1 (C1), 33.4 (C2), 72.9(C3), 28.5 (C4), 32.7 (C5), 27.6 (C6), 72.3 (C7), 34.2 (C8). 20:^{1}H NMR ($CDCl_3$) δ 5.32 (C_2H, dd, J=8.3, 3.5 Hz), 4.60 (C_1H, C_3H, C_6H, m), 4.28 (C_7H, ddd, J=11.6, 5.1, 4.5 Hz), 2.96 (C_8H, ddd, J=14.7, 11.6, 11.6 Hz), 2.75 (C_8H, ddd, J=14.7, 5.1, 2.5 Hz), 2.00 (C_4H_2,C_5H_2, m); ^{13}C NMR ($CDCl_3$) δ27.0 (C1), 78.0 (C2), 78.3, 84.4 (C3, C6), 26.3, 28.5 (C4, C5), 30.2 (C7), 43.7 (C8). 21: ^{1}H NMR ($CDCl_3$) δ 5.32 (C_2H, dd, J=6.6, 6.5 Hz), 4.60 (C_3H, C_6H, C_7H, m), 4.28 (C_1H, ddd, J=8.9, 6.5, 2.5 Hz), 2.39 (C_8H_2, m); ^{13}C NMR ($CDCl_3$) δ 26.5 (C1), 78.8 (C2), 79.3 (C3), 26.6 (C4), 30.2 (C5), 82.1 (C6), 32.5 (C7), 43.1 (C8). 22: ^{1}H NMR ($CDCl_3$)δ5.26 (C_1H, ddd, J= 11.7, 6.0, 6.0 Hz), 4.48 (C_3H, C_7H, m), 4.32 (C_2H, dd, J=6.0, 6.0 Hz), 4.08 (C_6H, dd, J=6.0, 6.0 Hz), 2.60 (C_8H_2, m); ^{13}C NMR ($CDCl_3$) δ 70.8 (C1), 68.6 (C2), 19.7 (C3), 32.6 (C4), 29.4 (C5), 70.1 (C6), 23.7 (C7), 39.1 (C8). 23:^{1}H NMR ($CDCl_3$) δ 5.56 (C_1H, ddd, J=10.4, 7.4, 7.0 Hz), 4.72 (C_2H, dd, J=7.0, 4.0 Hz), 4.58 (C_6H, dd, J=6.0, 3.3 Hz), 4.48 (C_7H, ddd, J=9.0, 9.0, 6.0 Hz), 4.72 (C_2H, dd, J=7.0, 4.0 Hz); ^{13}C NMR ($CDCl_3$) δ 72.4 (C1), 80.3, 80.1 (C2, C7), 25.0 (C3), 34.0 (C4), 38.0, 38.3 (C5, C8), 31.7 (C6). 24:^{1}H NMR ($CDCl_3$) δ5.33 (C_2H, dd, J=11.1, 5.8 Hz), 4.71 (C_1H, ddd, J=13.1, 11.1, 6.1 Hz), 4.54 (C_6H, ddd, J=10.0, 8.5, 6.3 Hz), 4.06 (C_3H, dd, J=5.8, 5.8 Hz), 3.64 (C_7H, 6.3, 6.1 Hz), 3.34 (C_8H, ddd, J=14.5, 6.1, 6.1 Hz), 2.82 (C_8H, dddd, J=14.5, 13.1, 6.3, 1.0 Hz), 2.40 (C_5H_2, m), 2.04 (C_4H, m), 1.77 (C_4H, dt, J=14.0, 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 23.8 (C1), 76.6 (C2), 68.7 (C3), 26.5 (C4), 33.6 (C5), 27.4 (C6), 73.5 (C7), 39.8 (C8). 27: ^{1}H NMR ($CDCl_3$)δ6.99 (C_7H, dd, J=10.3, 4.5 Hz), 6.39 (C_8H, d, J=10.3 Hz), 4.73 (C_6H, brt, J=4.5 Hz), 4.32 (C_3H, m), 4.25 (C_2H, br d, J=5.5 Hz), 2.38-2.20 (C_4H_2, C_5H, m), 1.56 (C_5H, m); ^{13}C MNR ($CDCl_3$) δ 192.0 (C1), 78.9 (C2), 18.9 (C3), 28.6 (C4), 28.7 (C5), 67.6 (C6), 148.7 (C7), 129.4 (C8). 28: ^{1}H NMR ($CDCl_3$) δ 4.90 (C_7H, dddd, J=8.2, 4.0, 4.0, 1.2 Hz), 4.54 (C_3H, dddd, J=8.5, 6.0, 3.0, 1.0 Hz), 4.42 (C_6H, ddd, J=11.2, 4.2, 4.0 Hz), 4.02 (C_2H, d, J=8.5 Hz), 2.88 (C_8H, dd, J=19.5, 4.0 Hz), 2.80 (C_8H, dd, J=19.5, 8.2 Hz), 2.48 (C_4H, m), 2.36 (C_5H, m), 2.22 (C_4H, m), 1.93 (C_5H, dddd, J=14.6, 11.2, 11.2, 1.2 Hz); ^{13}C NMR ($CDCl_3$)δ 209.9 (C1), 78.7, 80.3 (C2, C7), 24.6 (C3), 32.8, 38.1, 39.1 (C4, C5, C8), 31.6 (C6).

(Received in UK 29 December 1989)