Tetrahedron Letters,Vol.29,No.17,pp 2097-2100,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

TRICYCLIC OXONIUM-DIRECTED ADDITION: REGIOCHEMISTRY AND STEREOCHEMISTRY OF THE ELECTROPHILIC ADDITIONS TO EPOXY CYCLOALKENOLS.

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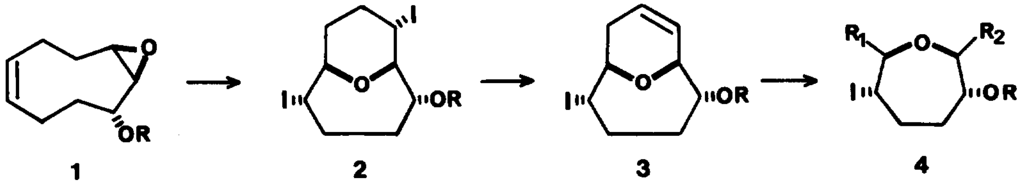
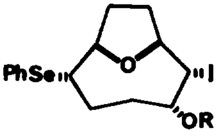
SUMMARY: The regio- and stereochemistry of electrophile-promoted transannular ring expansion of cyclo 1,5- and 1,6-epoxyalkenes and cyclo trans-1,5-bisepoxides were studied. The results are rationalized in terms of tricyclic oxonium intermediates showing the directing ability of oxygen substituents in the regio- and stereocontrol observed.

In the preceding communication,[1] we established that iodine induced cyclization of cyclic 1,2-epoxy-5-enes occurs with neighbouring group participation of the epoxide oxygen in the opening of iodonium ions to give bicyclic tetrahydrofuran and tetrahydropyran derivatives. In the model substrate studied, (Z)-trans-2,3-epoxycyclonona-6-en-1-ol (1,R=H), the isomer ratio in the formation of trisubstituted 10-oxabicyclo[5.2.1]decane derivatives strongly depends on substituents at position 1. As a consequence of these findings, a combination of current chiral epoxidation methodology using adjacent hydroxy groups, regiocontrolled iodine induced ring expansion, followed by chemoselective hydrogen iodide elimination and readily oxidative olefin cleavage, should provide a short and efficient entry into the enantioselective preparation of cis-α,α'-dialkylated β,β'-heterosubstituted oxepanes as depicted in the following scheme (Scheme 1).



Scheme 1

We now describe that this sequence of transformations with another representative electrophile gave similar results. Thus, reaction of 1,R=Ac with benzeneselenyl iodide at r.t. in CH_2Cl_2 proceeded to give after hydrolysis, a 4:6 mixture of 5,R=H and 6,R=H in a combined yield of 92%. The reaction seemed to proceed via transannular nucleophilic attack of the epoxide oxygen toward an olefin-$PhSe^{\oplus}$-π complex affording exo-cyclized benzeneselenyl ethers. To test if the 4:6 ratio of 5 and 6 came from direct cyclization or from equilibration of the selenide products, a 9:1 mixture of 5/6 was treated with 0.5 equiv of PhSeI at 25°C for 24 h in THF. There was no increase in the level of 6 on analysis by ^{13}C n.m.r. The assignment of 10-oxabicyclo[5.2.1]- and 10-oxabicyclo[4.3.1]-decane ring systems for 5 and 6 was based on their respective ^{1}H n.m.r., 2-D COSY, ^{13}C n.m.r. and ^{13}C-^{1}H COSY spectroscopy and chemical transformations. The presence of the tetrahydropyran ring in 6 was established e.g. by base treatment (DBN/ΦH/reflux/96%) of 6,R=H to give the alkenes 7 and 8 in a 2:6 ratio, respectively.



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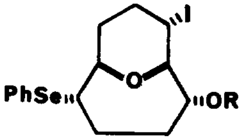

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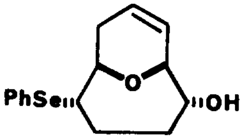

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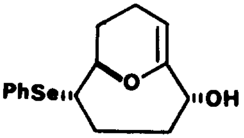

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We have explored in greater detail the stereoselectivity of electrophile-promoted transannular cyclizations of γ and δ cyclo epoxyalkenes to shed more light on this chemistry. Iodine induced cyclization experiments were conducted on compounds 9 and 15, which bear an allylic oxygen substituents, and compared with Lewis acid-catalyzed ring expanded cyclization from the bis-epoxide 20. The results of these studies are shown in Scheme 2.

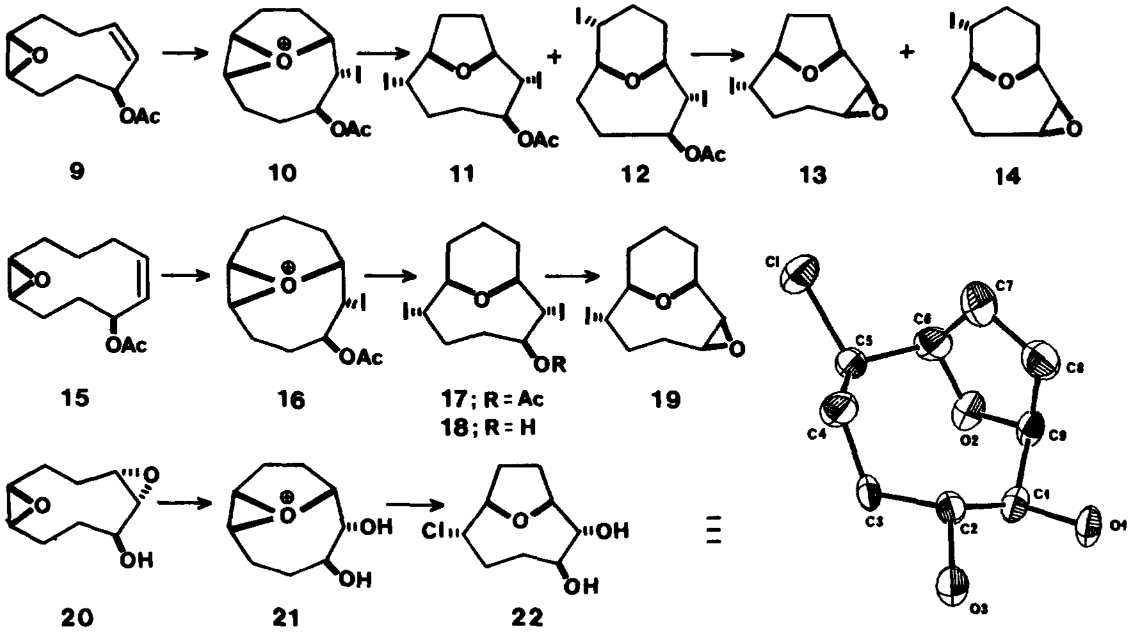
The syn-epoxy acetates 9 and 15 were respectively prepared upon treatment of (Z,Z)-1-acetoxy-cyclonona-2,6-diene[1] and (Z,Z)-1-acetoxy-cyclodeca-2,7-diene[2] with mCPBA/$NaHCO_3/CH_2Cl_2$/r.t. in 96% and 94% yields, respectively. The origin of the stereoselection observed is difficult to ascribe with confidence due to the kinetically controlled nature of the epoxidations.

The reaction of 9 with I_2/CH_2Cl_2/r.t./5 h led to a mixture of 11 and 12 (G.C.), whose relative amounts (1:1) were determined by ^{1}H n.m.r. spectroscopy of the crude mixture (87% combined yield). The mixture was treated with K_2CO_3/acetone to give a 1:1 mixture of two epoxides which were separated by chromatography and identified by spectroscopic methods as trans-6-iodo-cis-2,3-epoxy-10-oxabicyclo[5.2.1]decane (13) (43%) and trans-7-iodo-cis-2,3-epoxy-10-oxabicyclo[4.3.1]decane (14) (48%). Furthermore, compound 13 could be synthesized in 75% yield by sequential iodination of (Z,Z)-1-hydroxy-cyclonona-2,6-diene to give trans-6-iodo-10-oxabicyclo[5.2.1]deca-2-ene (85%) followed by mCPBA exo-epoxidation[3] to give 13 (88%).

Under similar conditions the reaction of 15 with I_2/CH_2Cl_2/r.t/3 h afforded exclusively the ring expanded bicyclic ether 17 (97%), which was further treated with base (K_2CO_3/acetone/r.t/2 h) to give 18 and the epoxide 19. After 12h of base treatment the epoxide 19 was obtained as a single product.

The trans-bisepoxide 20 was prepared as a single diepoxide by oxidation of 1,R=H with mCPBA(-78°C) in CH_2Cl_2(97%). Although there is excellent precedent for H$^+$-assisted polyepoxide ring expansion in acyclic systems;[4] unexpectedly, when 20 was treated with HCl/MeOH or with excess of HOAc, no bicyclic ethers were detected or were observed only to a limited extent (15%). However, treatment of 20 (6.5 mmol) with $TiCl_2(OPr^i)_2$ (13 mmol) in CH_2Cl_2 at -78°C resulted in an efficient conversion (84%) to the expanded cyclic ether 22.

The regiochemistry of the additions seems to be determined by the selectivity of attack on tricyclic oxonium intermediates such as 10, 16 and 21, which shown the directing ability of the allylic oxygen substituents to give exo-cyclized ethers. These intermediates predict that in these electrophile-mediated cyclizations the regioselectivity of the reaction does not depending on which electrophile is used, although they alone cannot explain the intercepting nucleophile regioselectivity observed in the cyclizations induced on 15 and 20. All new compounds gave spectroscopic[5] and analytical data entirely in accord with the structures shown, and in the case of 22 an X-ray cristallographic analysis[6] confirmed the expected stereochemistry for this compound and its progenitors (ORTEP plot, Figure 1).



Scheme 3

Figure 1

Further work is underway to test this rationale and to apply this methodology to the selective functionalizations of medium and large synthetic intermediates.

ACKNOWLEDGEMENTS: Support of this work by DGICT through grant PB86-0608 and by CAICYT grant 1184-84 is gratefully acknowledged. E.M. thanks the AIETI Foundation (Madrid) for a fellowship, E.A. and D.Z. thank the Spanish M.E.C. for a fellowship.

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3. The endo approach to trans-6-iodo-10-oxabicyclo[5.2.1]deca-2-ene of active oxygen to C_3,C_4 double bond might be sterically hindered by the C_6 -endo iodine atom [see ref. 1].

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5. ^{1}H- and ^{13}C-n.m.r. spectra of selected compounds follow. 5(R=H): ^{1}H-n.m.r. ($CDCl_3$) δ 3.60 (C_6H,ddd,J=12.8,3.8,3.6 Hz), 4.18 (C_3H,br s), 4.52 (C_2H,dd, J=4.0,3.5 Hz), 4.63 (C_1H and C_7H,m); ^{13}C-n.m.r. ($CDCl_3$) δ 83.8 (C-1), 47.8 (C-2), 71.8 (C-3), 33.1 (C-4), 22.3 (C-5), 48.6 (C-6), 83.6 (C-7), 25.4 (C-8), 27.7 (C-9). 6(R=H): ^{1}H-n.m.r. ($CDCl_3$) δ 3.58 (C_5H,ddd,J=12.0,3.0,3.0 Hz), 4.46 (C_2H,ddd,J=10.2,7.3,7.3 Hz), 4.31 (C_9H,br s), 4.14 (C_1H and C_6H, m); ^{13}C-n.m.r. ($CDCl_3$) δ 75.6 (C-1), 72.4 (C-2), 30.4 (C-3), 23.5 (C-4), 47.1 (C-5), 72.8 (C-6), 24.5 (C-7), 30.1 (C-8), 21.3 (C-9). 7: ^{1}H-n.m.r. ($CDCl_3$) δ3.66 (C_5H,ddd,J=9.0,5.1,3.4 Hz), 4.12 (C_2H,br s), 4.27 (C_1H and C_6H,m), 5.98 (C_9H,d,J=10.2 Hz), 6.01 (C_8H,d,J=10.2 Hz). 8: ^{1}H-n.m.r. ($CDCl_3$) δ 3.55 (C_5H,ddd,J=12.0,6.0,1.2 Hz), 4.60 (C_2H and C_6H,m), 5.89 (C_9H,ddd,J=7.6,7.6, 1.2 Hz). 9: ^{1}H-n.m.r. ($CDCl_3$) δ 1.96 (s,3H), 2.87 (br d,J=12.7 Hz,1H), 3.00 (ddd,J=9.8,4.8,4.8 Hz,1H), 5.14 (t,J=10.7 Hz,1H), 5.54 (ddd,J=10.5,10.5,3.5 Hz,1H), 5.82 (br dd,J=19.5,10.7 Hz,1H). 13: ^{1}H-n.m.r. ($CDCl_3$) δ 2.64 (C_2H,d, J=4.0 Hz), 2.96 (C_3H,m), 4.37 (C_6H,ddd,J=12.0,5.0,4.8 Hz), 4.61 (C_7H,m), 4.71 (C_1H,br d,J=6.7 Hz). 14: ^{1}H-n.m.r. ($CDCl_3$) δ 2.80 (C_2H,dd,J=4.2,2.3 Hz), 3.24 (C_3H,ddd,J=4.2,3.8,3.8 Hz), 4.01 (C_7H,ddd,J=6.2,4.4,4.4 Hz), 4.37 (C_6 H,ddd,J=11.3,6.2,2.3 Hz), 4.50 (C_1H,br d,J=4.4 Hz). 15: ^{1}H-n.m.r. ($CDCl_3$) δ 2.01 (s,3H), 2.44 (m,2H), 2.85 (dd,J=13.6,3.4 Hz,1H), 2.94 (dd,J=13.6,3.3 Hz,1H), 5.29 (ddd,J=8.8,8.8,1.4 Hz,1H), 5.55 (m,2H). 19: ^{1}H-n.m.r. ($CDCl_3$) 2.87 (C_2H,dd,J=4.2,1.8 Hz), 3.30 (C_3H,m), 4.08 (C_6H,dddd,J=8.0,4.5,3.6,0.6 Hz), 4.27 (C_7H,ddd,J=12.9,4.5,4.5 Hz), 4.37 (C_1H,ddd,J=6.7,5.6,1.8 Hz); C-n.m.r. ($CDCl_3$) δ 73.7 (C-1), 58.8 (C-2), 55.2 (C-3), 39.1 (C-4), 26.6 (C-5), 33.7 (C-6), 76.5 (C-7), 25.8 (C-8), 34.1 (C-9), 25.9 (C-10). 20: H-n.m.r. ($CDCl_3$) δ 1.81 (m,2H), 2.02 (m,1H), 2.24 (m,2H), 2.76 (m,2H), 2.90 (ddd,J=9.8,4.5,4.5 Hz,1H), 3.05 (ddd,J=9.8,4.5,4.5 Hz,1H), 3.52 (ddd,J=11.5 9.3,4.5 Hz,1H); ^{13}C-n.m.r. ($CDCl_3$) δ 21.2 (t), 22.3 (t), 22.3 (t), 30.2 (t), 56.1 (d), 56.6 (d), 57.5 (d), 60.3 (d), 68.0 (d). 22: ^{1}H-n.m.r. ($CDCl_3$)δ 1.80 (m,2H), 2.02 (m, 2H), 3.53 (m, 2H), 4.02 (m, 1H), 4.38 (br s,2H); ^{13}C-n.m.r. ($CDCl_3$)δ 24.6 (t), 25.4 (t), 31.6 (t), 33.1 (t), 61.5 (d), 75.0 (d), 77.3 (d), 81.4 (d), 82.7 (d).

6. Crystal data for compound 22: $C_9H_{15}ClO_3$, monoclinic, a=11.627(2), b=7.486(4) c=11.625(5) Å, β=109.5(1)°, V=954.0(8) Å^3, space group $P2_1/a$, Z=4. Data were measured on a Siemens AED4 diffractometer with Cu-Kα radiation (graphite monochromator) using $\omega:\theta$ scans. The structure was solved by direct methods using the MULTAN 80 program. Anisotropic temperature factors were used for the refinement of the non-H atoms. The final discrepancy index was R=0.081 for 1151 observed reflections [$I>2\sigma(I)$, $3° < 2\theta < 110°$]. The details of the crystal structure will be given in a full paper.

(Received in UK 19 February 1988)