## STEREOCHEMICAL STUDIES ON THE INTRAMOLECULAR DIELS ALDER REACTION OF FURANS WITH DOUBLY ACTIVATED DIENOPHILES.

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The stereochemical outcome of intramolecular Diels-Alder reactions of furans with Z- and E-2-ene-1,4-dione units attached by a bridging chain to C-2 of the furan results from modification of the steric demands of the bridging chain by the preference of the external activating group to adopt an *endo*- stereochemistry.

We are currently studying the intramolecular Diels-Alder reaction of furans (IMDAF),<sup>1</sup> particularly applied to the stereospecific formation of 7-6 fused carbobicycles, with a view to developing methodology for the construction of the polycyclic frameworks found in the phorbol and daphnane diterpenes.<sup>2</sup> We have previously reported that such cycloadditions, whilst frequently disfavoured at atmospheric pressure, are accelerated by the application of high (5-19 kbar) pressure.<sup>3</sup> Our initial studies using  $\alpha$ , $\beta$ -unsaturated ketone units as dienophiles demonstrated that ease of cycloaddition is dictated by the degree of substitution of the furan nucleus, length of the bridging chain, and the position of the carbonyl group; with internal activation of the dienophile (ie. the carbonyl group making up part of the bridging chain) being more efficient than external activation. In addition we found that the stereochemistry of the cycloaddition is directed by the length of the bridging chain. Closure to furnish 6-6 fused carbocycles results in cycloadducts having *exo*-stereochemistry at the bridgehead position under both kinetic and thermodynamic conditions; whereas 7-6 cycloadducts are formed initially with *exo*-bridgehead stereochemistry followed by conversion to the *endo*-cycloadducts.

We now report results of our studies on the use of Z- and E- doubly activated activated dienophiles (1) and (2) as substrates for the IMDAF, in an effort to enhance reaction rate and obtain greater stereocontrol in the cycloaddition.



Modified McMurry coupling<sup>4</sup> of 5-methyl-2-furaldehyde gave the difuryl alkene (3) in 52% yield which furnished (4a) in 35% yield on hydrogenation, accompanied by tetrahydrofuran containing by-products.<sup>5</sup> Difurans (4b, c) were prepared in 67% and 82% yield respectively by deprotonation of 5-methylfuran at C-2 with *n*-butyllithium at -78°C followed by addition of 1,3-dibromopropane or 1,4-dibromobutane (0.5 equiv.) to the resultant anion [The difuran (4a) could not be prepared in an analogous manner to (4b, c), as addition of 1,2-dibromoethane to 2-lithio-5-methylfuran resulted in formation of 2-bromo-5-methylfuran instead of alkylation]. Intermediates (4a - c) were cleaved oxidatively to the desired Z-enedione IMDAF substrates (1a - c) in 55%, 74% and 63% yield respectively, based on recovered starting material, with *metachloroperbenzoic acid* (0.5 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> at -10°C.<sup>6</sup> Use of a deficiency of peracid ensured that over-oxidation to the tetraketones was minimised (5a 4%, 5b 4%, 5c 12%).



Substrates (1a-c) showed no tendency to undergo IMDAF on storage or on heating and, in keeping with our earlier observations,<sup>3</sup> (1a) furnished no 5-6 fused ring IMDAF products under any conditions; whilst cycloaddition was observed for (1b, c) when subjected to high pressure (19 kbar,  $CH_2Cl_2$ , 20°C, 24h). After such treatment, followed immediately by hydrogenation of the crude reaction mixture in order to minimise any cycloreversion of adducts, the 6-ring precursor (1b) was found to furnish the 6-*exo*-7-*exo*-cycloadduct (6) in 27% isolated yield. This product was accompanied by 7% of (7) resulting from eliminative cleavage of the oxygen bridge of (6) and 30% of the isomeric ring opened product (8) (Figure 2). The formation of (8) can be ascribed to initial cycloaddition to the 6-*endo*-7-*endo*-adduct (9), with subsequent elimination during work-up, due to the observation of a second unstable cycloadduct in the NMR spectrum of the crude reaction mixture before hydrogenation.

The 7-6 ring IMDAF precursor (1c) furnished 7-endo-8-endo-cycloadduct (10), as the only isolable material after hydrogenation of the crude cycloaddition mixture, in 35% yield.<sup>7a</sup> Inspection of the NMR spectrum of the crude cycloaddition mixture both before or after hydrogenation did not permit identification of any other material, the remainder of the material being polymeric.



Conversion of the Z-enediones (1a - c) to the corresponding IMDAF substrates (2a - c) containing the *E*-enedione moiety was achieved with a catalytic quantity of iodine in CHCl<sub>3</sub> at room temperature. Isolation of pure (2a) and (2c) was possible in 68% and 67% yield respectively and these materials proved to be stable on prolonged storage. Indeed substrate (2a) furnished no cycloadducts under any high pressure conditions. However, under the isomerisation conditions, (2b) spontaneously underwent partial IMDAF to the 5-exo-6-endo-cycloadduct (11) with the ratio of cyclised and starting materials being *circa* 1.4 : 1.0 by NMR. All attempts to separate the components of this mixture by chromatography were frustrated by re-equilibration on silica.<sup>8</sup> However, subjecting this equilibrium mixture of (2b) and (11) to 19 kbar pressure resulted in total conversion to (11) as judged by NMR analysis of the crude reaction mixture (Figure 3). Prepared under these circumstances adduct (11) was relatively stable to cycloreversion, but traces of acid reestablished the equilibrium mixture. Reduction of this material permitted isolation of (12) in 54% yield. Alternatively, mild reduction of the equilibrium mixture (H<sub>2</sub>, 20 psi, Lindlar cat., CHCl<sub>3</sub>, 7 d) led to selective hydrogenation of the non-conjugated double bond of (11) in the presence of (2b), permitting isolation of (12) in 50% yield with no other identifiable material being obtained. Substrate (2c) after subjecting to the high pressure conditions followed by immediate hydrogenation, furnished 7-endo-8-exo-adduct (13) as the major product (25% isolated)<sup>7b</sup> accompanied by 7-exo-8-endo-adduct (14) (5% isolated)<sup>7c</sup> as the only identifiable products.



Figure 3

With our proposed IMDAF based synthetic approach to the phorbol system in mind, we investigated the potential for selective stereochemical modification of the 7-endo-8-endo-cycloadduct (10) at C-7 in an attempt to establish phorbol-type relative stereochemistry at the four stereocentres of the 7-oxabicyclo[2.2.1]heptane unit. In seeking such selectivity for bridgehead epimerisation, we were encouraged by our previous observation of regioselective eliminations of the cycloaddition products from (1b) to furnished solely C-7 epimerised material (14) as judged by NMR analysis, permitting its isolation in 84% yield. Models indicate reduced torsional strain about the ring fusion in the 7-6 system (14) compared with the 6-6 systems and this might explain the absence of any elimination in this instance. The 7-endo-8-exo-adduct (13) proved to be unaffected under the epimerisation conditions.



These stereochemical results may be interpreted as a superimposition of an *endo*- stereochemical requirement for the external activating group upon the steric demand of the bridging chain during IMDAF. In the formation of 6,6-fused carbobicycles the bridging chain favours the *exo*-configuration. Consequently the two effects work in opposition in the Z-enedione (1b); whereas in E-enedione (2b) they reinforce each other, giving high stereocontrol. Conversely, in the 7,6-system stereoselection appears dominated by the requirement of the bridging chain to have an *endo*- relationship in the final cycloadduct. This is enhanced by the demands of the external activating group in the Z-enedione (1c); whereas in the *E*-enedione (2c) they work in opposition. The regioselective epimerisation of (10) to (14) appears to be under kinetic control.

In conclusion, good stereocontrol in the IMDAF using doubly activated dienophiles is dependent upon the stereochemistry of the dienophile and the size of the carbocyclic ring formed by the bridging chain. Furthermore, in the case of 7-endo-8-endo adduct (10), regioselective epimerisation of the bridgehead position under kinetic conditions furnishes 7-exo-8-endo adduct (14), opening the way for a synthetic assault on the phorbol skeleton based upon an IMDAF strategy.

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5. All novel products isolated gave spectroscopic and microanalytical data in keeping with their assigned structures. The yields quoted are averaged over several runs but were not optimised. The relatively low yields of isolated cycloadducts are the result of extensive polymerisation under the reaction conditions; no other identifiable

material was formed. Selected data: (6)  $v_{max}$  (film) 1705 cm<sup>-1</sup>;  $\delta_{H}$  (500 MHz, CDCl<sub>3</sub>) 1.45 (3H, s), 1.63-1.91 (6H, m), 2.09-2.29 (3H, m), 2.15 (3H, s), 2.59 (1H, m), 2.61 (1H, d J 9Hz), 3.45 (1H, d J 9 Hz);  $m/_{z}$ (C.I., NH<sub>3</sub>) 240 (MNH<sub>4</sub><sup>+</sup>), 223 (MH<sup>+</sup>); Found, C, 69.96; H. 8.06, C<sub>12</sub>H<sub>19</sub>O<sub>2</sub> requires C, 70.25; H. 8.16%.

(8)  $v_{max}$  (CHCl<sub>3</sub>) 3590, 3410, 1705, 1660 cm<sup>-1</sup>;  $\delta_{H}$  (300 MHz, CDCl<sub>3</sub>) 1.33 (3H, s), 1.51 (1H, bs, removeable with D<sub>2</sub>O), 1.58 (1H, m), 1.88-2.08 (3H, m), 2.23-2.65 (6H, m), 2.48 (3H, s), 3.81 (1H,s);  $m_{z}$  (IBEI) 222 (M<sup>+</sup>), 162, 147, 134; Found, C. 70.53; H. 8.46, C<sub>12</sub>H<sub>12</sub>O<sub>2</sub> requires C. 70.25; H. 8.16%; m.p. (Et<sub>2</sub>0) 110-2°C.

147, 134; Found, C, 70.53; H, 8.46.  $C_{13}H_{18}O_3$  requires C, 70.25; H, 8.16%; m.p. (Et<sub>2</sub>0) 110-2°C. (12)  $v_{max}$  (CHCl<sub>3</sub>) 1700 cm<sup>-1</sup>;  $\delta_{H}$  (500 MHz, CDCl<sub>3</sub>) 1.46 (1H, ddt J 12 Hz, J' 5.5 Hz, J' 2.5 Hz), 1.63 (1H, ddd J 12 Hz, J' 9 Hz, J' 3.5 Hz), 1.66 (3H, s), 1.71 (1H, dt J 12 Hz, J' 3.5 Hz), 1.83 (1H, ddd, J 12 Hz, J' 9 Hz, J' 5.5 Hz), 1.91 (1H, m), 1.96-2.02 (1H, m), 2.03 (1H, ddd, J 14.5 Hz, J' 13 Hz, J' 4 Hz), 2.15 (1H, m), 2.26 (3H, s), 2.32 (1H, m), 2.47 (1H, m), 2.99 (1H, d, J 4.5 Hz), 3.53 (1H, dd, J 4.5 Hz, J' 2.5 Hz); m/z (IBEI) 222 (M<sup>+</sup>), 180, 179, 151, 123, 108, 43; Found, C, 70.20; H, 8.45.  $C_{13}H_{18}O_3$  requires C, 70.25; H, 8.16%; m.p. (pentane) 58°C 6. P. D. Williams and E. LeGoff, *Tetrahedron Lett.*, 1985, 1367.

7. All data for crystallographic analyses were measured  $(2\theta_{max} = 150^{\circ}C)$  on and Enraf Nonius CAD4 diffractometer using Cu-K<sub>a</sub> radiation and  $\omega$  - 2 $\theta$  scans. Structures were solved by direct methods and refined by least squares using the CRYSTAL package. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Centre.

(a) (10): Crystal data:  $C_{14}H_{20}O_3$ , M = 236.31, orthorhombic:  $P2_12_12_1$ , a = 9.469; b = 9.652; c = 13.949 Å, U = 1274.1 Å<sup>3</sup>, Z = 4,  $D_c = 1.232$  g cm<sup>-3</sup>, F(000) = 512,  $\mu$ (Cu  $K_{\alpha}$ ) = 6.498 cm<sup>-1</sup>. 1479 Independent reflections with I > 307(I) were used in the analysis. Final R = 4.9, final Hamiltonian weighted R = 6.4.

(b) (13): Crystal data:  $C_{14}H_{20}O_3$ , M = 236.31, monoclinic :  $P2_1/n$ , a = 10.474; b = 16.950; c = 7.357 Å,  $\beta = 90.87^\circ$ , U = 1306 Å<sup>3</sup>, Z = 4,  $D_c = 1.202$  g cm<sup>-3</sup>, F(000) = 512,  $\mu(Cu K_{\alpha}) = 6.339$  cm<sup>-1</sup>. 2181 Independent reflections with  $I>3\sigma(I)$  were used in the analysis. Final R = 5.8, final Hamiltonian weighted R = 7.8. (c) (14): Crystal data:  $C_{14}H_{20}O_3$ , M = 236.31, orthorhombic : Pcab, a = 10.775; b = 12.340; c = 19.297 Å, U = 2565.8 Å<sup>3</sup>, Z = 8,  $D_c = 1.224$  g cm<sup>-3</sup>, F(000) = 1024,  $\mu(Cu K_{\alpha}) = 6.454$  cm<sup>-1</sup>. 2418 Independent reflections with  $I>3\sigma(I)$  were used in the analysis. Final R = 6.1, final Hamiltonian weighted R = 7.8.



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