

## Synthetic Approaches to Phorbols *via* the Intramolecular Diels–Alder Reaction of Furans: Stereocontrol of the *A–B* Ring Junction

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A carbocycle (**9**) related to the phorbol skeleton has been constructed *via* low temperature intramolecular Diels–Alder reaction of furans at ambient pressure, permitting control of the relative stereochemistry between the *trans*-fused *A–B* ring junction and the stereocentres established in the 7-oxabicyclo[2.2.1]hept-2-ene moiety of the adduct.

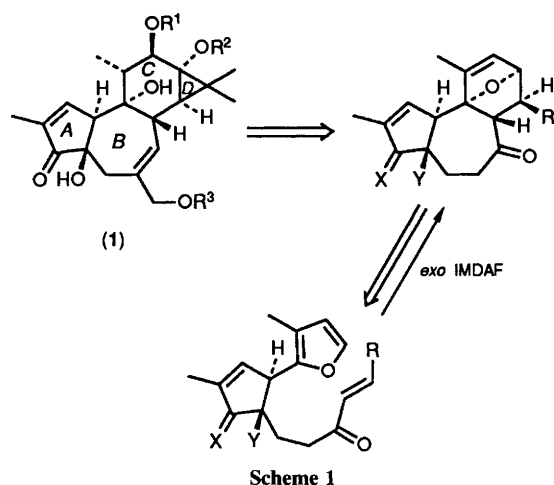
We have been conducting a series of investigations<sup>1a–c</sup> into the scope and limitations of the intramolecular Diels–Alder reaction of furans (IMDAF)<sup>2</sup> with the aim of applying the methodology to the synthesis of the polycyclic frameworks found in the phorbol diterpenes (**1**),<sup>3</sup> following a general approach outlined retrosynthetically in Scheme 1.

Our conclusions on the high pressure mediated IMDAF of simple model systems leading to 6-6 carbocycles have been confirmed by similar subsequent work by Keay.<sup>4</sup> Additionally we have shown that high pressure (10–20 kbar<sup>†</sup>) is necessary, and the presence of internal activation of the dienophile desirable, for efficient cycloaddition of precursors leading to

7-6 fused carbocycles; demonstrating the generality of our initial conclusions<sup>1a</sup> that the *exo*-cycloadducts are the kinetically preferred products under these circumstances. However, whilst we had demonstrated control of relative stereochemistry about the periphery of the newly formed 7-oxabicyclo[2.2.1]hept-2-ene moiety in simple polymethylene bridged models, the questions still remained regarding the possibility of influencing the relative stereochemistry at the *A–B* ring junction of a potential phorbol precursor molecule. In this communication we report the successful realisation of our aim of achieving such stereocontrol.

Our model substrate for study was prepared according to the reaction sequence shown in Scheme 2. Following the procedure of Lipschutz,<sup>5</sup> lithium di(2-furyl)cyanocuprate was reacted with 3-allylcyclopent-2-enone in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to give a *ca.* 3:1 mixture of the *trans*- and

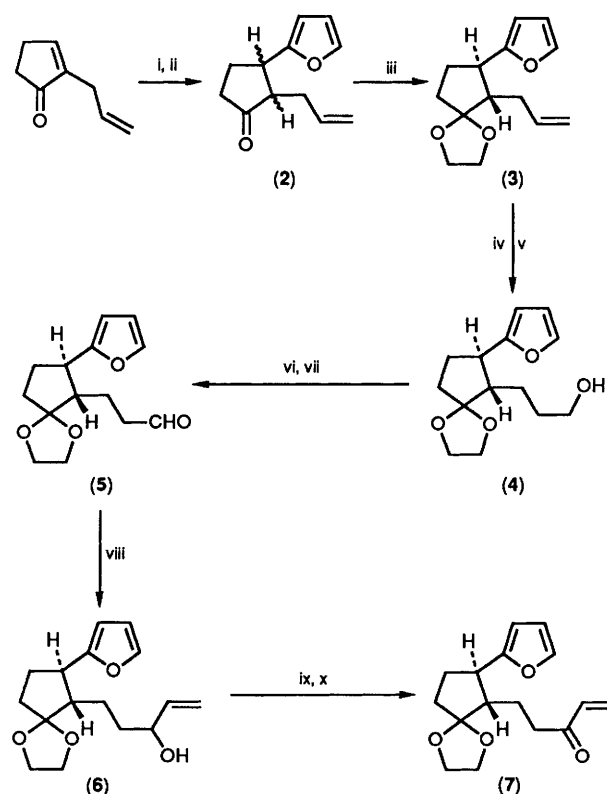
<sup>†</sup> 1 bar =  $10^5$  Pa.



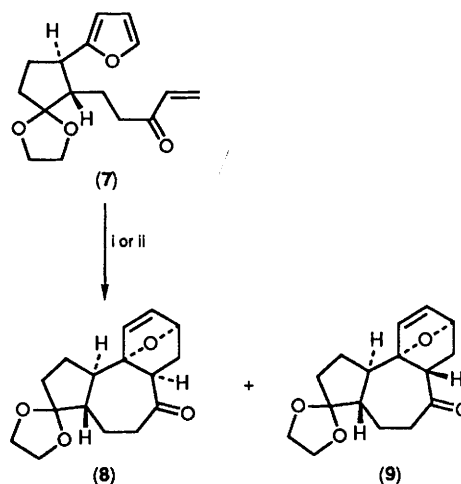
Scheme 1

*cis*-conjugate addition products (2).<sup>‡</sup> After epimerisation with NaOMe/MeOH, the diastereoisomeric ratio was changed to *ca.* 9 : 1 in favour of the *trans*-adduct which could be isolated in 28% yield after chromatography, although the crude product, obtained in 54% yield, was suitable for further elaboration. Conversion of *trans*-(2) to the ethylene ketal (3), followed by reaction of the terminal alkene with diborane and oxidative work-up gave the alcohol (4) in 68% purified yield over the two steps. Swern oxidation<sup>6</sup> of (4) gave the unstable aldehyde (5) which was not purified but reacted immediately with vinyl magnesium bromide to furnish the allylic alcohol (6) in 62% purified yield from (4). The alcohol (6) was oxidised using Swern conditions to give the crude IMDAF precursor (7) in quantitative yield.

However, attempts at removing traces of impurities in the crude material by chromatography on silica led to a marked alteration of the sample and the appearance of new peaks in the NMR spectrum indicating the presence of cycloaddition products.<sup>7</sup> The preferred means of effecting this transformation involved stirring a solution of (7) in chloroform in the presence of 20 times its weight of silica at room temperature for 16 h. At this stage, the reaction mixture could be shown to consist of starting material and two new



Scheme 2. Reagents and conditions: i, lithium di(2-furyl)cyanocuprate, BF<sub>3</sub>·Et<sub>2</sub>O, tetrahydrofuran (THF), -78°C; ii, NaOMe, MeOH, room temp., 54% crude *trans*-(2), 28% pure; iii, HOCH<sub>2</sub>CH<sub>2</sub>OH, H<sup>+</sup>, toluene, reflux, quant.; iv, B<sub>2</sub>H<sub>6</sub>, THF; v, H<sub>2</sub>O<sub>2</sub>, aq. NaOH, 68%; vi, (COCl)<sub>2</sub>, dimethyl sulphoxide (DMSO), CH<sub>2</sub>Cl<sub>2</sub>, -50°C; vii, Et<sub>3</sub>N, quant. (crude); viii, CH<sub>2</sub>=CHMgBr, THF, 64%; ix, (COCl)<sub>2</sub>, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -50°C; x, Et<sub>3</sub>N, quant. (crude).



Scheme 3. Reagents and conditions: i, SiO<sub>2</sub>, CHCl<sub>3</sub>, room temp., 16 h [(7):(8):(9) *ca.* 1:2:1]; ii, -12°C, 7 days [(8):(9) *ca.* 1:2].

components in the ratio *ca.* 1 : 2 : 1 (Scheme 3). All attempts to separate these components using chromatography failed; in all instances leading to re-establishment of the equilibrium mixture of components.

The major unknown was obtained in pure form by crystallisation from the crude mixture on standing at -12°C; permitting its elucidation as the *endo*-cycloadduct (8), initially on the basis of spectroscopic analysis,<sup>‡</sup> but later confirmed by

<sup>‡</sup> All novel compounds isolated gave spectroscopic data in accord with their assigned structures. With the exception of the aldehyde (5) and IMDAF precursor (7) all gave acceptable combustion analyses. Selected spectroscopic data: (7)  $\nu_{\max}$  (film) 1680 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 1.55–2.10 (6 H, m), 2.15–2.30 (1 H, m), 2.40–2.67 (2 H, m), 2.80–3.00 (1 H, m), 3.85–4.05 (4 H, m), 5.74 (1 H, dd, *J* 9 Hz, *J'* 1.5 Hz), 6.07 (1 H, d, *J* 1.5 Hz), 6.10–6.40 (3 H, m), 7.33 (1 H, bs);  $\delta_{\text{C}}$  (50 MHz; CDCl<sub>3</sub>) 22.0 (t), 27.8 (t), 35.2 (t), 37.3 (t), 42.3 (d), 49.9 (d), 64.3 (t), 64.4 (t), 104.7 (d), 110.2 (d), 127.7 (t), 136.7 (d), 141.1 (d), 157.9 (s), 201.0 (s).

(8)  $\nu_{\max}$  (CHCl<sub>3</sub>) 1695 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) 1.50–1.62 (1 H, m), 1.81 (1 H, m), 1.88–1.95 (6 H, m), 1.99 (1 H, ddd, *J* 11 Hz, *J'* 7 Hz, *J''* 4 Hz), 2.26 (1 H, m), 2.44–2.51 (1 H, m), 2.63 (1 H, dt, *J* 4 Hz, *J'* 1.5 Hz), 3.20 (1 H, dd, *J* 6 Hz, *J'* 3 Hz), 3.90–4.00 (4 H, m), 4.97 (1 H, dd, *J* 5 Hz, *J'* 1.5 Hz), 5.98 (1 H, d, *J* 5 Hz), 6.42 (1 H, dt, *J* 5 Hz, *J'* 1.5 Hz);  $\delta_{\text{C}}$  (50 MHz; CDCl<sub>3</sub>) 21.3 (t), 23.9 (t), 28.5 (t), 34.9 (t), 42.3 (t), 47.9 (d), 55.2 (d), 64.4 (t), 65.1 (t), 78.9 (d), 91.8 (s), 117.2 (s), 129.6 (d), 138.4 (d), 209.0 (s); *m/z* (DCI) 294 (MNH<sub>4</sub><sup>+</sup>), 277 (MH<sup>+</sup>), 259, 206, 99; m.p. (ether) 115°C.

(9)  $\nu_{\max}$  (CHCl<sub>3</sub>) 1695 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) 1.38 (1 H, dd, *J* 11 Hz, *J'* 7 Hz), 1.63–1.70 (3 H, m), 1.77–1.85 (2 H, m), 1.90–1.97 (1 H, m), 2.00–2.11 (1 H, m), 2.23 (1 H, dt, *J* 10.5 Hz, *J'* 3 Hz), 2.47 (1 H, dt, *J* 11.5 Hz, *J'* 5 Hz), 2.50–2.63 (2 H, m), 2.88 (1 H, dd, *J* 7 Hz, *J'* 4 Hz), 3.98 (4 H, m), 5.08 (1 H, dd, *J* 4 Hz, *J'* 1.5 Hz), 6.38 (1 H, d, *J* 6 Hz), 6.41 (1 H, m); *m/z* (CI) 294 (MNH<sub>4</sub><sup>+</sup>), 277 (MH<sup>+</sup>); m.p. 108–112°C.

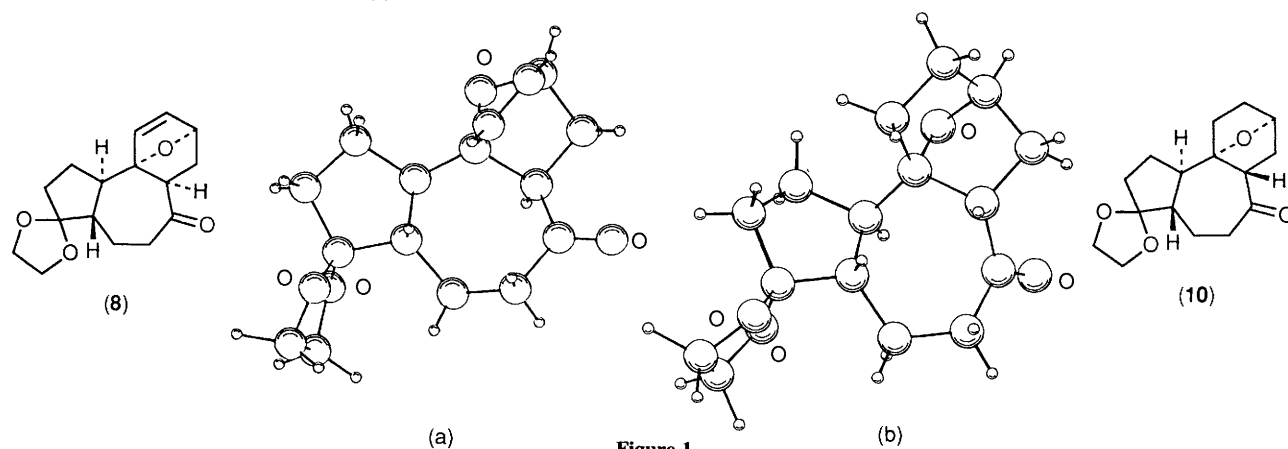


Figure 1

X-ray crystallographic analysis [Figure 1(a)].§ The fact that the *endo*-cycloadduct is more stable with regard to cycloreversion than the *exo*-material is totally in accordance with our observations in the previous model studies.<sup>1a,b</sup> This reaction is noteworthy as the first example of the formation of a 6,7-carbocyclic system by IMDAF without recourse to the application of ultra-high pressures. This increased ease of the cycloaddition compared with the model systems is in line with the documented accelerative effect of branching on the tethering chain upon the IMDAF in other substrates.<sup>8</sup>

Although a pure sample of the minor product could not be obtained at this stage due to its lability, spectroscopic analysis of the crude mixture indicated that it was a cycloadduct isomeric with (8). Gratifyingly it was found that storage of the neat IMDAF precursor (7) at  $-12^{\circ}\text{C}$  for 16 days resulted in the unknown cycloadduct (9) being formed as the major product [ca. 1 : 2, (8) : (9)] and crystallising from the mixture as pure material. Spectroscopic analysis of the pure material permitted its assignment as the *exo*-adduct (9). This was confirmed by X-ray crystallographic analysis of the dihydro derivative (10) [Figure 1(b)].<sup>8</sup> This result can be rationalised by the cycloaddition following the kinetically determined pathway to form *exo*-cycloadduct (9) preferentially, which crystallises out of the mixture and does not re-equilibrate.

The two cycloadducts (8) and (9) thus differ in stereochemistry only at the C–D ring junction (which we have shown to be epimerisable, favouring *exo*-stereochemistry<sup>1c</sup>) and the kinetically favoured *exo*-cycloadduct (9) possesses the correct phorbol relationship at all five stereocentres. Of fundamental importance for our future synthetic efforts is the control of the stereochemical relationship between the A–B ring junction and the 7-oxabicyclo[2.2.1]hept-2-ene moiety in the cycloadducts. This, coupled with the greater ease of IMDAF when the tethering chain possesses additional substituents, augers well

§ Crystal data for (8):  $\text{C}_{16}\text{H}_{20}\text{O}_4$ ,  $M = 276$ , monoclinic,  $P2_1/a$ ,  $a = 7.228$ ,  $b = 31.809$ ,  $c = 5.941$  Å,  $\beta = 102.2^{\circ}$ ,  $U = 1335$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.375$  g cm<sup>-3</sup>,  $F(000) = 592$ ,  $\mu(\text{Cu-K}\alpha) = 7.548$  cm<sup>-1</sup>. 1678 Independent reflections with  $I > 3\sigma(I)$  were used in the analysis. Final  $R = 5.9$ , final Hamiltonian weighted  $R = 7.1$ .

Crystal data for (10):  $\text{C}_{16}\text{H}_{22}\text{O}_4$ ,  $M = 276$ , monoclinic,  $P2_1/n$ ,  $a = 5.665$ ,  $b = 7.839$ ,  $c = 31.567$  Å,  $\beta = 93.7^{\circ}$ ,  $U = 1399$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.312$  g cm<sup>-3</sup>,  $F(000) = 592$ ,  $\mu(\text{Cu-K}\alpha) = 7.238$  cm<sup>-1</sup>. 1970 Independent reflections with  $I > 3\sigma(I)$  were used in the analysis. Final  $R = 4.9$ , final Hamiltonian weighted  $R = 6.2$ .

Data for crystallographic analyses were measured ( $2\theta_{\text{max}} = 150^{\circ}$ ) on an Enraf-Nonius CAD 4 diffractometer using Cu-K $\alpha$  radiation and  $\omega$ - $2\theta$  scans. Structures were solved by direct methods and refined by least squares using the CRYSTAL package. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors Issue No. 1.

for the application of this approach to the construction of the phorbol framework.

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