

## Synthetic Approaches to Phorbols *via* the Intramolecular Diels–Alder Reaction of Furans: Influence of the Dienophile upon the Stereochemical Control

Laurence M. Harwood,<sup>\*a</sup> Brian Jackson,<sup>b</sup> Geraint Jones,<sup>c</sup> Keith Prout,<sup>b</sup> Royston M. Thomas,<sup>a</sup> and Fiona J. Witt<sup>a</sup>

<sup>a</sup> Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

<sup>b</sup> Chemical Crystallography Laboratory, University of Oxford, Parks Road, Oxford OX1 3PD, U.K.

<sup>c</sup> ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield SK10 4TG, U.K.

A carbocyclic (13) having the same relative stereochemistry as the phorbols at 6 centres has been constructed *via* stereoselective intramolecular Diels–Alder reaction of furans (IMDAF) of a precursor (7) possessing a *Z*-vinylogous ketoester followed by selective epimerisation at C-10 of the initial cycloadduct (11); whereas the corresponding *E*-isomer (8) or alkyne (3) show no stereoselection in the IMDAF.

In the preceding communication<sup>1</sup> we have described the stereoselective construction of a carbocyclic compound with the goal of developing a synthetic approach to the phorbol diterpenes.<sup>2</sup> The key step involves an intramolecular Diels–Alder reaction of a furan diene (IMDAF)<sup>3</sup> in which the cycloaddition stereochemistry has been shown to be sensitive to the stereochemistry at the points of attachment of the additional 5-membered ring to the bridging chain. Following our earlier model studies,<sup>4a–c</sup> we expected the use of a doubly activated dienophile to result in an even higher degree of stereochemical control, together with increased propensity for cycloaddition. Furthermore, the model studies<sup>4c</sup> predicted that the desired phorbol stereochemistry at 4 sites associated with the oxabicyclo[2.2.1]heptene moiety would be achieved by *endo*-cycloaddition of a substrate possessing a *Z*-dienophile, followed by selective epimerisation at C-10 of the initial cycloadduct (Scheme 1).

The synthesis of the IMDAF substrate commenced with the known aldehyde (1)<sup>1</sup> which was reacted with the lithiated derivative of ethyl propiolate to furnish the propynylic alcohol (2) as a 1 : 1 mixture of diastereoisomers at the newly formed asymmetric centre in 42% isolated yield [ $\nu_{\max}$  (film) 3420,

2240, 1710  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  4.43 (1 H, m, CH–O)] (Scheme 2).<sup>†</sup> Attempts to oxidise this alcohol with activated  $\text{MnO}_2$  gave none of the expected product (3) but resulted in a material from which the two cycloadducts (4) [ $\nu_{\max}$  ( $\text{CHCl}_3$ ) 1725, 1690, 1630  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  5.64 (1 H, d,  $J$  1.5 Hz, 12-H), 7.19 (1 H, d,  $J$  5 Hz, 14-H), 7.32 (1 H, dt,  $J$  5 Hz,  $J'$  1.5 Hz)] and (5) [ $\nu_{\max}$  ( $\text{CHCl}_3$ ) 1715, 1700, 1650  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  5.66 (1 H, d,  $J$  2 Hz, 12-H), 6.82 (1 H, d,  $J$  5 Hz, 14-H), 7.32 (1 H, dt,  $J$  5 Hz,  $J'$  2 Hz, 13-H)] were isolated in 5 and 7% yield respectively as the only monomeric products. It would appear that the decreased steric demand and increased dienophilicity of the alkyne in (3)

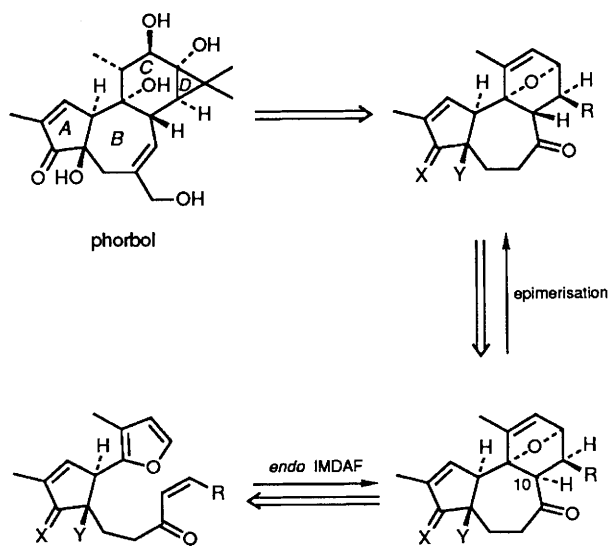
<sup>†</sup> All novel compounds isolated gave spectroscopic data in accord with their assigned structures. With the exception of (7) and (8) all gave acceptable combustion analyses. *Selected spectroscopic data:* (7)  $\nu_{\max}$  (film) 1720, 1625  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.27 (3 H, t,  $J$  7 Hz), 1.64–2.09 (6 H, m), 2.19 (1 H, m), 2.55 (2 H, m), 2.92 (1 H, m), 3.84–4.03 (4 H, m), 3.19 (2 H, q,  $J$  7 Hz), 5.95 (1 H, d,  $J$  12 Hz), 6.05 (1 H, d,  $J$  1.5 Hz), 6.28 (1 H, dd,  $J$  1.5 Hz,  $J'$  1 Hz), 6.38 (1 H, d,  $J$  12 Hz), 7.32 (1 H, d,  $J$  1.5 Hz);  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 13.7 (q), 21.3 (t), 27.7 (t), 35.2 (t), 40.4 (t), 42.2 (t), 42.2 (d), 49.7 (d), 60.9 (t), 64.2 (t), 64.4 (t), 104.8 (d), 110.2 (d), 124.7 (d), 141.2 (d), 141.6 (d), 157.8 (s), 165.5 (s), 203.8 (s);  $m/z$  (CI) 366 ( $\text{MNH}_4^+$ ), 349 ( $\text{MH}^+$ ), 304.

(8)  $\nu_{\max}$  (film) 1725, 1705, 1635  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.33 (1 H, t,  $J$  7 Hz), 1.62–2.08 (6 H, m), 2.22 (1 H, m), 2.57 (2 H, m), 3.82–4.05 (4 H, m), 4.27 (2 H, q,  $J$  7 Hz), 6.07 (1 H, d,  $J$  1.5 Hz), 6.29 (1 H, dd,  $J$  1.5 Hz,  $J'$  1 Hz), 6.59 (1 H, d,  $J$  16 Hz), 6.97 (1 H, d,  $J$  16 Hz), 7.34 (1 H, d,  $J$  1.5 Hz);  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 13.9 (q), 21.6 (t), 27.7 (t), 35.1 (t), 39.1 (t), 42.2 (d), 49.6 (d), 61.2 (t), 64.2 (t), 64.3 (t), 104.8 (d), 110.2 (d), 117.2 (s), 130.5 (d), 139.6 (d), 141.2 (d), 157.7 (s), 165.8 (s), 200.0 (s);  $m/z$  (CI) 366 ( $\text{MNH}_4^+$ ), 349 ( $\text{MH}^+$ ).

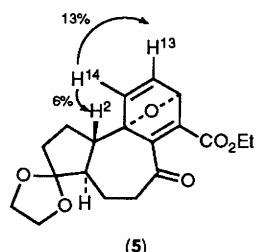
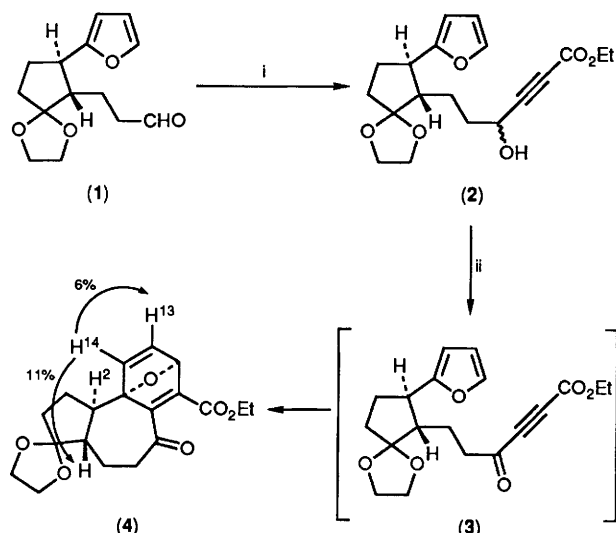
(10) M.p. 79–80 °C;  $\nu_{\max}$  ( $\text{CHCl}_3$ ) 1725, 1695  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz;  $\text{C}_6\text{D}_6$ ) 0.88 (3 H, t,  $J$  7 Hz), 0.96 (1 H, ddd,  $J$  13 Hz,  $J'$  9 Hz,  $J''$  4 Hz), 1.26 (1 H, ddt,  $J$  13 Hz,  $J'$  4.5 Hz,  $J''$  2.5 Hz), 1.37 (1 H, ddd,  $J$  12 Hz,  $J'$  9 Hz,  $J''$  4.5 Hz), 1.44–1.52 (3 H, m), 1.58–1.63 (2 H, m), 1.70–1.74 (2 H, m), 1.86–1.92 (1 H, m), 2.03 (1 H, m), 2.33 (1 H, dt,  $J$  19.5 Hz,  $J'$  3.5 Hz), 2.72 (1 H, ddd,  $J$  13 Hz,  $J'$  10 Hz,  $J''$  8 Hz), 3.38–3.46 (4 H, m), 3.62 (1 H, d,  $J$  4.5 Hz), 3.85 (1 H, dd,  $J$  4.5 Hz,  $J'$  2.5 Hz), 3.89 (2 H, m), 4.80 (1 H, d,  $J$  5.5 Hz);  $m/z$  (EI) 350 ( $\text{M}^+$ ), 99.

(12) M.p. 183–187 °C;  $\nu_{\max}$  ( $\text{CHCl}_3$ ) 1730, 1715  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz;  $\text{C}_6\text{D}_6$ ) 0.93–1.00 (2 H, m), 1.11 (3 H, t,  $J$  7 Hz), 1.40–1.61 (6 H, m), 1.67 (1 H, m), 1.73–1.83 (2 H, m), 2.09 (1 H, ddd,  $J$  12.5 Hz,  $J'$  11 Hz,  $J''$  6.5 Hz), 2.31 (1 H, ddd,  $J$  10 Hz,  $J'$  8.5 Hz,  $J''$  5 Hz), 2.35 (1 H, d,  $J$  9 Hz), 2.40 (1 H, dt,  $J$  12.5 Hz,  $J'$  5 Hz), 2.95 (1 H, d,  $J$  9 Hz), 3.33–3.46 (4 H, m), 4.21 (2 H, q,  $J$  7 Hz), 4.93 (1 H, d,  $J$  5 Hz);  $m/z$  (EI) 350 ( $\text{M}^+$ ), 99.

(13) M.p. 112–114 °C;  $\nu_{\max}$  ( $\text{CHCl}_3$ ) 1725, 1705  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz;  $\text{C}_6\text{D}_6$ ) 0.86 (3 H, t,  $J$  7 Hz), 1.32 (1 H, ddd,  $J$  10.5 Hz,  $J'$  7 Hz,  $J''$  2 Hz), 1.46–1.72 (9 H, m), 1.76–1.82 (1 H, m), 1.93 (1 H, ddd,  $J$  10.5 Hz,  $J'$  9 Hz,  $J''$  4 Hz), 2.11 (1 H, ddd,  $J$  13 Hz,  $J'$  11 Hz,  $J''$  6 Hz), 2.30 (1 H, ddd,  $J$  10.5 Hz,  $J'$  9 Hz,  $J''$  6 Hz), 2.52 (1 H, dt,  $J$  13 Hz,  $J'$  6 Hz), 3.33–3.47 (4 H, m), 3.37 (1 H, d,  $J$  7 Hz), 3.79–3.90 (2 H, m), 4.19 (1 H, ddd,  $J$  7 Hz,  $J'$  5 Hz,  $J''$  2 Hz), 4.60 (1 H, t,  $J$  5 Hz);  $m/z$  (EI) 350 ( $\text{M}^+$ ), 99.



Scheme 1

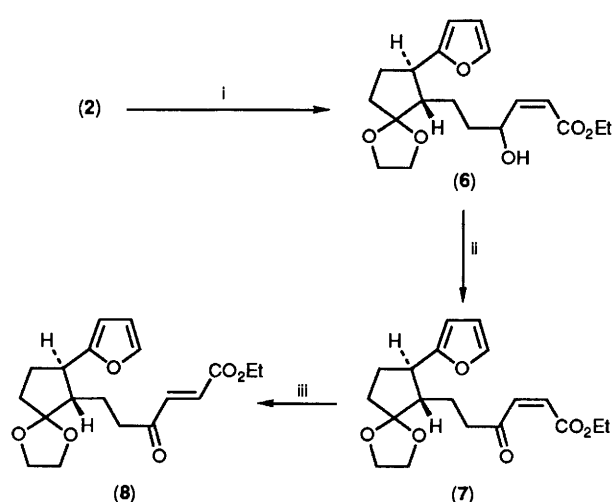


**Scheme 2.** Reagents and conditions: i,  $\text{LiC}\equiv\text{CCO}_2\text{Et}$ , tetrahydrofuran (THF),  $-70^\circ\text{C}$ ; ii,  $\text{MnO}_2$ ,  $\text{CCl}_4$ , room temp. (percentage figures represent NOE difference results).

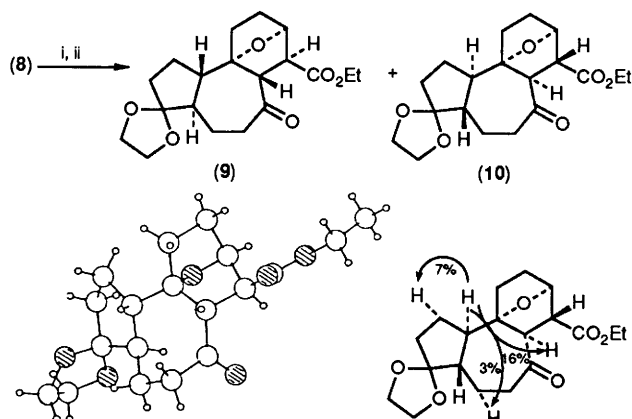
results in indiscriminate reaction where all control of the relative stereochemistry between the *A*-*B* ring junction and the oxygen bridge is lost. The relative stereochemistry of each cycloadduct was demonstrated by NOE difference measurements. In addition, the NMR spectrum of (4) showed the presence of a 5 bond coupling (1.5 Hz) between H-2 and H-13<sup>5</sup> indicating a high degree of coplanarity of the 6 connecting atoms.<sup>6</sup>

Consequently, the propynyl alcohol (2) was first reduced to the *Z*- $\alpha,\beta$ -unsaturated ester (6) with Lindlar catalyst in 67% purified yield. The geometry of the alkene could be inferred from the appearance of two signals in the NMR spectrum at  $\delta$  5.81 and 6.83 showing a mutual coupling constant of 12 Hz. Subsequent oxidation of this alcohol with activated  $\text{MnO}_2$  proceeded as expected to furnish the desired *Z*-configured vinylogous ketoester (7) in 65% isolated yield [ $\nu_{\text{max}}$  ( $\text{CCl}_4$ ) 1720, 1705  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  5.95 (1 H, d, *J* 12 Hz), 6.38 (1 H, d, *J* 12 Hz)]<sup>†</sup> which was rapidly (<30 s) and quantitatively converted by treatment with a trace of iodine to the *E*-isomer (8) [ $\delta_{\text{H}}$  6.59 (1 H, d, *J* 16 Hz), 6.97 (1 H, d, *J* 16 Hz)]<sup>†</sup> (Scheme 3).

In keeping with our observations of other *E*-enedione systems,<sup>4c</sup> (8) was found to undergo IMDAF on stirring with silica to furnish an inseparable mixture of starting material and cycloadducts which underwent re-equilibration during all attempts at purification. However, exposure of (8) to a pressure of 19 kbar<sup>‡</sup> for 5 min resulted in almost total



**Scheme 3.** Reagents and conditions: i,  $\text{H}_2$  (1 atm), Lindlar cat.; ii, activated  $\text{MnO}_2$  (excess),  $\text{CCl}_4$ , room temp., 15 min; iii,  $\text{I}_2$ ,  $\text{CHCl}_3$ , 15 min.

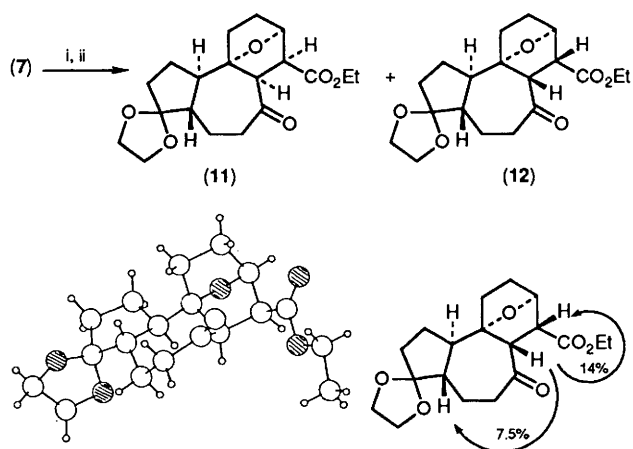


**Scheme 4.** Reagents and conditions: i, 19 kbar,  $\text{CH}_2\text{Cl}_2$ , 5 min; ii,  $\text{H}_2$  (15 atm),  $\text{EtOAc}$ ,  $\text{Pd/BaSO}_4$ . *X*-Ray structure of (9) and NOE enhancements for (10).

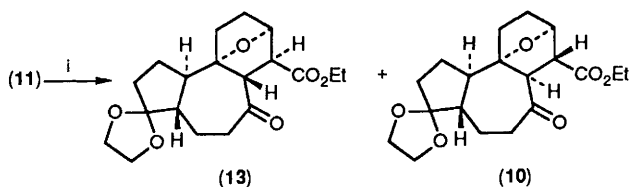
conversion to two new products, and hydrogenation of this crude mixture permitted isolation of reduced cycloadducts (9) and (10) in 11 and 48% yields respectively (Scheme 4). The minor product (9) furnished crystals suitable for *X*-ray crystallographic analysis<sup>§</sup> and the stereochemistry of the major product (10) was deduced from a combination of COSY and NOE difference experiments in  $\text{C}_6\text{D}_6$  at 500 MHz.<sup>†</sup>

<sup>§</sup> *Crystal data* for (9):  $\text{C}_{19}\text{H}_{26}\text{O}_6$ ,  $M = 350.4$ , triclinic,  $P\bar{1}$ ,  $a = 10.801$ ,  $b = 11.821$ ,  $c = 14.282$  Å,  $\alpha = 78.4$ ,  $\beta = 80.0$ ,  $\gamma = 89.8^\circ$ ,  $U = 1757$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.325$  g  $\text{cm}^{-3}$ ,  $F(000) = 752$ ,  $\mu(\text{Cu-K}\alpha) = 7.681$   $\text{cm}^{-1}$ . 6630 Independent reflections with  $I > 3\sigma(I)$  were used in the analysis. Final  $R = 6.7$ , final Hamiltonian weighted  $R = 7.0$ . *Crystal data* for (11):  $\text{C}_{19}\text{H}_{26}\text{O}_6$ ,  $M = 350.4$ , monoclinic,  $P2_1/c$ ,  $a = 5.870$ ,  $b = 15.131$ ,  $c = 19.610$  Å,  $\beta = 93.7^\circ$ ,  $U = 1736$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.339$  g  $\text{cm}^{-3}$ ,  $F(000) = 752$ ,  $\mu(\text{Cu-K}\alpha) = 7.764$   $\text{cm}^{-1}$ . 3562 Independent reflections with  $I > 3\sigma(I)$  were used in the analysis. Final  $R = 5.5$ , final Hamiltonian weighted  $R = 8.1$ . Data for crystallographic analyses were measured ( $2\theta_{\text{max}} = 150^\circ$ ) on an Enraf-Nonius CAD 4 diffractometer using  $\text{Cu-K}\alpha$  radiation and  $\omega$ - $2\theta$  scans. Structures were solved using SHELXS (9) or MULTAN (11) 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 Centre. See Notice to Authors, Issue No. 1.

<sup>‡</sup> 1 bar =  $10^5$  Pa.



**Scheme 5.** Reagents and conditions: i, 19 kbar,  $\text{CH}_2\text{Cl}_2$ , 5 min; ii,  $\text{H}_2$  (15 atm), EtOAc, Pd/BaSO<sub>4</sub>. X-Ray structure of (11) and NOE enhancements for (12).



**Scheme 6.** Reagents and conditions: i, NaOEt (cat.), EtOH, room temp.

The *Z*-isomer (7) behaved similarly to (8) on treatment with silica and exposure to 19 kbar pressure for 5 min. Thus, the crude mixture obtained from the high pressure treatment of (7) was hydrogenated and two cycloadducts (11) and (12) were isolated in 38 and 18% yields respectively (Scheme 5). The major cycloadduct (11) was analysed by X-ray crystallography<sup>§</sup> and the stereochemistry of the minor cycloadduct (12) was deduced from COSY and NOE difference experiments.<sup>†</sup> Both materials have stereochemistry differing from that corresponding to phorbol at one site; C-10 for (11) and C-11 for (12).

In keeping with our earlier studies,<sup>4c</sup> selective stereochemical inversion of (11) at C-10 proved possible under equilibrating conditions despite the fact that both C-10 and C-11 are potentially epimerisable positions. Treatment of (11) in

ethanol at 20 °C with a catalytic quantity of NaOEt resulted in conversion to two new products in a 5 : 1 ratio (Scheme 6). The minor product was identified as (10) on the basis of GC-MS and NMR comparison with the material obtained as the major product from IMDAF of the *E*-configured substrate (8). The stereochemistry of the major product (13) was demonstrated by COSY and NOE difference experiments.<sup>†</sup> Thus selective epimerisation had occurred at C-10 of cycloadduct (11) to furnish (13), possessing relative stereochemistry corresponding to phorbol at all 6 asymmetric centres.

In conclusion, we have demonstrated that IMDAF of a substrate possessing a *Z*-vinyllogous ketoester as dienophile, followed by selective epimerisation at one centre in the cycloadduct permits the construction of a carbocycle (13) in which the relative stereochemistry at all asymmetric centres agrees with that required for the construction of phorbol derivatives. Further studies are in progress to refine this approach to our ultimate goal.

We thank the SERC for a Quota award (to F. J. W.), SERC and ICI Pharmaceuticals for a CASE award (to R. M. T.), and Dr A. E. Derome and Mrs E. McGuiness for valuable assistance in obtaining the NMR spectra.

Received, 17th January 1990; Com. 0/00272K

## References

- L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas, and D. Watkin, *J. Chem. Soc., Chem. Commun.*, 1990, preceding communication.
- 'Naturally Occurring Phorbol Esters,' ed. F. J. Evans, C. R. C. Press, 1986. For the first reported total synthesis of phorbol see: P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger, R. S. Wilhelm, and P. D. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 8957; P. A. Wender, H. Y. Lee, R. S. Wilhelm, and R. S. Williams, *ibid.*, 1989, **111**, 8954, and references cited therein.
- For reviews see: B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795; K. Hayakawa and K. Kanematsu, *J. Synth. Org. Chem. Jpn.*, 1986, **44**, 109; D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187.
- (a) S. J. Burrell, A. E. Derome, M. S. Edenborough, L. M. Harwood, S. A. Leeming, and N. S. Isaacs, *Tetrahedron Lett.*, 1985, **26**, 2229; (b) L. M. Harwood, N. S. Isaacs, G. Jones, J. Pickard, R. M. Thomas, and D. Watkin, *ibid.*, 1988, **29**, 5107; (c) L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas, and D. Watkin, *ibid.*, 1988, **29**, 5825.
- S. H. Grover and J. B. Stothers, *J. Am. Chem. Soc.*, 1969, **91**, 4331.
- For a related example where 5 bond coupling was instrumental in distinguishing between two isomers see: W. M. Grootaert and P. J. De Clerq, *Tetrahedron Lett.*, 1982, **23**, 3291.