Synthetic Approaches to Phorbols *via* the Intramolecular Diels–Alder Reactions of Furans (IMDAF): Oxygen Bridge Cleavage and High Stereocontrol during Cycloaddition using α′-Benzylthio Substituted Furan Substrates

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High pressure mediated IMDAF of the α′-benzylthiofuran substrate **1** results in efficient and highly stereoselective cycloaddition; subsequent epimerisation of the cycloadduct **6** is regiospecific and the oxygen bridge may be opened by elimination or hydrolysis.

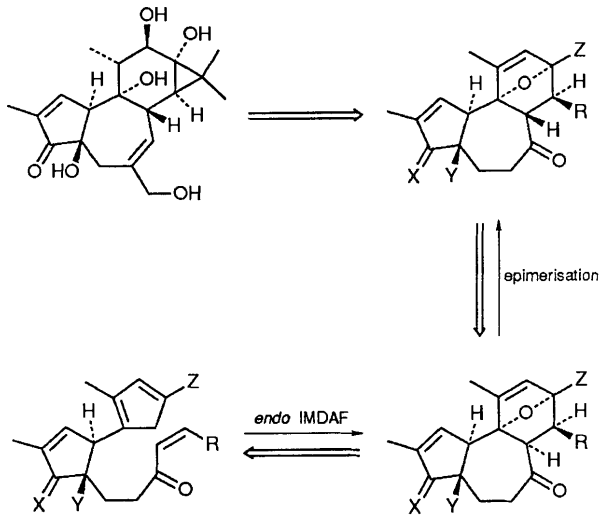
We have previously demonstrated the utility of the intramolecular Diels–Alder reaction of furans (IMDAF)[1] for the rapid stereoselective construction of carbotricycles having synthetic potential for phorbol construction.[2] The approach hinges upon the high pressure mediated IMDAF of a substrate possessing a *Z*-dienophile to furnish the *endo*-cycloadduct as the major product, followed by regioselective epimerisation affording an intermediate with correct phorbol stereochemistry at six vital stereocentres (Scheme 1).[3]

We now report that the modification of this approach by utilising an α′-benzylthiofuran precursor not only permits cleavage of the oxygen bridge of the resultant cycloadduct, but leads to greatly improved yield and stereoselectivity in the cycloaddition step as well as total regiocontrol in the subsequent epimerisation step.

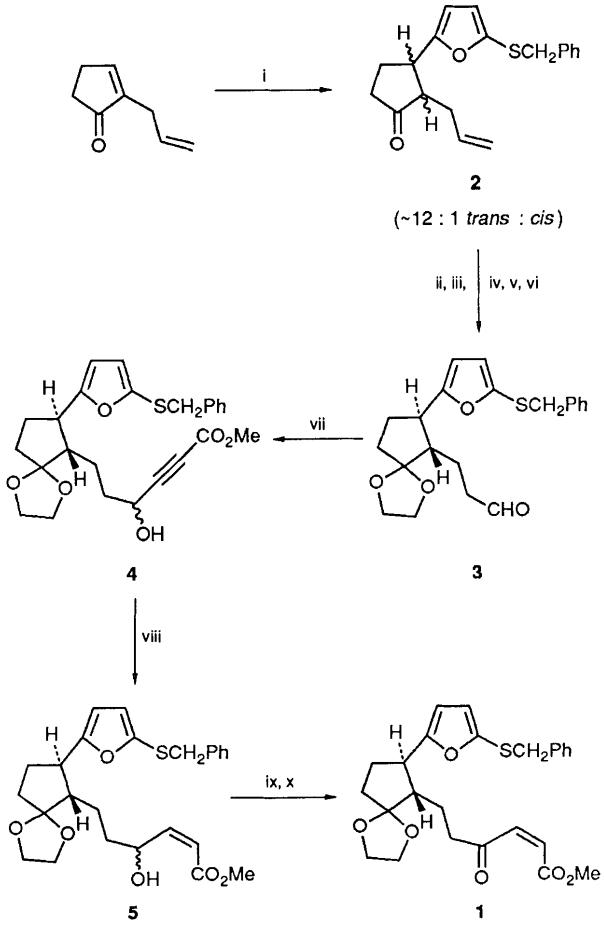
At the outset of this phase of our investigations we envisaged that the use of a Diels–Alder substrate possessing a heteroatom at the α′-position of the furan would form a

cycloadduct capable of undergoing hydrolytic cleavage of the oxygen bridge, a key feature of the envisaged synthetic approach. Initial studies with α′-oxygenated furan derivatives indicated that such materials did not possess sufficient stability to permit their use in prolonged synthetic sequences. However, following successful reports of the use of 2-methylthiofuran in intermolecular Diels–Alder reactions, and simple cleavage of the resultant cycloadducts,[4] we turned our attention to the construction and reactions of the IMDAF substrate **1**. This was prepared according to the sequence shown in Scheme 2. Following the procedure of Kraus,[5] 2-benzylthiofuran underwent trimethylsilyl iodide mediated 1,4-addition to 2-allylcyclopentenone in the presence of an acid scavenger to give **2** in 75% purified yield as a mixture of *trans*- and *cis*-isomers in *ca.* 12 : 1 ratio which did not alter on treatment with NaOMe–MeOH.† Successive elaboration of **2** following the previously reported method[3] gave the unstable aldehyde **3** which was immediately treated with methyl 3-lithiopropynoate to afford the propynylic alcohol **4** as a 1 : 1 mixture of diastereoisomers. The desired *Z*-configurated α,β-unsaturated ester **5** was obtained after hydrogenation using unpoisoned 5% $Pd/BaSO_4$ (Lindlar catalyst resulted in no reaction; presumably the presence of sulphur in the substrate is sufficient to deactivate the catalyst) and subsequent Swern oxidation gave the required IMDAF substrate **1**.

Substrate **1** showed no tendency to undergo cycloaddition at ambient pressure, but subjecting a *ca.* 0.1 mol dm^{-3} solution of **1** in dichloromethane to 19 kbar pressure (1 bar = 10^5 Pa) at



Scheme 1



Scheme 2 *Reagents and conditions*: i, 2-benzylthiofuran, Me_3SiI, $Me_2C{=}CHMe$, CH_2Cl_2, −70 °C, 75%; ii, $HOCH_2CH_2OH$, H^+, benzene, reflux, 97%; iii, B_2H_6, tetrahydrofuran (THF); iv, H_2O_2, aq. NaOH, 77%; v, $(COCl)_2$, dimethyl sulphoxide (DMSO), CH_2Cl_2, −60 °C; vi, Et_3N, quant. (crude); vii, $LiC{\equiv}CCO_2Me$, THF, −80 °C, 82%; viii, H_2 (1 bar), 5% $Pd–BaSO_4$, EtOAc, quant. (crude); ix, $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C; x, Et_3N, 73%

† All novel intermediates isolated during the course of this work, including those not expressly described in this communication, gave spectroscopic data in accord with their assigned structures. With the exception of **1**, **3** and **5**, all gave acceptable combustion analyses. *Selected spectroscopic data:* **1**, ν_{max}/cm^{-1} (film) 1722, 1700 and 1625; δ_H (200 MHz, $CDCl_3$) 1.60–2.08 (6H, m), 2.10–2.28 (1H, m), 2.50–2.65 (2H, m), 2.88 (1H, q), 3.73 (3H, s), 3.90–4.00 (4H, m), 3.96 (2H, s), 5.98 (1H, d, *J* 12.2 Hz), 6.01 (1H, d, *J* 3.0Hz), 6.27 (1H, d, *J* 3.0 Hz), 6.42 (1H, d, *J* 12.2 Hz) and 7.10–7.30 (5H); *m/z* (DCI, NH_3) 474 (MNH_4^+), 457 (MH^+), 439, 425, 395, 365, 333, 315, 297, 267, 99, 91 and 55 (DCI = desorption chemical ionisation).

2, *trans*, ν_{max}/cm^{-1} (film) 1740 and 1640; δ_H (200 MHz, $CDCl_3$) 1.90–2.60 (7H, m), 3.05–3.25 (1H, m), 3.94 (2H, s), 5.60 (1H, d, *J* 10.5 Hz), 5.62 (1H, d, *J* 17.0 Hz), 5.55–5.75 (1H, m), 6.03 (1H, d, *J* 3.1 Hz), 6.32 (1H, d, *J* 3.1 Hz), 7.10–7.20 (2H, m) and 7.20–7.35 (3H, m); *m/z* (DCI, NH_3) 330 (MNH_4^+), 313 and 91.

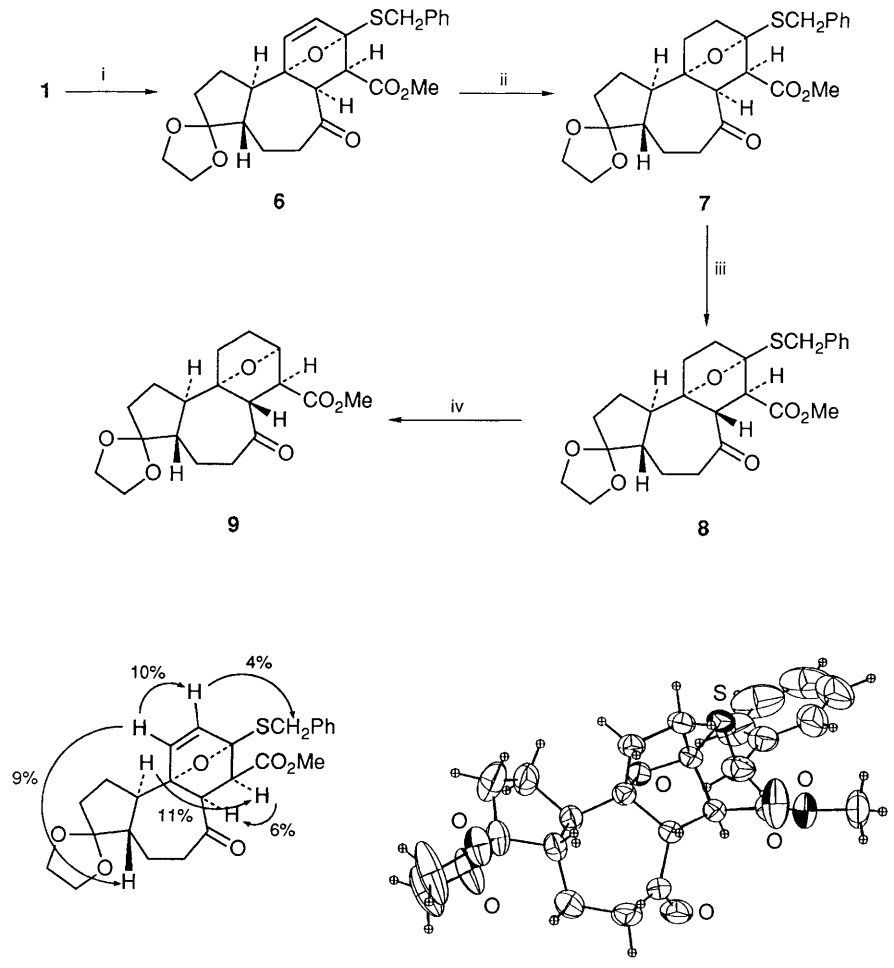
6, m.p. 115–118 °C; ν_{max}/cm^{-1} (Nujol) 1740 and 1692; δ_H (300 MHz, $CDCl_3$) 1.50–1.65 (1H, m), 1.75 (1H, t, *J* 11.0 Hz), 1.80–2.00 (5H, m), 2.26 (1H, ddd, *J* 19.0, *J′* 12.5, *J″* 6.0 Hz), 2.35–2.50 (1H, m), 2.63 (1H, dt, *J* 19.0, *J′* 3.7, *J″* 3.7 Hz), 3.20 (1H, d, *J* 9.2 Hz), 3.64, (3H, s), 3.92 (1H, d, *J* 9.2 Hz), 3.98 (6H, s), 6.14 (1H, d, *J* 5.6 Hz), 6.76 (1H, d, *J* 5.6 Hz) and 7.20–7.37 (5H, m); *m/z* (DCI, NH_3) 474 (MNH_4^+), 457 (MH^+), 395, 365, 333, 297, 267, 193, 113, 99, 91 and 55.

8, m.p. 174.5–176 °C; ν_{max}/cm^{-1} (Nujol) 1724 and 1704; δ_H (300 MHz, $CDCl_3$) 1.60–2.13 (11H, m), 2.18–2.30 (1H, m), 2.52 (1H, ddd, *J* 13.0, *J′* 11.0, *J″* 6.0 Hz), 2.63 (1H, dt, *J* 13.0, *J′* 6.0 *J″* 6.0 Hz), 3.53 (1H, d, *J* 6.4 Hz), 3.72 (3H, s), 3.88–4.00 (5H, m), 4.05 (1H, d, *J* 12.0 Hz), 4.14 (1H, d, *J* 12.0 Hz), 7.20–7.34 (3H, m) and 7.40 (2H, dd, *J* 8.5, *J′* 1.6 Hz); *m/z* (DCI, NH_3) 476 (MNH_4^+), 459 (MH^+), 441, 427, 409, 398, 367, 335, 303, 293, 181, 99, 91, 86 and 55.

10, m.p. 140–142 °C; ν_{max}/cm^{-1} (Nujol) 3430, 1722, 1665 and 1532; δ_H (500 MHz, $CDCl_3$) 1.60–1.84 (6H, m), 1.94–1.98 (1H, m), 2.04 (1H, s, exchanges with D_2O), 2.35–2.41 (1H, m), 2.49–2.56 (1H, m), 2.62–2.68 (1H, m), 3.73 (3H, s), 3.83–3.94 (4H, m), 4.11 (1H, d, *J* 13.0 Hz), 4.16 (1H, d, *J* 13.0 Hz), 4.14 (1H, s), 6.09 (1H, d, *J* 10.0 Hz), 6.52 (1H, d, *J* 10.0 Hz), 7.25–7.30 (1H, m) and 7.30–7.38 (4H, m); *m/z* (DCI, NH_3) 456 (M^+), 439, 407, 320, 99, 91, 86 and 55.

11, m.p. 159–161 °C (softens at 90 °C and then resolidifies); ν_{max}/cm^{-1} (Nujol) 3530, 3330, 1700 and 1680; δ_H (500 MHz, $CDCl_3$) 1.58–1.92 (9H, m), 1.65 (1H, s, exchanges with D_2O), 2.45–2.50 (1H, m), 2.48 (1H, ddd, *J* 12.5, *J′* 9.0, *J″* 4.4 Hz), 2.68 (1H, dddd, *J* 18.6, *J′* 10.7, *J″* 6.7, *J‴* 1.2 Hz), 2.80 (1H, ddd, *J* 18.6, *J′* 6.5, *J″* 1.6 Hz), 2.87 (1H, ddd, *J* 12.5, *J′* 10.4, *J″* 7.5 Hz), 3.66 (3H s), 3.85–3.95 (5H, m), 4.09 (1H, d, *J* 12.5 Hz), 4.13 (1H, d, *J* 12.5 Hz), 7.24–7.28 (1H, m), 7.32 (2H, t, *J* 8.5 Hz) and 7.38 (2H, d, *J* 8.5 Hz); *m/z* (DCI, NH_3) 459 (MH^+), 441, 427, 409, 367, 349, 335, 319, 127, 99, 91, 86, 65 and 55.

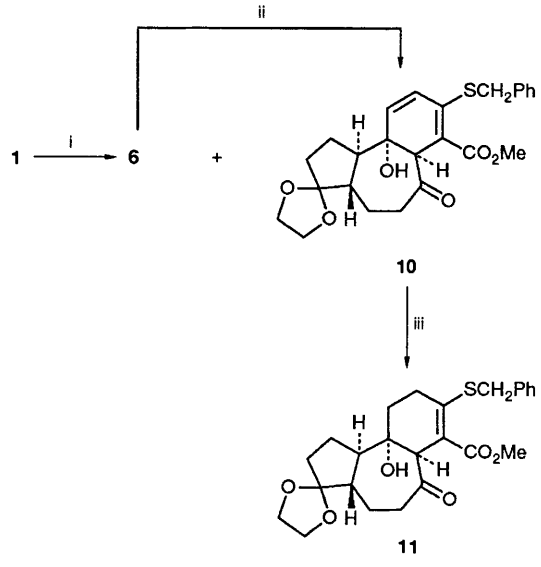
12, m.p. 178–181 °C; ν_{max}/cm^{-1} (Nujol) 3520, 3440, 1740, 1727 and 1700; δ_H (200 MHz, $CDCl_3$) 1.60–2.08 (4H, m), 2.08–2.60 (9H, m), 2.70–3.03 (2H, m), 3.64 (1H, d, *J* 12.9 Hz), 3.75 (3H, s) and 4.35 (1H, d, *J* 12.9 Hz); *m/z* (DCI, NH_3) 326 (MNH_4^+), 309 (MH^+), 291, 171, 137 and 55.



Scheme 3 *Reagents and conditions*: i, 19 kbar, CH_2Cl_2 (*ca.* 0.1 mol dm^{-3}), 13 h, 68%; ii, H_2 (17 bar), 5% Pd–$BaSO_4$, EtOAc, 83%; iii, NaOMe (cat.), MeOH, room temp., 84%; iv, Raney Ni(W-2), MeOH, reflux, 82%. Key NOE enhancements for **6** and X-ray structure of **8**.

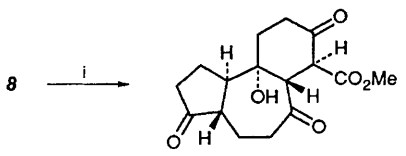
20 °C for 13 h resulted in smooth conversion to a single cycloadduct **6**. This could be isolated pure as a colourless solid (m.p. 115–118 °C) in 68% yield by removal of solvent and trituration of the residue with diethyl ether. The stereochemistry was deduced as that resulting from *endo*-cycloaddition by analysis of a combination of COSY and NOE difference ^1H spectra at 500 MHz (Scheme 3). Catalytic reduction of the cycloadduct afforded the dihydro-derivative **7** in 83% yield which, on treatment with methanolic sodium methoxide at room temperature, gave a single epimerised product **8** in 84% yield. That epimerisation had occurred selectively α- to the carbonyl group was initially indicated by Raney nickel desulphurisation of **8** to **9**, the NMR spectum of which (C_6D_6) gave a superimposable signal pattern with that of the previoulsy reported analogous ethyl ester,[3b] with the exception of the ester residue. Subsequent X-ray analysis of **8** confirmed our initial assignment.‡

‡ *Crystal data* for **8**: $C_{25}H_{30}O_6S$, triclinic, $P\bar{1}$, $a = 8.303$, $b = 9.804$, $c = 15.196$ Å, $\alpha = 101.7$, $\beta = 92.6$, $\gamma = 74.4°$, $U = 1166.5$ Å^3, $Z = 2$, $D_c = 1.299$ g cm^{-3}, $F(000) = 484$, μ(Cu-Kα) = 15.083 cm^{-1}. 3427 Independent reflections with $I > 3\sigma(I)$ were used in the analysis. Final $R = 4.9$, final Hamiltonian weighted $R = 5.5$. Data for crystallographic analysis were measured ($2\theta_{max} = 150°$) on an Enraf-Nonius CAD 4 diffractometer using Cu-Kα radiation and ω-2θ scans. Structures were solved by direct methods and refined by least squares using the CRYSTALS package. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors Issue No. 1.



Scheme 4 *Reagents and conditions*: i, 19 kbar, CH_2Cl_2 (*ca.* 0.02 mol dm^{-3}), 15 h; ii, HCl–MeOH (cat.), THF, 77%; iii, H_2 (17 bar), 5% Pd–$BaSO_4$, EtOAc, 86%

During attempts to optimise the IMDAF reaction of **1** it was observed that dilute solutions (*ca.* 0.02 mol dm^{-3}) led to marked reduction in the yield of the required adduct **6** and the appearance of a second material identified as **10** by spectro-



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Scheme 5 *Reagents and conditions*: i, $HgCl_2$, aq. MeCN, 50 °C, 8 days, 57%

scopic analysis (ratio **6**:**10** *ca.* 1:2). The advent of this product, resulting from eliminative cleavage of the oxygen bridge of **6** was presumed to be due to the effect of traces of acid present in the dichloromethane (Scheme 4). Indeed, treatment of a tetrahydrofuran solution of **6** with a catalytic amount of 1 mol dm^{-3} HCl in methanol afforded the cleavage product in 77% isolated yield as a colourless solid (m.p. 140—142 °C). It is noteworthy that the ethylene ketal remains intact under these mild reaction conditions. The stability of **10** towards aromatisation *via* E1 or E2 elimination may be due to a combination of the *syn*-relationship of the tertiary hydroxy group with the α-hydrogen and the fact that acid catalysed loss of water would lead to a tertiary cation which is destabilised owing to conjugation with the carbonyl carbon of the ester group. Hydrogenation of **10** ($Pd/BaSO_4$, H_2, 17 bar) yielded the dihydro-derivative **11**.

A wide range of attempts at oxygen bridge cleavage of the epimerised material **8** led to decomposition. However, $HgCl_2$ in aqueous acetonitrile at 50 °C for 8 days was found to lead to a 57% yield of the ketol **12** (Scheme 5) in which desired hydrolytic cleavage of the oxygen bridge has been accompanied by deketalisation.

In summary, the use of the α′-benzylthiofuran substrate **1** not only permits oxygen bridge cleavage of the resultant cycloadducts, but results in increased efficiency in both the IMDAF and the subsequent epimerisation, making this route applicable to the preparation of synthetically useful quantities of carbotricyclic intermediates. This work constitutes a significant advance in our synthetic progress towards phorbol.

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References

1 For useful reviews see: M. E. Jung, *Synlett*, 1990, 186; D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187; K. Hayakawa and K. Kanematsu, *J. Synth. Org. Chem. Jpn.*, 1986, **44**, 109; B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795.

2 *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 P. D. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 8954, and references cited therein.

3 (*a*) L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas and D. Watkin, *J. Chem. Soc., Chem. Commun.*, 1990, 605; (*b*) L. M. Harwood, B. Jackson, G. Jones, K. Prout, R. M. Thomas and F. J. Witt, *J. Chem. Soc., Chem. Commun.*, 1990, 608, and references cited therein.

4 H. Kotsuki, Y. Mori, T. Ohtsuka, H. Nishizawa, M. Ochi and K. Matsuoka, *Heterocycles*, 1987, **26**, 2347.

5 G. A. Kraus and P. Gottschalk, *Tetrahedron Lett.*, 1983, **24**, 2727.