Synthetic approaches towards phorbols *via* the ultra-high-pressure mediated intramolecular Diels–Alder reaction of furans (IMDAF): effect of furan substitution

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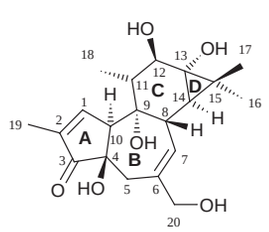
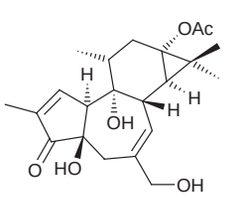
Tricyclic structures having the functionality and stereochemistry inherent in phorbol and its analogues may be rapidly constructed by an ultra-high pressure IMDAF reaction. The nature of the 2-thioether substituent on the furan diene is critical for the success of the key cycloaddition reaction.

Introduction

Phorbol (**1**) was first isolated in 1934 by Bohm[1] as a hydrolysis product of *Croton tiglium* oil, but it was not until 1967 that Hecker[2] used X-ray crystallography to elucidate its core structure. Phorbol esters are abundant within the genus *Euphorbiaceae* encompassing a range of plants, amongst which is the Spurge family and ornamental house plants such as the poinsettia (*E. plucherrima*). The genus owes its name to King Juba the 3rd of Mauritania (25 BC), who honoured his physician Euphorbos by naming the species after him.[3] In folklore medicine the plant extracts were used to treat tumours, migraine, parasite infections, venereal disease, skin conditions and were effective purgatives and abortifacients.[4] Despite their use in medicine, the toxicological properties of these plants are very severe, inducing intense inflammation on contact[5] and any such treatment probably had a rather efficient "kill or cure" result.[6] The toxic extract from *E. poisonii* has been used as an arrow tip poison[7] and as a fish poison.[8] The *Pimelea* species have been responsible for cattle poisoning[9] but are also used by farmers as stockade plants to keep predators out.[10] In Nigeria, extracts from *E. balsamifera* have been used to treat gonorrhoea and gingivitis while the extract of *Elaeophorbia drupifera* Stapf, despite being a severe blistering agent, is used against snake and insect bites, warts and ringworm.[11] Prostatin (**2**), (12-deoxyphorbol acetate), is of medical interest due to its cyto-protective effect in human lymphocytic cells infected with HIV-1.[12] Probably the most important physiological property of the phorbol esters is their capacity to act as tumour promoters[13] and tetradodecanoyl phorbol acetate is the most potent tumour promoter known to man, being active at levels of 0.02 μmol.[14] The origin of such activity was identified in 1982, when Castagna[15] showed that tetradecanoyl phorbol acetate bound to the ubiquitous enzyme protein kinase C.



(**1**)
Phorbol



(**2**)
Prostatin

Phorbols are diterpene members of the tigliane family possessing a tetracyclic framework consisting of a *trans*-hydroazulene (A,B rings) *trans*-fused, and a *gem*-dimethyl-cyclopropyl (D ring) *cis*-fused to a cyclohexane ring (C ring). The complex polycyclic structure of phorbol, together with intense interest in structure–activity relationship studies to map the basis of the tumour promotion activity have fuelled extensive efforts towards establishing efficient synthetic routes to phorbol and its derivatives, culminating in Wender's total synthesis of phorbol[16] which has also been developed in the enantiomerically pure series.[17] The approach was based upon an intramolecular oxopyrilium cycloaddition to construct the B-ring following earlier investigations which used a divinylcyclo-propane rearrangement.[18] An alternative approach adopted by Shibasaki[19] is based upon diastereocontrolled elaboration of carvone which acts as the C-ring template and provides a route which is amenable to the synthesis of enantiomerically pure material. Rigby has concentrated his synthetic efforts on the intermolecular Diels–Alder reaction of dienes to cyclopropenes to establish the CD ring system within phorbol.[20] Bullman-Page has shown the versatility of the intramolecular Diels–Alder reaction for the rapid construction of the BC ring system of the tigliane skeleton, subsequently reporting the introduction of the C-12 and C-13 hydroxy functions and cyclopropanation providing tetracyclic phorbol analogues.[21] Dauben has reported the synthesis of the tigliane ring system using a stereospecific rhodium(II) acetate-catalysed cycloaddition reaction to furnish the BC ring system,[22] and McMills later described a similar approach to the tigliane ABC ring system.[23] Paquette has reported the serendipitous but concise synthesis of an enantio-merically pure tigliane-type skeleton[24] and Little has described initial studies on diyl trapping reactions as an approach to the carbon framework of phorbol.[25]

The retrosynthetic analysis adopted by our group has involved the intramolecular Diels–Alder reaction of furan (IMDAF) utilising a suitable dienophile tether to furnish, in one step, the ABC tricycle of phorbol possessing strategically situated functionality for further elaboration.

Our initial retrosynthetic analysis, invoking an intra-molecular *exo*-cycloaddition of an (*E*)-bis-activated tethered dienophile onto a suitably functionalised furan was modified in the light of our extensive model studies in which we demonstrated that ultra-high pressures are necessary to obtain

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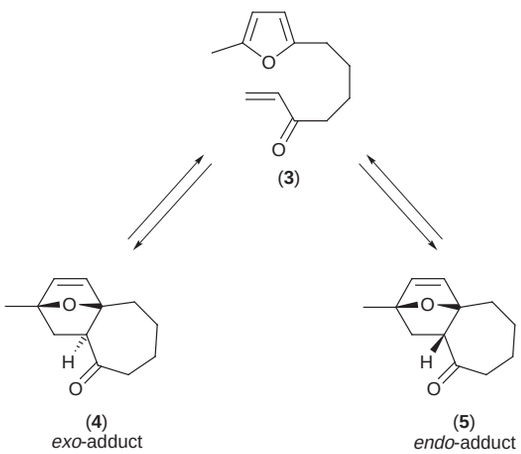
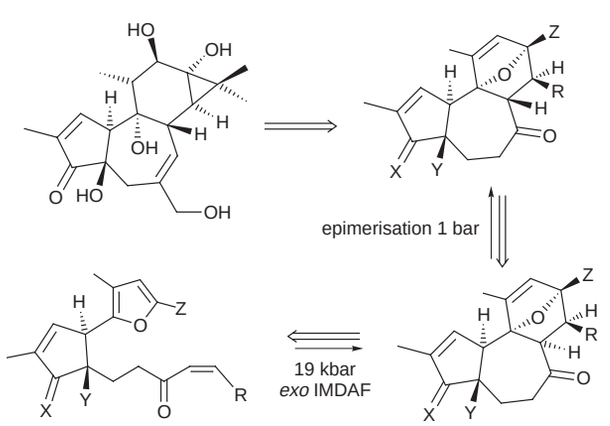
an efficient IMDAF reaction with a 5-carbon tether and that, at high pressure, the more sterically hindered (and hence smaller) *endo*-product is thermodynamically preferred.[26] Molar volume measurements on model substrate **3** and reduced derivatives of *exo*- and *endo*-cycloadducts **4** and **5** gave values of 183 cm^3 mol^{-1}, 169 cm^3 mol^{-1} and 164 cm^3 mol^{-1} respectively in agreement with this observation (Scheme 1).[27]



Scheme 1

Such an observation is at variance with our results using 4-atom tethers between furan and a dienophile, where the stereocontrol is the same as obtained by others such as Parker[28] and DeClerq.[29] In addition, we were able to demonstrate that cycloaddition products with a 5-carbon tether underwent cycloreversion at standard pressure while the cycloadducts with 4-carbon tethers were stable. Hydrogenation of the double bond of the 5-carbon tether *endo*-cycloadducts gave materials which could be selectively epimerised at the ring junction.[30] Subsequent to these publications on stereocontrol in the high pressure mediated IMDAF, Keay reported studies which effectively repeated that portion of our work relating to high pressure mediated generation of decalin-derived systems using 4-carbon tethers, apparently unaware of our previous disclosures.[31]

Our model studies led to a revision of our synthetic approach to hinge upon high pressure mediated *endo*-IMDAF of a (*Z*)-doubly activated dienophile, followed by regioselective epimerisation of the reduced cycloadduct at standard pressure, establishing the required stereochemistry at the B–C ring junction (Scheme 2). Using this approach, we were able to access



Scheme 2

cycloadducts containing six stereocentres commensurate with our needs for access to phorbol[32] but we still had to address the cleavage of the oxabicyclo[2.2.1]heptane moiety.

Results and discussion

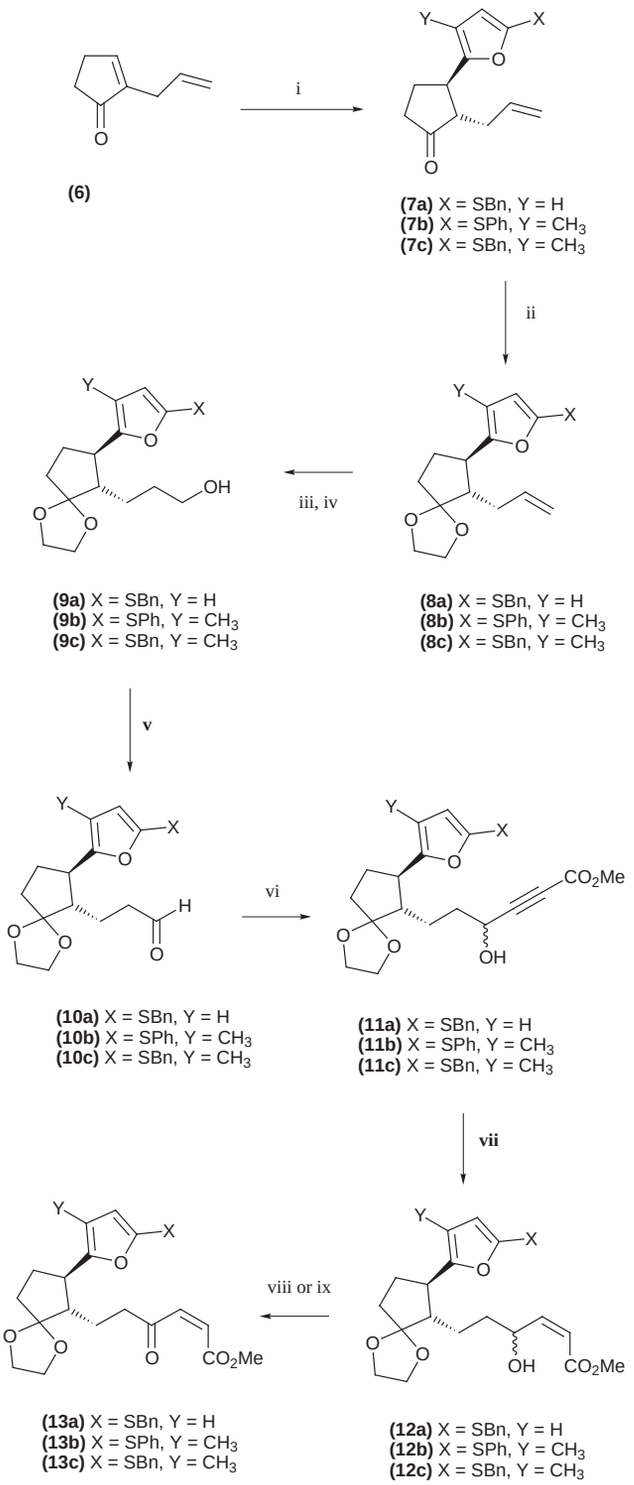
Kotsuki *et al.*[33] had previously reported that using 2-(methylthio)furan in the high pressure mediated intermolecular Diels–Alder reaction permitted cleavage of the oxygen bridge of the resultant cycloadducts and we decided to adopt this approach for further functionalisation of the C-ring of our cycloadducts. The 1,4 adduct **7a** was prepared using the procedure reported by Kraus,[34] adding 2-(benzylthio)furan to **6** in the presence of trimethylsilyl iodide at −78 °C to furnish the adducts in a 12:1 ratio in favour of the *trans*-isomer **7a** in an overall yield of 75%.[35] Using methodology previously established within the group,[32,35] treatment of **7a** with ethylene glycol under acid catalysis gave a virtually quantitative yield of the ketal **8a**. Subsequent hydroboration and oxidation of **8a** afforded alcohol **9a** in a yield of 77%. Swern oxidation gave the unstable aldehyde **10a** which was directly treated with methyl 3-lithiopropynonate to give the propynylic alcohol **11a** in an overall yield of 80%. The partial hydrogenation of **11a** was performed in the presence of 5% Pd–$BaSO_4$ to afford the crude α,β-unsaturated ester **12a**. Since this compound was prone to lactonisation, it was directly subjected to Swern oxidation conditions to give the IMDAF precursor **13a** in 73% yield (Scheme 3).

The precursor (**13a**) was subjected to 19 Kbar pressure at room temperature in dichloromethane for 15 h to afford a single cycloadduct (**14a**) in 65% yield which, after hydrogenation, was shown to be the *endo*-product **15a**. Epimerisation furnished the C-10 epimer (**16a**) in 84% yield and this structure was confirmed by X-ray spectroscopic analysis,[35] no epimerisation being observed at C-2. Hydrolytic cleavage of the oxygen bridge using mercuric chloride in aqueous acetonitrile afforded the tricycle **17a** in 58% yield. Thus the α′-benzylthiofuran substrate not only permitted oxygen bridgehead cleavage but also enhanced the IMDAF step to yield a cycloadduct which could be readily manipulated to furnish a tricycle with the correct relative stereochemistry at C-1, C-2, C-6, C-7 and C-11 (Scheme 4).

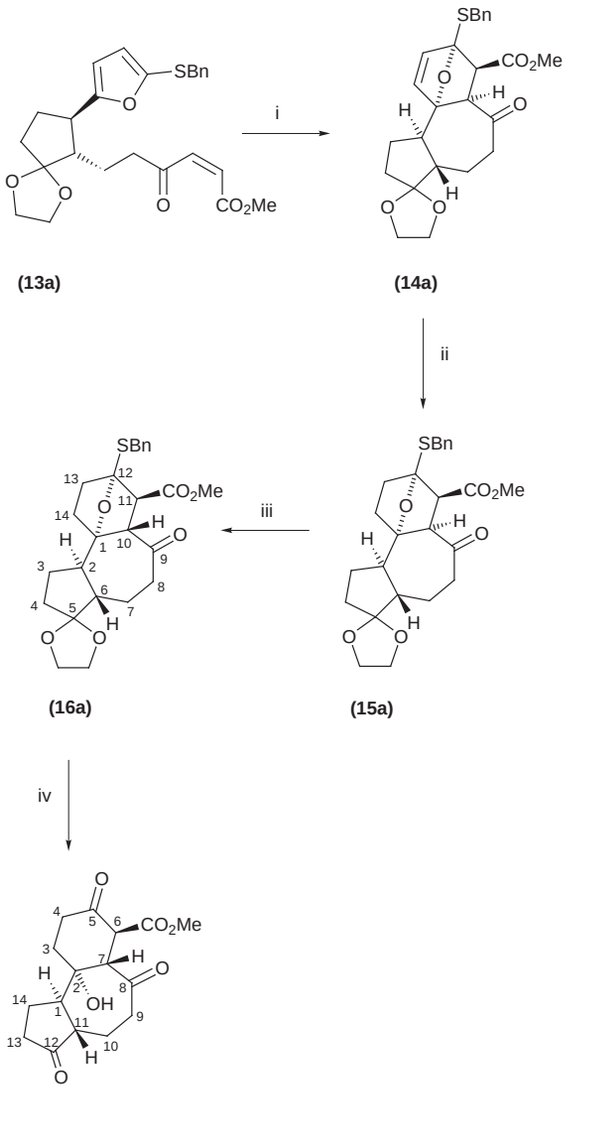
At this stage we wished to synthesise a Diels–Alder precursor in which the furan possessed an additional methyl substituent, in order to generate cycloadducts possessing a methyl group corresponding to that at C-11 on phorbol. Initial studies indicated that 4-methyl-2-(phenylthio)furan was synthetically more accessible than the corresponding benzylthio derivative[36] and so this was incorporated in the synthetic sequence to furnish **13b** (Scheme 3, series **b**). Disconcertingly, it was found that a range of high pressure conditions with substrate **13b** led either to the recovery of starting material or decomposition and no conditions could be established which led to cycloadducts (Scheme 5).

Molecular modelling calculations[37] indicated two possible sources for this reluctance to undergo the key cycloaddition step. Firstly, in the transition state, steric interactions between the methylene protons of the cyclopentane ring and the methyl group of the furan appeared to disfavour cycloaddition and secondly the 2-(phenylthio)-substituent was no longer enhancing electron density of the HOMO of the furan, both possible reasons for the lowered propensity for substrate **13b** to undergo cycloaddition.

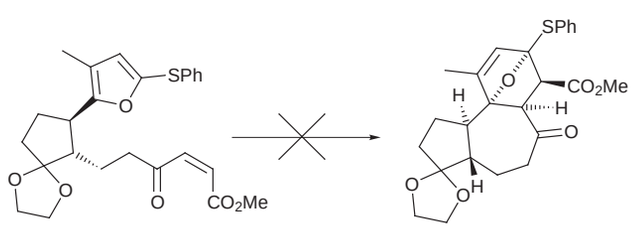
From these observations it seemed that our synthetic strategy might be fatally flawed if the steric problems of introducing the additional methyl group on the furan were sufficient to tip the balance of a reluctant IMDAF to one which would not even occur under high pressure conditions. It was therefore imperative that we establish the reason for the above failure and it was decided initially to return to incorporation of the benzylthioether functionality to see if this would favour cycloaddition. This required a reproducible route for synthesis of large quantities of 4-methyl-2-(benzylthio)furan **22**. We had previously examined the literature procedure[38] and found the



Scheme 3 *Reagents and conditions*: (i) 2-(benzylthio)furan (series a) or 2-phenylthio-4-methylfuran (series b) or 2-benzylthio-4-methylfuran (series c), CH_3SiI, $(CH_3)_2C{=}CHCH_3$, −78 °C; (ii) $HOCH_2CH_2OH$, PTSA, toluene, Δ; (iii) B_2H_6, THF; (iv) H_2O_2, NaOH, H_2O; (v) $(COCl)_2$, DMSO, DCM, Et_3N, −50 °C, quant.; (vi) $LiC{\equiv}CCO_2Me$ THF, −80 °C; (vii) H_2, Pd–$BaSO_4$, rt, quant.; (viii) $(COCl)_2$, DMSO, DCM, Et_3N, −50 °C (**13a** and **13b**); (ix) Dess–Martin periodinane, CH_2Cl_2 (**13c**).



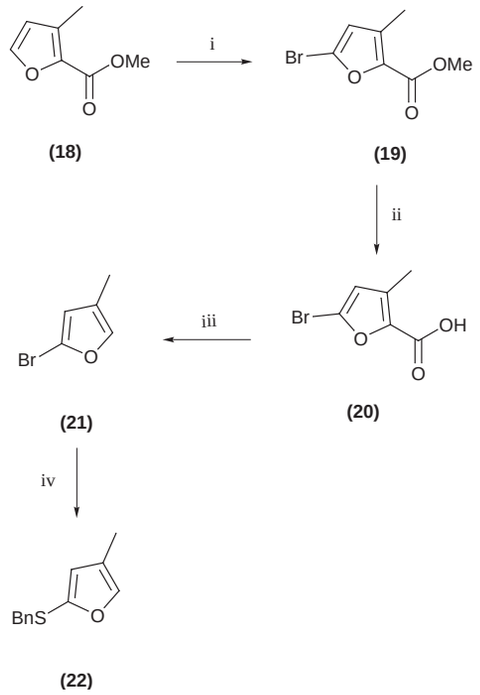
Scheme 4 *Reagents and conditions*: (i) 19 Kbar, DCM, 15 h, 65%; (ii) H_2 (15 atm), EtOAc, Pd–$BaSO_4$, 83%; (iii) NaOMe cat., MeOH, rt, 84%; (iv) $HgCl_2$, aq. CH_3CN, 50 °C, 8 days, 58%.



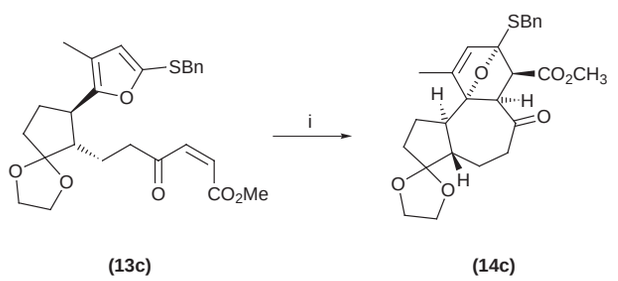
Scheme 5

copper–quinoline mediated decarboxylation step to be highly capricious, producing only minute quantities of the desired material at the very best (it was this observation which had caused us to investigate the 2-(phenylthio)furan series described above). However, after much experimentation it was found that steam distillation of substrate **20**, prepared from ester **18** *via* bromo-adduct **19** following the literature procedure,[39] in the presence of mercury(II) chloride[39] led to efficient decarboxylation under mild conditions, permitting the desired, highly volatile **21** to be isolated in a reproducible 64% yield (Scheme 6). Lithium–halogen exchange by treatment of the bromide **21** with *n*-butyllithium and quenching with dibenzyl disulfide permitted isolation of the target thioether **22** in 74% distilled yield.

With access to **22** established, our previous route was followed (Scheme 3, series **c**) to furnish precursor **13c**, the sole modification being that the final oxidation step was carried out using Dess–Martin reagent. Precursor **13c** was then subjected to the standard ultra-high pressure conditions (19 kbar, DCM, rt, 17 h) (Scheme 7) and we were rewarded with the isolation of a single cycloadduct in 45% recrystallised yield which proved



Scheme 6 *Reagents and conditions*: (i) Br_2, CH_2Cl_2, −5 °C, 85%; (ii) KOH, MeOH, H_2O, 90%; (iii) $HgCl_2$, H_2O, reflux, 64%; (iv) *t*-BuLi, THF, −78 °C, $(BnS)_2$, distil, 74%.



Scheme 7 *Reagents and conditions*: (i) 19 Kbar, DCM, 17 h, 45%.

more stable than previous cycloadducts, enabling X-ray crystallographic analysis to confirm the predicted structure (Fig. 1).[40]

Whatever the steric effect resulting from inclusion of the methyl group on the furan, its presence clearly has a beneficial effect on the stability of the cycloadduct. The effect of the 2-thioether substituent on success or failure of the high pressure mediated IMDAF reaction was an unexpected and disconcerting element in our studies but the fact that cycloaddition is possible with substrate **13c** has placed our synthetic approach on a firm footing for future synthetic efforts leading to the total synthesis of phorbol.

Experimental

All melting points were determined on a Kofler hot stage microscope. IR spectra were obtained on a Perkin-Elmer 1750 FT-IR spectrophotometer or on a Perkin-Elmer PARAGON 1000 FT-IR spectrophotometer using KBr discs or thin films as noted. NMR spectra were recorded on a Varian Gemini 200 MHz, Bruker AC200, WM250, DPX250, WH300, AMX500 MHz or JEOL EX400 MHz spectrometers. Mass spectra were recorded on VG TRIO 1, VG TRIO 1000, VG 20-250, or VG autospec mass spectrometers using either electron impact or chemical ionisation with ammonia. Elemental analyses were determined by the Dyson Perrins Laboratory, University of Oxford, or MEDAC LTD Brunel Science Centre, Surrey. X-Ray crystallography was carried out at the University of Reading. Column chromatography was performed on silica gel 60 (Merck 9385) or on alumina (Fluka 0630). TLC analyses were carried out using 0.25 mm silica gel precoated plastic backed sheets with fluorescent indicator UV_{254}. Diethyl ether and tetrahydrofuran were distilled over sodium benzophenone ketyl radical. Dichloromethane was distilled by refluxing over calcium hydride. Benzene was distilled over sodium and stored over calcium hydride.

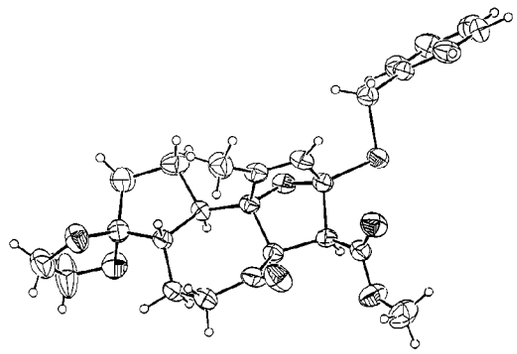


Fig. 1 X-Ray structure of **14c**.

2-Allylcyclopent-2-enone ethylene ketal[41]

n-Butyllithium (6.6 mL, 2.5 M solution in hexane, 16.6 mmol) was added to a stirred solution of thiophenol (1.7 mL, 16.6 mmol) in dry ether (16 mL) under nitrogen at 0 °C. The resulting anion was slowly added *via* cannula to a stirred suspension of CuI (3.2 g, 16.8 mmol) in dry ether (16 mL) at room temperature. After 30 min the yellow heterogeneous mixture obtained was cooled to −78 °C and a precooled (−78 °C) solution of 2-lithiocyclopent-2-en-1-one ethylene ketal in ether [prepared by reaction of 2-bromocyclopent-2-enone ethylene ketal (3.3 g, 16.2 mmol) with *n*-butyllithium (7.2 mL, 2.5 M solution in hexane, 18 mmol) at −78 °C in dry ether (33 mL)],[42,43] was slowly added *via* cannula. After 1 h at −78 °C allyl bromide (2.0 mL, 23 mmol) was added. The reaction mixture was stirred for 1 h at −78 °C then allowed to warm to 20 °C and stirred overnight. Then the reaction was quenched by the addition of saturated ammonium chloride solution (4 mL). The yellow precipitate formed was removed by filtration through Celite mixed with $MgSO_4$. The filtrate was concentrated *in vacuo* to give 2-allylcyclopent-2-enone ethylene ketal as a brown oil. This was used crude in the next step. δ_H (250 MHz, $CDCl_3$) 6.00–5.80 (1H, m), 5.75–5.70 (1H, m), 5.14–4.97 (2H, m), 4.20–4.09 (2H, m), 4.03–3.90 (2H, m), 2.85–2.75 (2H, m), 2.36–2.24 (2H, m), 2.09–1.97 (2H, m).

2-Allylcyclopent-2-enone 6

To the crude 2-allylcyclopent-2-enone ethylene ketal (2.7 g, 16.2 mmol) was added silica gel (10.0 g), then $FeCl_3$–SiO_2 (3.0 g)[44] was slowly added and the resultant mixture was stirred at 20 °C for 4 h. The crude product was extracted from the silica gel with ether (3 × 200 mL) and the filtrate concentrated *in vacuo*. Pure 2-allylcyclopent-2-enone **6** (1.3 g, 67% over two steps) was obtained as a colourless oil after flash chromatography on silica, eluting with light petroleum–ether 9:1; ν_{max} (film) 1703, and 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.31–7.10 (1H, m), 5.88–5.63 (1H, m), 5.09–4.88 (2H, m), 2.93–2.73 (2H, m), 2.58–2.44 (2H, m), 2.36–2.22 (2H, m); δ_C (62.9 MHz, $CDCl_3$) 208.1, 157.5, 143.7, 139.9, 115.8, 33.7, 28.6, 25.8; *m/z* (CI) 122 (M^+).

2-(Benzylthio)furan[37]

n-Butyllithium (48 mL, 1.6 M solution in hexane, 76.8 mmol) was added dropwise to a stirred solution of furan (5.0 g, 73.5 mmol) in dry THF (50 mL) under nitrogen at −30 °C. The reaction mixture was stirred at −30 °C for 45 min and then recooled to −65 °C. A solution of benzyl bromide (12.9 g, 75.4 mmol) in dry THF (10 mL) was added dropwise and the result-

ing mixture was allowed to warm to room temperature. After addition of ice-water (100 mL), the mixture was extracted with ether (2 × 50 mL). The organic layers were combined, washed with 1 M HCl solution (2 × 50 mL), and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Pure 2-(benzylthio)furan (8.7 g, 62%) was obtained as a pale yellow oil after distillation, bp 96–102 °C (0.8 mmHg), lit.,[45] bp 67–71 °C (0.07 mmHg).

5-Bromo-3-methylfuran-2-carboxylic acid 20[38]

Methyl 3-methyl-2-furoate **18** (25.0 g, 178.6 mmol)[46] was treated with bromine (12 mL, 234 mmol) as previously described[47] to give methyl 5-bromo-3-methyl-2-furoate **19**. The crude mixture was added portionwise to a stirred solution of KOH (19.0 g, 338 mmol) in water (10 mL) and methanol (150 mL) at 0 °C. The reaction mixture was stirred overnight at 20 °C, then diluted with water (200 mL) and extracted with ether (2 × 200 mL). The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid before being extracted with ether (3 × 150 mL). The combined layers were washed with saturated aqueous sodium thiosulfate (50 mL), water (170 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a solid. Pure 5-bromo-3-methylfuran-2-carboxylic acid **20** (32.8 g, 90%) was obtained as a white solid, mp 166–168 °C after recrystallisation (methanol); ν_{max} (KBr disc) 3034, 1676 and 1479 cm^{-1}; δ_H (500 MHz, d_6-DMSO) 6.63 (1H, s), 2.22 (3H, s); δ_C (125 MHz, d_6-DMSO) 159.1, 144.5, 134.7, 126.2, 117.1, 12.0; *m*/*z* (CI) 224/222 (MNH_4^+), 204/206 (MH^+, 28%).

2-Bromo-4-methylfuran 21[39]

A solution of the carboxylic acid **20** (30.0 g, 146 mmol), and mercuric chloride (39.7 g, 146 mmol) in water (500 mL) was heated to reflux. The steam distillate was collected in a solid CO_2-cooled round bottom flask over a period of 1 h. The distillate was allowed to warm to room temperature and the layers were separated. The aqueous layer was extracted with ether (2 × 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and the ether was distilled off through a 50 cm Vigreux column to give the 2-bromo-4-methylfuran **21** (15.0 g, 64%) as a colourless oil; ν_{max} (film) 2929, 1470 and 918 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.21 (1H, s), 6.19 (1H, s), 2.03 (3H, s); δ_C (125 MHz, $CDCl_3$) 141.2, 123.2, 121.9, 113.8, 9.7.

Preparation of furan thioethers

2-Phenylthio-4-methylfuran. *t*-Butyllithium (81 mL, 1.5 M solution in hexane, 121.5 mmol) was added dropwise to a stirred solution of 2-bromo-4-methylfuran **21** (15.0 g, 93.2 mmol) in THF (400 mL) under nitrogen at −78 °C. After 30 min, diphenyl disulfide (26.5 g, 121.7 mmol) was rapidly added in one portion under increased nitrogen flow. The reaction mixture was allowed to warm to 20 °C, then quenched with ice-water (200 mL), and extracted with ether (3 × 200 mL). The extract was washed with water (2 × 200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil. Pure 2-phenylthio-4-methylfuran (9.9 g, 56%) was obtained after Kugelrohr distillation, bp 155 °C (0.1 mmHg) (Found C, 69.45, H, 5.63, S, 16.85%; $C_{11}H_{10}OS$ requires C, 69.44, H, 5.30, S, 16.85%); ν_{max} (film) 2927, 1708, 1624, 1583, 1479 and 1440 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.37 (s, 1H), 7.35–7.04 (5H, m), 6.62 (1H, s), 2.07 (3H, s).

2-Benzylthio-4-methylfuran 22. Compound **22** (14.0 g, 74%) was obtained as a yellow oil after distillation, bp 155 °C (4 mmHg) (Found C, 70.32, H, 6.18, S, 15.83%; $C_{12}H_{12}OS$ requires C, 70.56, H, 5.92, S, 15.69%); ν_{max} (film) 2927, 1495, 1454 and 1112 cm^{-1}; δ_H(200 MHz, $CDCl_3$) 7.31–7.19 (6H, m), 6.21 (1H, s), 3.96 (2H, s), 1.97 (3H, s); δ_C (125 MHz, $CDCl_3$) 142.2, 137.7, 134.5, 128.9, 128.4, 127.2, 121.8, 119.9, 40.7 and 9.8; *m*/*z* (CI) 204 (M^+).

1,4-Additions to 2-allylcyclopent-2-enone

(2α,3β)-3-(5-Benzylthio-2-furyl)-2-(prop-2-enyl)cyclopentanone 7a. Trimethylsilyl iodide (16.0 mL, 110 mmol) was added dropwise to a stirred solution of allylcyclopentenone **6** (11.0 g, 90 mmol) in CH_2Cl_2 (300 mL) under nitrogen at −78 °C. After 20 min, 2-(benzylthio)furan (15.4 g, 75 mmol) in CH_2Cl_2 (50 mL) was slowly added *via* cannula over 15 min at −78 °C, and 2-methylbut-2-ene (23 mL, 217 mmol) was added concomitantly. The mixture was stirred at −78 °C for 4 h, then warmed to −40 °C and quenched with 1 M HCl solution (200 mL). The resulting mixture was poured into ice-water (50 mL), and extracted with ether (2 × 200 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (200 mL), water (200 mL), brine (200 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The pure ketone **7a** (21.0 g, 75%) was obtained as a colourless oil after flash chromatography on silica, eluting with light petroleum–ether 9:1 (Found C, 72.93, H, 6.70%; $C_{19}H_{20}O_2S$ requires C, 73.04, H, 6.45%); ν_{max} (film) 3063, 2925, 1740, 1640 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.10 (5H, m), 6.32 (1H, d, *J* 3.1), 6.03 (1H, d, *J* 3.1), 5.75–5.55 (1H, m), 5.01–4.95 (2H, m), 3.94 (2H, s), 3.25–3.05 (1H, m), 2.60–1.90 (7H, m); *m*/*z* (CI) 330 (MNH_4^+), 313 (MH^+).

(2α,3β)-3-(5-Phenylthio-3-methyl-2-furyl)-2-(prop-2-enyl)-cyclopentanone 7b. Ketone **7b** (14.3 g, 74%) was obtained from 2-phenylthio-4-methylfuran, as a colourless oil after flash chromatography on silica, eluting with light petroleum–ether 9:1; ν_{max} (film) 3063, 2925, 1742 and 1640 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.08 (5H, m), 6.57 (1H, s), 5.70–5.45 (1H, m), 5.10–4.90 (2H, m), 3.26–3.07 (1H, m), 2.68–2.40 (2H, m), 2.39–2.26 (3H, m), 2.01 (3H, s); *m*/*z* (CI) 330 (MNH_4^+), 313 (MH^+).

(2α,3β)-3-(5-Benzylthio-3-methyl-2-furyl)-2-(prop-2-enyl)-cyclopentanone 7c. Ketone **7c** (19.7 g, 80%) was obtained from furan **22** as a white solid, mp 53–54 °C, after flash chromatography on silica, eluting with light petroleum–ether 9:1 (Found C, 73.69, H, 6.44, S, 9.60%; $C_{20}H_{22}O_2S$ requires C, 73.58, H, 6.79, S, 9.82%); ν_{max} (KBr disc) 3063, 2925, 1741 and 1640 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.28–7.13 (5H, m), 6.18 (1H, s), 5.61–5.53 (1H, m), 5.01–4.95 (2H, m), 3.97 (2H, s), 3.11–3.05 (1H, m), 2.52–2.46 (1H, m), 2.34–2.31 (1H, m), 2.26–2.22 (1H, m), 2.22–2.06 (4H, m), 1.90 (3H, s); δ_C (125 MHz, $CDCl_3$) 217.8, 153.4, 142.3, 137.8, 134.7, 128.8, 128.3 127.1, 121.0, 117.2, 117.1, 53.1, 41.1, 38.5, 38.0, 32.0, 26.4, 9.6; *m*/*z* (CI) 344 (MNH_4^+), 327 (MH^+).

Ketalisations of ketones 7

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-2-furyl)-2-(prop-2-enyl)cyclopentane 8a. In a flask equipped with a Dean and Stark apparatus under nitrogen were placed cyclopentanone **7a** (5.74 g, 18.4 mmol), ethylene glycol (1.9 mL, 34 mmol), pyridinium toluene-*p*-sulfonate (93 mg, 0.37 mmol) and benzene (155 mL). This mixture was refluxed under nitrogen for 17 h, then washed with 1 M NaOH solution (3 × 60 mL), brine (2 × 60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The pure ketal **8a** (6.3 g, 96%) was obtained as a colourless oil after column chromatography on silica, eluting with light petroleum–ether 4:1 (Found C, 70.73, H, 7.06%; $C_{21}H_{24}O_3S$ requires C, 70.76, H, 6.79%); ν_{max} (film) 3063, 2925, 1645 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.15 (5H, m), 6.25 (1H, d, *J* 3.0), 5.97 (1H, d, *J* 3.0), 5.85–5.63 (1H, m), 5.01–4.95 (2H, m), 4.26–4.05 (4H, m), 3.93 (2H, s), 3.00–2.83 (1H, m), 2.40–1.75 (7H, m); *m*/*z* (CI) 374 (MNH_4^+), 357 (MH^+).

(2α,3β)-1,1-Ethylenedioxy-3-(5-phenylthio-3-methyl-2-furyl)-2-(prop-2-enyl)cyclopentane 8b. Ketal **8b** (4.0 g, 62%) was obtained as a colourless oil after column chromatography on silica, eluting with light petroleum–ether 4:1; ν_{max} (film) 2972,

2880, 1640, 1453, 1434 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.34–7.03 (5H, m), 6.52 (1H, s), 5.72–5.46 (1H, m), 5.01–4.73 (2H, m), 4.06–3.81 (4H, m), 3.09–2.85 (1H, m), 2.53–2.17 (2H, m), 1.97 (3H, s), 2.17–1.73 (5H, m); *m*/*z* (CI) 357 (MH^+, 45%).

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-3-methyl-2-furyl)-2-(prop-2-enyl)cyclopentane 8c. Ketal **8c** (5.1 g, 75%) was obtained as a colourless oil after column chromatography on silica, eluting with light petroleum–ether, 4:1; ν_{max} (film) 2972, 2880, 1640, 1453, 1434 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 7.21–7.13 (5H, m), 6.09 (1H, s), 5.60–5.52 (1H, m), 4.94–4.80 (2H, m), 3.94–3.89 (6H, m), 2.86 (1H, m), 2.39–2.36 (1H, m), 2.23–2.19 (1H, m), 2.00–1.98 (2H, m), 1.89–1.80 (3H, m), 1.84 (3H, s); δ_C (100 MHz, $CDCl_3$) 155.4, 141.5, 137.9, 137.4, 128.8, 128.3, 127.1, 120.9, 117.2, 116.5, 114.5, 64.6, 64.4, 50.4, 41.0, 40.1, 35.6, 32.3, 27.0, 9.71; *m*/*z* (EI) 370 (M^+), 279, 91; $C_{22}H_{26}O_3S$ requires 370.1603, found 370.1602.

Anti-Markownikoff hydration

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-2-furyl)-2-(3-hydroxypropyl)cyclopentane 9a. Borane–dimethyl sulfide complex (7.0 mL, 2 M solution in THF, 14 mmol) was added dropwise to a stirred solution of the ketal **8a** (3.56 g, 10 mmol) in dry THF (35 mL) under nitrogen at 0 °C. The mixture was allowed to warm to 20 °C, then stirred for 2 h. The reaction was cooled to 0 °C, then water (1.1 mL, 60 mmol), 2 M NaOH solution (7.5 mL, 15 mmol) and hydrogen peroxide (1.1 mL, 18.5 M solution, 20 mmol) were added. The mixture was allowed to warm to 20 °C, then stirred for 1 h. The reaction mixture was poured into ether (60 mL) and washed with brine (25 mL). The aqueous phase was further extracted with ethyl acetate (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a pale yellow oil. The pure alcohol **9a** (2.9 g, 77%) was obtained as a colourless oil after flash chromatography on silica, eluting with ether (Found C, 67.56, H, 7.29, S, 8.24%; $C_{21}H_{26}O_4S$ requires C, 67.35, H, 7.00, S, 8.56%); ν_{max} (film) 3400, 1618, 1583, 1479 and 1441 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.15 (5H, m), 6.25 (1H, d, *J* 3.0), 5.98 (1H, d, *J* 3.0), 4.26–4.05 (4H, m), 3.94 (2H, s), 3.60–3.55 (2H, m), 2.95–2.80 (1H, m), 2.40–2.15 (1H, m), 2.05–1.30 (8H, m); *m*/*z* (CI) 374 (M^+), 313, 99, 91.

(2α,3β)-1,1-Ethylenedioxy-3-(5-phenylthio-3-methyl-2-furyl)-2-(3-hydroxypropyl)cyclopentane 9b. Alcohol **9b** (2.8 g, 75%) was obtained as a colourless oil after flash chromatography on silica, eluting with ether (Found C, 67.13, H, 6.60, S, 8.15%; $C_{21}H_{26}O_4S$ requires C, 67.35, H, 7.00, S, 8.56%); ν_{max} (film) 3436, 1618, 1583, 1479, 1441 cm^{-1}; δ_H(200 MHz, $CDCl_3$) 7.35–7.06 (5H, m), 6.54 (1H, s), 4.08–3.81 (4H, m), 3.59–3.39 (3H, m), 3.05–2.83 (1H, m), 2.35 (1H, dt, *J* 11.8, *J′* 5.9), 2.00 (3H, s), 2.05–1.74 (4H, m), 1.46–1.11 (4H, m); *m*/*z* (CI) 392 (MNH_4^+), 375 (MH^+).

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-3-methyl-2-furyl)-2-(3-hydroxypropyl)cyclopentane 9c. Alcohol **9c** (3.8 g, 87%) was obtained as a colourless oil after flash chromatography on silica, eluting with ether; ν_{max} (film) 3453, 2941, 1495 and 1453 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.14 (5H, m), 6.11 (1H, s), 3.97–3.91 (4H, m), 3.91 (2H, s), 3.52–3.46 (2H, m), 2.87–2.82 (1H, m), 2.32–2.28 (1H, m), 1.88 (3H, s), 1.88–1.79 (4H, m), 1.55–1.50 (1H, m), 1.43–1.28 (4H, m); δ_C (100 MHz, $CDCl_3$) 155.6, 141.6, 137.8, 128.8, 128.3, 127.0, 120.9, 117.4, 116.4, 64.5, 64.4, 63.3, 49.8, 40.9, 40.8, 35.4, 30.4, 27.3, 24.1, 9.7; *m*/*z* (EI) 388 (M^+), 326, 235, 203, 91; $C_{22}H_{28}O_4S$ requires 388.1708, found 388.1709.

Alcohol oxidation by the Swern method

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-2-furyl)-2-(3-oxopropyl)cyclopentane 10a. Dimethyl sulfoxide (3.3 mL, 46 mmol) was added dropwise to a stirred solution of oxalyl chloride (2.4 mL, 27.5 mmol) in CH_2Cl_2 (18 mL) under nitrogen over 10 min at −78 °C. The temperature of the reaction did not rise above −58 °C. The mixture was stirred for 10 min, then a solution of the alcohol **9a** (2.88 g, 7.7 mmol) in CH_2Cl_2 (24 mL) was added dropwise. The resultant mixture was stirred for 40 min at −78 °C, then triethylamine (10 mL, 72 mmol) was added dropwise and the reaction was allowed to warm to 20 °C. The suspension was diluted with CH_2Cl_2 (300 mL) and washed with water (60 mL), saturated aqueous copper sulfate (2 × 60 mL), 2 M NaOH solution (2 × 60 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude aldehyde **10a** (2.8 g, quant.) as an orange oil. This was used in the next step without further purification; ν_{max} (film) 2946, 2883, 1720, 1495, 1454 cm^{-1}; δ_H(200 MHz, $CDCl_3$) 9.68 (1H, t, *J* 1.3), 7.35–7.16 (5H, m), 6.27 (1H, d, *J* 3.1), 6.01 (1H, d, *J* 3.1), 3.95–3.81 (4H, m), 3.74 (2H, s), 2.95–2.80 (1H, m), 2.37 (2H, dt, *J* 7.4, *J′* 1.3), 2.30–2.15 (1H, m), 2.05–1.60 (6H, m); *m*/*z* (CI) 373 (M^+), 267, 99, 91.

(2α,3β)-1,1-Ethylenedioxy-3-(5-phenylthio-3-methyl-2-furyl)-2-(3-oxopropyl)cyclopentane 10b. Aldehyde **10b** (2.7 g, 94%) was isolated as a highly unstable yellow oil and used immediately in the next step.

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-3-methyl-2-furyl)-2-(3-oxopropyl)cyclopentane 10c. Aldehyde **10c** (2.84, 95%) was obtained as an orange oil; ν_{max} (film) 2946, 2883, 1723, 1495, 1454 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 9.62 (1H, t, *J* 1.5), 7.35–7.16 (5H, m), 6.15 (1H, s), 3.95–3.81 (4H, m), 3.75 (2H, s), 2.87–2.81 (1H, m), 2.31–2.17 (3H, m), 1.95–1.87 (6H, m), 1.83 (3H, s); δ_C (100 MHz, $CDCl_3$) 202.4, 154.8, 141.9, 137.8, 128.8, 128.4, 127.0, 120.8, 116.9, 116.7, 64.5, 64.4, 49.2, 41.8, 40.9, 40.4, 35.1, 29.5, 19.6, 9.6; *m*/*z* (EI) 386 (M^+), 91; $C_{22}H_{26}O_4S$ requires 386.1552, found 386.1560.

Addition of methyl 3-lithiopropynoate to aldehydes 10

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-2-furyl)-2-(3-hydroxy-5-methoxycarbonylpent-4-ynyl)cyclopentane 11a. *n*-Butyllithium (4.2 mL, 1.6 M solution in hexane, 6.7 mmol) was added dropwise to a stirred solution of methyl propynoate (555 mL, 6.2 mmol) in dry THF (8 mL) under nitrogen at −78 °C. The mixture was stirred for 20 min, then a solution of aldehyde **10a** (1.93 g, 5.2 mmol) in dry THF (13 mL) cooled to −78 °C was slowly added *via* cannula. The reaction was stirred for a further 40 min at −78 °C, then quenched with saturated aqueous ammonium chloride (9 mL) and allowed to warm to 20 °C. The reaction was poured into ether (85 mL) and washed with water (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a red oil. The pure alkyne **11a** was obtained as a colourless oil (1.9 g, 80%) after flash chromatography on silica, eluting with hexane–ethyl acetate, 2:1 (Found C, 65.52, H, 6.38%; $C_{25}H_{28}O_6S$ requires C, 65.77, H, 6.18%); ν_{max} (film) 3420, 2235, 1710 and 1254 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.15 (5H, m), 6.26 (1H, d, *J* 3.1), 6.00 (1H, d, *J* 3.1), 4.31 (1H, t, *J* 6.1), 4.10–3.90 (4H, m), 3.84 (2H, s), 3.76 (3H, s), 3.06–2.83 (1H, m), 2.50–2.10 (2H, m), 2.10–1.45 (7H, m); *m*/*z* (CI) 474 (MNH_4^+), 456 (MH^+).

(2α,3β)-1,1-Ethylenedioxy-3-(5-phenylthio-3-methyl-2-furyl)-2-(3-hydroxy-5-methoxycarbonylpent-4-ynyl)cyclopentane 11b. Alcohol **11b** was obtained as a yellow oil (1.4 g, 72%) after flash chromatography on silica, eluting with light petroleum–ether, 1:1 (Found C, 65.89, H, 6.18, S, 7.05%; $C_{25}H_{28}O_6S$ requires C, 66.77, H, 6.18, S, 7.02%); ν_{max} (film) 3452, 1717 and 1254 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.05 (5H, m), 6.54 (1H, s), 4.35 (1H, t, *J* 6.1), 4.08–3.82 (5H, m), 3.78 (3H, s), 3.06–2.83 (1H, m), 2.43–2.14 (2H, m), 2.00 (3H, s), 2.14–1.71 (7H, m); *m*/*z* (CI) 474 (MNH_4^+), 457 (MH^+).

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-3-methyl-2-furyl)-2-(3-hydroxy-5-methoxycarbonylpent-4-ynyl)cyclopentane 11c. Alcohol **11c** was obtained as a yellow oil (1.5 g, 60%) after flash chromatography on silica, eluting with light petroleum–ethyl acetate, 2:1; ν_{max} (film) 3418, 3062, 3029, 1720, 1716, 1454 and 1435 cm^{-1}; δ_H (400 MHz, C_6D_6) 7.37–7.17 (5H, m), 6.20 (1H, s), 4.32–4.30 (1H, m), 3.92 (2H, s), 3.76–3.61 (4H, m), 3.40 (3H, s), 3.11–3.06 (1H, m), 2.59–2.50 (1H, m), 2.06–1.42 (9H, m), 1.84 (3H, s); δ_C (100 MHz, C_6D_6) 155.7, 153.9, 142.9, 138.5, 128.5, 128.3, 127.1, 121.3, 117.4, 116.7, 89.2, 76.5, 64.5, 64.4, 62.1, 52.1, 50.1, 41.1, 40.9, 35.7, 35.2, 27.4, 23.6, and 9.5; *m/z* 470 (M^+), 409, 326, 91; $C_{26}H_{30}O_6S$ requires 470.17063, found 470.1749.

Catalytic hydrogenation of the alkyne to a (*Z*)-alkene

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-2-furyl)-2-[(4*Z*)-3-hydroxy-5-methoxycarbonylpent-4-enyl)cyclopentane 12a. A solution of the alkyne **12a** (958 mg, 2.1 mmol) and palladium on barium sulfate (700 mg, 5%) in ethyl acetate (24 mL) was vigorously stirred under hydrogen at atmospheric pressure for 3 h, then the reaction was filtered through a pad of Celite washed with ethyl acetate (80 mL) and the filtrate concentrated *in vacuo* to give the allylic alcohol **11a** (962 mg, quant.) as an orange oil. This compound was used in the next step without further purification; ν_{max} (film) 3450, 2951, 2881, 1718, 1645 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.15 (5H, m), 7.15 (2H, d, *J* 7.7), 6.24 (1H, d, *J* 3.0), 6.24–6.20 (1H, m), 5.99 (1H, d, *J* 3.0), 5.82 (1H, d, *J* 11.8), 4.83–4.80 (1H, m), 4.05–3.95 (4H, m), 3.93 (2H, s), 3.73 (3H, s), 3.40 (1H, s), 2.90–2.85 (1H, m), 2.30–2.10 (1H, m), 2.10–1.35 (8H, m); *m/z* (CI) 459 (MH^+).

(2α,3β)-1,1-Ethylenedioxy-3-(5-phenylthio-3-methyl-2-furyl)-2-[(4*Z*)-3-hydroxy-5-methoxycarbonylpent-4-enyl]cyclopentane 12b. Alcohol **12b** (962 mg, quant.) was obtained as a brown oil. This compound was very prone to lactonisation and was therefore used immediately in the next step.

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-3-methyl-2-furyl)-2-[(4*Z*)-3-hydroxy-5-methoxycarbonylpent-4-enyl]cyclopentane 12c. Alcohol **12c** (1.0 g, quant.) was obtained as a brown oil; ν_{max} (film) 3467, 2951, 2881, 1721, 1716, 1698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.15 (5H, m), 6.20 (1H, d, *J* 11.7), 6.12 (1H, s), 5.80–5.75 (1H, m), 4.72–4.69 (1H, m), 4.26 (2H, s), 4.09–4.02 (4H, m), 3.61 (3H, s), 2.90–2.85 (1H, m), 2.33–2.30 (1H, m), 1.98–1.85 (4H, m), 1.90 (3H, s), 1.70–1.32 (5H, m); δ_C (100 MHz, $CDCl_3$) 167.0, 155.4, 152.8, 141.6, 137.8, 128.8, 128.4, 127.0, 120.9, 119.6, 117.3, 116.4, 68.4, 65.8, 64.4, 51.5, 49.8, 40.9, 40.7, 35.4, 34.3, 27.0, 23.4, 9.6; *m/z* 440 ($M^+ - CH_3OH$), 396, 91; $C_{25}H_{28}O_5S$ requires 440.1657, found 440.1628.

Oxidation of alcohols 12

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-3-methyl-2-furyl)-2-[(4*Z*)-3-oxo-5-methoxycarbonylpent-4-enyl]cyclopentane 13c. A solution of the allylic alcohol **12c** (962 g, 2.1 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of Dess–Martin periodinane (980 mg, 2.3 mmol),[48,49] in CH_2Cl_2 (24 mL) under nitrogen at 20 °C. The reaction was stirred for 20 min, then poured into saturated aqueous sodium sulfate (30 mL) and extracted with ether. The extract was washed with saturated aqueous sodium sulfate (2 × 30 mL), saturated aqueous sodium bicarbonate (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *cis*-enedione **13c** (950 mg, 95%) as a yellow oil; ν_{max} (film) 3016, 2908, 1730, 1704, 1507 and 1496 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.14 (5H, m), 6.33 (1H, d, *J* 12.1), 6.14 (1H, s), 5.94–5.90 (1H, m), 3.96–3.91 (6H, m), 3.69 (3H, s), 2.51–2.36 (3H, m), 2.28–2.23 (1H, m), 1.96–1.77 (4H, m), 1.87 (3H, s), 1.73–1.51 (2H, m); δ_C (100 MHz, $CDCl_3$) 203.3, 199.5, 166.1, 155.2, 142.0, 141.6, 137.8, 129.9, 128.9, 127.3, 120.9, 117.2, 116.7, 64.6, 64.3, 52.3, 49.3, 41.0, 40.8, 39.9, 35.2, 27.1, 21.3, 9.7; *m/z* 470 (M^+), 91; $C_{26}H_{30}O_6S$ requires 470.1763, found 470.1770.

(2α,3β)-1,1-Ethylenedioxy-3-(5-benzylthio-2-furyl)-2-[4*Z*)-3-oxo-5-methoxycarbonylpent-4-enyl]cyclopentane 13a. Ester **13a** (699 mg, 73%) was obtained as a yellow oil; ν_{max} (film) 3450, 2908, 1718, 1645 and 1496 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.04 (5H, m), 6.30–6.24 (1H, m), 6.24 (1H, d, *J* 3.0), 5.99 (1H, d, *J* 3.0), 5.82 (1H, d, *J* 11.8), 4.80–4.78 (1H, m), 4.05–3.90 (4H, m), 3.89 (2H, s), 3.73 (3H, s), 3.40–3.35 (1H, m), 2.89–2.85 (1H, m), 2.30–2.10 (1H, m), 2.10–1.35 (8H, m); *m/z* (CI) 459 (MH^+, 1%), 427 (100%).

(2α,3β)-1,1-Ethylenedioxy-3-(5-phenylthio-3-methyl-2-furyl)-2-[4*Z*)-3-oxo-5-methoxycarbonylpent-4-enyl]cyclopentane 13b. Ester **13b** (708 mg, 74%) was obtained as a yellow oil; ν_{max} (film) 3016, 2908, 1726, 1704, 1624 and 1496 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35–7.04 (5H, m), 6.54 (1H, s), 6.34 (1H, d, *J* 12.1), 5.97 (1H, d, *J* 12.1), 4.09–3.84 (4H, m), 3.73 (3H, s), 3.09–2.83 (1H, m), 2.62–2.17 (4H, m), 2.00 (3H, s), 2.10–1.72 (5H, m); *m/z* (CI) 457 (MH^+).

Ultra-high pressure mediated IMDAF

(2α,6β,10α,11α)-12-Benzylthio-5,5-ethylenedioxy-11-methoxycarbonyl-15-oxatetracyclo[10.2.1.0^{3,12}.0^{7,11}]pentadeca-13-en-9-one 14a.‡ The *cis*-enedione **13a** (250 mg, 532 mmol) in CH_2Cl_2 (5 mL) was subjected to high pressure conditions of 19 Kbar for 15 h at 20 °C. The reaction solution was filtered through a plugged pipette containing cotton wool and washed with CH_2Cl_2 (15 mL). The filtrate was concentrated *in vacuo* to give a brown oil which was triturated with ether to form a yellow foam. The pure cycloadduct **14a** (165 mg, 68%) was obtained as a colourless fine needles mp 115–118 °C after recrystallisation (hexane–CH_2Cl_2) (Found C, 65.47, H, 6.23%; $C_{25}H_{28}O_6S$ requires C, 65.77, H, 6.18%); ν_{max} (KBr disk) 1740 and 1692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.20 (5H, m), 6.76 (1H, d, *J* 5.6), 6.14 (1H, d, *J* 5.6), 4.05–3.95 (6H, m), 3.92 (1H, d, *J* 9.2), 3.64 (3H, s), 3.20 (1H, d, *J* 9.2), 2.63 (1H, ddd, *J* 19.0, *J′* 3.7, *J″* 3.7), 2.50–2.35 (1 H, m), 2.26 (1H, ddd, *J* 19.0, *J′* 12.5, *J″* 6.0), 2.00–1.80 (5H, m), 1.75 (1H, t, *J* 11.0), 1.65–1.50 (1H, m); *m/z* (CI) 474 (MNH_4^+), 457 (MH^+).

(2α,6β,10α,11α)-12-Benzylthio-5,5-ethylenedioxy-11-methoxycarbonyl-14-methyl-15-oxatetracyclo[10.2.1.0^{3,12}.0^{7,11}]-pentadeca-13-en-9-one 14c.‡ Tetracycle **14c** (113 mg, 45%) was obtained as a colourless solid, mp 121–122 °C after recrystallisation (ether–light petroleum); ν_{max} (KBr disk) 2951, 2882, 1734, 1710 and 1242 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.21 (5H, m), 6.44 (1H, s), 4.00–3.93 (7H, m), 3.62 (3H, s), 3.13 (1H, d, *J* 9.2), 2.70–2.64 (1H, m), 2.48–2.29 (2H, m), 2.08–1.79 (7H, m), 1.78 (3H, s); δ_C (62.5 MHz, $CDCl_3$) 205.6, 170.6, 143.1, 139.6, 138.0, 135.9, 129.1, 128.3, 126.8, 116.8, 93.9, 92.5, 65.2, 64.5, 62.4, 53.6, 51.6, 48.7, 48.1, 43.0, 34.5, 23.4, 21.7, 15.9; *m/z* (CI) 471 (MH^+); $C_{26}H_{31}O_6S$ requires 471.1841, found 471.1854.

(2α,6β,10α,11α)-12-Benzylthio-5,5-ethylenedioxy-11-methoxycarbonyl-15-oxatetracyclo[10.2.1.0^{3,12}.0^{7,11}]pentadecan-9-one 15a.‡ A mixture of the cycloadduct **14a** (112 mg, 245 μmol) and palladium on barium sulfate (555 mg, 5%) in ethyl acetate (20 mL) was vigorously stirred under hydrogen at 15 bar for 24 h, then the reaction was filtered through a pad of Celite washed with ethyl acetate (80 mL) and the filtrate concentrated *in vacuo*. Pure **15a** (93 mg, 83%) was obtained as colourless prisms, mp 142–145 °C after recrystallisation (methanol) (Found C, 65.73, H, 6.69%; $C_{25}H_{30}O_6S$ requires C, 65.48, H,

‡ The α and β stereodescriptors in this name refer to the orientation of the hydrogen atoms with respect to the plane of the cycloheptane ring, α being below the plane, and β above the plane.

6.59%); ν_{max} (KBr disk) 1738 and 1691 cm^{-1}; δ_H(500 MHz, $CDCl_3$) 7.40–7.20 (5H, m), 4.00–3.85 (6H, m), 3.64 (1H, dd, *J* 11.5, *J′* 2.1), 3.63 (3H, s), 3.09 (1H, dd, *J* 11.5, *J′* 2.4), 2.90–2.80 (1H, m), 2.61 (1H, ddd, *J* 19.0, *J′* 3.8, *J″* 3.8), 2.51–2.45 (1H, m), 2.32 (1H, ddd, *J* 19.0, *J′* 13.0, *J″* 4.4), 1.95–1.70 (7H, m), 1.67–1.57 (2H, m), 1.50–1.45 (1H, m); *m/z* (CI) 459 (MH^+).

(2α,6β,10β,11α)-12-Benzylthio-5,5-ethylenedioxy-11-methoxycarbonyl-15-oxatetracyclo[10.2.1.0^{3,12}.0^{7,11}]pentadecan-9-one 16a.‡ To a solution of the *cis-endo*-cycloadduct **15a** (147 mg, 322 μmol) in dry methanol (15 mL) was added sodium methoxide solution (3 mL, 3.3 mmol). The mixture was allowed to stand at room temperature for 20 h. After concentration of the reaction mixture, water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic layers were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Epimerised material **16a** (270 mg, 84%) was obtained as colourless prisms, mp 175–176 °C by trituration of the residual solid with ether (Found C, 65.28, H, 6.45%; $C_{25}H_{30}O_6S$ requires C, 65.48, H, 6.59%); ν_{max} (KBr disk) 1724 and 1704 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.20 (5H, m), 4.14 (1H, d, *J* 12.0), 4.05 (1H, d, *J* 12.0), 4.00–3.88 (5H, m), 3.73 (3H, s), 3.53 (1H, d, *J* 6.4), 2.63 (1H, ddd, *J* 13.0, *J′* 6.0, *J″* 6.0), 2.52 (1H, ddd, *J* 13.0, *J′* 11.0, *J″* 6.0), 2.30–2.18 (1H, m), 2.13–1.60 (11H, m); *m/z* (CI) 476 (MNH_4^+), 459 (MH^+).

(1α,6α,7β,11β)-Methyl 2-hydroxy-5,8,12-trioxotricyclo[9.3.0.0^{2,7}]tetradecane-6-carboxylate.‡ A mixture of **16a** (640 mg, 140 μmol) and mercuric chloride (76 mg, 280 μmol) in acetonitrile–water (4:1, 3 mL) was stirred at 50 °C under nitrogen for 8 days. After addition of ethyl acetate (30 mL) and water (20 mL), the mixture was filtered through Celite and the layers separated. The aqueous solution was extracted with ethyl acetate (2 × 20 mL), the organic layers combined, washed with brine (4 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Pure **17a** (280 mg, 57%) was obtained as a colourless solid, mp 178–181 °C after flash chromatography on silica, eluting with ethyl acetate–chloroform, 2:1; ν_{max} (KBr disk) 3520, 3340, 1740, 1727 and 1700 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.35 (1H, d, *J* 12.9), 3.75 (3H, s), 3.64 (1H, d, *J* 12.9), 3.03–2.70 (2H, m), 2.60–2.08 (9H, m), 2.08–1.60 (4H, m); *m/z* (CI) 326 (MNH_4^+), 309 (MH^+).

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