Enantiopure Didemnenones *via* Kinetic Resolution

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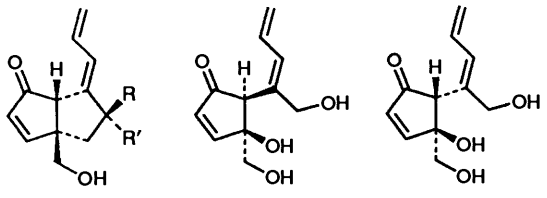
Kinetic resolution in an enantioselective Diels–Alder process provided the starting material for an improved and simplified approach to all the didemnenones *via* the lactone **16**.

In addition to cyclic peptides of unusual structure and interesting biological activity, the caribbean tunicates provide the so called didemnenones A and B **1**,[1] which are a mixture of epimeric lactols, as well as the didemnenones C and D **2** which represent the corresponding diols.

For a variety of reasons, these comparatively small molecules immediately aroused the interest of synthetic chemists.[2–4] First, they have been shown to exhibit both toxicity against leukemia cell lines as well as antibacterial and antifungal activity.[1] Second, since they are molecules with diverse functionality, every carbon atom is, in fact, functionalized, their synthesis represents a special challenge. Some help may be expected from the fact, however, that methanol under slightly acidic conditions converts the epimeric lactols **1a** and **1b** into one single crystalline acetal **1c**, thus rendering this easily characterized material the molecule of choice for synthesis. Third, the absolute configuration of didemnenone C **2a** which was isolated from *Didemnum voeltzkowi* turned out to be different from that of didemnenone A and B isolated from *Tridemnum cyanophorum*. This is an interesting stereochemical aspect indicating that two different organisms produce related metabolites in an enantiomeric series.



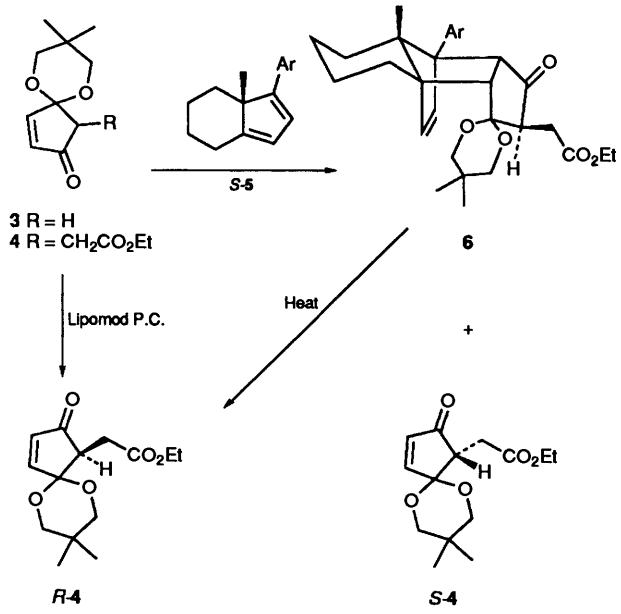
1 **2a** **2b**

a R = H, R' = OH
b R = OH, R' = H
c R = H, R' = OMe

Scheme 1

Taken together, these reasons provide a good case for the development of an enantioselective synthesis, offering high configurational flexibility, to afford both enantiomers. This last requirement was, unfortunately, not met by our first synthetic approach,[4] since in that case the chiral starting material was prepared *via* kinetic resolution of the ester **4** (see Scheme 2) with the lipase Lipomod P.C. This provided the starting material only for the didemnenones A and B, the other enantiomer being hydrolysed to the corresponding acid. This, owing to the acid labile ketal group, created serious problems in all our efforts to isolate and purify the enantiomer.

Since the stereogenic centre in this compound is located next to a carbonyl group, non-racemizing conditions for resolution, work-up and purification were highly desirable and we were, therefore, pleased to note that the enantiopure cyclopentadiene **5** reacted almost exclusively with the '*R*'-enantiomer of **4** at room temperature under high pressure conditions[5] (12 kbar), to form the Diels–Alder adduct **6**. The corresponding '*S*'-enantiomer ('*S*'-**4**) was added only to a very small extent



Scheme 2

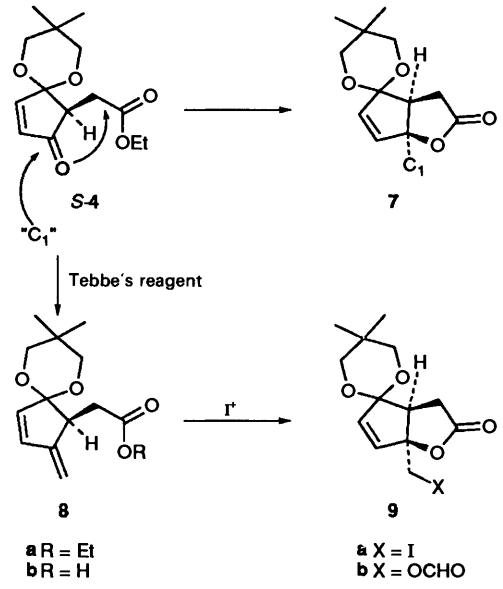
(≃4%), which guaranteed a very high enantiomeric excess (>98%ee) for this remaining enantiomer. The adduct **6** could easily be purified by flash chromatography to yield exactly 50% of the sterically homogenous adduct **6** which, under high vacuum pyrolysis (300 °C), reverted to the '*R*'-**4** enantiomer (>98%ee) and the constitutionally as well as configurationally unchanged cyclopentadiene **5** (quantitative yield).

Having the '*R*'-**5** enantiomer available too,[6] makes available '*R*'-**4** without the thermal retro-process. Since these possibilities give access to **1a** and **1b** as well as to the enantiomeric triols **2a**/**2b** and their corresponding antipodes, this approach is shown to be of high configurational flexibility.

In continuing our investigations we decided to concentrate on the '*S*'-**4** keto ester which can give access to the not yet available, non-natural enantiomer of the didemnenones A and B and to the, as yet, unsynthesized didemnenones C and D.

The problem of absolute configurations being solved, we focussed on the selection of the C_1-nucleophile which is needed to convert '*S*'-**4** into the general lactone intermediate **7**. In our first generation synthesis,[4] a thioketal had been used for this purpose, but this proved less than satisfactory because it led to mercury salt deketalization and gave the wrong oxidation state for the corresponding carbon-atom; this resulted in an additional reduction step at a later stage of the synthesis.

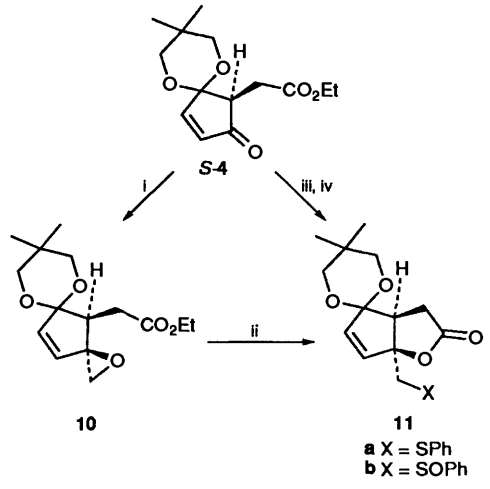
In our first alternative we employed Tebbe's reagent[7] instead and were indeed able to secure a high yield of the diene ester **8a** which, after hydrolysis to the acid **8b**, underwent very efficient iodolactonization to provide pure **9a** in 72% yield. The subsequent attempted nucleophilic displacement of the iodo



Scheme 3

atom, however, proved to be an unsatisfactory process, an array of polar solvents together with potassium formate combined with crown ethers failing to give yields >65%; this line of investigation was terminated when selective hydrolysis of the formate in the presence of the lactone group proved to be impossible.

In an attempt to overcome the problem of steric hindrance which is, of course, due to the neighbouring quaternary carbon atom, we also prepared the epoxide **10** and the sulfoxide **11b** (see Scheme 4). In the first case we hoped to benefit from

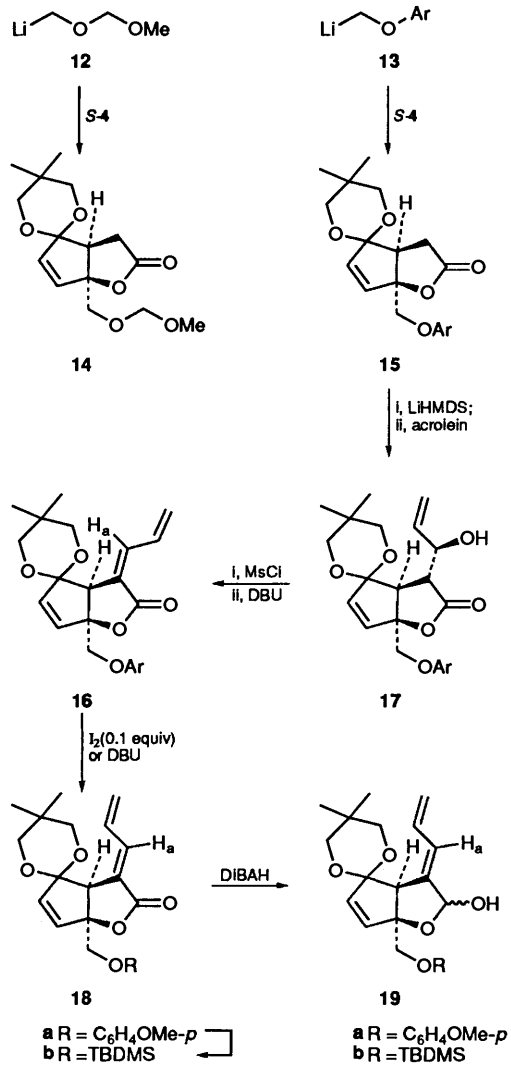


Scheme 4 *Reagents:* i, $Me_3S^+I^-$, base; ii, 1. PhSH, 2. IO_4^-; iii, $LiCH_2SPh$; iv, IO_4^-

cleavage of the three-membered ring and in the second case assistance was expected from the fact that in the crucial Pummerer rearrangement[8] primary attack takes place at the more distant oxygen atom of the sulfoxide.

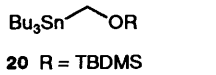
The epoxide **10** was easily prepared in 85% yield by employing Corey's sulfur-ylide[9] and **11b** was obtained either from the lithium salt of thioanisole, followed by an oxidation with metaperiodate (overall yield 50%) or, in a straightforward manner, by nucleophilic opening of the epoxide **10**. Although the nucleophilic attack at the carbonyl group of the five-membered ring took place with excellent diastereoselectivity in both cases, all attempts to open the epoxide selectively or to induce a Pummerer rearrangement with the sulfoxide **11b** met with failure.

To incorporate the oxygen atom properly into the nucoeophile from the very start, we next concentrated on nucleophilic C_1-ether derivatives such as **12** and **13** (see Scheme 5).



Scheme 5

Both were smoothly prepared from the corresponding tin compounds[10,11] in an efficient transmetallation process. Interestingly, the tin precursor of the hydroquinone ether **13** is unrecorded in the literature but was easily prepared by nucleophilic substitution with the corresponding phenolate and tributyl(iodomethyl)stannane.[11] This new C_1-nucleophile combined high efficiency with excellent diastereoselectivity and since deprotection was achieved with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile (see below) we considered this material the reagent of choice for our purpose. It should also be mentioned at this stage, that other possible candidates such as compounds **20**–**22** gave unsatisfactory results in this



20 R = TBDMS
21 R = $CH_2C_6H_4OMe$-*p*
22 R = SEM

reaction. Thus, compound **20** in spite of a smooth transmetallation failed to attack at all, probably owing to its spatial requirements, compound **21** suffered from a fast transprotonation of the more acidic benzylic protons once the lithium derivative was formed, and the SEM-ether **22** simply decomposed under the reaction conditions employed.

In contrast to this, compounds **12** and **13** gave rise to the corresponding lactones **14** and **15** in an acceptable chemical yield (≃ 60%) and with high diastereoselectivity and, since subsequent experiments disclosed quite forcing and prohibitive reaction conditions for the deprotection of the MOM-derivative **14**, we focussed on the lactone **15** as the most promising intermediate.

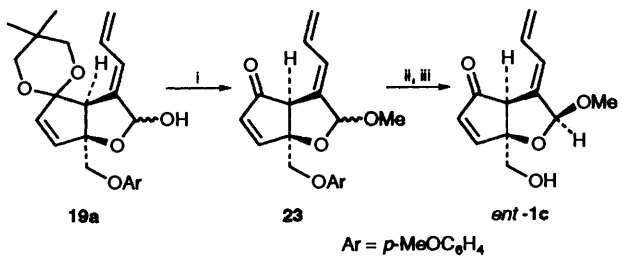
As experienced in our first generation synthesis[4] the subsequent aldol addition of acrolein provided one single diastereoisomer **17** in 70% yield, which is absolutely in line with the Zimmerman–Traxler transition-state model. As reported before, the base catalysed E_2 elimination of the corresponding mesylate generated, under kinetically controlled conditions, the non-natural *Z*-configuration of the exocyclic double bond exclusively (see **16**), although Takano[3] and his colleagues in a very similar case had secured a 61:26 *Z*/*E* ratio, providing at least a small amount of the desired (*E*)-butadiene.

In our first approach, we had gained access to this particular material by retreating to the *syn*-elimination mode of an E_{ICB} process.[4] Since, however, the yield of the E_2 elimination was consistently higher (≃ 90%), than the one of the E_{ICB} route (≃ 50%), we decided to explore the *E*/*Z* equilibration of the butadiene system too. In this endeavour we were encouraged by experiments from Takanos group,[3] who had observed a successful *E*/*Z* isomerization on treatment of similar butadienes with lithium 1-methylethanethiolate at room temperature, which provided a 75:25 ratio in favour of the desired *E*-isomer. When these conditions were applied to our pure *Z*-isomer **16** the result was a meagre and synthetically unacceptable 1:5 *E*/*Z* ratio, favouring strongly the unwanted *Z*-isomer. From the mechanistic point of view one is certainly dealing here with a nucleophilic key step; however, as Sonnet in his excellent review article[12] demonstrated, there is a wide range of possibilities available and, thus, we decided to investigate electrophilic processes too. Although with an electron poor butadiene such as **16** there were doubts as to its ability to take part in such reactions, since Hollingworth and Sweeney[13] had already used iodine in dichloromethane very successfully with unsaturated lactones, we treated **16** under Sweeney's conditions and were pleased to observe its slow but clean conversion into the pure *E*-isomer **18a** in quantitative yield.

An even simpler, although slower, solution of the problem was provided by a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated elimination of the mesylate at room temperature. This gave clean conversion of the kinetically controlled *Z*-isomer **16** into the more stable *E*-isomer in excellent yield. This procedure saves one step and provides direct access from aldol **17** to the desired diene **18a**.

The stereochemical problems having thus been solved, straightforward functional group manipulation alone was left. This started with the quite reliable diisobutyl aluminium hydride (DIBAH) reduction[14] to generate the lactol **19a** in 96% yield. Subsequent treatment with methanol and toluene-*p*-sulfonic acid led not only to methyl ether formation but also, simultaneously, deketalization which provided, directly, a 75% yield of the cyclopentenone **23** (Scheme 6).

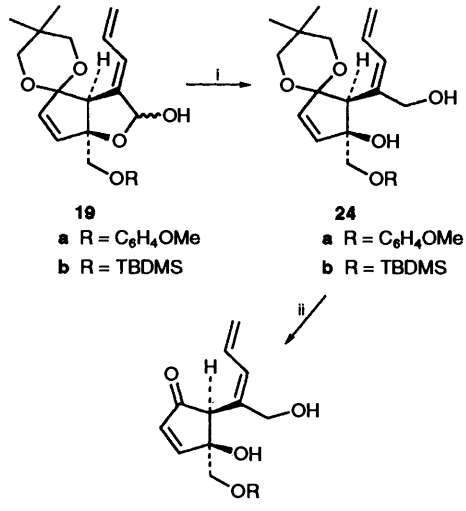
The final step called for oxidative cleavage of the hydroquinone ether in the presence of a hidden aldehyde group and, since such reactions are generally carried out in aqueous acetonitrile, some concern was certainly justified. To our great delight, however, deprotection with CAN (2.4 equiv.) followed by treatment with methanol and acid, gave rise to a high yield of



Scheme 6 *Reagents and conditions:* i, MeOH, *p*-TsOH; ii, CAN, $MeCN/H_2O$, 0 °C; iii, MeOH, *p*-TsOH

the methyl ether corresponding to the enantiomer of didemnenone A.

For the preparation of didemnenone C, we went back to the DIBAH reduction of the lactone **18a** and found that the corresponding lactol **19a**, even with a surplus of the reducing reagent, was not converted into the corresponding diol. However, a number of successful Wittig reactions with lactols[15] prove, very clearly, that ring opening of this moiety to the corresponding aldehyde does take place in the presence of a proton-accepting species. With these results in mind we treated compounds **19a** and **19b** with borohydride in the presence of potassium *tert*-butoxide and found that they were cleanly reduced to a moderately polar material, which proved to be the diols **24a** and **24b**. Our experience with compound **24** suggested that deprotection of compound **25a** would be difficult, and this proved to be the case. Thus, following a similar procedure to that adopted for compound **19a**, **24a** was hydrolysed to give the diol **25a**, but the subsequent attempted oxidation with CAN failed. With the silyl ether **24b**, however, opening of the ketal with catalytic amounts of hydrochloric acid in aqueous acetone at 40 °C was accompanied by hydrolysis of the silyl ether to provide didemnenone C **2a**.



Scheme 7 *Reagents and conditions:* i, $NaBH_4$, KOBu^t, Pr^{i}OH; ii, cat. HCl, acetone/H_2O, 40 °C

Experimental

UV spectra were measured in methanol on a Beckman 3600 instrument and IR spectra on a Perkin-Elmer 581 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 200 instrument and δ values are given relative to tetramethylsilane; *J* values are given in Hz. Mass spectra were determined with a Finnigan MAT 312 instrument at 70 eV. Optical rotations were

measured in chloroform on a Perkin-Elmer 241 polarimeter, using the sodium-D line; values are recorded as 10^{-1} deg cm^2 g^{-1}. For flash chromatography silica gel (300–600 mesh, Baker) was used at 0.4 bar. All solvents were dried by the standard methods. Ether refers to diethyl ether and light petroleum refers to the fraction with b.p. 45–60 °C.

(3aR*,6aR*)-6a-(*Iodomethyl*)-5'5'-*dimethyl*-3a,6a-*dihydrospiro*[4H-*cyclopenta*[*b*]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **9a**. —Methyllithium (4.1 mmol) was added to a cooled (0 °C) solution of titanocene dichloride (0.5 g, 2 mmol) in dry ether (10 cm^3) under an atmosphere of argon and in the dark. The mixture was allowed to warm to room temperature and stirring was continued for 15 min, after which ice–water (3 cm^3) was added slowly. The phases were separated and the organic layer was dried ($MgSO_4$) and, at 20 °C in the dark, evaporated to yield the Tebbe reagent (0.280 g, 91%). To a solution of the keto ester **4** (100 mg, 0.373 mmol) in dry toluene (15 cm^3) was added the Tebbe reagent (194 mg, 0.933 mmol), and the mixture was stirred in the dark at 75 °C for 5 days. The solution was poured into aqueous ammonium chloride (saturated) and extracted with ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (ether–light petroleum, 1:2) to yield the diene **8a** (70 mg, 71%); $\nu_{max}(CHCl_3)$/cm^{-1} 1728 and 1120; $\delta_H(CDCl_3$, 200 MHz) 0.78 (3 H, s), 1.16 (3 H, s), 1.27 (3 H, tr, *J* 7), 2.36 (1 H, dd, *J* 16/7), 2.72 (1 H, dd, *J* 16/7), 3.19–3.86 (5 H, m), 4.19 (2 H, q, *J* 7), 4.86 (1 H, m), 5.04 (1 H, d, *J* 2), 6.41 (1 H, d, *J* 6) and 6.77 (1 H, dd, *J* 6/2); *m/z* 266 (M$^+$, 36%).

Compound **8a** (140 mg, 0.526 mmol) was immediately hydrolysed with sodium carbonate (280 mg, 2.64 mmol, 5 equiv.) in methanol–water (1:1; 12 cm^3) under reflux for 4 h after which the mixture was evaporated. The crude residue was redissolved in saturated aqueous sodium hydrogen carbonate (4 cm^3) and, at 0 °C, treated with a solution of iodine (135 mg, 0.531 mmol) in ether (10 cm^3). Stirring at 0 °C was continued for 10 min, after which the mixture was allowed to warm to room temperature. After 3 h the reaction mixture was poured into aqueous sodium thiosulfate (15%) and extracted with ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. Subsequent purification of the residue by flash chromatography (ether–light petroleum, 1:2) afforded the iodo lactone **9a** (136 mg, 71%); $\nu_{max}(CHCl_3)$/cm^{-1} 1784, 1196 and 1008; $\delta_H(CDCl_3$, 200 MHz) 0.94 (3 H, s), 1.07 (3 H, s), 2.77–3.00 (2 H, m), 3.21 (1 H, dd, *J* 12/6), 3.36–3.77 (6 H, m), 6.12 (1 H, d, *J* 6) and 6.51 (1 H, d, *J* 6); *m/z* 364 (M$^+$, 4%) (Found: M, 364.016 179. $C_{13}H_{17}IO_4$ requires *M*, 364.017 162).

(3aR*,3aR*)-6a-(*Formyloxymethyl*)-5'5'-*dimethyl*-3a,6a-*dihydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **9b**.—A solution of the iodo lactone **9a** (30 mg, 0.082 mmol) and sodium formate (56 mg, 0.966 mmol, 12 equiv.) in dimethylformamide (3 cm^3) was stirred at 65 °C for 5 days. After standard work-up (see above) the formate **9b** (14 mg, 60%) was isolated; $\nu_{max}(CHCl_3)$/cm^{-1} 1780, 1728 and 1088; $\delta_H(CDCl_3$, 200 MHz) 0.93 (3 H, s), 1.07 (3 H, s), 2.75–2.95 (2 H, m), 3.11 (1 H, dd, *J* 11/6), 3.32–3.74 (4 H, m), 4.21 (1 H, dd, *J* 12/1), 4.51 (1 H, dd, *J* 12/1), 6.08 (1 H, d, *J* 6), 6.60 (1 H, d, *J* 6) and 8.07 (1 H, tr, *J* 1); *m/z* 282 (M$^+$, 1%) [Found: 254.114 633. $C_{13}H_{18}O_5$ (*M*-CO) requires 254.115 424). Further experiments with this substitution were discontinued when selective hydrolysis met with failure.

(3aR*,6aR*)-5'5'-*Dimethyl*-6a-(*phenylsulfanylmethyl*)-3a,6a-*dihydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **11a**.—A solution of trimethylsulfonium iodide (93 mg, 0.458 mmol) in dry dimethyl sulfoxide (3 cm^3) was added to a cooled (0 °C) suspension of sodium hydride (11 mg, 0.458 mmol) in dry tetrahydrofuran (3 cm^3) and the mixture stirred for 1 h. Subsequently, the keto ester **4** (100 mg, 0.373 mmol), dissolved in tetrahydrofuran (3 cm^3), was added and stirring was continued for a further 10 min. The reaction mixture was allowed to warm to room temperature and then poured into brine. The aqueous mixture was extracted with ether and the extract washed with brine, dried ($MgSO_4$) and evaporated to afford the crude product, which was subjected to flash chromatography (ether–light petroleum, 1:1) to yield the pure epoxide **10** (89 mg, 85%); $\nu_{max}(CHCl_3)$/cm^{-1} 1724, 1608 and 1026; $\delta_H(CDCl_3$, 200 MHz) 0.8 (3 H, s), 1.18 (3 H, s), 1.26 (3 H, tr, *J* 7), 2.27 (1 H, dd, *J* 16/8), 2.66 (1 H, dd, *J* 16/6.5), 3.37–3.84 (4 H, m), 4.19 (2 H, q, *J* 7), 5.80 (1 H, d, *J* 6) and 6.93 (1 H, d, *J* 6); *m/z* 282 (M$^+$, 52%) (Found: M, 282.146 088. $C_{15}H_{22}O_5$ requires *M*, 282.146 724).

This above-prepared material was immediately ring-opened with lithium thiophenolate which was prepared in the following way. A cooled (0 °C) solution of thiophenol (30 mg, 0.28 mmol) in dry tetrahydrofuran (6 ml) under argon was treated with butyllithium (0.28 mmol). After 15 min a solution of the epoxide **10** (80 mg, 0.287 mmol) in dry tetrahydrofuran (6 cm^3) was added. This mixture was kept at 0 °C for 1 h and then allowed to warm to room temperature when it was poured into saturated aqueous ammonium chloride. The reaction mixture was extracted with ether and the extract dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (ether–light petroleum, 1:1) to give the sulphide **11a** (66 mg, 60%); $\nu_{max}(CHCl_3)$/cm^{-1} 1724, 1604 and 1084; $\delta_H(CDCl_3$, 200 MHz) 0.95 (3 H, s), 1.03 (3 H, s), 2.76 (1 H, dd, *J* 13/10), 2.82 (1 H, dd, *J* 13/7), 3.13 (1 H, dd, *J* 10/7), 3.24–3.70 (6 H, m), 6.06 (1 H, d, *J* 6), 6.42 (1 H, d, *J* 6) and 7.15–7.51 (5 H, m); *m/z* 346 (M$^+$, 18%) (Found: M, 346.123 810. $C_{19}H_{22}O_4S$ requires *M*, 346.123 881).

The same material was obtained from the keto ester **4** in the following way. To a cooled (0 °C) solution of thioanisole (94 mg, 0.76 mmol) in dry tetrahydrofuran (6 ml) was added butyllithium (0.76 mmol) and the resulting mixture was stirred for 30 min at this temperature. After the mixture had been cooled to −78 °C a solution of the keto ester **4** (200 mg, 0.74 mmol) in dry tetrahydrofuran (6 cm^3) was added to it and stirring was continued at −78 °C for a further 1 h. The solution was then poured into saturated aqueous ammonium chloride and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated to yield, after flash chromatography (ether–light petroleum, 1:2), the sulphide **11a** (156 mg, 60%). Spectroscopic data and sulfoxide formation see above.

The sulfoxide **11b**. The sulfoxide **11b** was prepared from the sulphide **11a** with sodium metaperiodate under standard conditions in 90% yield; $\nu_{max}(CHCl_3)$/cm^{-1} 1724, 1607, 1084 and 1060; $\delta_H(CDCl_3$, 200 MHz) 0.96 (3 H, s), 1.05 (3 H, s), 2.76 (1 H, dd, *J* 15/11), 2.98 (1 H, dd, *J* 15/7), 2.16 (1 H, dd, *J* 11/7), 3.28–3.76 (6 H, m), 6.26 (1 H, d, *J* 6), 6.55 (1 H, d, *J* 6) and 7.43–7.75 (5 H, m); *m/z* 362 (9%).

(5S)-5-*Ethoxycarbonylmethyl*-5',5'-*dimethylspiro*[*cyclopent*-2-*ene*-1,2'-[1,3]*dioxan*]-4-*one* 'S'-**4** *and the Diels–Alder Adduct* **6**.—A solution of the racemic keto ester **4** (1 g, 3.73 mmol) and the enantiopure cyclopentadiene '*S*'-**5** (895 mg, 3.73 mmol) in dichloromethane (1.6 cm^3) was sealed in a Teflon tube and subjected to a pressure of 12 kbar for 7 days at ambient temperature. The solvent was removed and the residue was separated by flash chromatography on silica gel, eluting with ether–light petroleum (1:4 then 1:1), to yield the adduct **6** as an oil (947 mg, 50%); [α] −27.1 (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 2956, 1732, 1516, 1252 and 1128; $\delta_H(CDCl_3$, 200 MHz) 0.66 (1 H, d br, *J* 13), 0.79 (3 H, s), 0.81 (3 H, s), 1.12 (3 H, s), 1.20 (3 H,

tr, *J* 7), 1.34–1.79 (5 H, m), 2.02 (1 H, d tr, *J* 13/3), 2.25 (1 H, d br, *J* 11), 2.51 (1 H, d, *J* 3), 2.55 (1 H, d, *J* 3), 3.20–3.43 (4 H, m), 3.62–3.83 (3 H, m), 3.79 (3 H, s), 4.10 (2 H, q, *J* 7), 6.05 (1 H, d, *J* 6), 6.29 (1 H, d, *J* 6), 6.83–6.90 (2 H, m) and 7.26–7.33 (2 H, m); *m/z* 508 (M^+, 1%), 266 (12), 240 (100), 225 (12), 141 (14) and 109 (10) (Found: M^+, 508.2823. $C_{31}H_{40}O_6$ requires *M*, 508.2825); along with unchanged diene '*S*'-**5** (280 mg) and enantiopure keto ester '*S*'-**4** (450 mg, 45%); [α] −29.4 (*c* 1.00, $CHCl_3$); λ_{max}(MeOH)/nm 212; ν_{max}($CHCl_3$)/cm^{-1} 2961, 1725, 1470, 1400 and 1350; δ_H($CDCl_3$, 200 MHz) 0.82 (3 H, s), 1.19 (3 H, s), 1.26 (3 H, tr, *J* 7), 2.65 (2 H, dd, *J* 8/6), 3.04 (1 H, dd, *J* 8/6), 3.43 (2 H, m), 3.72 (1 H, d, *J* 12), 3.81 (1 H, d, *J* 12), 4.17 (2 H, q, *J* 7), 6.31 (1 H, d, *J* 6.5) and 8.12 (1 H, d, *J* 6.5); *m/z* 268 (M^+, 43%), 240 (81), 167 (82) and 109 (100) (Found: M, 268.1312. $C_{14}H_{20}O_5$ requires *M*, 268.1311).

(5R)-5-*Ethoxycarbonylmethyl*-5',5'-*dimethylspiro*[*cyclopent*-2-*ene*-1,2'-[1,3]*dioxan*]-4-*one* 'R'-**4**.—The Diels–Alder adduct **6** (100 mg, 0.197 mmol) was subjected to high vacuum flash pyrolysis (300 °C, $0.8*10^{-2}$ mbar) to give, after separation by flash chromatography on silica gel (ether–petroleum, 1:2), the diene **5** (47 mg, 99%) and the enantiomerically pure keto ester '*R*'-**4** (53 mg, 100%); [α] +31.0 (*c* 1.01, $CHCl_3$).

4-*Methoxyphenoxymethyl*(*tributyl*)*stannane*.—To a solution of *p*-methoxyphenol (9.5 g, 76.5 mmol) in dry dimethylformamide (70 ml) were added potassium carbonate (10.6 g, 76.5 mmol) and iodomethyl(tributyl)stannane (18 g, 41.8 mmol) as well as a catalytic amount of 18-crown-6. The reaction mixture was stirred at 40 °C for 2 days until completion of the reaction (TLC monitoring). The mixture was poured into light petroleum (130 cm^3) and washed with water (×2) then with brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (neat petroleum) to yield the title compound (11.6 g, 65%); ν_{max}($CHCl_3$)/cm^{-1} 2956, 2924, 1612, 1512 and 1248; δ_H($CDCl_3$, 200 MHz) 0.80–1.05 (15 H, m), 1.24–1.55 (12 H, m), 3.74 (3 H, s), 4.12 (2 H, s) and 6.83 (4 H, s); *m/z* 427 (M^+, 5%), 371 (40), 291 (100), 233 (54) and 179 (87).

(3aS,6aS)-6a-(*Methoxymethoxymethyl*)-5',5'-*dimethyl*-3a,6a-*dihydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **14**.—Methoxymethoxymethyl(tributyl)stannane (1.021 g, 2.795 mmol, 1.5 equiv.) was dissolved in dry tetrahydrofuran (7 cm^3) and butyllithium (2.799 mmol, 1.6 equiv.) was added at − 78 °C under an atmosphere of argon. After 10 min the mixture was added slowly to a cooled (−78 °C) solution of the keto ester '*S*'-**4** (500 mg, 1.866 mmol) in dry tetrahydrofuran (7 cm^3) *via* a double-ended needle, and the reaction mixture was stirred for 15 min. The cold solution was quenched with saturated aqueous ammonium chloride and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was separated by flash chromatography on silica gel (ether–light petroleum, 1:2) to give the lactone **14** (305 mg, 55%); R_F 0.21 (ether–light petroleum, 1:1); ν_{max}($CHCl_3$)/cm^{-1} 2960, 1772, 1088 and 1040; δ_H($CDCl_3$, 200 MHz) 0.92 (3 H, s), 1.07 (3 H, s), 2.70–2.88 (2 H, m), 3.05 (1 H, dd, *J* 10/6), 3.36 (3 H, s), 3.38–3.54 (4 H, m), 3.60 (2 H, s), 3.63 (1 H, d, *J* 10), 3.83 (1 H, d, *J* 10), 4.65 (2 H, s), 6.08 (1 H, d, *J* 6) and 6.59 (1 H, d, *J* 6); *m/z* 298 (M^+, 7%), 269 (28), 183 (38), 167 (65), 137 (42) and 109 (100) (Found: M, 298.1412. $C_{15}H_{22}O_6$ requires *M*, 298.1416).

(3aS,6aS)-6a-(4-*Methoxyphenoxymethyl*)-5',5'-*dimethyl*-3a,6a-*dihydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **15**.—4-Methoxyphenoxymethyl(tributyl)stannane (1.345 g, 3.172 mmol, 1.7 equiv.) was dissolved in dry tetrahydrofuran (7 cm^3) and, under an atmosphere of argon, butyllithium (2.985 mmol, 1.6 equiv.) was added at −78 °C. After 15 min the resulting mixture was added slowly to a solution of the keto ester '*S*'-**4** (500 mg, 1.866 mmol) in dry tetrahydrofuran (7 cm^3) at −78 °C *via* a double-ended needle. The reaction mixture was stirred for 15 min after which it was poured into saturated aqueous ammonium chloride and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was subjected to flash chromatography on silica gel (ether–light petroleum, 1:3) to yield the lactone **15** (396 mg, 59%); R_F 0.14 (ether–light petroleum, 1:1); [α] 31.0 (*c* 0.960, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2956, 1772, 1508, 1232 and 1088; δ_H($CDCl_3$, 200 MHz) 0.91 (3 H, s), 1.07 (3 H, s), 2.75–2.93 (2, m), 3.16 (1 H, dd, *J* 10/6), 3.37–3.70 (4 H, m), 3.76 (3 H, s) 3.97 (1 H, d, *J* 10), 4.19 (1 H, d, *J* 10), 6.17 (1 H, d, *J* 6), 6.63 (1 H, d, 6 H) and 6.80–6.90 (4 H, m); *m/z* 360 (M^+, 3%), 240 (11), 168 (33), 124 (80) and 109 (100) (Found: M^+, 360.1572. $C_{20}H_{24}O_6$ requires *M*, 360.1573).

(3R,3aS,6aS)-6a-(4-*Methoxyphenoxymethyl*)-5',5'-*dimethyl*-3-[(1R)-1-*hydroxyallyl*]-3a,6a-*dihydrospiro*[4H-*cyclopenta*-[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **17**.—To a cooled (−78 °C) solution of lithium hexamethyldisilazanide (2.332 mmol, 1.4 equiv.) in dry tetrahydrofuran (5 cm^3) was added the lactone **15** (600 mg, 1.666 mmol), dissolved in dry tetrahydrofuran (6 cm^3), under an atmosphere of argon. The mixture was stirred at the same temperature for 30 min after which a solution of acrolein (168 mg, 3 mmol, 1.8 equiv.) in tetrahydrofuran (1 cm^3) was added. After being stirred for a further 30 min at − 78 °C, the reaction mixture was poured into standard aqueous ammonium chloride and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. Subsequent purification of the residue by flash chromatography on silica gel (ether–light petroleum, 1:3) afforded the aldol **17** (485 mg, 70%); [α] +34.6 (c 0.951, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3492, 2956, 1768, 1508, 1232 and 1088; δ_H($CDCl_3$, 200 MHz) 0.81 (3 H, s), 1.20 (3 H, s), 3.07, (1 H, d, *J* 4), 3.28–3.65 (5 H, m), 3.77 (3 H, s), 3.94 (1 H, d, *J* 10), 4.19 (1 H, d, *J* 10), 4.60 (1 H, m), 5.32 (1 H, dtr, *J* 10/1), 5.46 (1 H, dtr, *J* 17/1), 5.94 (1 H, ddd, *J* 17/10/6), 6.20 (1 H, d, *J* 6), 6.81 (1 H, d, *J* 6) and 6.81–6.85 (4 H, m); *m/z* 416 (M^+, 10%), 360 (9), 237 (13), 183 (15), 138 (35), 124 (100) and 109 (41) (Found: M, 416.1843. $C_{23}H_{28}O_7$ requires *M*, 416.1835).

(3aS,6aS)-3-[(*Z*)-*Allylidene*]-6a-(4-*methoxyphenoxymethyl*)-5',5'-*dimethyl*-3a,6a-*dihydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **16**.—To a cooled (0 °C) solution of the aldol **17** (450 mg, 1.082 mmol) and triethylamine (219 mg, 2 equiv.) in dry dichloromethane (9 cm^3) was added mesyl chloride (186 mg, 1.624 mmol, 1.5 equiv.). After being stirred for 15 min, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ether. The combined extracts were washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in dichloromethane (9 cm^3) and DBU (329 mg, 2.164 mmol, 2 equiv.) was added. Stirring was continued for 1 h, after which the mixture was poured into water and extracted with ether. The organic phases were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (ether–light petroleum, 1:3) to yield the butadiene **16** (388 mg, 90%); [α] −17.0 (*c* 0.950, $CHCl_3$); λ_{max}(MeOH)/nm 263; ν_{max}($CHCl_3$)/cm^{-1} 2956, 1748, 1648, 1508, 1232 and 1040; δ_H($CDCl_3$, 200 MHz) 0.80 (3 H, s), 1.21 (3 H, s), 3.44–3.72 (5 H, m), 3.75 (3 H, s), 4.01 (1 H, d, *J* 10), 4.14 (1 H, d, *J* 10), 5.53 (1 H, dtr, *J* 10/1), 5.60 (1 H, dtr, *J* 17/1), 6.20 (1 H, d, *J* 6), 6.79–6.84 (4 H, m), 6.86 (1 H, d, *J* 6) and 7.82 (1 H, ddd, *J* 17/12/10); *m/z* 399 (M + 1, 10%), 261 (100), 175 (54) and 149 (59) [Found: *m/z* 261.1134. $C_{15}H_{17}O_4$ requires (M − 137), 261.1127).

(3aS,6aS)-3[(E)-*Allylidene*]-6a-(4-*methoxyphenoxymethyl*)-5',5'-*dimethyl*-3a,6a-*dihydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **18a**.—*Method A*. A solution of the butadiene **16** (150 mg, 0.377 mmol) and iodine (9.6 mg, 0.0377 mmol, 0.1 equiv.) in dichloromethane (6 cm^3) was stirred at room temperature for 8 days until the *Z*-diene had disappeared (TLC monitoring). The mixture was then poured into saturated aqueous sodium thiosulfate and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford the pure (*E*)-butadiene **18a** (150 mg, 100%); [α] −17.8 (*c* 0.960, $CHCl_3$); λ_{max}(MeOH)/nm 263; ν_{max}($CHCl_3$)/cm^{-1} 2960, 1752, 1636, 1508, 1232 and 1040; δ_H($CDCl_3$, 200 MHz) 0.77 (3 H, s), 1.20 (3 H, s), 3.40–3.74 (5 H, m), 3.75 (3 H, s), 4.02 (1 H, d, *J* 10), 4.12 (1 H, d, *J* 10), 5.62 (1 H, d br, *J* 10), 5.72 (1 H, d br, *J* 17), 6.23 (1 H, d, *J* 6), 6.77–6.81 (4 H, m), 6.84 (1 H, ddd, *J* 17/12/10), 6.96 (1 H, d, *J* 6) and 7.32 (1 H, dd, *J* 12/2); *m*/*z* 399 (M + 1, 11%), 261 (100), 175 (50), 147 (49) and 123 (21) (Found: *m*/*z* 261.1126. $C_{15}H_{17}O_4$ requires (M − 137), 261.1135).

Method B. When the above mentioned elimination (see butadiene **16**) was run for a longer period of time (2–3 days), the butadiene **18a** was isolated instead of the butadiene **16** in 77% yield.

(3aS,6aS)-3-[(E)-*Allylidene*-6a-(tert-*butyldimethylsilyloxymethyl*)-5',5'-*dimethyl*-3a,6a-*dihydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2(3H)-*one* **18b**.—To a cooled (0 °C) and vigorously stirred solution of the butadiene **18a** (150 mg, 0.377 mmol) in acetonitrile–water (8:2; 10 cm^3) was added ceric ammonium nitrate (496 mg, 0.905 mmol, 2.4 equiv.) in one portion. After 15 min the mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in dichloromethane (8 cm^3) and imidazole (33 mg, 0.490 mmol, 1.3 equiv.) as well as *tert*-butyl(chloro)dimethylsilane (74 mg, 0.490 mmol, 1.3 equiv.) were added. The mixture was stirred at room temperature for 3 h and then poured into saturated aqueous sodium hydrogen carbonate and extracted with ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. The residue was subjected to flash chromatography on silica gel (ether–light petroleum, 1:5) to yield the butadiene **18b** (110 mg, 72%); [α] −24.4 (*c* 0.950, $CHCl_3$); λ_{max}(MeOH)/nm 263; ν_{max}($CHCl_3$)/cm^{-1} 2965, 1750, 1660, 1470, 1460, 1360 and 1090; δ_H($CDCl_3$, 200 MHz) 0.03 (6 H, s), 0.72 (3 H, s), 0.79 (9 H, s), 1.15 (3 H, s), 3.32–3.76 (5 H, m), 3.60 (1 H, d, *J* 11), 3.83 (1 H, d, *J* 11), 5.56 (1 H, ddd, *J* 10/2/1.5), 5.65 (1 H, ddd, *J* 17/2/1.5), 6.07 (1 H, d, *J* 6), 6.79 (1 H, ddd, *J* 17/11.5/10), 6.91 (1 H, d, *J* 6) and 7.12 (1 H, dd, *J* 11.5/2); *m*/*z* 406 (M^+, 6%), 350 (100), 263 (40), 261 (41), 181 (30), 174 (31) and 147 (30) (Found: M, 406.2177. $C_{22}H_{34}O_5Si$ requires *M*, 406.2175).

(3aS,6aS)-3-[(E)-*Allylidene*-6a-(4-*methoxyphenoxymethyl*)-5',5'-*dimethyl*-2,3,3a,6a-*tetrahydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxan*]-2-*ol* **19a**.—To a cooled (−78 °C) solution of the butadiene **18a** (150 mg, 0.377 mmol) in dry ether (6 cm^3) was slowly added DIBAL (0.566 mmol, 1.5 equiv.). After 15 min the reaction mixture was quenched with methanol at −78 °C and poured into aqueous citric acid (2 mol dm^{-3}). The mixture was extracted with chloroform, and the extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford the pure lactol **19a** as a mixture of diastereoisomers (145 mg, 96%); λ_{max}(MeOH)/nm 235; ν_{max}($CHCl_3$)/cm^{-1} 3490, 2960, 1508, 1360, 1232 and 1090; δ_H($CDCl_3$, 200 MHz) 0.76/0.80 (3 H, s), 3.40–3.74 (5 H, m), 3.76 (3 H, s br), 3.86/4.17 (1 H, d, *J* 10), 3.96/4.43 (1 H, d, *J* 10), 5.23–5.44 (2 H, m), 5.64/5.71 (1 H, dd, *J* 11/1), 6.16/6.33 (1 H, d, *J* 6), 6.40 (1 H, tr d, *J* 11/1), 6.66/6.73 (1 H, d, *J* 6) and 6.80–6.88 (4 H, m); *m*/*z* 400 (M^+, 11%), 383 (3), 263 (41), 177 (19), 149 (26), 123 (100) and 109 (33) (Found: M, 400.1882. $C_{23}H_{28}O_6$ requires *M*, 400.1886).

(3aS,6aS)-3-*Allylidene*-6a-(tert-*butyldimethylsilyloxymethyl*)-5',5'-*dimethyl*-2,3,3a,6a-*tetrahydrospiro*[4H-*cyclopenta*[b]*furan*-4,2'-[1,3]*dioxane*-2-*ol* **19b**.—The lactol **19b** was obtained as a mixture of diastereoisomers according to the procedure described for the lactol **19a**; λ_{max}(MeOH)/nm 235; ν_{max}($CHCl_3$)/cm^{-1} 3480, 2960, 1470, 1460, 1360 and 1090; δ_H($CDCl_3$, 200 MHz) 0.06/0.08 (6 H, s), 0.75/0.77 (3 H, s), 0.85/0.87 (9 H, s), 1.16 (3 H, s), 3.28–3.94 (7 H, m), 5.16–5.40 (2 H, m), 5.45/5.52 (1 H, dd, *J* 11/1.5), 6.01/6.04 (1 H, d, *J* 6), 6.31 (1 H, dd, *J* 11.5/1.5), 6.57–6.87 (1 H, m) and 6.68/6.81 (14 H, d, *J* 6); *m*/*z* 408 (M^+, 0%), 353 (10), 264 (18), 248 (17), 220 (11), 146 (14) and 75 (100).

(3aS,6aS)-3-*Allylidene*-2-*methoxy*-6a-(4-*methoxyphenoxymethyl*)-2,3,3a-6a-*tetrahydro*[4H-*cyclopenta*[b]*furan*]-4-*one* **23**.—A solution of the lactol **19a** (100 mg, 0.25 mmol) and catalytic amounts of toluene-*p*-sulfonic acid in methanol (2 cm^3) was stirred at room temperature for 1.5 h. After addition of small amounts of solid sodium hydrogen carbonate to the mixture it was evaporated and the residue distributed between water and ether. The aqueous phase was extracted with ether and the combined extracts were dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography on silica gel (ether–light petroleum, 1:1) gave **23** as a mixture of diastereoisomers (62 mg, 75%); λ_{max}(MeOH)/nm 236; ν_{max}($CHCl_3$)/cm^{-1} 2960, 1720, 1508, 1228 and 1036; δ_H($CDCl_3$, 200 MHz) 3.32/3.44 (3 H, s), 3.67/3.77 (1 H, d, *J* 2), 3.77 (3 H, s), 4.10 (1 H, d, *J* 10), 4.17/4.22 (1 H, d, *J* 10), 5.30–5.47 (3 H, m), 6.21/6.24 (1 H, d, *J* 6), 6.34 (1 H, ddbr, *J* 10/2), 6.80–6.96 (5 H, m) and 7.62/7.64 (1 H, d, *J* 6); *m*/*z* 328 (M^+, 38%), 297 (8), 205 (20), 173 (52), 145 (67), 124 (100) and 109 (51) (Found: M, 328.1311. $C_{19}H_{20}O_5$ requires *M*, 328.1311).

Didemnenone Glycoside **1c**.—To a cooled (0 °C) and vigorously stirred solution of compound **23** (62 mg, 0.189 mmol) in acetonitrile–water (4:1; 2.5 cm^3) was added ceric ammonium nitrate (249 mg, 0.454 mmol, 2.4 equiv.) in one portion. After 5 min the mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in dry methanol (2 cm^3) and, after addition of catalytic quantities of toluene-*p*-sulfonic acid, the mixture was stirred at ambient temperature for 1 h. Small amounts of solid sodium hydrogen carbonate were added to the mixture which was then evaporated and the residue partitioned between water and dichloromethane. The aqueous phase was separated and extracted with dichloromethane, and the combined organic phase and extracts were washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography on silica gel (ether–light petroleum, 1:2) gave the didemnenone glycoside **1c** (30 mg, 72%); λ_{max}(MeOH)/nm 234; ν_{max}($CHCl_3$)/cm^{-1} 3590, 3450, 2956, 1718, 1605, 1590, 1460, 1075 and 1020; δ_H($CDCl_3$, 200 MHz) 3.31/3.50 (3 H, s), 3.51/3.61 (1 H, d, *J* 2), 3.70 (1 H, d, *J* 11), 3.90/3.93 (1 H, d, *J* 11), 5.34 (1 H, s), 5.36 (1 H, dd, *J* 10/2), 5.39 (1 H, dd, *J* 17/2), 6.18/6.20 (1 H, d, *J* 6), 6.30 (1 H, dd, *J* 10.5/2), 6.85 (1 H, ddd, *J* 17/10.5/10) and 7.50/7.54 (1 H, d, *J* 6); *m*/*z* 222 (M^+, 6%), 221 (27), 190 (92), 160 (77), 145 (60), 117 (59) and 77 (100) (Found: M, 222.0891. $C_{12}H_{15}O_4$ requires *M*, 222.0892).

(4S,5S)-5-[1-(*Hydroxymethyl*)-(E)-*buta*-1,3-*dienyl*]-4-(4-*methoxyphenoxymethyl*)-5',5'-*dimethylspiro*[*cyclopent*-2-*ene*-

1,2'-[1,3]*dioxan*]-4-*ol* **24a**.—The lactol **19a** (230 mg, 0.575 mmol) was dissolved in dry isopropyl alcohol (6 cm^3) and sodium borohydride (48 mg, 1.265 mmol, 2.2 equiv.) together with potassium *tert*-butoxide (6.6 mg, 0.0575 mmol, 0.1 equiv.) were added to the stirred solution at 0 °C. The mixture was allowed to warm to room temperature and stirring was then continued for 12 h. The mixture was extracted with dichloromethane, and the extract washed with brine, dried ($MgSO_4$) and evaporated to provide a residue which on purification by flash chromatography on silica gel (ether–light petroleum, 1:1) provided the diol **24a** (138 mg, 60%); λ_{max}(MeOH)/nm 234; ν_{max}($CHCl_3$)/cm^{-1} 3564–3532, 2956, 1508, 1232 and 1036; δ_H($CDCl_3$, 200 MHz) 0.86 (6 H, s), 2.60–2.74 (2 H, s br), 3.26–3.51 (5 H, m), 3.78 (3 H, s), 3.90 (1 H, d, *J* 10), 4.04 (1 H, d, *J* 10), 4.28 (1 H, d br, *J* 13), 4.63 (1 H, d br, *J* 13), 5.26 (1 H, d, *J* 10), 5.31 (1 H, d, *J* 17), 5.94 (1 H, d, *J* 6), 6.00 (1 H, d, *J* 6), 6.23 (1 H, dd, *J* 10/1), 6.78 (1 H, dr, *J* 17/10), 6.87 (4 H, s br); *m/z* 402 (M^+, 8%), 298 (8), 175 (52), 161 (34), 149 (16), 133 (25) and 124 (100) (Found: M, 402.2048. $C_{23}H_{30}O_6$ requires *M*, 402.2042).

(4S,5S)-4-(tert-*Butyldimethylsiloxymethyl*]-5-[1-(*hydroxymethyl*)-(E)-*buta*-1,3-*dienyl*]-5',5'-*dimethylspiro*[*cyclopent*-2-*ene*-1,2'-[1,3]*dioxan*]-4-*ol* **24b**.—The diol **24b** was obtained according to the procedure described for the diol **24a**; λ_{max}(MeOH)/nm 235; ν_{max}($CHCl_3$)/cm^{-1} 3672, 3616, 2964, 1452, 1372, 1236 and 1088; δ_H($CDCl_3$, 200 MHz) 0.06 (3 H, s), 0.08 (3 H, s), 0.90 (9 H, s), 0.95 (3 H, s), 0.97 (3 H, s), 3.20 (1 H, s), 3.49 (1 H, d, *J* 10), 3.58 (1 H, d, *J* 10), 3.43–3.62 (6 H, m), 4.19 (2 H, s), 5.16 (1 H, dd, *J* 10/2), 5.23 (1 H, dd, *J* 16/2), 6.03 (1 H, d, *J* 6), 6.07 (1 H, d, *J* 11), 6.35 (1 H, d, *J* 6) and 6.80 (1 H, ddd, *J* 16/11/10); *m/z* 410 (M^+, 1.4%), 395 (4), 307 (7), 265 (20), 249 (46), 161 (27), 141 (61), 128 (25) and 75 (100) (Found: M, 410.249 634. $C_{22}H_{38}O_5Si$ requires *M*, 410.248 853).

(4S,5S)-4-*Hydroxy*-5-[1-(*hydroxymethyl*)-(E)-*buta*-1,3-*dienyl*]-4-(4-*methoxyphenoxymethyl*)*cyclopent*-2-*enone* **25a**.—A solution of the diol **24a** (113 mg, 0.281 mmol) in acetone–water (6:1; 3.5 cm^3) containing catalytic amounts of hydrochloric acid was stirred at 40 °C for 6 h. Small amounts of solid sodium hydrogen carbonate were then added to the mixture which was then evaporated and the residue partitioned between water and dichloromethane. The aqueous phase was separated and back-extracted with dichloromethane, and the combined organic phase and extracts were then washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography on silica gel (ether–light petroleum, 1:2) afforded the deprotected ketone **25a** (62 mg, 70%); ν_{max}($CHCl_3$)/cm^{-1} 3698, 3616, 3392, 2962, 1708, 1508, 1228 and 1044; δ_H($CDCl_3$, 200 MHz) 3.78 (4 H, s br), 4.07 (2 H, s br), 4.13 (1 H, d, *J* 12), 4.55 (1 H, d, *J* 12), 5.16 (1 H, d, *J* 10), 5.33 (1 H, d, *J* 15), 6.31 (1 H, d, *J* 6), 6.34–6.44 (2 H, m), 6.86 (4 H, s br) and 7.53 (1 H, d, *J* 6); *m/z* 316 (M^+, 4%), 300 (2), 175 (6), 162 (7), 137 (11), 124 (100) and 109 (30) (Found: M, 316.1311. $C_{18}H_{20}O_5$ requires *M* 316.1311).

Didemnenone C **2a**.—A solution of the diol **24b** (38 mg, 0.093 mmol) in acetone–water (6:1; 1.75 cm^3) containing catalytic amounts of hydrochloric acid was stirred at 40 °C for 36 h. Small amounts of sodium hydrogen carbonate were added to the mixture which was then evaporated and the residue was partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organic phase and extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was subjected to flash chromatography on silica gel (ether neat) to afford the didemnenone C **2a** (9 mg, 46%); λ_{max}(MeOH)/nm 234; ν_{max}($CHCl_3$)/cm^{-1} 3532, 2928, 1712 and 1084; δ_H($CDCl_3$, 200 MHz) 3.25 (1 H, s), 3.76 (2 H, s br), 4.34 (1 H, dd, *J* 12/1), 4.58 (1 H, dd, *J* 12/1), 5.20–5.35 (2 H, m), 6.08 (1 H, d br, *J* 12), 6.29 (1 H, d, *J* 6), 6.56 (1 H, ddd, *J* 17/11/10) and 7.55 (1 H, d, *J* 6); *m/z* 210 (M^+, 9%), 192 (16), 179 (14), 163 (28), 149 (43), 105 (73), 79 (80) and 71 (100) (Found: M, 210.089 483. $C_{11}H_{14}O_4$ requires *M*, 210.089 211).

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