Synthetic studies towards the clerodane insect antifeedant jodrellin A: preparation of a polycyclic model compound with antifeedant activity

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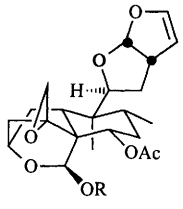
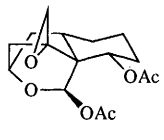
Synthetic studies towards the insect antifeedant jodrellin A 1a are reported. This work delineates a synthetic strategy that affords a polycyclic epoxy diacetate model compound 2 which contains most of the structural features found in the natural product. This material was also shown to possess mild insect antifeedant activity against *Spodoptera littoralis*.

There is a need to develop more ecologically acceptable methods of insect pest control. For this reason plant natural products which display behaviour-modifying properties, such as antifeedants that deter insects from feeding, are becoming increasingly important.[1] For several years, we have been studying these compounds in an effort to define the structural features responsible for their activity.[2] Clerodane diterpenes are often endowed with antifeedant and other biological properties.[3] In particular, the natural products isolated from *Scutellaria woronowii* have been shown to be especially potent antifeedants.[4] Here, we report in full[5] on our synthetic studies towards jodrellin A **1a**, an important member of this class of compounds. The work describes a general strategy we have developed for the synthesis of compound **2**, which may also be applied to the construction of **1** itself. Furthermore, the preparation of model compounds such as **2** gives us the opportunity to probe the biological activity of structural motifs embedded in the complex natural product and to define the functional groups responsible. The unusual polycyclic framework present in these molecules represents a challenging synthesis problem.



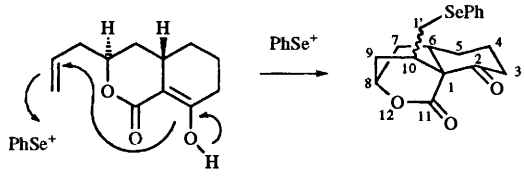
1a R = Ac
1b R = COPr^i



2

Our strategy for the preparation of **2** involves a selenium-mediated cyclization[6a] as a key step in the pathway, as illustrated in Scheme 1. We had shown previously that this approach is an attractive way to form carbon–carbon bonds by the coupling of β-keto esters with alkenes in the presence of selenating agents.[6b,c] In order to test this concept, we needed to prepare the alkenyl β-keto lactone **3** as the starting material in the anticipation that it would undergo conversion into the tricyclic selenides upon treatment with an electrophilic selenium reagent, in which the newly formed carbon–carbon bond neatly establishes the required skeleton of the natural product (Scheme 1).

Several routes for the synthesis of **3** were considered and were briefly investigated.[7] We report here, however, only the successful sequence and its related chemistry. Obviously compounds similar to **3** with appropriate substitution patterns might also serve as precursors for the synthesis of the natural products **1a** and **1b** themselves.



3

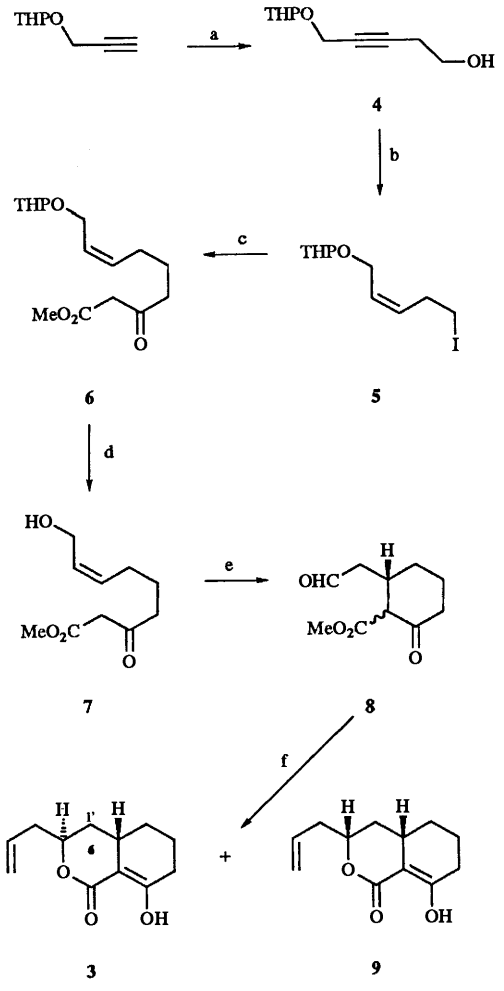
Scheme 1

Results and discussion

The compound **3** was readily prepared from a prop-2-ynyl alcohol derivative according to the sequence outlined in Scheme 2. Prop-2-ynyl alcohol, protected as its tetrahydropyranyl derivative, was treated with butyllithium followed by quenching with ethylene oxide in tetrahydrofuran (THF) in the presence of *N*,*N*′-dimethyl-*N*,*N*′-propyleneurea (DMPU)[8] † to give the alcohol **4**.[9] This was readily transformed into the iodide **5** by Lindlar reduction, followed by iodide displacement of an intermediate mesylate, in the normal fashion, in 82% overall yield. During the Lindlar reduction step, however, we encountered some scale-up difficulties owing to over-reduction or failure of the reaction to proceed to completion. This was overcome by introducing hydrogen into the reaction *via* a sintered glass frit to disperse the gas. Under these conditions reliable and selective hydrogenation could be achieved on scales of up to 40 g without difficulty.

Next, kinetic γ-alkylation of the dianion derived from methyl 3-oxobutanoate with **5** gave the product **6** in 82% yield. The use of low-temperature conditions in this reaction (−60 °C) minimised the formation of the unwanted dialkylation by-product. Deprotection of **6** using 1 mol dm^{-3} HCl in THF, afforded the alcohol **7** in excellent yield. Alternative conditions

† With stoichiometric equivalents of DMPU the reaction worked well, but it proved difficult to separate the product alcohol from DMPU. When smaller amounts of DMPU (10%) was used, however, a smooth conversion into the product was observed, with a slight retardation of the rate in comparison with the stoichiometric procedure.



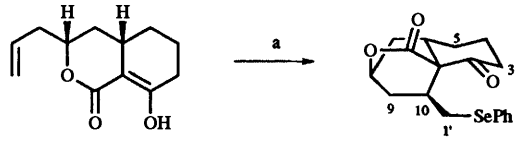
Scheme 2 *Reagents and conditions:* a: BuLi, DMPU, ethylene oxide, THF, (76%); b: i, H_2, $Pd/CaCO_3$, quinoline, EtOAc; ii, MsCl, Et_3N, CH_2Cl_2, 0 °C; iii, NaI, acetone, reflux, (82% over three steps); c: methyl acetoacetate, NaH, BuLi, THF, −60 °C, (82%); d: 1 mol dm^{-3} HCl-THF (1:1), (90%); e: PDC, AcOH, 3 Å molecular sieves, CH_2Cl_2, (85%); f: i, NaH, THF, 0 °C; ii, $Li[Ti(allyl)(OPr^i)_4]$, −78 °C, (80%, 6:1, **3**:**9**).

for this reaction, such as the use of toluene-*p*-sulfonic acid (TPSA) in methanol, led to substantial formation of a contaminating product identified as the dimethyl acetal derivative of the 3-oxo group in compound **7**.

The construction of the β-keto ester **3** mentioned before, required the oxidation of the allylic alcohol to an α,β-unsaturated aldehyde necessary for the allylation and *in situ* lactonization. We recognized, however, that the intermediate enal which would be formed in this reaction, could undergo spontaneous cyclization to the desired product **8** given the correct conditions. While it was possible to oxidise **7** with MnO_2 or $BaMnO_4$, we found that using pyridinium dichromate (PDC) with catalytic acetic acid, in the presence of 3 Å molecular sieves [10] directly afforded **8** in 85% yield, after simple work-up involving filtration through a short pad of Florisil®.

This aldehyde **8** could then be used in the next reaction, without further purification. For the selective addition of an allyl group to the aldehyde carbonyl unit of **8** we required rather special conditions, since this molecule has a high enol content and consequently provides a source of acidic protons. Moreover, it is susceptible to concomitant nucleophilic attack at the keto carbonyl centre. Furthermore, there is also a diastereoselectivity problem associated with addition to the aldehyde moiety, in that only one diastereoisomer, **3** is required, as opposed to the alternative reaction addition which would afford the isomer **9**. In the event, we found that the use of allyl titanium 'ate' species‡ to be a most satisfactory solution to the problems discussed above. Although this reagent showed preference for aldehydes, better results were obtained when the ketone was enolised. The optimised conditions required initial deprotonation of the β-keto ester moiety in the aldehyde **8** with sodium hydride at 0 °C followed by addition of $Li[Ti(allyl)(OPr^i)_4]$ at −78 °C; this mixture when warmed to room temperature gave a 6:1 ratio of **3** to **9** in a pleasing 80% yield (Scheme 2). The 'ate' species used in this reaction was generated from allyltributyltin by reaction with butyllithium followed by addition of titanium(IV) isopropoxide [$Ti(OPr^i)_4$]. Any other conditions used for this process gave inferior yields and/or poor selectivity. The stereochemistry of the newly created asymmetric centre of both C(4) isomers was confirmed on the basis of NMR studies. For example, the ^{13}C NMR spectrum is in accord with the assignment shown, since comparison of the chemical shift of each pair of C(4) epimeric compounds reveals that resonances of C(6) and C(1′) atoms are both shifted upfield in compound **3** owing to the γ-effect between the allyl chain and C(6) [$\delta_C(6)$ = 29.63 ppm, $\delta_{C(1')}$ = 38.84 ppm and $\delta_{C(6)}$ = 32.84 ppm and $\delta_{C(1')}$ = 40.05 ppm for **3** and **9**, respectively]. The two diastereoisomeric lactones were subsequently separated by HPLC and subjected to cyclization, in order to confirm the stereochemical outcome in the key step.

We were now in a position to examine the crucial cyclization of **3**.[12a] Initially, we considered a radical based process using $Mn(OAc)_3$[12b,c] to effect carbon–carbon bond formation and ring closure of this substrate, owing to the expected regioselectivity and mild reaction conditions under which the reaction is performed.[12d] It proved, however, to be unsatisfactory under a variety of conditions. Instead we turned to methodology developed some years ago in our laboratories involving selenium-mediated cyclization of β-keto esters with alkenes.[6] This process proved to be extremely successful in achieving the desired transformation. In an initial model study we found that the unwanted β-keto lactone, diastereoisomer **9**, reacted with *N*-phenylselenophthalimide (NPSP), and ZnI_2 in CH_2Cl_2 to give the expected selenide **10** in 61% yield (Scheme 3). The structure of **10** was confirmed by COSY and NOE



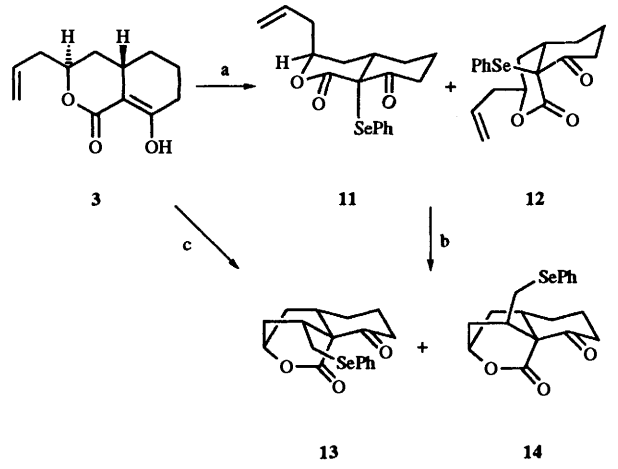
Scheme 3 *Reagents and conditions:* a: NPSP, ZnI_2, CH_2Cl_2, (61%)

NMR experiments. Irradiation at 10-H gave an enhancement of the signals corresponding to 1′-H, 9_{ax}-H, 5_{ax}-H and 3_{ax}-H, which would only arise with the structure shown.

More importantly, compound **3**, which has the correct stereochemistry, also reacted with NPSP, in the absence of Lewis acids, to give the selenides **11** and **12**. Although the observation was in accord with our previous studies on related systems,[6] since these are not especially stable they were immediately treated with Lewis acids to effect cyclization (Scheme 4).

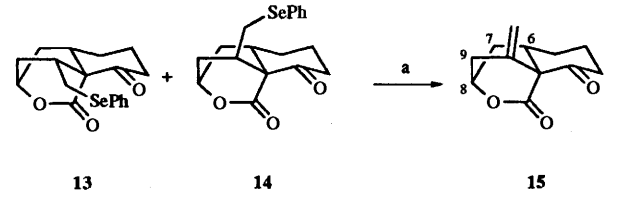
Unfortunately, reaction with $SnCl_4$ proved to be a little too vigorous and led to decomposition by deselenation even at −78 °C. Treatment of **11** and **12** as a mixture, however, with ZnI_2 in CH_2Cl_2 at room temperature over 24 h, gave a 95% yield of the two diastereoisomeric selenides **13** and **14**, in a 4:1 ratio respectively (Scheme 4). It was also possible to treat **3** with NPSP and ZnI_2 to give **13** and **14** directly in excellent yield (Scheme 4). The proof of structures of **13** and **14** followed from

‡ Better results were obtained when allyllithium was used instead of Grignard reagents.



Scheme 4 *Reagents and conditions:* a: NPSP, CH_2Cl_2; b: ZnI_2, CH_2Cl_2, (95% over two steps); c: NPSP, ZnI_2, CH_2Cl_2, (95%)

detailed NMR studies and further reactions reported below. Although it was possible to readily separate **13** and **14** this was not necessary from the synthetic perspective, since oxidation and *syn* elimination of both selenide isomers would give the same alkene. An excess of the oxidant (*e.g.* hydrogen peroxide, oxaziridine) is generally used, but over-oxidation of sensitive functionalities in the substrate was problematic. Thus, the use of hydrogen peroxide [13a] tended to give mixtures of compounds while the use of the Davis oxaziridine [13b] transformed the mixture of selenide isomers into **15** in low yield.[7] A successful alternative was the use of *tert*-butyl hydroperoxide (TBHP) which proved to be superior for the oxidative *syn*-elimination. Thus, a mixture of both isomers **13** and **14** when treated with Bu^tOOH and catalytic $Ti(OPr^i)_4$ [13c] followed by heating at reflux, gave a single product alkene **15** (Scheme 5). The



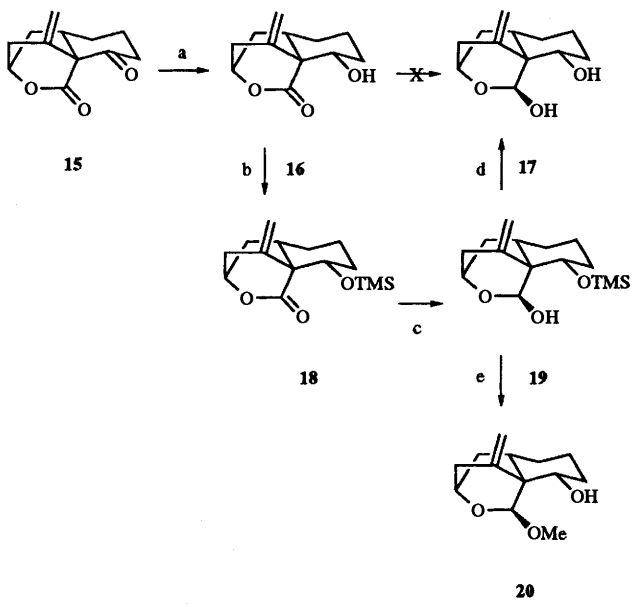
Scheme 5 *Reagents and conditions:* a: TBHP, $Ti(O^iPr)_4$, dihydropyran, CH_2Cl_2, reflux, (92%)

structure of **15** was confirmed by COSY and NOE experiments. Irradiation at 7_{ax}-H gave an enhancement of the signals corresponding to 9_{ax}-H, 8-H, 7_{eq}-H and 6-H, in accordance with the structure shown.

Although use of the $Mn(OAc)_3$ cyclization procedure [12] with **3** gave compound **15** directly, even under optimized conditions we could never realize better than a 39% yield of product. The selenium-based approach therefore proved to be much more satisfactory for this particular cyclisation.

Once construction of the tricyclic framework was complete, the next objective in the synthesis was the conversion of the tricyclic compound **15** into the model compound **2**. Careful planning and extensive experimentation was necessary in order to obtain the required substitution pattern in a minimum of steps.

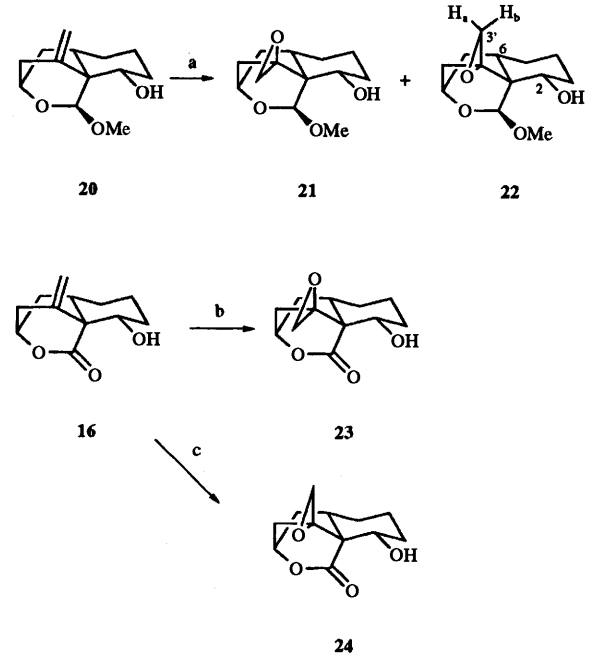
Although stereoselective sodium borohydride reduction of the ketone group in **15** proceeded well, introduction of further functionality was not straightforward. Attempts to reduce the lactone group in **16** to provide **17** directly with, for example, diisobutylaluminium hydride (DIBAL-H), failed and consequently a multistep operation was required. Thus, initial trimethylsilylation of **16** with trimethylsilyl triflate (TMSOTf) gave **18**, which subsequently reacted with DIBAL-H in toluene at −78 °C to give the lactol **19** on work-up (Scheme 6). This



Scheme 6 *Reagents and conditions:* a: $NaBH_4$, CH_3OH, 0 °C, (95%); b: TMSOTf, Et_3N, CH_2Cl_2, −78 °C, (95%); c: DIBAL-H, PhMe, −78 °C, (92%); d: PPTS, THF–H_2O (1:1), (80%); e: PPTS, MeOH, (68%)

compound could then be converted into **17** by deprotection with pyridinium tosylate (PPTS). The stereochemical assignment of the newly created centre in **17**, was that expected from ring opening and closure to the more thermodynamically stable arrangement, and in accordance with literature precedent.[3b] Treatment of **19** with PPTS in methanol gave the acetal exchange product **20** in reasonable yield.

At this stage we believed it would be possible to epoxidize stereoselectively these substrates using a hydroxy group directed approach as in our earlier work.[14] Reaction of **20**, however, with *m*-chloroperbenzoic acid (*m*-CPBA) gave the epoxides **21** and **22**, but in a reverse 3:1 ratio to that required (Scheme 7). The relative stereochemistry of the oxirane moiety was confirmed by NOE experiments. In fact, irradiation of 3_b'-H in the minor isomer, compound **22**, caused enhancement of

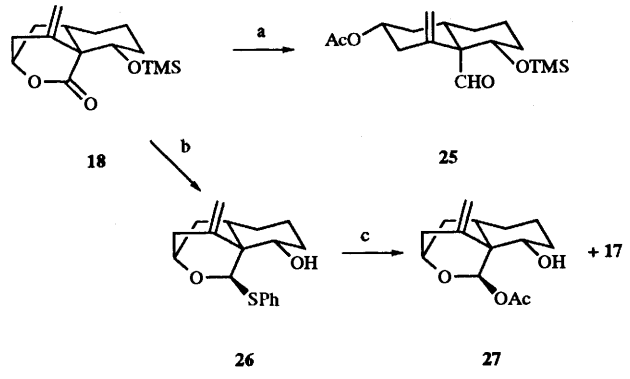


Scheme 7 *Reagents and conditions:* a: *m*-CPBA, CH_2Cl_2-sat. aq. $NaHCO_3$, 0 °C, (87%, 3:1, **21**:**22**); b: *m*-CPBA, CH_2Cl_2-sat. aq. $NaHCO_3$, 0 °C, (75%); c: TBHP, $Ti(OPr^i)_4$, benzene, reflux

the signals corresponding to 6-H and 2-H, which only would arise with a structure in which these protons and the ethylene of the epoxide are in a *cis* relationship. Similarly, oxidation of **16** afforded the epoxide **23** in 75%.

Owing to the failure of the *m*-CPBA reactions, we studied alternative epoxidations conditions. Treatment of **16** with Bu^{t}OOH in benzene in the presence of vanadyl acetylacetonate [$VO(acac)_2$][15] gave recovered starting material only. When **20** was treated with TBHP and $Ti(OPr^i)_4$[16] in benzene under reflux on a small scale, some of the desired epoxide **24** was formed. This was indicated by NMR analysis of the crude mixture but the reaction proved to be extremely capricious and could not be repeated consistently, especially on a larger scale.

We assume these complications arose from a preferential approach of the oxidizing agent from the presumably less hindered face. Consequently, we investigated an alternative route involving intermediate formation of bromohydrins. Initially, however, we studied methods for installing the ester at the crucial bridging lactol position. This transformation was of concern, since an early attempt to acylate **19** with acetic anhydride in Et_3N containing 4-(dimethylamino)pyridine (DMAP) as catalyst, afforded the ring-opened product **25** as the only isolable material in 55% yield (Scheme 8). This ring



Scheme 8 *Reagents and conditions:* a; i, DIBAL-H, PhMe, −78 °C; ii, Ac_2O, Et_3N, DMAP, CH_2Cl_2, (51%); b: i, DIBAL-H, PhMe, −78 °C; ii, PhSH, PPTS, CH_2Cl_2, (71%); c: $AgOCOCF_3$, Me_4NOAc, 3 Å molecular sieves, (32%)

opening was possibly a consequence of the steric bulk of the trimethylsilyl ether.

Next, we examined the anomeric exchange of **19** with sodium acetate in acetic acid; however, only starting material was recovered in this process. On the other hand, on treatment of the sulfide intermediate **26** (prepared by reaction of **18** with benzenethiol and PPTS in 71% yield), with silver trifluoroacetate (silver acetate failed to react) and tetramethylammonium acetate, a fast reaction occurred, to give the desired acetate **27** (32%) along with diol **17** as the major product in 60% yield.

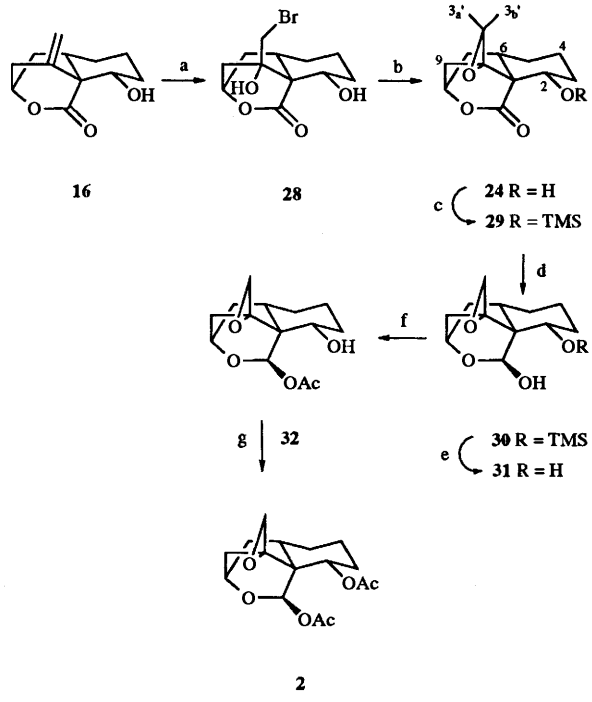
Finally, we found that the optimum conditions were the treatment of the diol **17** with acetyl chloride and pyridine in dichloromethane at room temperature, in which the mono acetylated compound **27** is isolated in 50%. These conditions also proved to be satisfactory during the preparation of the real epoxide model system (*vide infra*).

Ultimately, the best sequence involved hydrobromination of **16** with bromine in acetonitrile and saturated ammonium chloride, to give the hydroxy bromide **28**, which was converted into the required epoxide **24**, using basic Amberlite IRA 420 resin (Scheme 9). As the product was very polar this was best handled as its corresponding trimethylsilyl ether **29**. The structure and stereochemistry of **29** was unambiguously assigned by COSY and NOE experiments after which the previous assignments were confirmed from the 1-D and 2-D ^1H NMR spectra (Table 1).

Compound **29** was then reduced using the previously established conditions, with DIBAL-H in toluence, to give

Table 1 ^1H nuclear Overhauser effect data of compound **29**

Irradiation	Response
2-H	$3'_b$-H (+6.61%), 6-H (+3.3%), 3_{eq}-H (+2.6%), 4_{ax}-H (+2.4%)
$3'_b$-H	2-H (+7.6%), $3'_a$-H (+16.1%), 6-H (+1.5%)
$3'_a$-H	$3'_b$-H (+14.41%), 2-H (−0.27%), 9_{ax}-H (+0.34%)



Scheme 9 *Reagents and conditions:* a: Br_2, MeCN–NH_4Cl (1 : 1), (76%); b: Amberlite® IRA-420, CH_2Cl_2; c: TMSOTf, Et_3N, CH_2Cl_2, −78 °C, (90%, over two steps); d: DIBAL-H, PhMe, −78 °C, (89%); e: PPTS, THF–H_2O (1 : 1), (81%); f: AcCl, Py, DMAP, CH_2Cl_2; g: Ac_2O, Py, DMAP, 0 °C, (85%)

lactol **30**, which was hydrolysed to **31** on treatment with PPTS in THF–water in excellent overall yield. Finally, stepwise acylation of **31**, firstly with acetyl chloride, pyridine and DMAP in CH_2Cl_2 afforded the monoacetate **32** which subsequently reacted with acetic anhydride, pyridine and DMAP to give the final model epoxy diacetate **2** (Scheme 9). Attempted direct double acylation of **31**, which was successful in other systems,[2f] failed in this example. This selective hydroxy group functionalisation, is a useful strategy for introducing an ester group at the anomeric position and, consequently, may find application on the synthesis of jodrellin B **1b** also isolated from *Scutellaria woronowii*.[4] This is the most potent clerodane antifeedant described so far.[3c]

Pleasingly, the model compound **2** showed moderate antifeedant activity against *Spodoptera littoralis*.[5] Full details of these effects and of other model systems will be reported separately. These studies once again confirm that smaller fragment motifs of the natural products can display antifeedant activity.[2a,c]

In conclusion, we have developed a highly efficient synthesis of compound **2** which we believe paves the way to more complex systems and in particular, the synthesis of the natural products themselves, which contain the same polycyclic framework.

Experimental

General

^1H NMR spectra were recorded in $CDCl_3$ at 200, 400 and 500 MHz on Bruker AM-200, Bruker AM-400 and Bruker DRX-

500 spectrometers, respectively. Residual protic solvent, *i.e.* $CDCl_3$ (δ_H = 7.26) was used as internal reference. *J* Values are recorded in Hz. ^{13}C NMR were recorded in $CDCl_3$ at 125.8 MHz on a Bruker DRX-500, at 100.12 MHz on a Bruker AM-400 and at 50 MHz on a Bruker AM-200 spectrometers using the resonance of $CDCl_3$ (δ_C = 77.00) as internal reference. COSY spectra required to confirm NMR assignments were recorded on a Bruker AM-400 or DRX-500 spectrometer. IR spectra were recorded on a Perkin-Elmer 983G or FTIR 1620 spectrometers. Mass spectra were recorded using VG-707B, VG 12–253 and VG ZAB-E instruments at the Department of Chemistry, Imperial College and at the EPSRC Mass Spectrometry Service at the University of Swansea. Additional spectra were recorded on a Kratos MS890MS spectrometer at the Department of Chemistry, University of Cambridge. Microanalyses were performed in the microanalytical laboratories at Imperial College and Cambridge University and at MEDAC Ltd., Department of Chemistry, Brunel University. Melting points were determined on a Reichert hot-stage apparatus. Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Normal phase HPLC was carried out on a Gilson system on a DYNAMAX 60A Si column, using an UV detector. Analytical TLC was performed using pre-coated glass-backed plates (Merck Kieselgel F_{254}) and visualised by acidic ammonium molybdate (IV). Florisil® refers to 230–300 US mesh Florisil, as supplied by BDH Ltd. Diethyl ether and THF were distilled from sodium–benzophenone ketyl radical, dichloromethane from calcium hydride, toluene from sodium, acetonitrile from calcium hydride and methanol from magnesium. Light petroleum refers to the fraction boiling in the range 40–60 °C, which was distilled prior to use. Other solvents and reagents were purified by standard procedures as necessary. Aqueous solutions are saturated unless specified otherwise.

5-Tetrahydropyranyloxypent-3-yn-1-ol 4

BuLi (2.5 mol dm^{-3} in hexanes; 120 cm^3, 0.30 mol) was added to a stirred solution of the tetrahydropyranyl ether of prop-2-ynyl alcohol (38.2 g, 0.273 mol) and DMPU (3.30 cm^3, 27.3 mmol) in THF (300 cm^3) at −78 °C, under argon. Ethylene oxide (55 cm^3, 1.09 mol) was condensed into a CO_2(s)-cooled, jacketed pressure-equalizing dropping funnel and added to the reaction mixture over 20 min. The reaction mixture was stirred at −78 °C for 1.5 h, allowed to reach room temperature and then stirred for 4 h. The reaction mixture was poured into water (200 cm^3) and extracted with diethyl ether (3 × 200 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was subjected to flash chromatography through a short column (65% diethyl ether–light petroleum) to afford the alcohol **4** (37.9 g, 76%) as a colourless oil, whose spectroscopic properties were identical with those reported previously.[9b]

(*Z*)-1-Iodo-5-tetrahydropyranyloxypent-3-ene 5

Lindlar's catalyst (0.80 g) was slurried with quinoline (6 cm^3) and then added to a stirred solution of the alcohol **4** (30.2 g, 0.164 mol) in EtOAc (400 cm^3). The reaction mixture was saturated with argon after which hydrogen was bubbled through the suspension using a gas inlet tube with a sintered tip. The reaction was complete after 2 h, as verified by gas chromatography. The suspension was filtered through a short pad of Florisil®, washed with EtOAc, and evaporated under reduced pressure. The residue (30.2 g, 0.164 mol) was taken up in CH_2Cl_2 (500 cm^3) under argon and Et_3N (68 cm^3, 0.492 mol) was added at 0 °C to the solution followed by methanesulfonyl chloride (13.3 cm^3, 0.172 mol), added dropwise. After 1 h the reaction mixture was poured into 50% aqueous $NaHCO_3$ (400 cm^3) and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 250 cm^3) and the combined organic layer and extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The mesylate obtained (0.164 mol) was dissolved in dry acetone (500 cm^3), sodium iodide (49.1 g, 0.328 mol) was added portionwise to this solution and the mixture heated to gentle reflux. After 2.5 h the cooled reaction mixture was poured into brine and extracted with CH_2Cl_2 (3 × 250 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography (8% diethyl ether–light petroleum) gave the *iodide* **5** (39.8 g, 82%) as a pale yellow oil (Found: C, 40.6; H, 5.9. $C_{10}H_{17}IO_2$ requires C, 40.6; H, 5.8%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3018, 2942, 2869, 1664, 1440, 1387, 1340, 1321, 1242, 1201, 1172, 1118, 1077, 1027 and 972; δ_H(500 MHz) 5.76–5.71 (1 H, m, 4-H), 5.58–5.52 (1 H, m, 3-H), 4.63 (1 H, dd, *J* 4.0 and 3.1, 1′-H), 4.25 (1 H, ddt, *J* 12.4, 6.2 and 0.7, 5-H), 4.06 (1 H, ddd, *J* 12.4, 7.2 and 1.3, 5-H), 3.87 (1 H, ddd, *J* 11.2, 8.0 and 3.2, $5'_{ax}$-H), 3.55–3.50 (1 H, m, $5'_{eq}$-H), 3.16 (2 H, t, *J* 7.1, 1-H), 2.69 (2 H, q, *J* 7.1, 2-H) and 1.87–1.49 (6 H, m, 2′-H, 3′-H and 4′-H); *m/z* (EI) 295 ($M^+ - H$), 212 ($M^+ - C_5H_8O$) and 195 ($M^+ - C_5H_9O_2$).

(*Z*)-Methyl 3-oxo-9-tetrahydropyranyloxynon-7-enoate 6

Methyl acetoacetate (14.6 cm^3, 0.137 mol) was added dropwise to a stirred suspension of sodium hydride (80% dispersion in oil; 4.10 g, 0.136 mol) in THF (700 cm^3), under argon at 0 °C. After 30 min of continuous stirring, the reaction mixture was cooled to −78 °C and BuLi (2.5 mol dm^{-3} solution in hexanes; 54.7 cm^3, 0.137 mol) was added dropwise to it; the mixture was then stirred for a further 30 min. After this, the iodide **5** (27.0 g, 91.2 mmol) was added to the mixture which was then allowed to warm to −60 °C and stirred overnight at this temperature. The reaction mixture was then warmed slowly to room temperature, poured into 50% aqueous $NaHCO_3$ (450 cm^3) and extracted with diethyl ether (2 × 200 cm^3) and then CH_2Cl_2 (3 × 200 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by flash chromatography (gradient elution, 35–40% diethyl ether–light petroleum) to afford the keto ester **6** (21.3 g, 82%) as a colourless oil (Found: C, 63.2; H, 8.6. $C_{15}H_{24}O_5$ requires C, 63.4; H, 8.5%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3458, 2949, 2871, 1743, 1718, 1437, 1409, 1321, 1238, 1200, 1117, 1077, 1054 and 1035; δ_H(500 MHz) 5.64–5.59 (1 H, m, 8-H), 5.56–5.49 (1 H, m, 7-H), 4.63 (1 H, t, *J* 3.6, 1′-H), 4.24 (1 H, ddd, *J* 12.1, 6.1 and 1.1, 9-H), 4.05 (1 H, dd, *J* 12.1 and 7.2, 9-H), 3.87 (1 H, ddd, *J* 11.2, 7.9 and 3.2, $5'_{ax}$-H), 3.74 (3 H, s, OMe), 3.53–3.49 (1 H, m, $5'_{eq}$-H), 3.45 (2 H, s, 2-H), 2.55 (2 H, t, *J* 7.3, 4-H), 2.11 (2 H, q, *J* 7.3, 6-H), 1.68 (2 H, quint., *J* 7.3, 5-H), 1.86–1.79, 1.74–1.64 and 1.61–1.51 (1 H, 1 H and 4 H, 3 × m, 2 × 2′-H, 2 × 3′-H and 2 × 4′-H); *m/z* (EI) 183 ($M^+ - C_5H_9O_2$), 151 [$M^+ - (C_5H_9O_2 + OMe)$], 109 [$M^+ - (C_5H_9O_2 + CH_2CO_2Me)$] and 85 ($C_5H_9O^+$).

(*Z*)-Methyl 9-hydroxy-3-oxonon-7-enoate 7

The keto ester **6** (21.2 g, 74.6 mmol) was stirred in THF–1 mol dm^{-3} HCl (2:1; 250 cm^3) at room temperature. After 30 min, the reaction mixture was poured into diethyl ether (150 cm^3), the organic layer separated and the aqueous solution extracted with CH_2Cl_2 (3 × 250 cm^3). The combined organic layer and extracts were washed with brine, dried ($MgSO_4$) filtered and evaporated under reduced pressure. Flash chromatography of the resulting residue (gradient elution 70–80% diethyl ether–light petroleum) afforded the *alcohol* **7** (13.4 g, 90%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3419, 3014, 2951, 1745, 1714, 1651, 1437, 1410, 1370, 1323, 1265, 1178, 1034 and 1003; δ_H(500 MHz) 5.68–5.63 (1 H, m, 8-H), 5.50–5.45 (1 H, m, 7-H), 4.16 (2 H, br d, *J* 6.8, 9-H), 3.74 (3 H, s, OMe), 3.45 (2 H, s, 2 × 2-H), 2.56 (2 H, t, *J* 7.1, 2 × 4-H), 2.11 (2 H, q, *J* 7.4, 2 × 6-H) and 1.69 (2 H, quint, *J* 7.2, 2 × 5-H); *m/z* (FAB) 201 (MH^+), 183 ($M^+ - OH$), 167 ($M^+ - MeOH$), 157 [$M^+ - (OH +$

MeOH)], 137 ($M^+ - CH_2CO_2Me$) [Found (FAB): MH^+, 201.1141. $C_{10}H_{17}O_4$ requires *M*, 201.1127].

(4*S,6*S**)-4-Allyl-2-oxo-3-oxabicyclo[4.4.0]dec-1(10)en-10-ol 3 and (4*R**,6*S**)-4-allyl-2-oxo-3-oxabicyclo[4.4.0]dec-1(10)-en-10-ol 9**

Pyridinium dichromate (5.60 g, 15.0 mmol) was added in portions over 30 min, to a vigorously stirred suspension of the alcohol **7** (2.00 g, 10.0 mmol), acetic acid (0.5 cm^3) and 3 Å powdered molecular sieves (5.6 g) in CH_2Cl_2 (100 cm^3) at room temperature. After 1.5 h, the reaction mixture was diluted with EtOAc and filtered through a short pad of Florisil®, eluting with EtOAc. The filtrate was evaporated under reduced pressure and the residual aldehyde **8** (1.69 g, 85%) was used immediately in the next reaction. BuLi (2.5 mol dm^{-3} solution in hexanes; 8.52 cm^3, 21.3 mmol) was added dropwise to a stirred solution of allyl(tributyl)tin (6.60 cm^3, 21.3 mmol), under argon in THF (35 cm^3) at −78 °C causing a bright yellow solution of allyllithium to form immediately. This was stirred for 20 min, before $Ti(OPr^i)_4$ (6.39 cm^3, 21.3 mmol) was added which caused the yellow solution to turn to a deep red-brown due to the allyltitanium species. This was stirred at 0 °C for 30 min and then recooled to −78 °C. A solution of the aldehyde **8** (1.69 g, 8.52 mmol) in THF (15 cm^3) under argon, was added *via* a cannula to a stirred suspension of NaH (80% dispersion in mineral oil; 0.37 g, 10.2 mmol) in THF (40 cm^3) at 0 °C. The resulting solution was added at 0 °C *via* a cannula to the allyltitanium species' solution at −78 °C; the reaction mixture was then allowed to warm slowly to room temperature overnight. After 48 h the mixture was poured into 1 mol dm^{-3} HCl (150 cm^3) and extracted with CH_2Cl_2 (3 × 250 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the resulting oil was purified by flash chromatography (gradient elution, 15–20% diethyl ether–light petroleum) to yield a 6:1 mixture of diastereoisomeric *keto esters* **3** and **9** (1.43 g, 80%) as a light yellow oil. These could be separated by HPLC using EtOAc–hexane (2.5:97.5) as eluent to afford, in order of elution the *keto ester* **3** as a white solid, mp 67–69 °C (from EtOAc–hexane) (Found: C, 69.1; H, 7.8. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3078, 2937, 2865, 1644, 1446, 1409, 1374, 1301, 1229, 1213, 1165, 1101, 1070, 1044, 1007, 994 and 913; δ_H(500 MHz) 13.29 [1 H, s, OH(enol)], 5.78 (1 H, ddt, *J* 16.8, 10.3 and 7.1, 2′-H), 5.14 (1 H, d, *J* 17.4, $3'_Z$-H), 5.13 (1 H, d, *J* 9.8, $3'_E$-H), 4.56 (1 H, q, *J* 6.4, 4-H), 2.65–2.57 (2 H, m, 9-H and 1′-H), 2.40–2.37 (2 H, m, 6-H and 9-H), 2.33 (1 H, dt, *J* 14.9 and 7.5, 1′-H), 2.00–1.80 (3 H, m, 8_{eq}-H, 5_{eq}-H and 7_a-H), 1.74–1.66 (1 H, m, 7_b-H), 1.63 (1 H, td, *J* 13.3 and 5.3, 5_{ax}-H) and 1.17 (1 H, br q, *J* 12.5, 8_{ax}-H); δ_C(100.12 MHz) 175.15 (C-10), 171.15 (C-2), 133.05 (C-2′), 118.46 (C-3′), 96.86 (C-1), 77.88 (C-4), 38.84 (C-1′), 31.86 (C-5), 29.63 (C-6), 29.06 (C-8), 27.79 (C-9) and 21.07 (C-7); *m/z* (EI) 208 (M^+), 167 ($M^+ - C_3H_5$), 165 ($M^+ - C_3H_7$), 125, 123, 112, 86 and 84; and the *keto ester* **9** as a white solid, mp 72–74 °C (from EtOAc–hexane) (Found: C, 68.9; H, 7.7. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2933, 2861, 1726, 1639, 1450, 1407, 1323, 1297, 1221, 1167, 1123, 1068 and 863; δ_H(500 MHz) 13.19 (1 H, s, OH-enol), 5.82 (1 H, ddt, *J* 17.2, 10.0 and 7.1, 2′-H), 5.13 (1 H, d, *J* 17.2, $3'_Z$-H), 5.12 (1 H, d, *J* 9.7, $3'_E$-H), 4.34 (1 H, dtd, *J* 11.9, 5.9 and 1.8, 4-H), 2.50–2.45 (2 H, m, 6-H and 1′-H), 2.40–2.35 (3 H, m, 9_{eq}-H, 9_{ax}-H and 1′-H), 1.95–1.85 (3 H, m, 5_{eq}-H, 7_b-H and 8_{eq}-H), 1.68–1.59 (1 H, m, 7_a-H), 1.29 (1 H, q, *J* 12.5, 5_{ax}-H) and 1.14 (1 H, br q, *J* 12.5, 8_{ax}-H); δ_C(100.12 MHz) 174.87 (C-10), 171.69 (C-2), 132.61 (C-2′), 118.61 (C-3′), 97.03 (C-1), 79.35 (C-4), 40.05 (C-1′), 34.95 (C-5), 32.84 (C-6), 29.59 (C-8), 29.06 (C-9) and 20.92 (C-7); *m/z* (EI) 208 (M^+), 190 ($M^+ - H_2O$), 167 ($M^+ - C_3H_5$), 165 ($M^+ - C_3H_7$), 125, 123, 86 and 84.

(1*R,6*S**,8*S**,10*R**)-2,11-Dioxo-10-phenylselanylmethyl-12-oxatricyclo[6.2.2.0^{1,6}]dodecane 10**

N-(Phenylselanyl)phthalimide (704 mg, 2.46 mmol) was added in one portion to a stirred solution of the keto ester **9** (256 mg, 1.23 mmol) in CH_2Cl_2 (10 cm^3) at room temperature, under argon, followed by zinc iodide (785 mg, 2.46 mmol). After 24 h of continuously stirring the reaction mixture was poured into 1 mol dm^{-3} aqueous NaOH (20 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography (gradient elution, 0–10% methanol–diethyl ether) afforded the *selenide* **10** (273 mg, 61%) as a light yellow solid, mp 134–136 °C (from methanol–diethyl ether) (Found: C, 59.3; H, 5.5. $C_{18}H_{20}O_3Se$ requires C, 59.5; H, 5.55%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3055, 2934, 2867, 1763, 1701, 1577, 1478, 1450, 1437, 1364, 1337, 1324, 1256, 1231, 1185, 1144, 1110, 1073, 1022, 1000, 983, 738 and 694; δ_H(400 MHz) 7.48–7.46 (2 H, m, 2 × ArH), 7.28–7.27 (3 H, m, 3 × ArH), 4.64 (1 H, br s, 8-H), 2.83 (1 H, dd, *J* 12.3 and 2.8, 1′-H), 2.62 (1 H, dddd, *J* 11.8, 10.7, 6.1 and 3.2, 10-H), 2.44 (1 H, t, *J* 12.3, 1′-H), 2.42–2.28 (3 H, m, 7_{eq}-H, 6-H and 3_{eq}-H), 2.17 (1 H, ddd, *J* 14.2, 9.9 and 1.7, 9_{ax}-H), 1.98–1.82 (4 H, m, 9_{eq}-H, 5_{eq}-H, 4_a-H and 3_{ax}-H) 1.68–1.58 (2 H, m, 5_{ax}-H and 4_b-H) and 1.30 (1 H, dd, *J* 12.8, 4.8, 7_{ax}-H); *m/z* (EI) 364 (M^+), 207 (M^+ − SePh), 163 [$M^+ - (SePh + CO_2)$] and 157 (SePh).

(1*S,6*S**,8*R**,10*R**)-2,11-Dioxo-10-phenylselanylmethyl-12-oxatricyclo[6.2.2.0^{1,6}]dodecane 13 and (1*S**,6*S**,8*R**,10*S**)-2,11-dioxo-10-phenylselanylmethyl-12-oxatricyclo[6.2.2.0^{1,6}]-dodecane 14**

N-(Phenylselanyl)phthalimide (415 mg, 1.45 mmol) was added in one portion to a stirred solution of the keto ester **3** (151 mg, 725 μmol) in CH_2Cl_2 (6 cm^3) at room temperature under argon, followed by zinc iodide (462 mg, 1.45 mmol). After 24 h, the reaction mixture was poured into 1 mol dm^{-3} aqueous NaOH (20 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. After flash chromatography (gradient elution, 40–50% diethyl ether–light petroleum) a 4:1 diastereoisomeric mixture of selenides **13** and **14** (250 mg, 95%) was obtained as a light yellow oil. Only the major diastereoisomer, the *selenide* **13** was fully characterized (Found: C, 59.2; H, 5.6%; M^+, 364.0578. $C_{18}H_{20}O_3Se$ requires C, 59.5; H, 5.55%; *M*, 364.0577); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2933, 2864, 1742, 1712, 1479, 1437, 1372, 1338, 1156, 1138, 1126, 1071, 1027, 738 and 691; δ_H(400 MHz) 7.60–7.52 (2 H, m, 2 × ArH), 7.30–7.19 (3 H, m, 3 × ArH), 4.74 (1 H, quint, *J* 1.9, 8-H), 3.93 (1 H, dd, *J* 11.9 and 2.5, 1′-H), 3.07 (1 H, ddd, *J* 13.5, 12.7 and 6.3, 3_{ax}-H), 2.53 (1 H, dddd, *J* 12.0, 8.3, 5.8 and 2.5, 10-H), 2.42 (1 H, br d, *J* 12.5, 9_{eq}-H), 2.16 (1 H, t, *J* 12.0, 1′-H), 2.13–1.85 (5 H, m, 7_{eq}-H, 6-H, 5_{eq}-H, 4_{eq}-H and 3_{eq}-H), 2.00 (1 H, ddd, *J* 13.5, 10.1 and 1.6, 7_{ax}-H), 1.69–1.63 (1 H, m, 9_{ax}-H), 1.59 (1 H, qt, *J* 13.8 and 3.7, 4_{ax}-H) and 1.47 (1 H, qd, *J* 13.0 and 3.4, 5_{ax}-H); *m/z* (EI) 364 (M^+), 207 (M^+ − SePh), 163 [$M^+ - (SePh + CO_2)$] and 157 (SePh).

(1*S,6*S**,8*R**)-10-Methylidene-2,11-dioxo-12-oxatricyclo-[6.2.2.0^{1,6}]dodecane 15**

From the keto ester 3. $Mn(OAc)_3$ (125 mg, 539 μmol) and $Cu(OAc)_2 \cdot H_2O$ (54 mg, 269 μmol) were added in one portion to a stirred solution of the keto ester **3** (56 mg, 269 μmol) in AcOH (25 cm^3) at room temperature. After 20 h, 10% aq. Na_2SO_3 (3 cm^3) was added to the mixture which was then stirred for 10 min. After this time, the reaction mixture was poured into 10% aq. Na_2SO_3 (7 cm^3) and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (gradient elution, 55–60% diethyl ether–light petroleum) to afford the keto ester **15** (22 mg, 39%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2993, 2866, 1738, 1715, 1643, 1447, 1426, 1368, 1325, 1285, 1261, 1228, 1147, 1127, 1067 and 1014; δ_H(500 MHz) 5.85 (1 H, t, *J* 2.3, 1′-H), 5.18 (1 H, t, *J* 2.1, 1′-H), 4.76 (1 H, quint, *J* 1.9, 8-H), 2.83–2.75 (2 H, m, 3_{ax}-H and

9_{eq}-H), 2.55 (1 H, dquint, *J* 15.8 and 2.2, 3_{eq}-H), 2.53 (1 H, dq, *J* 15.4 and 1.8, 9_{eq}-H), 2.37 (1 H, dddd, *J* 13.0, 10.1, 5.0 and 4.2, 6-H), 2.17 (1 H, ddd, *J* 14.1, 10.3 and 1.4, 7_{ax}-H), 2.00 (1 H, dtd, *J* 13.2, 6.4 and 3.4, 4_{eq}-H), 1.91 (1 H, dtd, *J* 13.8, 3.7 and 1.9, 5_{eq}-H), 1.82 (1 H, dq, *J* 13.9 and 3.9, 7_{eq}-H), 1.70 (1 H, qt, *J* 13.5 and 3.9, 4_{ax}-H) and 1.51 (1 H, qd, *J* 13.3 and 3.4, 5_{ax}-H); *m/z* (FAB) 207 (MH^+), 165 ($M^+ - C_3H_5$), 154, 136 and 107 [Found (FAB): MH^+ 207.1030. $C_{12}H_{15}O_3$ requires *M*, 207.1021].

From the mixture of selenides 13 and 14. $Ti(OPr^i)_4$ (0.068 cm^3, 228 μmol) was added to a stirred solution of the selenides **13** and **14** (0.83 g, 2.28 mmol), *tert*-butyl hydroperoxide (3 mol dm^{-3} in isooctane; 1.52 cm^3, 4.57 mmol) and dihydropyran (397 mm^3 4.57 mmol) in CH_2Cl_2 (20 cm^3) at room temperature under argon. The mixture was then heated to gentle reflux. After 4 h, the reaction mixture was allowed to cool to room temperature when it was treated with 10% aq. Na_2SO_3 (20 cm^3). The mixture was stirred for 20 min after which the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography (gradient elution, 55–60% diethyl ether–light petroleum) afforded the keto ester **15** (0.43 g, 92%) as a colourless oil, the spectroscopic data of which were identical with those for the compound prepared above.

(1*S**,2*S**,6*S**,8*R**)-10-Methylidene-11-oxo-12-oxatricyclo-[6.2.2.$0^{1,6}$]dodecan-2-ol 16

Sodium borohydride (238 mg, 6.30 mmol) was added to a stirred solution of the keto ester **15** (430 mg, 2.10 mmol) in methanol (25 cm^3) at 0 °C. After 1 h of continuously stirring, the reaction mixture was poured into 1 mol dm^{-3} hydrochloric acid (30 cm^3) and extracted with CH_2Cl_2 (4 × 40 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (gradient elution, 50–60% diethyl ether–light petroleum) to afford the *alcohol* **16** (411 mg, 95%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3534, 2935, 2862, 1729, 1648, 1449, 1407, 1370, 1327, 1282, 1222, 1200, 1114, 1065, 1007 and 982; δ_H(500 MHz) 5.45 (1 H, t, *J* 2.1, 1′-H), 5.11 (1 H, t, *J* 2.0, 1′-H), 4.72 (1 H, br t, *J* 3.7, 8-H), 3.85 (1 H, td, *J* 11.5 and 5.0, 2-H), 3.15 (1 H, d, *J* 11.9, OH), 2.79 (1 H, dquint, *J* 17.5 and 3.0, 9_{eq}-H), 2.52 (1 H, dd, *J* 17.5 and 1.5, 9_{ax}-H), 2.08 (1 H, dd, *J* 14.1 and 10.8, 7_{ax}-H), 2.08–2.01 (1 H, m, 3_{eq}-H), 1.94 (1 H, qd, *J* 12.7 and 4.0, 3_{ax}-H), 1.83 (1 H, dddd, *J* 14.0, 9.1, 4.1 and 4.3, 6-H), 1.76 (1 H, dquint, *J* 13.7 and 3.4, 4_{eq}-H), 1.69–1.62 (2 H, m, 7_{eq}-H and 5_{eq}-H), 1.30 (1 H, qt, *J* 13.4 and 3.5, 4_{ax}-H) and 1.05 (1 H, qd, *J* 13.3 and 3.4, 5_{ax}-H); *m/z* (EI) 208 (M^+), 190 ($M^+ - H_2O$), 164 ($M^+ - C_3H_8$), 146 [$M^+ - (C_3H_8 + H_2O)$], 135, 131, 118 and 108 [Found (EI): M^+, 208.1100. $C_{12}H_{16}O_3$ requires *M*, 208.1099].

(1*S**,2*S**,6*S**,8*R**)-10-Methylidene-11-oxo-2-trimethylsilyloxy-12-oxatricyclo[6.2.2.$0^{1,6}$]dodecane 18

TMSOTf (0.965 cm^3, 5.00 mmol) was added to a stirred solution of the alcohol **16** (260 mg, 1.24 mmol) and Et_3N (2.09 cm^3, 15.0 mmol) in CH_2Cl_2 (12 cm^3) at −78 °C under argon. After 30 min, the reaction mixture was poured into saturated aq. $NaHCO_3$ (25 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography (gradient elution, 40–45% diethyl ether–light petroleum) yielded the *silyl ether* **18** (330 mg, 95%) as a crystalline solid, mp 94–97 °C (from diethyl ether–light petroleum) (Found: C, 64.2; H, 8.7. $C_{15}H_{24}SiO_3$ requires C, 64.2; H, 8.6%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2932, 2856, 1758, 1645, 1462, 1448, 1426, 1362, 1329, 1249, 1228, 1203, 1176, 1140, 1101, 1069, 1036, 1013, 989, 945, 875, 840 and 753; δ_H(500 MHz) 5.19 (1 H, br s, 1′-H), 5.02 (1 H, t, *J* 2.0, 1′-H), 4.62 (1 H, s, 8-H), 3.99 (1 H, dd, *J* 11.6 and 4.8, 2-H), 2.76 (1 H, dt, *J* 17.2 and 3.0, 9_{eq}-H), 2.46 (1 H, dd, *J* 17.2 and 1.5, 9_{ax}-H), 2.30 (1 H, dq, *J* 12.7 and 4.0, 3_{ax}-H), 2.00 (1 H, dd, *J* 13.7 and 10.4, 7_{ax}-H), 1.84–1.70 (3 H, m, 3-H, 4_{eq}-H and 3_{eq}-H), 1.61–1.56 (2 H, m, 7_{eq}-H and 5_{eq}-H), 1.29 (1 H, qt, *J* 13.5 and 3.7, 4_{ax}-H), 1.09 (1 H, qd, *J* 13.3 and 3.5, 5_{ax}-H) and 0.13 (9 H, s, $SiMe_3$); *m/z* (EI) 265 ($M^+ - CH_3$), 221 [$M^+ - (CH_3 + CO_2)$], 203, 145, 131, 117, 105 and 91.

(1*S**,2*S**,6*S**,8*R**,11*S**)-10-Methylidene-12-oxatricyclo-[6.2.2.$0^{1,6}$]dodecane-2,11-diol 17

DIBAL-H solution (1.5 mol dm^{-3} in toluene; 1.18 cm^3, 1.77 mmol) was added dropwise to a stirred solution of the lactone **18** (330 mg, 1.18 mmol), under argon, in toluene (20 cm^3) at −78 °C. After 15 min $Na_2SO_4 \cdot 10H_2O$ (6 g) was added cautiously to the reaction mixture which was then allowed to warm slowly to room temperature over 1 h. After this, anhydrous Na_2SO_4 (12 g) was added to the mixture and stirring continued for a further 30 min. The suspension was then filtered through a short pad of silica gel, eluting with ethyl acetate, and the filtrate evaporated under reduced pressure. The resultant residue was dissolved in THF–water (2:1; 12 cm^3) and PPTS (10 mg) was added to the solution which was then stirred at room temperature. After 15 min the reaction mixture was poured into saturated aq. $NaHCO_3$ (15 cm^3) and extracted with CH_2Cl_2 (5 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography (gradient elution, 70–80% diethyl ether–light petroleum) afforded, in order of elution. The deprotected alcohol **16** with spectroscopic data identical with those for the compound prepared above (33 mg, 14%), and the *lactol* **17** (196 mg, 80%) as a colourless oil (Found: C, 68.7; H, 8.7. $C_{12}H_{18}O_3$ requires C, 68.5; H, 8.6%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3383, 2932, 2858, 1722, 1650, 1446, 1366, 1310, 1226, 1202, 1175, 1100, 1076, 1022, 1006, 993, 954, 935 and 885; δ_H(200 MHz) 5.68 (1 H, br d, *J* 3.1, 11-H), 5.33 (1 H, br s, 1′-H), 5.10 (1 H, br t, *J* 1.9, 1′-H), 4.18–4.10 (1 H, m, 8-H), 3.97 (1 H, td, *J* 6.5 and 3.1, 2-H), 3.77 [1 H, d, *J* 3.9, C(*11*)OH], 3.35 [1 H, d, *J* 6.5, C(2)OH], 2.89 (1 H, ddt, *J* 17.1, 5.8 and 2.9, 9_{eq}-H), 2.36 (1 H, dq, *J* 17.1, 1.9, 9_{ax}-H), 2.07–1.93 and 1.85–1.20 (1 H and 8 H, 2 × m, 7_{eq}-H, 7_{ax}-H, 6-H, 5_{ax}-H, 5_{eq}-H, 4_{ax}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H); *m/z* (EI) 210 (M^+), 193 (M^+ − OH), 164 (M^+ − OCHOH), 146 [$M^+ - (OCHOH + H_2O)$] and 131.

(1*S**,2*S**,6*S**,8*R**,11*S**)-11-Methoxy-10-methylidene-12-oxatricyclo[6.2.2.$0^{1,6}$]dodecan-2-ol 20

DIBAL-H (1.5 mol dm^{-3} in toluene; 0.308 cm^3, 432 μmol) was added dropwise to a stirred solution of the lactone **18** (57 mg, 205 μmol) in toluene (4 cm^3) at −78 °C under argon. After 15 min $Na_2SO_4 \cdot 10H_2O$ (2 g) was added cautiously to the reaction mixture which was then allowed to warm slowly to room temperature, before anhydrous Na_2SO_4 (4 g) was added to it and stirring continued for a further 30 min. The suspension was filtered through a short pad of silica gel eluting with ethyl acetate and the filtrate was evaporated under reduced pressure. The residue was dissolved in methanol (4 cm^3), PPTS (10 mg, cat.) was added to the solution which was then stirred at room temperature. After 30 min the reaction mixture was poured into saturated aq. $NaHCO_3$ (5 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography (30% diethyl ether–light petroleum) afforded the *alcohol* **20** (31 mg, 68%) as a colourless oil (Found: C, 69.6; H, 9.0. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3507, 2930, 1649, 1448, 1419, 1376, 1271, 1224, 1189, 1095, 1077, 1031, 1007, 984, 934, 882 and 813; δ_H(200 MHz) 5.26 (1 H, br s, 1′-H), 5.19 (1 H, s, 11-H), 4.99 (1 H, br s, 1′-H), 4.10 (1 H, m, 8-H), 3.89 (1 H, ddd, *J* 11.4, 6.7 and 4.6, 2-H), 3.66 (1 H, d, *J* 6.8, OH), 3.43 (3 H, s, OMe), 2.81 (1 H, dquint, *J* 17.0 and 2.8, 9_{eq}-H), 2.30 (1 H, dq, *J* 16.9 and 1.9, 9_{ax}-H), 2.05–1.96, 1.82–1.71 and 1.68–1.21 (1 H, 2 H and 6 H, 3 × m, 7_{ax}-H,

7_{eq}-H, 6-H, 5_{ax}-H, 5_{eq}-H, 4_{ax}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H); *m/z* (EI) 224 (M^+), 193 ($M^+ - OMe$), 175 [$M^+ - (OMe + H_2O)$], 164 ($M^+ - OCHOMe$) and 146 [$M^+ - (OCHOMe + H_2O)$].

(1*R,2*S**,6*S**,8*R**,10*S**,11*S**)-2-Hydroxy-11-methoxyspiro-[12-oxatricyclo[6.2.2.0^{1,6}]dodecane-10,2′-(oxacyclopropane)] 21 and (1*R**,2*S**,6*S**,8*R**,10*R**,11*S**)-2-hydroxy-11-methoxyspiro[12-oxatricyclo[6.2.2.0^{1,6}]dodecane-10,2′-(oxacyclopropane)] 22**

m-CPBA (90%; 54 mg, 312 μmol) was added portionwise to a stirred solution of the alcohol **20** (35 mg, 156 μmol) in CH_2Cl_2-saturated aq. $NaHCO_3$ (1 : 1; 3 cm^3) at 0 °C. After 30 min, 10% aq. Na_2SO_3 (1 cm^3) was added to the mixture which was then stirred for 5 min and finally poured into saturated aq. $NaHCO_3$ (10 cm^3). The solution was extracted with CH_2Cl_2 (4 × 15 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the resulting residue by flash chromatography (gradient elution, 50–100% diethyl ether–light petroleum) afforded, in order of elution the epoxy alcohol **21** (25 mg, 67%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3491, 2929, 2860, 1449, 1419, 1379, 1266, 1224, 1187, 1095, 1077, 1030, 1004, 987, 918, 896 and 878; δ_H(200 MHz) 5.20 (1 H, s, 11-H), 4.13 (1 H, dt, *J* 4.4 and 2.5, 8 H), 3.91 (1 H, d, *J* 7.3, OH), 3.54 (1 H, d, *J* 4.6, 3′-H), 3.45 (3 H, s, OMe), 3.30 (1 H, ddd, *J* 11.7, 6.9 and 4.8, 2-H), 2.74 (1 H, d, *J* 4.7, 3′-H), 2.59 (1 H, dt, *J* 14.8 and 2.8, 9_{eq}-H), 2.06–1.89, 1.72–1.63 and 1.56–1.14 (3 H, 1 H and 6 H, 3 × m, 9_{ax}-H, 7_{ax}-H, 7_{eq}-H, 6-H, 5_{ax}-H, 5_{eq}-H, 4_{ax}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H); *m/z* (EI) 240 (M^+), 209 ($M^+ - OMe$), 190 [$M^+ - (MeOH + H_2O)$], 180 ($M^+ - OCHOMe$) and 162 [$M^+ - (OCHOMe + H_2O)$] [Found (EI): M^+, 240.1349. $C_{13}H_{20}O_4$ requires *M*, 240.1361]; followed by the epoxy alcohol **22** (7 mg, 20%) as colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3482, 2927, 2853, 1461, 1417, 1376, 1362, 1348, 1247, 1105, 1082, 1055, 1030 and 982; δ_H(500 MHz) 5.19 (1 H, s, 11-H), 4.11 (1 H, dt, *J* 4.7 and 2.7, 8-H), 3.56 (1 H, d, *J* 1.2, OH), 3.50 (3 H, s, OMe), 3.46 (1 H, dd, *J* 11.5 and 4.7, 2-H), 3.13 (1 H, d, *J* 4.2, $3'_b$-H), 2.55 (1 H, dt, *J* 14.3 and 2.8, 11_{eq}-H), 2.54 (1 H, d, *J* 4.2, $3'_a$-H), 1.86–1.82 (2 H, m, 3-H and 7_{ax}-H), 1.75 (2 H, m, 11_{ax}-H and 6-H), 1.69–1.62 (1 H, m, 6-H), 1.57–1.47 (3 H, m, 4_{eq}-H, 5_{eq}-H and 7_{eq}-H) and 1.38–1.27 (2 H, m, 4_{ax}-H and 5_{ax}-H); *m/z* (EI) 242 (MH_2^+), 240 (M^+), 226 ($MH^+ - CH_3$), 223 ($M^+ - OH$), 209 ($M^+ - OMe$), 194 [$MH_2^+ - (MeO + OH)$], 180 ($M^+ - OCHOMe$) and 162 [$M^+ - (OCHOMe + H_2O)$] [Found (EI): M^+, 240.1359. $C_{13}H_{20}O_4$ requires *M*, 240.1361].

(1*R,2*S**,6*S**,8*R**,10*S**)-2-Hydroxy-11-oxospiro[12-oxatricyclo[6.2.2.0^{1,6}]dodecane-10,2′-(oxacyclopropane)] 23**

m-CPBA (90%; 102 mg, 591 μmol) was added portionwise to a stirred solution of the alcohol **16** (41 mg, 197 μmol) in CH_2Cl_2-saturated aq. $NaHCO_3$ (1 : 1; 4 cm^3) at 0 °C. After 45 min 10% aq. Na_2SO_3 (1 cm^3) was added to the solution which was then stirred for 5 min and finally poured into saturated aq. $NaHCO_3$ (10 cm^3). The solution was extracted with CH_2Cl_2 (4 × 15 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography (gradient elution, 60–70% diethyl ether–light petroleum) yielded the epoxy alcohol **23** (33 mg, 75%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3426, 2934, 2863, 1730, 1448, 1373, 1340, 1322, 1228, 1165, 1135, 1111, 1074, 1013 and 980; δ_H(200 MHz) 4.78–4.73 (1 H, m, 8-H), 4.01 (1 H, td, *J* 11.6 and 2.6, 2-H), 3.67 (1 H, d, *J* 4.5, 3′-H), 3.29 (1 H, d, *J* 2.6, OH), 2.77 (1 H, d, *J* 4.6, 3′-H), 2.51 (1 H, dt, *J* 15.4 and 3.2, 9_{eq}-H), 2.31–1.62 (7 H, m, 7_{ax}-H, 7_{eq}-H, 6-H, 5_{eq}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H), 1.86 (1 H, dd, *J* 15.4 and 1.8, 9_{ax}-H) and 1.34–0.86 (2 H, m, 5_{ax}-H and 4_{ax}-H); *m/z* 224 (M^+), 211, 206 ($M^+ - H_2O$), 193, 188, 163 [$M^+ - (H_2O + CO_2)$], 156, 147, 139 and 111 [Found (EI): M^+, 224.1052 $C_{12}H_{16}O_4$ requires *M*, 224.1049].

(1*S,2*S**,6*S**,8*R**,11*R**)-10-Methylidene-11-phenylsulfanyl-12-1-oxatricyclo[6.2.2.0^{1,6}]dodecan-2-ol 26**

DIBAL-H (1.5 mol dm^{-3} in toluene; 0.136 cm^3, 204 μmol) was added dropwise to a stirred solution of the lactone **18** (38 mg, 136 μmol) in toluene (4 cm^3), under argon, at −78 °C. After 15 min $Na_2SO_4 \cdot 10H_2O$ (2 g) was added cautiously to the reaction mixture which was then allowed to warm slowly to room temperature. After anhydrous Na_2SO_4 (4 g) had been added to the mixture, stirring was continued for a further 30 min before the suspension was filtered through a short pad of silica gel eluting with ethyl acetate. The filtrate was evaporated under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 (3 cm^3) to which benzenethiol (10 drops) and PPTS (10 mg) were added. The mixture was stirred at room temperature for 15 min after which it was poured into saturated aq. $NaHCO_3$ (5 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the resulting residue by flash chromatography (gradient elution, 10–20% diethyl ether–light petroleum) afforded the *alcohol* **26** (29 mg, 71%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3473, 2927, 2858, 1646, 1582, 1479, 1438, 1417, 1330, 1075, 1037, 990, 755 and 691; δ_H(200 MHz) 7.58–7.49 (2 H, m, 2 × ArH), 7.38–7.24 (3 H, m, 3 × ArH), 5.83 (1 H, s, 11-H), 5.46 (1 H, td, *J* 1.9 and 0.9, 1′-H), 5.13 (1 H, br s, 1′-H), 4.22–4.17 (1 H, m, 8-H), 3.92 (1 H, td, *J* 10.3 and 3.3, 2-H), 3.65 (1 H, d, *J* 9.6, OH), 3.24 (1 H, dquint, *J* 17.2 and 2.8, 9_{eq}-H), 2.39 (1 H, dq, *J* 17.2 and 1.8, 9_{ax}-H), 1.83 (1 H, t, *J* 11.4, 6-H), 2.04–1.95, 1.78–1.64 and 1.59–1.38 (1 H, 2 H and 5 H, 3 × m, 7_{ax}-H, 7_{eq}-H, 5_{ax}-H, 5_{eq}-H, 4_{ax}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H); *m/z* (EI) 302 (M^+, 193 ($M^+ - SPh$), 175 [$M^+ - (SPh + H_2O)$] and 147 [$M^+ - (OCHSPh + OH)$] [Found (EI): M^+, 302.1348. $C_{18}H_{22}O_2S$ requires *M*, 302.1340].

(1*S,2*S**,6*S**,8*R**,11*R**)-11-Acetoxy-10-methylidene-12-oxatricyclo[6.2.2.0^{1,6}]dodecan-2-ol 27**

$AgOCOCF_3$ (20.2 mg, 91.7 μmol) was added portionwise to a stirred solution of the alcohol **26** (25.2 mg, 83.3 μmol), NMe_4OAc (55.5 mg, 416 μmol) and 3 Å powdered molecular sieves (200 mg) in CH_2Cl_2 (4 cm^3) at room temperature under argon. After 5 h, the reaction mixture was filtered through a short plug of Florisil® and eluted with ethyl acetate. The filtrate was washed with saturated aq. $NaHCO_3$ (15 cm^3) and the aqueous layer re-extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (70% diethyl ether–light petroleum) to afford in order of elution the *acetate* **27** (7 mg, 32%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3492, 2934, 2861, 1746, 1649, 1375, 1272, 1233, 1220, 1200, 1094, 1080, 1009, 986 and 939; δ_H(400 MHz) 6.59 (1 H, s, 11-H), 5.20 (1 H, br s, 1′-H), 5.04 (1 H, br t, *J* 2.0, 1′-H), 4.20–4.16 (1 H, m, 8-H), 4.01 (1 H, ddd, *J* 11.4, 4.6 and 2.9, 2-H), 2.86 (1 H, dquint, *J* 17.2 and 2.9, 9_{eq}-H), 2.36 (1 H, dq, *J* 17.1 and 1.8, 9_{ax}-H), 2.17 (1 H, d, *J* 2.9, OH), 2.05 (3 H, s, OAc), 1.98–1.92 (1 H, m, 3_{ax}-H), 1.83–1.70 (2 H, m, 7_{ax}-H and 4_{eq}-H), 1.69–1.57 (2 H, m, 6-H and 3_{eq}-H), 1.54–1.49 (2 H, m, 7_{eq}-H and 5_{eq}-H) and 1.47–1.31 (2 H, m, 5_{ax}-H and 4_{ax}-H); *m/z* (FAB) 275 (MNa^+), 253 (MH^+), 235 ($M^+ - OH$), 209 ($M^+ - Ac$), 193 ($M^+ - OAc$), 175 [$M^+ - (OAc + H_2O)$] and 147 [$M^+ - (OAc + H_2O + CO)$] [Found (FAB): MH^+ 253.1421. $C_{14}H_{21}O_4$ requires *M*, 253.1440]; and the lactol **17** (10.8 mg, 60%) the properties of which were identical with those of the previously prepared sample.

(1*R,2*S**,6*S**,8*R**,10R*)-10-Bromomethyl-11-oxo-12-oxatricyclo[6.2.2.0^{1,6}]dodecane-2,10-diol 28**

Bromine (0.10 cm^3, 1.92 mmol) was added dropwise to a stirred solution of the alcohol **16** (133 mg, 639 μmol) in acetonitrile-saturated aq. NH_4Cl (1 : 1; 9 cm^3) at 0 °C under argon. After 15 min the reaction mixture was poured into water (10 cm^3) and

extracted with CH_2Cl_2 (5 × 15 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography (80% diethyl ether–light petroleum) afforded the hydroxy bromide **28** (148 mg, 76%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3406, 2933, 2864, 1738, 1450, 1410, 1376, 1335, 1250, 1223, 1150, 1112, 1077, 1015 and 958; δ_H(400 MHz) 4.75 (1 H, t, *J* 4.0, 8-H), 4.73 [1 H, s, C(10)OH], 3.90 (1 H, td, *J* 11.2, 5.5, 2-H), 3.71 (2 H, s, 1′-H), 3.29 [1 H, d, *J* 11.4, C(2)OH], 2.18 (1 H, ddd, *J* 14.7, 4.7 and 3.1, 7_{eq}-H), 2.13–1.95, 1.80–1.73, 1.63–1.56 and 1.33–1.20 (4 H, 2 H, 1 H and 2 H, 4 × m, 9_{ax}-H, 9_{eq}-H, 7_{ax}-H, 6-H, 5_{eq}-H, 4_{ax}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H) and 1.05 (1 H, qd, *J* 12.9 and 2.5, 5_{ax}-H); *m/z* (EI) 306 and 304 (M^+), 288 and 286 ($M^+ - H_2O$), 270 and 268 ($M^+ - 2H_2O$), 223 ($M^+ - H_2Br$), 207 ($M^+ - (Br + H_2O)$ and 189 [$M^+ - (Br + 2H_2O)$] [Found (EI): M^+, 304.0309. $C_{12}H_{17}{}^{79}BrO_4$ requires *M*, 304.0311].

(1*R,2*S**,6*S**,8*R**,10*R**)-2-Trimethylsilyloxy-11-oxospiro[12-oxatricyclo[6.2.2.0^{1,6}]dodecane-10,2′-(oxacyclopropane)] 29**

Amberlite IRA-420 (2 g) was added to a stirred solution of the hydroxy bromide **28** (156 mg, 510 μmol) in CH_2Cl_2 (10 cm^3) at room temperature. After 30 min the reaction mixture was filtered and evaporated under reduced pressure. The residual epoxy alcohol **24** was dissolved in CH_2Cl_2 (10 cm^3), under argon. The resulting solution was cooled at −78 °C and treated with Et_3N (0.811 cm^3, 5.82 mmol) and TMSOTf (0.375 cm^3, 1.94 mmol). After 30 min the reaction mixture was poured into saturated aq. $NaHCO_3$ (15 cm^3) and extracted with CH_2Cl_2 (5 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by flash chromatography (gradient elution, 80–100% diethyl ether–light petroleum) afforded the *silyl ether* **29** (136 mg, 90%) as a crystalline solid, mp 100–104 °C (diethyl ether–light petroleum); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2933, 2861, 1761, 1361, 1320, 1247, 1124, 1103, 1074, 1016, 991, 959, 875 and 840; δ_H(400 MHz) 4.64 (1 H, dq, *J* 3.7 and 1.8, 8-H), 3.44 (1 H, dd, *J* 11.3 and 4.7, 2-H), 3.05 (1 H, d, *J* 4.7, 3′-H), 2.62 (1 H, d, *J* 4.7, 3′-H), 2.28 (1 H, dt, *J* 14.7 and 3.2, 9_{eq}-H), 2.17 (1 H, qd, *J* 12.8 and 4.0, 3_{ax}-H), 2.05 (1 H, ddd, *J* 13.9, 10.1 and 1.0, 7_{ax}-H), 2.00 (1 H, dd, *J* 14.6 and 1.4, 9_{ax}-H), 1.92 (1 H, ddt, *J* 11.3, 11.2 and 4.2, 6-H), 1.72–1.58 (4 H, m, 7_{eq}-H, 5_{eq}-H, 4_{eq}-H and 3_{eq}-H), 1.21 (1 H, qt, *J* 13.6 and 3.4, 4_{ax}-H), 1.09 (1 H, qd, *J* 13.2 and 2.6, 5_{ax}-H) and 0.09 (9 H, s, $SiMe_3$); *m/z* (FAB) 297 (MH^+), 281 ($M^+ - CH_3$), 235 [$M^+ - (CH_3 + CH_2O_2)$], 207 ($M^+ - OSiMe_3$) and 161 [$M^+ - (OSiMe_3 + CH_2O_2)$] [Found (FAB): MH^+, 297.1504. $C_{15}H_{25}SiO_4$ requires *M*, 297.1522].

(1*R,2*S**,6*S**,8*R**,10*R**,11*S**)-2,11-Dihydroxyspiro[12-oxatricyclo[6.2.2.0^{1,6}]dodecane-10,2′(oxacyclopropane)] 31**

DIBAL-H (1.5 mol dm^{-3} in toluene; 0.378 cm^3, 567 μmol) was added dropwise to a stirred solution of the silyl ether **29** (112 mg, 378 μmol) in toluene (5 cm^3) under argon at −78 °C. After 15 min $Na_2SO_4 \cdot 10H_2O$ (3 g) was added cautiously to the reaction mixture which was then allowed to warm slowly to room temperature over 1 h. After this anhydrous Na_2SO_4 (6 g) was added to the mixture and stirring continued for a further 30 min. The suspension was filtered through a short pad of silica gel eluting with EtOAc and evaporated under reduced pressure. Purification of the resulting oil by flash chromatography (gradient elution, 80–100% diethyl ether–light petroleum) afforded the *lactol* **30** (100 mg, 89%) as a colourless oil, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3453, 3039, 2938, 2863, 1759, 1721, 1448, 1412, 1369, 1295, 1249, 1088, 1035, 1014, 965, 909, 870 and 843; δ_H(400 MHz) 5.70 (1 H, s, 11-H), 4.67 (1 H, s, OH), 4.13–4.10 (1 H, m, 8-H), 3.42 (1 H, dd, *J* 10.8 and 5.3, 2-H), 2.78 (1 H, d, *J* 4.7, 3′-H), 2.68 (1 H, dt, *J* 14.1 and 2.6, 9_{eq}-H), 2.39 (1 H, d, *J* 4.6, 3′-H), 1.73–1.17 (10 H, m, 9_{ax}-H, 7_{eq}-H, 7_{ax}-H, 6-H, 5_{ax}-H, 5_{eq}-H, 4_{ax}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H) and 0.10 (9 H, s, $SiMe_3$); *m/z* (FAB) 321 (MNa^+), 281 ($M^+ - OH$), 235 [$M^+ - (CH_3 + CH_3O_2)$], 191 and 169 [Found (FAB): MNa^+, 321.1525. $C_{15}H_{25}NaO_4Si$ requires *M*, 321.1498]. A catalytic amount of PPTS (~ 10 mg) was added to a stirred solution of the lactol **30** (100 mg, 335 μmol) in THF–H_2O (1:1; 8 cm^3) at room temperature. After 15 min, the reaction mixture was poured into saturated aq. $NaHCO_3$ (8 cm^3) and extracted with CH_2Cl_2 (6 × 15 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by flash chromatography (gradient elution, 90–100% AcOEt–light petroleum) to afford the *lactol* **31** (61 mg, 81%) as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3456, 2936, 2865, 1721, 1644, 1450, 1416, 1372, 1336, 1301, 1136, 1086, 1052, 1021 and 1001; δ_H(400 MHz) 5.78 (1 H, d, *J* 1.3, 11-H), 4.16 (1 H, dt, *J* 4.5 and 2.3, 8-H), 3.72 [1 H, d, *J* 1.6, C(11)OH], 3.55 (1 H, ddd, *J* 11.6, 4.7 and 1.6, 2-H), 3.48 [1 H, d, *J* 1.8, C(2)OH], 3.14 (1 H, d, *J* 3.9, 3′-H), 2.64 (1 H, dt, *J* 14.4 and 2.9, 9_{eq}-H), 2.58. (1 H, d, *J* 3.9, 3′-H), 1.87–1.49 (8 H, m, 9_{ax}-H, 7_{ax}-H, 7_{eq}-H, 6-H, 5_{eq}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H), 1.38 (1 H, qd, *J* 13.0 and 3.3, 5_{ax}-H) and 1.28 (1 H, qt, *J* 13.0 and 3.9, 4_{ax}-H); *m/z* (EI) 225 ($M^+ - H$), 209 ($M^+ - OH$), 180 ($M^+ - OCHOH$), 162 [$M^+ - (OCHOH + H_2O)$], 147, 133 and 118 [Found (EI): $M^+ - H$, 225.1123. $C_{12}H_{17}O_4$ requires *M*, 225.1127].

(1*R,2*S**,6*S**,8*R**,10*R**,11*R**)-2,11-Diacetoxyspiro[12-oxatricyclo[6.2.2.0^{1,6}]dodecane-10,2′-(oxacyclopropane)] 2**

Acetyl chloride (0.012 cm^3, 165 μmol) was added dropwise to a stirred solution of the lactol **31** (34 mg, 150 μmol), pyridine (0.036 cm^3, 450 μmol) and DMAP (cat) in CH_2Cl_2 (1 cm^3) at 0 °C. After 3 h, the reaction mixture was poured into 50% aq. $NaHCO_3$ (5 cm^3) and extracted with CH_2Cl_2 (5 × 5 cm^3). The combined extracts were dried (Na_2SO_4) filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography (gradient elution, 50–100% EtOAc–light petroleum) afforded the acetate **32** (16 mg, 40%) as a viscous oil. The mono acetate was not characterised but taken on directly to the next reaction. The acetate **32** (3 mg, 11.2 μmol) and DMAP (cat) were dissolved in pyridine (250 mm^3) and the solution cooled to 0 °C. Acetic anhydride (0.031 cm^3, 33.6 μmol) was added to the reaction mixture which was then stirred at 0 °C for 30 min, after which it was allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was then poured into 50% aq. $NaHCO_3$ (5 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The combined extracts were washed with brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by flash chromatography using diethyl ether as eluent afforded the *diacetate* **2** (2.9 mg, 85%) as a low-melting solid; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2931, 2864, 1738, 1731, 1433, 1376, 1254, 1203, 1168, 1087, 1069, 1038, 1022, 994 and 949; δ_H(400 MHz) 6.71 (1 H, s, 11-H), 4.73 (1 H, dd, *J* 11.3 and 5.3, 1′-H), 4.20–4.16 (1 H, m, 8-H), 2.99 (1 H, d, *J* 4.4, 3′-H), 2.55 (1 H, br d, *J* 14.4, 9_{eq}-H), 2.39 (1 H, d, *J* 4.4, 3′-H), 2.15 (3 H, s, OAc), 1.97 (3 H, s, OAc), 1.92–1.23 (8 H, m, 9_{ax}-H, 7_{ax}-H, 7_{eq}-H, 6-H, 5_{eq}-H, 4_{eq}-H, 3_{ax}-H and 3_{eq}-H) and 1.01–0.88 (2 H, m, 5_{ax}-H and 4_{ax}-H); *m/z* (EI) 267 ($M^+ - Ac$), 251 ($M^+ - OAc$), 208 [$M^+ - (OAc + Ac)$], 179 [$M^+ - (OCHOAc + Ac)$] and 162 [$M^+ - (OCHOAc + HOAc)$] [Found (EI): $M^+ - OAc$, 251.1285. $C_{14}H_{19}O_4$ requires *M*, 251.1283].

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