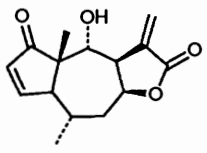
A Concise Synthesis of the Pseudoguaianolide Skeleton

Luiz-Claudio de Almeida Barbosa and John Mann
Department of Chemistry, Reading University, Whiteknights, Reading RG6 2AD, UK

We describe the conversion of 1,3-dimethyl-8-oxabicyclo[5.3.0]dec-3-ene-2,9-dione into 1,3-dimethyl-6-oxatricyclo[8.3.0.0^{3,7}]tridec-11-ene-2,5,13-trione (pseudoguaianolide skeleton) in eight steps. This completes a ten-stage synthesis of this system from the readily available 2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-one.

More than 2000 different sesquiterpene lactones have been identified, and of these, the pseudoguaianolides comprise the largest structural class. Almost without exception, these compounds possess some kind of biological activity.[1] For example, helenalin **1** acts as an anti-tumour agent, an anti-microbial agent, as an insect anti-feedant, and also possesses anti-inflammatory activity.



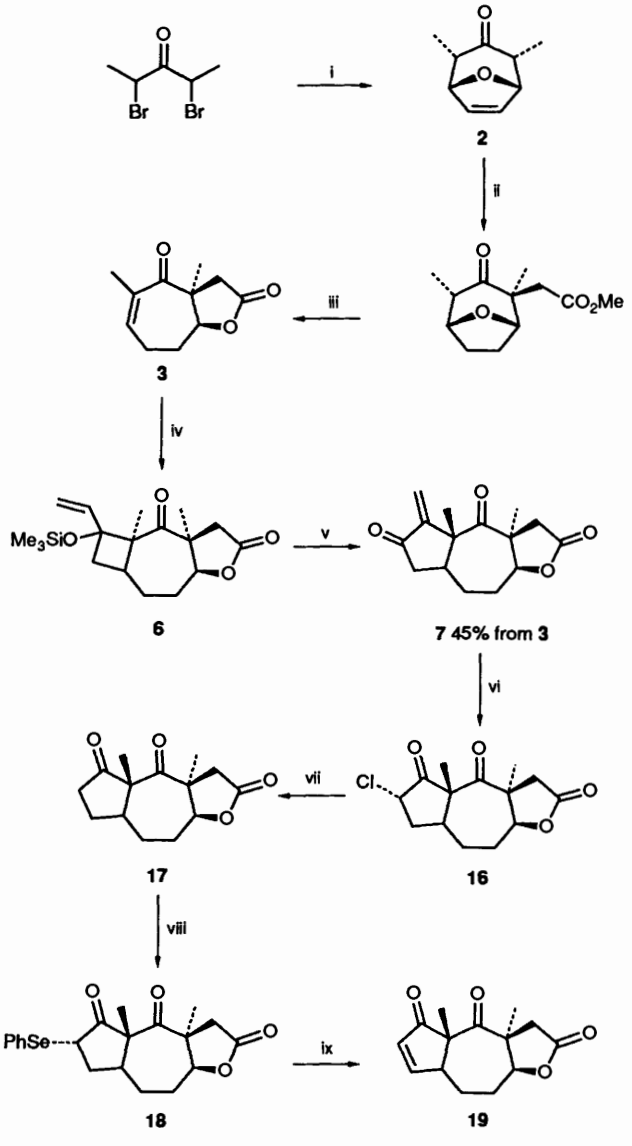
1

In consequence there have been numerous syntheses of the natural pseudoguaianolides,[2] but in almost every instance these have been multi-step and elegant rather than practical. In order to probe the particular structural requirements for biological activity, we required a short, flexible, and above-all, efficient synthesis of this ring-system. In this paper we report the attainment of this goal.

The overall route is shown in Scheme 1, and we have already given details[3] of our synthesis of 1,3-dimethyl-8-oxabicyclo-[5.3.0]dec-3-ene-2,9-dione **3** from 2,4-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one **2**. This latter compound can be prepared in large quantities from 2,4-dibromopentan-3-one and furan using oxyallyl methodology.[4,5] Our initial attempt to prepare a tricyclic system involved a copper-catalysed Grignard reaction of 2-(2-bromomagnesioethyl)-1,3-dioxolane with the lactone **3**, and subsequent trapping of the resultant enolate with bis-(trimethylsilyl)acetamide. This provided the silyl enol ether **4** as a mixture of isomers in 30% yield. Treatment of this mixture with titanium tetrachloride in dichloromethane (Mukaiyama aldol methodology)[6] yielded the tricyclic alcohols **5** in 78% isolated yield. However, the disappointing yield for the cuprate reaction coupled with the lack of stereoselectivity necessitated a change of strategy.

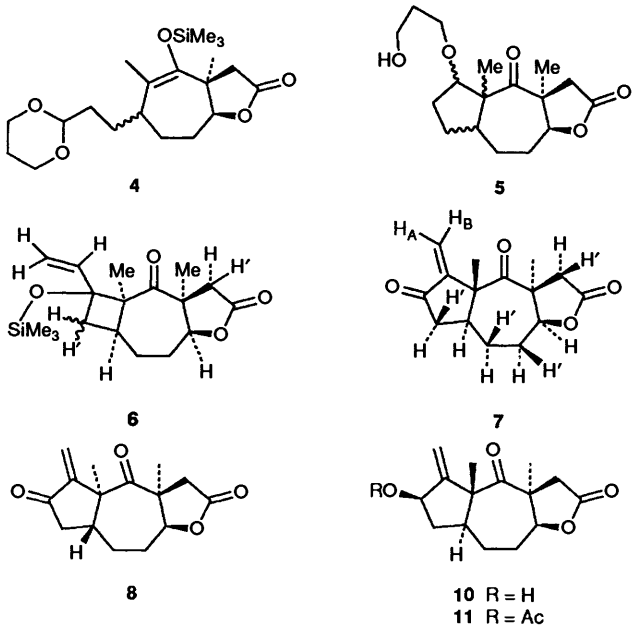
In a recent paper,[7] Demuth *et al.* described a novel cyclopentannelation procedure based upon a [2π + 2π] photocyclisation of 2-trimethylsiloxybuta-1,3-diene with 3-substituted cyclohex-2-enones, followed by a palladium-catalysed rearrangement to provide the desired products (Scheme 2). High regio- and stereo-selectivities were observed, and the nature of the 3-substituent seemed to be unimportant. With 2-methylcyclohept-2-enone, however, a complex mixture of products was obtained. Nonetheless, the simplicity of the procedure encouraged us to try the methodology on lactone **3**.

In the event, reaction of the lactone with a 12-fold excess of 2-trimethylsiloxybuta-1,3-diene in cyclohexane containing a little tetrahydrofuran (THF), under irradiation with two 500 W



Scheme 1 Summary of the synthesis of the pseudoguaianolide skeleton: *Reagents, conditions and yields:* i, NaI, Cu, furan, 60%; ii, H_2, Pd/C, LDA, $BrCH_2CO_2R$, 96%; iii, BF_3, KI, 55–65%; iv, CH_2=$CH(OSiMe_3)$=CH_2, *hν*; v, Pd $(PhCN)_2Cl_2$, *p*-benzoquinone; vi, $NaBH_4$, CCl_4/Ph_3P, $NaIO_4$, OsO_4, 62%; vii, Bu_3SnH, azoisobutyronitrile, 83%; viii, PhSeCl, 77%; ix, $NaIO_4$, 25%

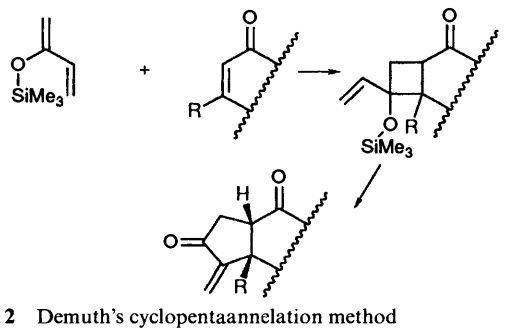
medium pressure lamps, led to complete consumption of the lactone after 21 h. On work-up, one pure crystalline product was obtained in 37% yield, together with a complex mixture of other photo-products. The crystalline product has been



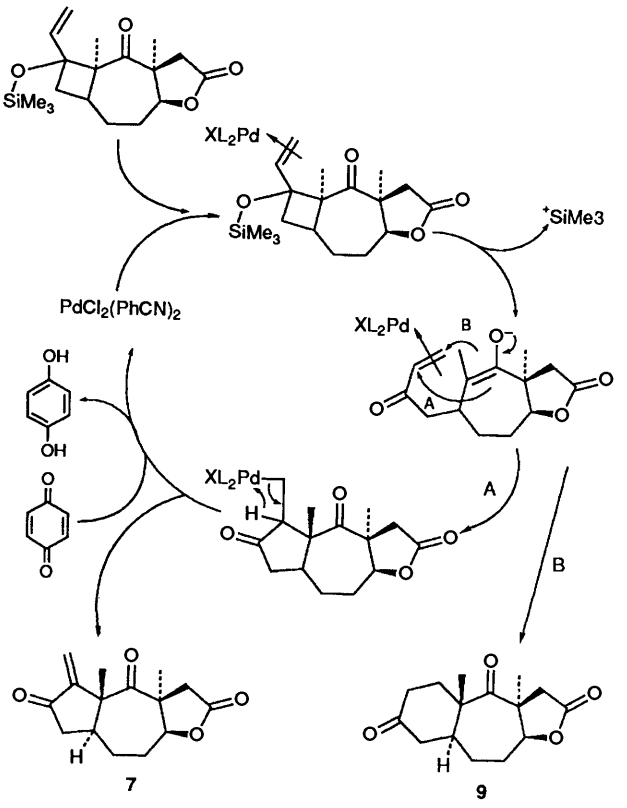
assigned structure **6** on the basis of a full spectral analysis of the rearrangement product **7**. It was clear that only one stereoisomer was present since the ^{1}H NMR spectrum possessed discrete signals for the vinyl hydrogens (three double doublets at δ 5.20, 5.32 and 6.00), and a six-proton singlet for the two methyl groups. Reaction of **6** with bis(benzonitrile)palladium(II) chloride (3 mol %) in refluxing THF resulted in a smooth rearrangement to provide the α-methylene ketone **7** in 95% isolated yield. The structure of **7** was confirmed by spectroscopic means. In particular, there were three carbonyl absorptions in the IR spectrum (1781, 1728 and 1709 cm^{-1}); discrete ^{1}H NMR signals for the methyls (δ 1.26 and 1.38) and the two α-methylene protons (δ 5.37 and 5.97); and there were significant NOE enhancements between 7-H and 10-H, and between 7-H and the 3-methyl group, with no enhancement between the two methyl groups, or between 10-H and the 1-methyl. The fortuitous formation of the desired *trans*-stereochemistry can probably be explained by the mechanism shown in Scheme 3, where enolate formation precedes construction of the cyclopentanone ring.

The low yield of **6** in the photochemical reaction was not as serious as we first imagined, since reaction of the complex mixture of photoadducts with Pd^{II} provided a further 17% of compound **7** together with compounds **8** (10%) and **9** (25%). This last compound is, we believe, formed *via* an alternative mode of ring closure during the rearrangement process (Scheme 3).

With the tricyclic system in hand, it was only necessary to change the functionality on the cyclopentanone ring in order to attain our synthetic goal. This proved to be surprisingly



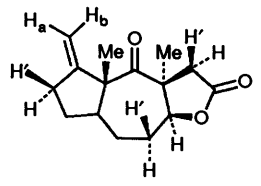
Scheme 2 Demuth's cyclopentaannelation method



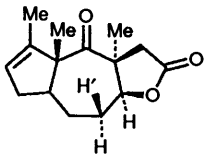
Scheme 3 Proposed mechanism for the palladium catalysed rearrangement

difficult. Regio- and stereo-selective reduction of the diketone could be achieved (in near quantitative yield) using $NaBH_4$ in admixture with $CeCl_3$,[8] and the resultant alcohol **10** was converted into the acetate **11**. In the ^{1}H NMR spectrum of this compound, 12-H appeared as triple triplet at δ 5.59, and the magnitudes of the coupling constants $J_{11,12}$ and $J_{11',12}$ (both 8 Hz) were consistent with the assigned structure. Further chemical and spectral evidence for this assignment was obtained after we had prepared the chloride **16** (*vide infra*). Oxidative cleavage of the double bond was then effected using a mixture of $NaIO_4$ and OsO_4 to afford the α-acetoxy ketone **14**, but attempted pyrolytic elimination of ethanoic acid was unsuccessful. At 200 °C and 10 mmHg the compound was stable, whilst at temperatures above 350 °C and atmospheric pressure, a complex mixture of products was obtained; and we were unable to find an appropriate set of conditions for the elimination. Attempted reductive removal of the acetate group using either Zn/HOAc or Zn/Ac_2O[9,10] proved unsuccessful, and the acetate was recovered unchanged from these reactions. This is probably not surprising since molecular models indicated that the acetoxy group was at an angle of 120° with respect to the plane of the carbonyl group, and orthogonality is required for facilitated reductive removal.[10] An alternative reductive method due to Sarma[11] using $NiCl_2$ and $NaBH_4$ provided an inseparable mixture of the alkenes **12** and **13** in 41% yield.

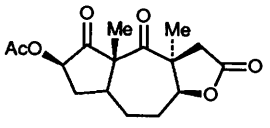
Ultimately, success was achieved *via* the route shown in Scheme 1. The alcohol **10** was converted into the chloride **15** using CCl_4/Ph_3P in an isolated yield of 71%, and oxidative cleavage as before yielded the α-chloro ketone **16**. Confirmation of the structure of this compound was achieved through extensive NOE experiments. In particular, there were significant enhancements between 12-H and 1-Me, 10-H and 3-Me, and between 10-H and 7-H. The 400 MHz ^{1}H NMR spectrum of **16** is reproduced in Fig. 1.



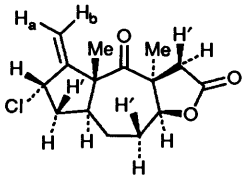
12



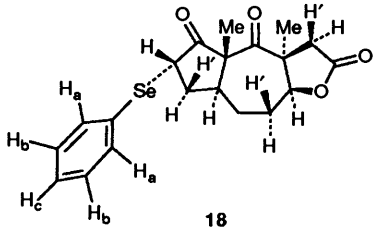
13



14

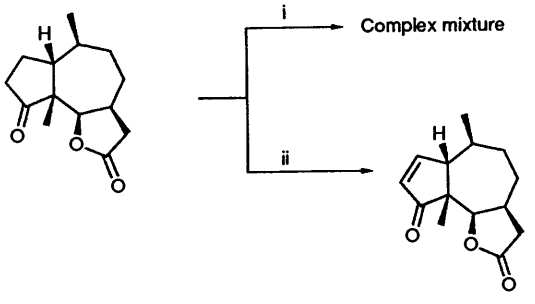


15



18

Attempts to eliminate HCl from the compound met with total failure. It was completely inert to $AgNO_3$ in ethanol at room temperature, reacted slowly with LiCl in DMF (at 40 °C), Li_2CO_3 in DMF (at 100 °C), DBU in THF (at 60 °C), and with Me_3SnMe_3[12] in toluene (at 40 °C) to produce complex mixtures of products, and the compound was completely decomposed by DBU in refluxing toluene. In consequence, the chlorine atom was removed using Bu_3SnH to provide an 83% yield of cyclopentanone **17**, and this was converted into the phenylselenenyl derivative **18** in 77% yield (PheSeCl in EtOAc). In the ^1H NMR spectrum, it was apparent that 10-H was deshielded by *ca.* 0.3 ppm with respect to 10-H in compound **17**, and this is in accord with the stereochemistry assigned to the selenide. Finally, oxidative elimination of phenylseleninic acid was achieved using sodium periodate in aqueous THF, though the yield of the desired lactone **19** was very poor (25%). Other oxidative methods were investigated, but none provided any improvement in yield. Heathcock experienced similar difficulties[13] in the conversion shown in Scheme 4, and eventually resorted to the use of bromination and dehydrobromination to introduce the double bond.



Scheme 4 *Reagents*: i, PhSeCl; ii, Me_3SiOTF/triethylamine, *N*-bromosuccinimide, $CaCO_3$, DMAC, 47%

Despite this problem with the final step, the rest of the synthesis was reasonably efficient, and all reactions as far as the ketone **17** have been carried out on the 0.5 to 5 g scale. Reasonable quantities of pseudoguaianolide-type compounds are thus now accessible for use in structure–biological activity correlation investigations.

Experimental

IR spectra were recorded with a Perkin-Elmer 881 double beam grating spectrophotometer. NMR spectra were recorded with a Perkin-Elmer R34 (220 MHz) instrument, a Bruker WH 400 spectrometer (400 MHz) at the University of Warwick or with a Varian T-60 (60 MHz) instrument, using tetramethylsilane as internal standard; all *J* values are given in Hz. Mass spectra were obtained at the University of Swansea using a VG ZAB-E high resolution spectrometer. Flash chromatography was performed using Crosfield Sorbsil C60 (40–60 μm). Solvents were purified according to Perrin,[14] and light petroleum refers to the fraction with b.p. 40–60 °C; ether refers to diethyl ether.

13-(3′-*Hydroxypropoxy*)-1,3-*dimethyl*-6-*oxatricyclo*-[8.3.0.$0^{3,7}$]*tridecane*-2,5-*dione* **5**.—A solution of Grignard reagent was prepared from magnesium turnings (320 mg, 13.3 mmol) and 2-(2-bromoethyl)-1,3-dioxane (1.95 g, 10 mmol) in THF (30 cm^3). The light grey solution was cooled to −78 °C and Me_2S·CuBr (822 mg, 4 mmol) was added *via* an addition tube, and the resultant mixture was stirred for 10 min at −78 °C and for 20 min at −24 °C. The lactone **3** (388 mg, 2 mmol) was added in THF (5 cm^3) over 20 min, and the mixture was allowed to warm to 0 °C and stirred for 5 h before addition of BSA (2.44 cm^3, 10 mmol). The resultant solution was stirred for 15 h at room temperature and then poured into a rapidly stirred ice-cooled solution of aqueous NH_4Cl (saturated) and NH_3 (conc.) (4:1; 50 cm^3). The solid material was removed by filtration and the two layers were separated. The aqueous phase was extracted with ether (3 × 50 cm^3) and the combined organic extracts were washed with saturated aqueous NH_4Cl (30 cm^3) and water (30 cm^3) and dried ($MgSO_4$). Removal of the solvent yielded a pale orange oil, which was purified by flash chromatography (1:2, ethyl acetate–light petroleum) to afford the required enol ether **4** as a colourless viscous oil (30%, 230 mg), R_f 0.45 (1:2, ethyl acetate–light petroleum); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 and 1660; δ_H(220 MHz; $CDCl_3$) 0.1 ($OSiMe_3$).

To a stirred solution of the enol ether **4** (170 mg, 0.44 mmol) in dry dichloromethane (4.5 cm^3) kept at −78 °C and under an atmosphere of nitrogen, a solution of $TiCl_4$ in dichloromethane (1 mol dm^{-3}; 0.6 cm^3, 0.6 mmol) was added. The resultant red solution was stirred at −78 °C for 1 h before addition of saturated aqueous $NaHCO_3$ (20 cm^3). The product was extracted into dichloromethane (3 × 20 cm^3) and the combined organic extracts were dried and concentrated to a clear oil, which was purified by column chromatography to afford the alcohol **5** in 78% yield (108 mg, 0.34 mmol) as a 1:1 mixture of two isomers (R_{f1} 0.32 and R_{f2} 0.23 in 4:1 ethyl acetate–light petroleum.

A pure sample of the isomer with R_f 0.23 was obtained but the stereochemistry has not been fully assigned, $\nu_{max}(CHCl_3)/cm^{-1}$ 3506, 2942, 2871, 1775, 1685, 1464, 1194, 1130, 1016 and 732; δ_H(220 MHz; $CDCl_3$) 1.04 and 1.51 (2 s, 3 H each, 1-Me and 3-Me), 1.35–2.40 (3 m, 11 H, 8-H_2, 9-H_2, 10-H, 11-H_2, 12-H_2 and 2′-H_2), 2.42 (d, 1 H, $J_{4,4'}$ 18.5, 4-H), 2.80–3.30 (br, 1 H, OH), 3.12 (d, 1 H, $J_{4',4}$ 18.5, 4′-H), 3.48 and 3.58–3.75 (td, 5 H, J_1 8 and J_2 4, and a multiplet, respectively, 13-H, 1′-H_2 and 3′-H_2) and 4.48 (dd, 1 H, J_1 11.5, J_2 1.5, 7-H); δ_C(22.49 MHz; $CDCl_3$) 11.76, 24.65, 25.85, 26.20, 28.25, 29.65, 32.05, 38.95, 57.41, 57.76, 61.63, 69.94, 84.74, 84.30, 93.90, 174.00 and 211.50 (Found: M^+, 310.1773. $C_{17}H_{26}O_5$ requires *M*, 310.1773); *m/z* 295, 292, 265, 251 and 235.

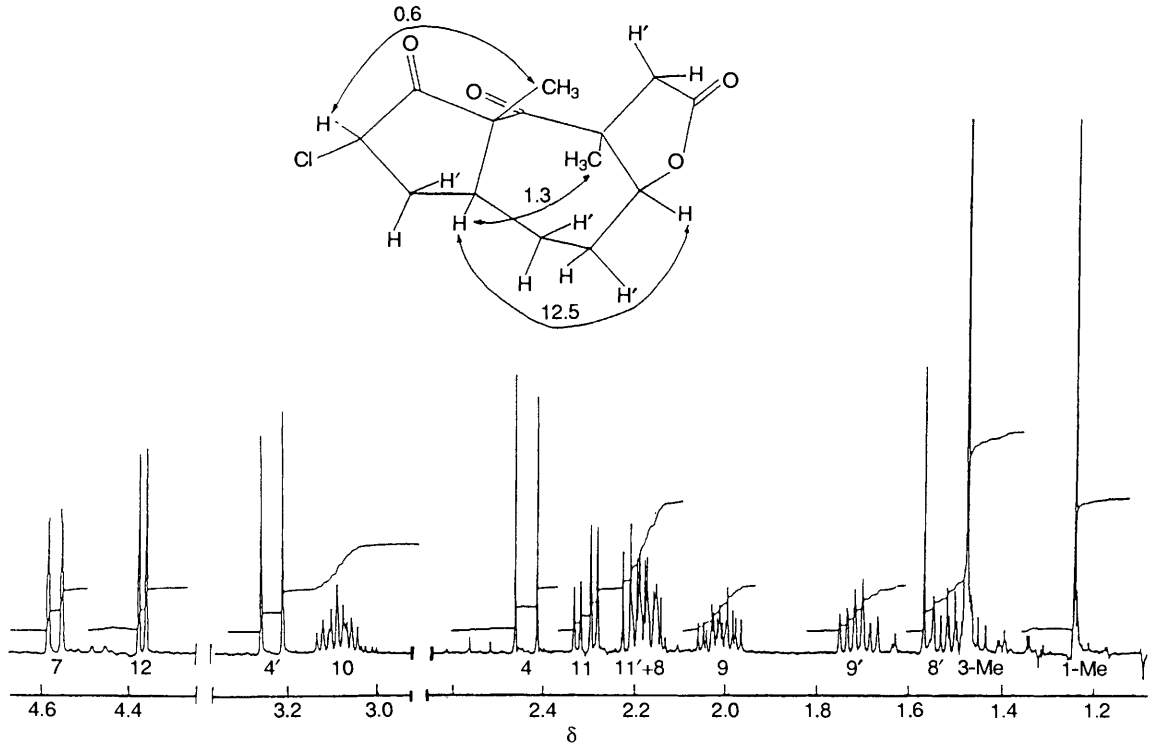


Fig. 1 400 MHz ^{1}H NMR spectrum of compound **16**. Major NOE (%) data are shown

1,3-*Dimethyl*-12-*trimethylsiloxy*-12-*vinyl*-6-*oxatricyclo*-[8.2.0.0^{3,7}]*dodecane*-2,5-*dione* **6**.—A solution of lactone **3** (1.0 g, 5.15 mmol) and 2-trimethylsilyloxybuta-1,3-diene (8.7 g, 61.8 mmol) in dry cyclohexane (200 cm^3) and THF (7 cm^3) contained in a Pyrex irradiation vessel, was degassed using nitrogen. It was then irradiated for 21 h with two 500 W medium pressure mercury lamps, with the temperature maintained at 20 °C. After removal of the solvent, ether (40 cm^3) was added to the white residue and the white solid formed was filtered off. This solid, obtained in 37% yield (638 mg, 1.9 mmol), was shown to be the required [2 + 2] cycloadduct **6**. The filtrate was concentrated under reduced pressure to yield a colourless oil, which was chromatographed (2:3, light petroleum–ether) to afford 54% (937 mg) of an isomeric mixture of photoproducts of unknown composition.

Compound **6**, white solid, R_f 0.41 (2:3, light petroleum–ether); m.p. 163 °C starts melting and then decomposes; $\nu_{max}(CHCl_3)/cm^{-1}$ 3087, 3025, 2958, 2872, 1784, 1696, 1641, 1465, 1299, 1253, 1191, 1023, 936, 845 (Si-Me) and 721; δ_H(220 MHz; $CDCl_3$) 0.10 (s, 9 H, $SiMe_3$), 1.36 (s, 6 H, 1-Me and 3-Me), 1.60–2.16 (m, 6 H, 10-H, 9-H_2, 8-H_2 and 11-H), 2.42 (dd, 1 H, J_1 10.5, J_2 8, 11'-H), 2.50 (d, 1 H, $J_{4,4'}$ 18, 4-H), 2.58 (1 H, $J_{4',4}$ 18, 4'-H), 4.46 [dd (complex), 1 H, J_1 10.5, J_2 4, 7-H), 5.20 (dd, 1 H, $J_{B,A}$ 10.5, $J_{B,C}$ 1, H_B), 5.32 (dd, 1 H, $J_{C,A}$ 17, $J_{C,B}$ 1, H_C), 6.00 (dd, 1 H, $J_{A,C}$ 17, $J_{A,B}$ 10.5, H_A) (Found: [M + 1]$^+$, 337.1835. $C_{18}H_{29}O_4Si$ requires *M*, 337.1827).

1β,3α- (**7**) *and* 1α,3α-*Dimethyl*-13-*methylene*-6-*oxatricyclo*-[8.3.0.0^{3,7}]*tridecane*-2,5,12-*trione* **8**, *and* 1α,3β-*Dimethyl*-12-*oxatricyclo*[9.3.0.0^{3,8}]*tetradecane*-2,6,13-*trione* **9**.—A solution of tricyclic lactone **6** (605 mg, 1.8 mmol), $Pd(PhCN)_2Cl_2$ (31 mg, 0.06 mmol), and *p*-benzoquinone (356 mg, 3.3 mmol) in dry THF (40 cm^3), maintained under an atmosphere of nitrogen, was refluxed at 70 °C for 4 h. The mixture was cooled to room temperature and ether (40 cm^3) and water (40 cm^3) were added. The two layers were separated and the aqueous phase was extracted with ether (5 × 40 cm^3). The combined organic extracts were washed with brine (2 × 40 cm^3) and aqueous $Na_2S_2O_3$ (2 mol dm^{-3}; 40 cm^3), dried ($MgSO_4$) and concentrated to a green residue, which was subsequently purified by chromatography (1:1, light petroleum–ether) to afford the tricyclic lactone **7** (92%, 435 mg). This compound was recrystallized from ether.

The isomeric mixture of photoproducts obtained in the previous reaction was also submitted to the same treatment with $Pd(PhCN)_2Cl_2$ and *p*-benzoquinone to afford 17% of **7**, 10% of its isomer **8**, and 25% of the cyclohexanone **9**.

Compound **7**, white solid, R_f 0.13 (1:1, light petroleum–ether), m.p. 161–163 °C from ether; $\nu_{max}(CHCl_3)/cm^{-1}$ 3007, 2978, 2940, 2871, 1781, 1728, 1709, 1632, 1449, 1384, 1265, 1192, 1111, 1022 and 698; δ_H(400 MHz, $CDCl_3$) 1.26 (s, 3 H, 1-Me), 1.38 (s, 3 H, 3-Me), 1.58–1.68 (m, 1 H, $J_{8',7}$ 12.2, 8'-H), 1.69–1.78 (m, 1 H, $J_{9',9} \approx 13$, $J_{9',8}$ 7.8, $J_{9',10}$ 4.9, 9'-H), 2.02–2.15 (m, 1 H, $J_{9,10}$ 4.9 9-H), 2.18 (ddd, 1 H, $J_{8,8'}$ 13.8, $J_{8,9'}$ 7.8, $J_{8,7}$ 1.5, 8-H), 2.24 (dd, 1 H, $J_{11',11}$ 17.6, $J_{11',10}$ 13, 11'-H), 2.46 (d, 1 H, $J_{4,4'}$ 18.8, 4-H), 2.51 (dd, 1 H, $J_{11,11'}$ 17.6, $J_{11,10}$ 7.1, 11-H), 2.59 (tdd, 1 H, $J_{10,11'}$ $J_{10,9'}$ 13, $J_{10,11}$ 7.1, $J_{10,9}$ 4.9, 10-H), 3.22 (d, 1 H, $J_{4',4}$ 18.8, 4'-H), 4.53 (dd, 1 H, $J_{7,8'}$ 12.2, $J_{7,8}$ 1.5, 7-H), 5.37 (s, 1 H, H_b), 5.97 (s, 1 H, H_a); *m/z* 262 (27%), 234 (60), 214 (8), 188 (12), 174 (20), 147 (18), 134 (30), 122 (100), 109 (24), 91 (35), 79 (62) and 69 (40) (Found: C, 68.7; H, 6.95%; M$^+$, 262.1246. $C_{15}H_{18}O_4$ requires C, 68.69; H, 6.92%; *M*, 262.1205.

Compound **8**, white solid, R_f 0.1 (ether), m.p. 165–170 °C from ethyl acetate–ether; $\nu_{max}(CHCl_3)/cm^{-1}$ 3026, 3009, 2935, 2869, 1787, 1730, 1702, 1641, 1446, 1338, 1276, 1183, 1008, 988 and 860; δ_H(400 MHz; $CDCl_3$) 1.42 (s, 3 H, 1-Me), 1.54 (s, 3 H, 3-Me), 1.58 (m, $J_{8',7} \approx 12.3$, $J_{8',8} \approx 12.2$, 8'-H), 1.77 (qm, $J \approx 12$, 9-H), 1.94–2.04 (m, 2 H, 9'-H and 10-H), 2.19 (dd, $J_{11,11'}$ 17.8, $J_{11,10}$ 12, 11-H), 2.24–2.30 (m, 1 H, 8-H), 2.44 (dd, $J_{11',11}$ 17.8, $J_{11',10}$ 7.4, 11'-H), 2.51 (d, 1 H, $J_{4,4'}$ 18.0, 4-H), 2.92 (d, 1 H, $J_{4',4}$ 18.0, 4'-H), 4.70 (dd, 1 H, $J_{7,8'}$ 12.3, $J_{7,8}$ 2.9, 7-H), 5.38 (s, 3 H, H_b) and 6.29 (s, 3 H, H_a) (Found: [M + NH_4]$^+$, 280.1549.* $C_{15}H_{22}O_4N$ requires *M*, 280.1549); *m/z* 234 (12%),

* This peak was obtained under CI conditions using NH_3.

174 (8), 146 (10), 135 (20), 122 (98), 109 (58), 91 (48), 79 (100), 69 (82) and 53 (70).

Compound **9**, white solid, R_f 0.05 (ether), m.p. 194–196 °C from ethyl acetate–ether; $\nu_{max}(CHCl_3)/cm^{-1}$ 3014, 2976, 2938, 1777, 1721, 1697, 1450, 1222, 1027 and 792; δ_H(400 MHz; $CDCl_3$) 1.28 (s, 3 H, 3-Me), 1.40–1.52 (m, 1 H, 10′-H), 1.50 (s, 3 H, 1-Me), 1.52–1.64 (m, 1 H, 9′-H), 1.70–1.83 (m, 1 H, 9-H), 1.86 (td, 1 H, $J_{4,4'}$ and J_2 13.8, J_3 4.7, 4-H), 1.97 (ddm, 1 H, $J_{4',4}$ 13.8, J_2 6, 4′-H), 2.06 (ddm, 1 H, $J_{10,10'}$ 14, J_2 7, 10-H), 2.23 (dd, 1 H, $J_{7',7}$ 15, $J_{7',8}$ 12.6, 7′-H), 2.26–2.36 (m, 2 H, 5-H and 7-H), 2.35 (dd, 1 H, $J_{14,14'}$ 18.7, J_2 1, 14-H), 2.41–2.55 (m, 2 H, 5′-H and 8-H), 3.23 (d, 1 H, $J_{14',14}$ 18.7, 14′-H) and 4.45 (d, 1 H, J 11.3, 11-H) (Found: $[M + NH_4]^+$, 282.1705.* $C_{15}H_{24}O_4N$ requires M, 282.1705); m/z 236 (12%), 137 (15), 124 (55), 109 (65), 95 (75), 67 (75) and 55 (100) (Found: C, 67.85; H, 7.65. $C_{15}H_{20}H_4$ requires C, 68.14; H, 7.63%).

12β-*Acetoxy*-1,3-*dimethyl*-13-*methylene*-6-*oxatricyclo*-[8.3.0.0^{3,7}]*tridecane*-2,5-*dione* **11**.—To a stirred solution of the enone **7** (262 mg, 1 mmol) and $CeCl_3 \cdot 7H_2O$ (372.6 mg, 1 mmol) in dichloromethane (1 cm^3) and methanol (4 cm^3), kept at room temperature, was added $NaBH_4$ (38 mg, 1 mmol). At this moment, a vigorous evolution of gas and an increase in temperature (to 35–40 °C) were observed. The resultant solution was stirred for 5 min before addition of water (40 cm^3), and extraction with dichloromethane (5 × 40 cm^3). The combined organic extracts were washed with water (30 cm^3), dried ($MgSO_4$) and concentrated to a white residue (263 mg, 100%). Infrared analysis of this residue showed that the enone **7** was completely reduced to alcohol **10**, R_f 0.37 (3:1, ethyl acetate–light petroleum); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600sh, 3440br, 3020, 2980, 2970, 2840, 1773, 1686 and 1190.

To a stirred, ice-cooled solution of alcohol **10** (203 mg, 0.77 mmol), in dry pyridine (1.5 cm^3) was added acetic anhydride (0.5 cm^3, ≈5 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 6 h, before addition of dichloromethane (100 cm^3). Subsequent washing with HCl (2 mol dm^{-3}; 30 cm^3), saturated aqueous $NaHCO_3$ (30 cm^3), and brine (30 cm^3), followed by drying ($MgSO_4$) and concentration, gave a white solid. This solid was purified by flash chromatography to afford 88% (208 mg, 0.68 mmol) of the required acetate **11**, R_f 0.33 (1:3, light petroleum–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3040, 1778, 1740, 1695 and 1541; δ_H(220 MHz; $CDCl_3$) 1.30 and 1.40 (2 s, 3 H, each, 1-Me and 3-Me), 2.10 (s, 3 H, OCMe), 1.20–1.50 (m, 7 H, 8-H_2, 9-H_2, 11-H_2 and 10-H), 2.42 (d, 1 H, $J_{4,4'}$ 18.5, 4-H), 3.24 (d, 1 H, $J_{4',4}$ 18.5, 4′-H), 4.50 (br d, 1 H, $J_{7,8'}$ 12, 7-H), 5.18 and 5.22 (2 d, 1 H each, J 1.8, H_a and H_b) and 5.59 (br tt, $J_{12,11'} \approx J_{12,11} \approx 8$, $J_{12a} \approx J_{12b} \approx 1.8$, 12-H).

1,3-*Dimethyl*-13-*methylene*-6-*oxatricyclo*[8.3.0.0^{3,7}]*tridec*-*ane*-2,5-*dione* **12** *and* 1,3,13-*Trimethyl*-6-*oxatricyclo*[8.3.0.0^{3,7}]-*tridec*-12-*ene*-2,5-*dione* **13**.—To a solution of the acetate **11** (190 mg, 0.62 mmol), in dry bis(2-methoxyethyl) ether (25 cm^3), was added $NiCl_2 \cdot 6H_2O$ (884 mg, 3.72 mmol) followed by $NaBH_4$ (283 mg, 7.45 mmol). After the mixture had been stirred for 5 min at room temperature, the formation of nickel boride as a black precipitate was observed. The reaction mixture was stirred for 3 h, and then dichloromethane (150 cm^3) and water (50 cm^3) were added. The two layers were separated and the aqueous phase was extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were washed with brine (40 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure by a vacuum pump (5 mmHg at 70 °C) to leave a clear residue. This residue was subjected to flash chromatography (1:3, light petroleum–ether) to afford alkenes **12** and **13** as a white solid (41%, 63 mg) in a ratio of 4:1, and 22% recovery of the starting acetate, R_f 0.5 (1:3 light petroleum–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3020, 2943, 2867, 1777, 1692, 1460, 1259, 1091, 1020, 909 and 720 (Found: M^+, 248.1412. $C_{15}H_{20}O_3$ requires M, 248.1412); m/z 248 (3%), 220 (10), 133 (20), 107 (100), 91 (35), 79 (32) and 41 (28).

Compound **12**: δ_H(220 MHz; $CDCl_3$) 1.06 and 1.33 (2 s, 1-Me and 3-Me), 2.31 (d, J 18.5, 4-H), 3.24 (d, J 18.5, 4′-H), 4.48 (br d, $J_{7,8'}$ 12, 7-H), 4.75 and 4.82 (2 t, $J_{a1,2'} \approx J_{a1,2'} \approx J_{b1,2'} \approx J_{b1,2} \approx 2$, H_a and H_b). All other proton signals appeared as a multiplet between δ 1.00 and 2.60.

Compound **13**: δ_H(220 MHz; $CDCl_3$) 1.00 and 1.38 (2 s, 1-Me and 3-Me), 1.58 (sharp m, 13-Me), 2.34 (d, J 18.5, 4-H), 3.12 (d, J 18.5 4′-H), 4.52 (dd, $J_{7,8'}$ 12, $J_{7,8}$ 1, 7-H) and 5.37 (m, 12-H).

12α-*Chloro*-1,3-*dimethyl*-13-*methylene*-6-*oxatricyclo*-[8.3.0.0^{3,7}]*tridecane*-2,5-*dione* **15**.—To a stirred solution of the alcohol **10** (554 mg, 2.1 mmol) in dry acetonitrile (8 cm^3) and CCl_4 (4 cm^3), kept at 0 °C and under nitrogen, was added triphenylphosphine (700 mg, 2.67 mmol) in dry CCl_4 (4 cm^3). The solution was allowed to warm up to room temperature and was stirred for 12 h. The solvent was removed and the residue obtained was purified by flash chromatography (1:2, ethy acetate–light petroleum) to afford the required allylic chloride (72%, 427 mg), R_f 0.43 (1:2, ethyl acetate–light petroleum); δ_H(220 MHz, $CDCl_3$) 1.15 and 1.55 (2 s, 3 H, each, 1-Me and 3-Me), 1.50–2.20 (2 m, 6-H, 8-H_2, 9-H_2 and 11-H_2), 2.45 (d, 1 H, J 18.5, 4-H), 2.90–3.10 (m, 1 H, 10-H), 3.25 (d, 1 H, J 18.5, 4′-H), 4.65 (dd, 1 H, $J_{7,8'}$ 12, $J_{7,8}$ 1.5, 7-H), 4.88 (br d, 1 H, $J_{12,11'}$ 6, 12-H), 5.38 and 5.42 (2 d, 1 H each, J 0.5, H_a and H_b).

12-*Chloro*-1,3-*dimethyl*-6-*oxatricyclo*[8.3.0.0^{3,7}]*tridecane*-2,5,13-*trione* **16**.—To a stirred solution of the allylic alkene **15** (362 mg, 1.28 mmol) in THF (8 cm^3) was added OsO_4 (2 cm^3 of a 2.5% w/w solution in *tert*-butyl alcohol, corresponding to 0.158 mmol of OsO_4) and $NaIO_4$ (1.5 g, 7 mmol) in water (8 cm^3). After the mixture had been kept at 50 °C for 3 d, ethyl acetate (50 cm^3) and water (50 cm^3) were added. The two layers were separated and the aqueous phase was extracted with ethyl acetate (4 × 30 cm^3). The combined organic extracts were washed with brine (30 cm^3), dried ($MgSO_4$), and concentrated to a brown residue. This residue was purified by flash chromatography (1:1, ethyl acetate–light petroleum) to afford the required chloro compound **16** as a white solid (65%, 236 mg), and 26% of the starting alkene, R_f 0.20 (1:1, ethyl acetate–light petroleum), m.p. 168 °C (decomp.); $\nu_{max}(CHCl_3)/cm^{-1}$ 3025, 2978, 2943, 2870, 1772, 1701, 1203, 1147, 1054, 910 and 823; δ_H(400 MHz; $CDCl_3$) 1.24 and 1.48 (2 s, 3 H each, 1-Me and 3-Me), 1.44–1.58 (m, 1 H, 8′-H), 1.71 (td, 1 H, J_1 13.1, J_2 13.1, J_3 6.6, 9′-H), 1.96–2.06 (m, 1 H, 9-H), 2.14–2.20 (m, 1 H, 8-H), 2.19 (dt, 1 H, $J_{11'11}$ 14.6, $J_{11'12} = J_{11'10}$ 6.6, 11′-H), 2.31 (dd, 1 H, $J_{1111'}$ 14.6, J_{1110} 5.8, 11-H), 2.44 (d, 1 H, $J_{44'}$ 18.9, 4-H), 3.04–3.12 (m, 1 H, 10-H), 3.23 (d, 1 H, $J_{4'4}$ 18.9, 4′-H), 4.37 (d, 1 H, $J_{1211'}$ 6.6, 12-H), 4.57 (dd, $J_{78'}$ 12.3, J_{78} 1.5, 7-H); m/z (CI, NH_3) 302.1159 ($[M+NH_4]^+$, $C_{14}H_{21}ClNO_4$ requires 302.1159, 70%), 268 (100), 251 (20), 212 (15) and 52 (8) (Found: C, 58.85; H, 6.1. $C_{14}H_{17}ClO_4$ requires C, 59.06; H, 6.02%).

1,3-*Dimethyl*-6-*oxatricyclo*[8.3.0.0^{3,7}]*tridec*-11-*ene*-2,5,13-*trione* **19**.—To a solution of ketone **17** (100 mg, 0.4 mmol) in ethyl acetate was added benzeneselenenyl chloride (86 mg, 0.45 mmol). The resultant mixture was stirred at room temperature for 3 d, ether (30 cm^3) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (2 × 10 cm^3). The ethereal solution was concentrated under reduced pressure to give a

* Only this peak was obtained under chemical ionization conditions using NH_3.

yellow oil, which was purified by chromatography (ether) to afford seleno compound **18** as a white solid (77%, 124 mg), R_f 0.29 (ether), δ_H(220MHz; $CDCl_3$) 1.22 and 1.53 (2 s, 3 H each, 1-Me and 3-Me), 1.20–2.30 (m, 7 H, 8-H_2, 9-H_2, 11-H_2 and 10-H), 2.42 (d, 1 H, *J* 18.5, 4-H), 2.88–3.07 (m, 1 H, 10-H), 3.20 (d, 1 H, *J* 18.5, 4′-H), 4.12 (m, 1 H, 12-H), 4.56 (br d, 1 H, $J_{7,8'}$ 12, 7-H), 7.25–7.35 (m, 3 H, H_B and H_C) and 7.55 (dd, 2 H, J_o 6.8, J_m 2.0, H_A).

A mixture of seleno ketone **18** (77 mg, 0.19 mmol) in THF (3 cm^3) and $NaIO_4$ (112 mg, 0.5 mmol) in water (0.5 cm^3) was stirred at room temperature for 3 h and then at 50 °C for 1.5 h. Ether (10 cm^3) and saturated aqueous $NaHCO_3$ (10 cm^3) were added and the two layers were separated. The aqueous phase was extracted with ether (2 × 10 cm^3), and the combined organic extracts were washed with water (10 cm^3), dried, and concentrated to a brown residue. This residue was submitted to flash chromatography (ether) to afford the required enone (25%, 12 mg), R_f 0.10 (ether), m.p. 145–151 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 3040, 2980, 1776, 1745, 1699, 1190 and 720; δ_H(400 MHz; $CDCl_3$) 1.38 (s, 3 H, 3-Me), 1.40 (s, 3 H, 1-Me), 1.71–1.81 (m, 1 H, 8′-H), 1.87–1.95 (m, six lines, 1 H, 9′-H), 2.12–2.26 (m, 2 H, 8-H and 9-H), 2.52 (d, 1 H, $J_{4,4'}$ 18.8, 4-H), 3.14 (d, 1 H, $J_{4',4}$ 18.8, 4′-H), 3.36 (dm, 1 H, $J_1 \approx$ 13.6, 10-H), 4.53 (dd, 1 H, J_1 12.1, J_2 1.2, 7-H), 6.13 (dd, 1 H, $J_{12,11}$ 5.9, $J_{12,10}$ 2.9, 12-H), 6.45 (dd, 1 H, $J_{11,12}$ 5.9, $H_{11,10}$ 2, 11-H) (Found: $[M + 1]^+$, 249.1127. $C_{14}H_{17}O_4$ requires *M*, 249.1127);* *m*/*z* 149(12%), 125 (10), 111 (20), 97 (32), 83 (30), 71 (50), 59 (5) and 43 (100).

* Only this peak was obtained under chemical ionization conditions using NH_3.

Acknowledgements

We thank the CNPq, Brazil for a Scholarship (L.-C. de A. B.) and Dr. Oliver Howarth for numerous NMR investigations.

References

1 A. K. Picman, *Biochem. Syst. Ecol.*, 1986, **13**, 255.
2 C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac and C. T. White, in *The Total Synthesis of Natural Products*, ed. J. ApSimon, Wiley, New York, 1983, **5**, p. 550; M. Vandewalle and P. De Clercq, *Tetrahedron*, 1985, **41**, 1767.
3 W. J. Cummins, M. G. B. Drew, J. Mann and A. J. Markson, *Tetrahedron*, 1988, **44**, 5151.
4 M. R. Ashcroft and H. M. R. Hoffmann, *Org. Synth.*, 1978, **58**, 17.
5 J. Mann, *Tetrahedron*, 1986, **42**, 4611.
6 T. Mukaiyama, *Angew. Chemie*, 1977, **16**, 817.
7 M. Demuth, B. Pandey, H. Said, J. Viader and B. Wietfeid, *Helv. Chim. Acta*, 1988, **71**, 1392.
8 A. L. Gemal and J. L. Luche, *Tetrahedron Lett.*, 1981, **22**, 4080.
9 R. S. Rosenfeld and T. F. Gallagher, *J. Am. Chem. Soc.*, 1955, **77**, 4367.
10 D. H. R. Barton and W. J. Roselfelder, *J. Chem. Soc.*, 1951, 1048.
11 D. N. Sarma and R. P. Sharma, *Tetrahedron Lett.*, 1985, **26**, 371 and 2581.
12 D. J. Carding and M. F. Lappert, *J. Chem. Soc., Chem. Commun.*, 1967, 1034.
13 C. H. Heathcock, C. M. Tice and T. C. Germoth, *J. Am. Chem. Soc.*, 1982, **104**, 6081.
14 D. D. Perrin and W. L. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., 1988, Pergamon, Oxford.

Paper 1/04943G
Received 25*th September* 1991
Accepted 18*th October* 1991