Pseudoguaianolides from Intramolecular Cycloadditions of Aryl Diazoketones: Synthesis of (±)-Confertin and an Approach to the Synthesis of (±)-Damsin

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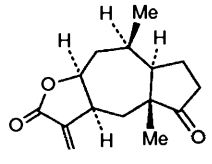
Rhodium(II) mandelate-catalysed cyclisation of α-diazoketones derived from 3-arylpropionic acids produces bicyclo[5.3.0]decatrienones, one of which has been used to synthesise an advanced (±)-confertin intermediate in six stages and 20% overall yield. The possibility of constructing intermediates for the synthesis of damsin-like pseudoguaianolides *via* catalysed diazoketone cyclisation is also examined and methods for the construction of polyfunctional 3-arylpropionic acids suitable for use as damsin precursors are presented.

In a recent paper[1] we described efforts to construct the tricyclic framework of the pseudoguaianolide confertin **1** by intramolecular cyclisation–ring expansion of aromatic diazoketones to which the characteristic γ-lactone ring of confertin was already attached. Although rhodium(II)-catalysed intramolecular reactions of these diazoketones could be brought about efficiently, we found that the presence of the lactone ring adversely affected the direction of cyclisation in the key confertin intermediate. While direct access to the pseudoguaianolide tricyclic framework using a diazoketone precursor with the γ-lactone already in place has the obvious attraction of brevity, most published syntheses of confertin proceed through bicyclohydroazulene intermediates, *e.g.* **2**,[2] **3**[3] and **4**,[4] to which the lactone moiety was added at a later stage. The recent enantiospecific synthesis of **4** by Quinkert and co-workers[4] provided a reference point for our proposed synthesis of this intermediate using the diazoketone methodology; a preliminary account of this approach has been published.[5]

Our scheme for constructing **4** envisaged the cyclisation of a



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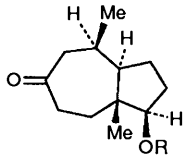
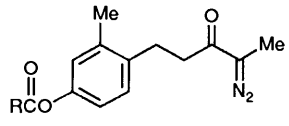


2; R = Bu^t
3; R = TMS
4; R = TBDMS



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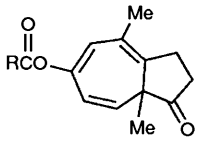

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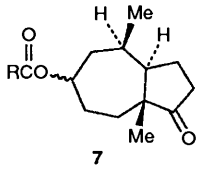
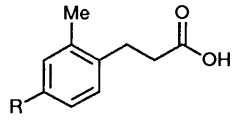


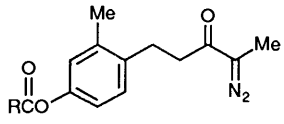
7

diazoketone of type **5** to the bicyclic trienone **6** with stereocontrolled hydrogenation of the latter to **7** along the lines discussed in our earlier paper,[1] the presumption having been made, based on the regiospecificity of cyclisation of the *ortho*-tolyl system,[6] that rhodium(II)-catalysed cyclisation of **5** would proceed in the desired direction. Stereoselective reduction of the keto function in intermediates such as **7** is a feature of several earlier syntheses of pseudoguaianolides,[7] the effect of the bridgehead methyl group being to favour formation of the *cis*-alcohol. However, within the context of a total synthesis of confertin, the question of stereocontrol of the hydroxy-bearing carbon atom is irrelevant since ultimately the keto group is to be regenerated at this position.

3-(4-Hydroxy-2-methylphenyl)propionic acid **8**[8] served as the diazoketone precursor. Two syntheses were pursued in parallel, one with the phenolic group of **8** protected as its acetate (as in **9**), and the other as its phenylacetate (as in **10**). The latter was included because it gave a somewhat clearer response on TLC analysis of the intermediates after cyclisation. Acetylation of **8** with potassium acetate in acetic anhydride furnished **9** which was then subjected to the diazoketone-forming routine of conversion into the acyl chloride, followed by exposure to ethereal diazoethane, affording diazoketone **11** in 75% yield. For the production of **10**, the carboxylate function of **8** was benzylated, the resulting product was esterified with phenylacetyl chloride, and the carboxylic acid group was released again by catalytic hydrogenolysis. This sequence was accomplished in 77% yield and conversion into diazoketone **12** in 63% yield completed the sequence.



8; R = OH
9; R = AcO
10; R = $PhCH_2CO_2$



11; R = Me
12; R = $PhCH_2$

Decomposition of **11** with rhodium(II) mandelate in hot dichloromethane furnished a single ring-expanded product in quantitative yield. The ^1H and ^{13}C NMR spectra of the product indicated that it consisted of an equilibrium mixture of bicyclic cycloheptatriene **13a** and tricyclic norcaradiene **13b**. This diagnosis was based on the location of H_A which appeared as a doublet at δ_H 3.54 and of the carbon atom bearing H_A which appeared as a doublet at δ_C 69.20. These values suggest that the norcaradiene form **13b** is, in fact, the dominant component of a mobile equilibrium at room temperature. This conclusion is also supported by Hannemann's recent NMR spectroscopic analysis[9] of substituent effects on the cycloheptatriene–norcaradiene equilibrium. The **13a**/**13b** pair represent an interesting addition to our earlier examples containing fused

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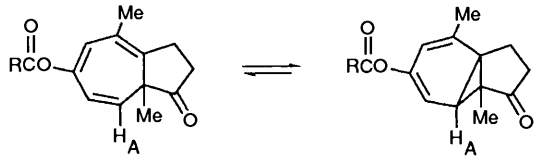
cyclopentanone rings.[6] The alternative diazoketone **12** could also be decomposed with rhodium(II) mandelate in dichloromethane to afford the **14a**/**14b** mixture, though here the extent

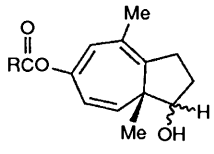


13a; R = Me
14a; R = $PhCH_2$

13b; R = Me
14b; R = $PhCH_2$

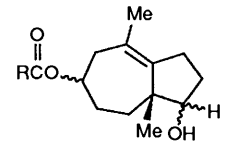
of cyclisation (85%) was somewhat less than that observed with diazoketone **11**.

Our original intention at this point was to hydrogenate the ring-expanded product. However, conditions for a clean reaction with hydrogen could not be found. Use of Adams' catalyst produced a complex mixture of products from **13**, at least one of which lacked the acetyl group and this option was not pursued further. Instead, the keto group of **13** was reduced. Use of lithium tri-*tert*-butoxyaluminium hydride in ether at 0 °C caused the tricyclic form to disappear, producing a mixture of epimeric alcohols **15** in 72% yield. That norcaradiene-type structures were now absent was indicated by the ^1H and ^{13}C NMR spectroscopic data for the H_A proton and its conjoining carbon arom. Integration of the H_A signals at δ_H 5.25 and 5.70 indicated an epimeric alcohol ratio of *ca.* 3:1. This analysis was confirmed by ^1H NMR spectra obtained using $Eu(tfc)_3$ shift reagent which further indicated that the preponderant isomer was that with the hydroxy group *cis* to the bridgehead methyl group. Sodium borohydride reduction of **13** also produced a mixture of alcohols **15** (77%), though here the preference for the *cis*-isomer was rather less than exhibited by the aluminium hydride reagent. Sodium borohydride reduction of the **14a**/**14b** mixture obtained from diazoketone **12** proceeded similarly to afford alcohols **16**.

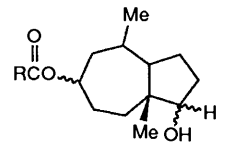


15; R = Me
16; R = $PhCH_2$

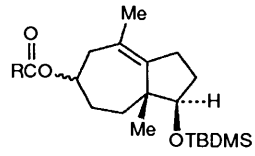
To continue the synthesis, **15** was hydrogenated at low pressure over 10% palladium on carbon to afford the tetrahydro derivative **17**, together with a small amount of the perhydroderivative **18** (total yield 93%) which were not separated, the identifications being on the basis of the ^1H NMR spectrum of the mixture. The product was then treated with an excess of *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide (DMF) at 70 °C to yield, after chromatographic purification, a mixture of **19** and **20** (the minor constituent) in 53% overall yield from **13**. As with **17** and **18**, the **19**–**20** mixture was not separated since both compounds were destined for the same target molecule. We presumed that the chromatographic purfication at this stage had removed the small amounts of minor components associated with the presence of the *trans*-epimer in alcohol mixture **15**. We presumed also that, excluding the uncertainty associated with the disposition of the acetoxy group in both **19** and **20** that these products had the realtive stereochemistry shown. These assignments could be confirmed when the acetoxy moiety in both compounds was removed by hydrolysis. Treatment of **19** and **20** with aqueous potassium hydroxide, followed by (without purification or separation) pyridinium chlorochromate in dichloromethane, afforded ketones **21** (62%) and **22** (21%) which were separable, ketone **22** being the target



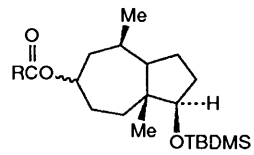
17; R = Me
17a; R = $PhCH_2$



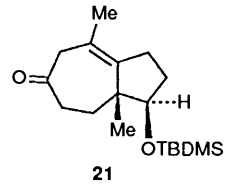
18; R = Me
18a; R = $PhCH_2$



19; R = Me
19a; R = $PhCH_2$



20; R = Me
20a; R = $PhCH_2$



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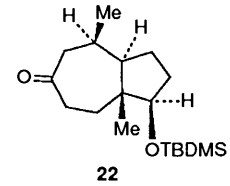
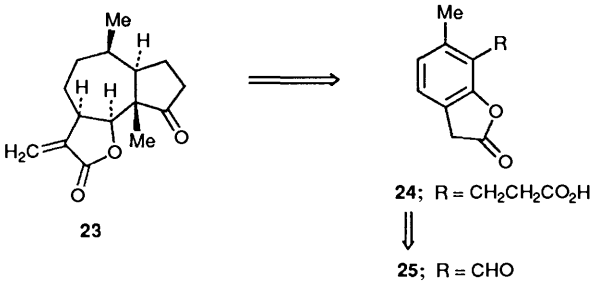


22

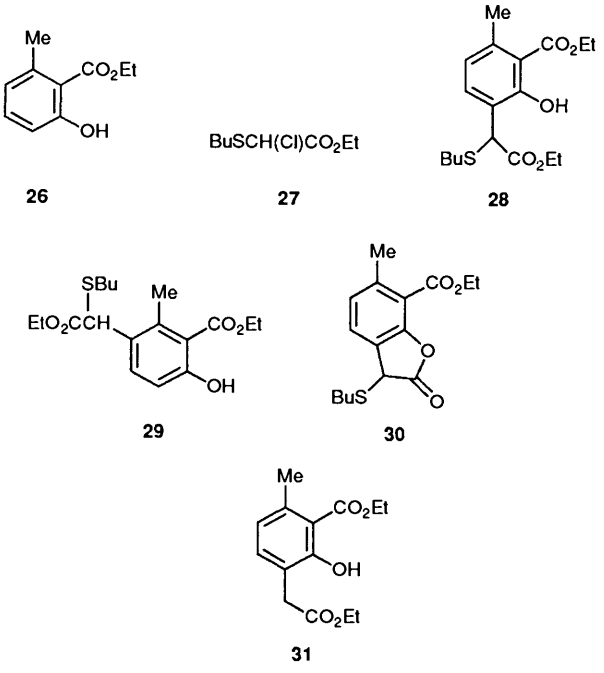
molecule. To complete the synthesis ketone **21** was hydrogenated (4.5 bar, 20 °C) over 5% rhodium on alumina according to Quinkert's[4] procedure, and the crude product was treated with pyridinium chlorochromate in dichloromethane (to re-oxidise the trace of alcohol produced during the hydrogenation) to furnish **22** (41%) (68% based on recovered alkene) along with about 10% of what appeared from the ^1H NMR spectrum (500 MHz) to be the *cis*-fused hydroazulene. Otherwise, the spectral data for **22**, and for its precursor **21**, were identical with those of (+)-**22** and (+)-**21** published by Quinkert and co-workers.[4]

Damsin **23** is another natural perhydroazulene derivative whose synthesis has attracted attention.[7] Though damsin is also a pseudoguaianolide and has features in common with confertin (*cf.* the bridgehead stereochemistry), the significant difference between the two is the relative orientation of the γ-lactone ring. In damsin, the seven-membered ring is oxygenated at the position adjacent to the bridgehead methyl group. With the intention of applying the carbenoid cyclisation methodology to damsin, we considered precursors capable of producing appropriately substituted ring-expanded intermediates. Thus, the aromatic precursor should have the diazobutanone side chain flanked by two *ortho* substituents, one methyl and the other an oxygenated group, the expectation being that the repulsive effect of the former on the direction of cyclisation would ensure the correct direction of cyclisation.

For this study we decided to have the lactone ring in position prior to the carbenoid cyclisation. Retrosynthetic analysis of the appropriate phenylpropionic acid **24** suggested that lactone aldehyde **25**, or its equivalent, would be a suitable intermediate target. Two syntheses were developed. In the first, ethyl 6-methylsalicylate[10] **26** was alkylated with chloro sulphide **27** with stannic chloride catalysis. This reaction displayed low regioselectivity, furnishing a mixture (85% yield) of the product of alkylation *ortho* to the phenolic group **28** and the unwanted *para*-isomer **29** in a 3:4 ratio. Unlike examples of this phenol alkylation route discussed earlier,[8] formation of **28** was not followed by spontaneous lactonisation. The two isomers were easily separated by flash chromatography and conversion of

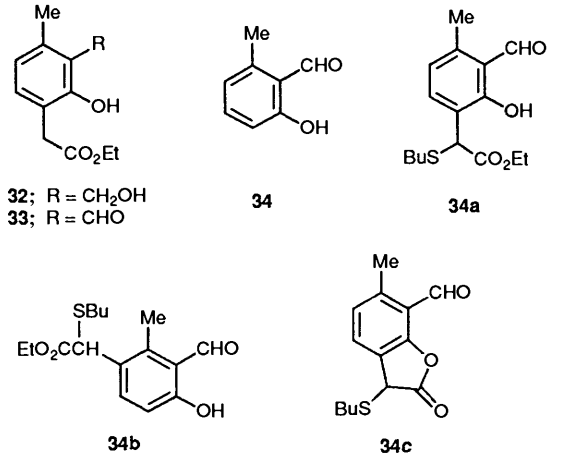


isomer **28** into lactone ester **30** on exposure to toluene-*p*-sulphonic acid in hot toluene confirmed our earlier tentative assignments based on the ^1H NMR spectra of the two isomers. The minor isomer **28** was treated with zinc in acetic acid to afford a sulphur-free product **31** which on sodium borohydride



reduction in ethyl acetate as solvent furnished a single primary alcohol **32** in 85% yield. The success of this selective reduction of the aromatic ester moiety in preference to the aliphatic ester, for which there is precedent,[11] can be attributed to involvement of the phenolic group with the borohydride ion and subsequent intramolecular hydride transfer *via* a six- rather than a seven-membered transition state. Oxidation of **32** to aldehyde **33** proved difficult: manganese dioxide produced only a 23% yield, though use of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) did eventually improve the yield to 50%. The lactone ring of **25** was then constructed (63% yield) by heating **33** with toluene-*p*-sulphonic acid in toluene. Although the lactone we needed was now in hand, there was obvious scope for improvement on the synthesis, in particular with respect to the unfavourable regioselectivity in the Friedel–Crafts alkylation step. In this regard we examined also the alkylation of 6-methylsalicylaldehyde **34** hoping to improve on this route to **25**. However, this route was equally unselective, furnishing **34a** and **34b** in about equal amounts. Isomers **34a** and **34b** were separable indirectly by the expedient of hydrolysing the ester moiety in the mixture and then treating the resulting acids in benzene with oxaloyl chloride, whereupon the proximal phenolic acid only cyclised to lactone **34c**.

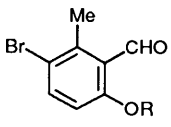
A solution to this regioselectivity problem was forthcoming



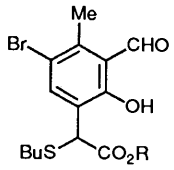
when we found that bromination of 6-methylanisaldehyde[12] proceeded regiospecifically to place the halogen atom adjacent to the methyl group, a protective detour which ensured that alkylation of the product **35** furnished only the arrangement appropriate to lactone formation. Demethylation of **35** with boron tribromide furnished **36** which was smoothly alkylated with chloro sulphide **27** and stannic chloride to form intermediate **37** in 38% yield based on **35**. Hydrolysis of **37** with sodium hydroxide in aqueous dioxane produced phenolic acid **38** (78%) and the lactone ring in **39** was then closed (85%) by exposing **38** to oxalyl chloride. The next phase of the synthesis was accomplished efficiently by a Wittig reaction between **39** and phosphorane **40** to yield **41**. Completion of the synthesis required reductive removal of the bromo and sulphide groups and saturation of the olefinic bond in the resulting cinnamate. In the event, exposure of **41** to Raney nickel in hot isopropyl alcohol accomplished all three objectives and afforded lactone ester **42** in 68% yield. Cleavage of the *tert*-butyl ester was brought about by TFA (trifluoroacetic acid) and exposure of the acid **43** thus formed to the usual diazo-forming sequence afforded diazoketone **44** in 82% yield.

When **44** was decomposed with rhodium(II) mandelate in refluxing dichloromethane we were unable to detect in the product any significant amounts of ring-expanded material. The product retained the aromatic ring; its structure has not been elucidated. Neither rhodium(II) trifluoroacetate nor other members of the rhodium(II) carboxylate series were any more successful; $Cu(acac)_2$ and $Pd(OAc)_2$ were also ineffective. A possible explanation for the failure of this cyclisation may lie in the very sterically congested transition state due to the accumulation of contiguous substituents at the point of reaction on the aromatic nucleus.

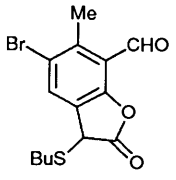
To establish the degree to which the presence of the lactone ring contributed to the failure of **44** to cyclise, we examined compound **49** as an alternative formulation of a diazoketone precursor which could be lactonised at a later stage in the synthesis. Compound **37** provided a convenient entry to this series. A standard Wittig reaction transformed **37** into cinnamate **45** which was then methylated at the phenolic group with ethereal diazomethane to form methyl ether **46** (62% yield). Exposure of **46** to Raney nickel in refluxing ethanol caused complete desulphurisation and debromination and almost complete hydrogenation to afford **47**. The small amount of residual olefinic material in the crude product was removed by catalytic hydrogenation over platinum oxide in ethanol at ambient pressure. The *tert*-butyl ester of **47** was selectively cleaved using TFA and the carboxylic acid function **48** so released was converted into diazoketone **49** in the usual way in excellent yield. Decomposition of **49** in dichloromethane was



35; R = Me
36; R = H



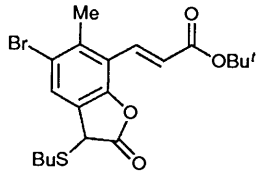
37; R = Et
38; R = H



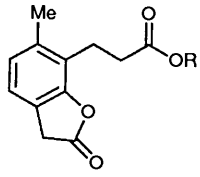
39

$Ph_3PCHCO_2Bu^t$

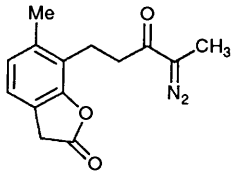
40



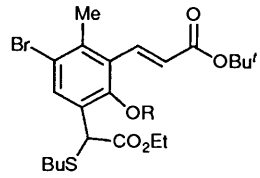
41



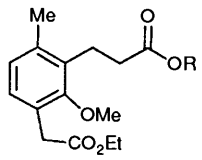
42; R = Bu^t
43; R = H



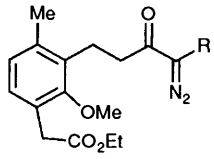
44



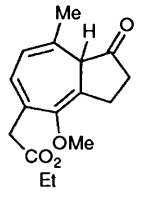
45; R = H
46; R = Me



47; R = Bu^t
48; R = H



49; R = Me
50; R = H



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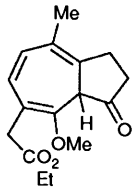


52

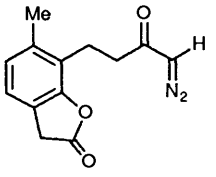
studied with a range of catalysts; none produced the desired ring-expansion reaction. The product in all cases appeared to be a dimeric structure in which the aromatic ring was intact. Thus, we concluded that *ortho*-disubstituted 2-diazo-5-phenylpentan-3-ones, probably for unfavourable steric reasons, are not suitable substrates for cycloheptatrienone formation *via* intramolecular-catalysed Buchner reactions.

In a final attempt to probe the steric argument for the failure of **44** and **49** to cyclise, we prepared the terminal diazoketone **50**, reasoning that replacement of the diazo methyl group by a hydrogen atom might lead to a less congested keto carbenoid with correspondingly better prospects for intramolecular cyclisation. Acid **48** was converted into diazoketone **50** *via* the normal two-step sequence of acid chloride formation followed by treatment with diazomethane. Upon decomposition with rhodium(II) mandelate in dichloromethane at room temperature, diazoketone **50** was found to produce, in 69% yield by NMR spectroscopic analysis, a mixture of both possible cyclisation products **51** and **52** in a 4:1 ratio, though which was which was not obvious. To conclude the investigation lactone acid **43** was converted into the terminal diazoketone **53** whose decomposition with rhodium(II) carboxylates also led to cyclisation (75% yield). Again, it was clear from NMR spectroscopic analysis that the product was a mixture of **54** and **55** (2:1 ratio, unassigned) indicating that both types of cyclisation were possible.

Such a dramatic change in the nature of these diazoketone decompositions as a result of replacing the terminal methyl group by a hydrogen atom tends to support the steric argument advanced above. Unfortunately, apropos of our original objective of producing damsin-like intermediates, the cyclisation products derived from **50** and **53** proved to be exceedingly reactive and very unsuitable for further manipulation. It is quite likely that the absence of the bridgehead methyl group in **51**/**52** and **54**/**55** contributes significantly to the mobility of the double bonds in the cycloheptatrienyl ring and ultimately to the destruction–reorganisation of the molecules even under mild conditions. For example, exposure of the **54**/**55** cycloheptatriene mixture to triethylamine in dichloromethane produced an instantaneous red colouration and led to the isolation of two crystalline substances, one red and the other orange. The spectroscopic data indicated that neither substance was cycloheptatrienyl in nature nor were they isomeric with the precursors, having lost two hydrogen atoms in the reaction. Presumably these compounds were formed by triethylamine-catalysed skeletal rearrangement followed by aerial oxidation. The ^1H NMR spectroscopic data for these two compounds is consistent with structures such as **56** and **57**, but these have not been established beyond doubt.

Experimental

3-(4-Acetoxy-2-methylphenyl)propionic Acid **9**.—A mixture of phenol **8** (0.89 g, 4.9 mmol) and potassium acetate (7.5 g, 76.5 mmol) in acetic anhydride (15 cm^3) was heated under reflux for 6 h, after which the hot solution was added to tepid water (150 cm^3) with stirring. The resulting aqueous solution was extracted with ether (3 × 10 cm^3) and the combined ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate (4 × 30 cm^3). The hydrogen carbonate extract was acidified with conc. hydrochloric acid and the resulting milky mixture was extracted with ether (3 × 4 cm^3). The ethereal extract was dried and concentrated at reduced pressure to afford **9** as an off-white crystalline solid (0.88 g, 77%), m.p. 103 °C (from dichloromethane–hexane) (Found: C, 64.9; H, 6.5. $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.3%); $\delta_H(CDCl_3)$ 2.24 (3 H, s, Ac), 2.28 (3 H, s, $ArCH_3$), 2.30–3.05 (4 H, m, CH_2CH_2), 6.60–7.20 (3 H, m, ArH) and 10.95 (1 H, s, CO_2H).



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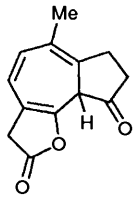

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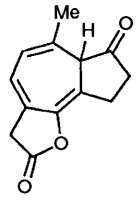

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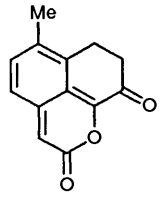

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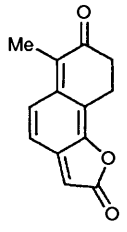

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1-(4-*Acetoxy*-2-*methylphenyl*)-4-*diazopentan*-3-*one* **11**.—A mixture of acid **9** (0.39 g, 1.76 mmol), oxaloyl chloride (0.4 cm^3, 4.7 mmol) and benzene (10 cm^3) was heated under reflux under nitrogen for 45 min. The cooled solution was stored under nitrogen until required for the next stage before which the solvent and excess of oxaloyl chloride were removed at reduced pressure. The residue was taken up in dry ether (10 cm^3) and added dropwise over 15 min to an ethereal solution (30 cm^3) of diazoethane [prepared from *N*-ethyl-*N*-nitrosourea (3 g, 26 mmol)] at −10 °C. After 1 h the solution was concentrated at reduced pressure to leave a claret-coloured oil (0.48 g). A portion of the product (0.34 g) was chromatographed on silica with dichloromethane as eluent to afford **11** as an oil (0.24 g, 75%); $\delta_H(CDCl_3)$, 1.94 (3 H, s, CN_2CH_3), 2.27 (3 H, s, Ac), 2.29 (3 H, s, $ArCH_3$), 2.50–3.05 (4 H, m, CH_2CH_3) and 6.60–7.20 (3 H, m, ArH); ν_{max}(film)/cm^{-1} 2070, 1755 and 1630.

3-(2-*Methyl*-4-*phenylacetoxyphenyl*)*propionic Acid* **10**.—Phenol **8** (1.22 g, 6.8 mmol) in acetonitrile (10 cm^3) was treated dropwise with DBU (1.05 cm^3, 7.5 mmol) at room temperature. After 10 min benzyl bromide (1.51 cm^3, 14.6 mmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was then diluted with dichloromethane (40 cm^3) and the resulting solution was washed with water (10 cm^3), saturated aqueous sodium hydrogen carbonate (10 cm^3), 5% hydrochloric acid (10 cm^3) and, finally, brine (10 cm^3). The dried solution was concentrated at reduced pressure to leave an oil from which residual benzyl bromide was removed by flash chromatography over silica with dichloromethane as eluent. The product, benzyl 3-(4-hydroxy-2-methylphenyl)propionate, was obtained as an oil in 93% yield and was acylated as follows without further purification.

A solution of phenylacetyl chloride (0.94 cm^3, 7.1 mmol) in dichloromethane (10 cm^3) was added dropwise to a solution of the above phenol ester (1.47 g, 5.44 mmol) and triethylamine (1.07 cm^3, 7.7 mmol) in dichloromethane (15 cm^3). After 15 min the solution was washed with water (10 cm^3), saturated aqueous sodium hydrogen carbonate (10 cm^3) and 5% hydrochloric acid (10 cm^3), dried and evaporated under reduced pressure to furnish *benzyl* 3-(4-*phenylacetoxy*-2-*methylphenyl*)*propionate* as an oil (2.02 g, 85%) (Found: C, 77.6; H, 6.2. $C_{25}H_{24}O_4$ requires C, 77.32; H, 6.19%). The ester moiety in this product was then cleaved as follows.

A mixture of the above compound (1.5 g, 3.87 mmol) and 10% palladium on carbon (95 mg) was hydrogenated at room temperature at 25 psi for 12 h. The catalyst was removed by filtration through a Celite bed and the filtrate was concentrated at reduced pressure to afford an oil which on purification by 'dry' flash chromatography over silica with dichloromethane as eluent yielded *acid* **10** as a crystalline solid (1.0 g, 87%), m.p. 83–85 °C (Found: C, 72.3; H, 6.1. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.0%); $\delta_H(CDCl_3)$ 2.27 (3 H, s, $ArCH_3$), 2.30–3.10 (4 H, m, CH_2CH_2), 3.77 (2 H, s, $ArCH_2$), 6.60–7.20 (3 H, m, ArH) and 7.31 (5 H, s, ArH).

2-*Diazo*-5-(2-*methyl*-4-*phenylacetoxyphenyl*)*pentan*-3-*one* **12**.—Acid **10** (1.0 g, 3.37 mmol) was dissolved in dry benzene (10 cm^3) containing oxaloyl chloride (0.5 cm^3, 5.9 mmol) and the solution was heated under reflux under nitrogen for 40 min. The solvent and residual oxaloyl chloride were then removed at reduced pressure and the oil remaining was taken up in dry ether (10 cm^3) and added dropwise over 15 min to an ethereal solution of diazoethane (100 cm^3) [prepared from *N*-ethyl-*N*-nitrosourea (7 g, 60 mmol)] at −10 °C. After 1.5 h the solution was concentrated at reduced pressure to leave an oil which on purification by flash chromatography over silica with dichloromethane as eluent furnished diazoketone **12** (0.66 g, 59%) as a green oil; $\delta_H(CDCl_3)$ 1.91 (3 H, s, CN_2CH_3), 2.26 (3 H, s, $ArCH_3$), 2.40–3.10 (4 H, m, CH_2CH_2), 3.78 (2 H, s, $ArCH_2$), 6.60–7.20 (3 H, m, ArH) and 7.31 (5 H, s, ArH); ν_{max}(film)/cm^{-1} 2080, 1760 and 1635.

6-*Acetoxy*-2,3-*dihydro*-4,8a-*dimethylazulen*-1(8aH)-*one* **13a**/**13b**.—A solution of diazoketone **11** (40 mg) in dichloromethane (16 cm^3) was added dropwise over 15 min to a boiling solution of rhodium(II) mandelate (1 mg) in dichloromethane (40 cm^3). After a further 5 min the solvent was removed at reduced pressure to afford a light brown oil in quantitative yield. Purification by flash chromatography on silica with dichloromethane as eluent furnished a colourless oil which partly solidified on storage at −10 °C for 12 h. NMR spectroscopic analysis confirmed that the product was **13a**/**13b** exclusively; ν_{max}(film)/cm^{-1} 1750 and 1710; $\delta_H(CDCl_3)$ 0.86 (3 H, bridgehead CH_3), 1.97 (3 H, s, vinylic CH_3), 2.18 (3 H, s, Ac), 2.30 (4 H, m, CH_2CH_2), 3.54 (1 H, d, 8-H, *J* 7.5), 5.66 (1 H, d, 7-H, *J* 7.5) and 5.88 (1 H, s, H-5); $\delta_C(CDCl_3)$ 8.8 (q), 20.9 (q), 20.7 (q), 25.1 (t), 33.1 (t), 35.2 (s), 69.2 (d), 77.9 (s), 113.4 (d), 120.8 (d), 133.5 (s), 147.7 (s), 169.5 (s) and 218.6 (s). The instability of the product precluded reliable microanalysis.

2,3-*Dihydro*-4,8a-*dimethyl*-6-*phenylacetoxyazulen*-1(8aH)-*one* **14a**/**14b**.—A solution of diazoketone **12** (100 mg) in dichloromethane (10 cm^3) was added dropwise over 10 min to a boiling solution of rhodium(II) mandelate (2 mg) in dichloromethane (40 cm^3). After a further 5 min the solvent was removed at reduced pressure to afford an oil whose NMR spectrum showed that it contained *ca.* 85% of the bicyclic ketones **14a**/**14b**; $\delta_H(CDCl_3)$ 0.84 (3 H, s), 1.91 (3 H, s), 2.10–2.43 (4 H, m), 3.54 (1 H, d, *J* 7.5), 3.67 (2 H, s), 5.64 (1 H, d, *J* 7.5), 5.85 (1 H, s) and 7.29 (5 H, s). Purification was not attempted. In later experiments this product was used without purification.

6-*Acetoxy*-1,2,3,8a-*tetrahydro*-4,8a-*dimethylazulen*-1-*ols* **15**.—A solution of diazoketone **11** (0.104 g) in dichloromethane (18 cm^3) was decomposed with rhodium(II) mandelate exactly as described above. The crude product was dissolved in dry ether

(6 cm^3) and added in one portion to a vigorously stirred suspension of lithium tri-*tert*-butoxyaluminiumhydride (0.203 g) in dry ether (2 cm^3) under nitrogen at 0 °C. The reaction mixture was allowed to come to room temperature and after 6 h saturated aqueous ammonium chloride (15 cm^3) was added. The ether layer and ethereal extracts (3 × 20 cm^3) of the aqueous layer were combined, dried and evaporated under reduced pressure to furnish a yellow oil which on chromatography over silica with dichloromethane as eluent furnished **15** as a colourless oil (0.063 g, 76% yield based on diazo ketone **11**), which solidified on prolonged storage at −10 °C.) The ^1H NMR spectrum of **15** in $CDCl_3$ containing $Eu(tfc)_3$ (0.1 equiv.) revealed separate signals for the bridgehead methyl groups whose integration indicated a 3:1 ratio for the *cis*- and *trans*-isomers.

When sodium borohydride was used to reduce **13a**/**13b** the product **15** consisted of a 1.9:1 mixture of *cis*- and *trans*-isomers; δ_H(270 MHz; $CDCl_3$) 0.83 (3 H, s, bridgehead CH_3), 1.86 (3 H, s, vinylic CH_3), 1.80 (2 H, m), 2.17 (3 H, s, Ac), 2.00–2.65 (2 H, m), 4.10 (1 H, m, CHOH), 5.25 (2/3 H, d, 8-H, *J* 10), 5.70 (1/3 H, d, 8-H, *J* 10), 5.85 (2/3 H, d, 7-H, *J* 10), 5.92 (1/3 H, d, 7-H, *J* 10) and 6.11 (1 H, s, 5-H).

Hydrogenation of Trienols **15**.—*6-Acetoxy-1,2,3,5,6,7,8,8a-octahydro-4,8a-dimethylazulen-1-ols* **17** *and the Corresponding Perhydro Derivative* **18**.—A mixture of trienols **15** (0.158 g, 0.68 mmol), 10% palladium on carbon (30 mg) and ethanol (3 cm^3) was stirred under a balloon of hydrogen at room temperature for 2.5 h. The catalyst was removed by filtration through a bed of Celite containing a thin layer of silica gel. Concentration of the filtrate furnished an oil (0.150 g) which was shown by NMR spectroscopy to consist chiefly (>93%) of **17** with a trace amount of a second component which was later identified as the perhydro derivative **18**. The product was used without further purification; $\delta_H(CDCl_3)$ 0.94 (3 H, s, angular Me), 1.60 (3 H, s, vinylic Me), 2.02 (3 H, s, Ac), 3.60 [1 H, brm, CH(OH)] and 4.60 (1 H, brm, CHOAc); $\delta_C(CDCl_3)$ 170.4, 142.7, 130.9, 128.8, 123.0, 84.3, 81.9, 73.9, 72.9, 46.8, 43.5, 40.0, 34.6, 31.1, 29.8, 26.7, 22.8, 21.5 and 14.9; ν_{max}(film)/cm^{-1} 3450 and 1730.

cis-6-*Acetoxy*-1,2,3,5,6,7,8,8a-*octahydro*-4,8a-*dimethyl*-1-*tert-butyldimethylsilyloxyazulenes* **19** *and the Corresponding Perhydro Derivative* **20**. Imidazole (0.210 g, 3.10 mmol) was added to a solution of the **17**–**18** mixture (0.150 g) in dimethylformamide (DMF) (2 cm^3), followed by *tert*-butyldimethylsilyl chloride (0.220 g, 1.5 mmol). The mixture was heated under nitrogen at 50 °C for 12 h and then for a further 24 h at 65–70 °C during which time further portions of *tert*-butyldimethylsilyl chloride (0.200 and 0.320 g, respectively), and imidazole (0.200 and 0.320 g, respectively) at 12 and 24 h respectively, were added. After a further 12 h period at room temperature the reaction mixture was diluted with ether and the ethereal layer and ethereal extracts (2 × 20 cm^3) of the lower layer were combined, washed with water (2 × 20 ml), dried and concentrated to afford an oil which was shown by TLC to contain two components. After chromatography over silica the mixture was isolated as an oil (0.126 g, 53% yield based on **15**); compound **19** $\delta_H(CDCl_3)$ 0.01 (3 H, s, Me), 0.02 (3 H, s, Me) 0.83 (3 H, s) 0.85 (9 H, s, Bu^t), 0.87 (3 H, s, Me), 1.26 (1 H, m), 1.45–2.10 (7 H, m), 1.57 (3 H, s, Me), 1.97 (3 H, s, Me), 2.22 (1 H, m), 2.60 (1 H, t), 3.54 (1 H, dd) and 4.62 (1 H, m).

cis-1-tert-*Butyldimethylsilyloxy*-1,2,3,7,8,8a-*hexahydro*-4,8a-*dimethylazulen*-6(5H)-*one* **21** *and the Corresponding Perhydro Derivative* **22** *from* **19**–**20**.—A solution of **19**–**20** (66 mg, 0.19 mmol) in ethanol (6 cm^3) was treated with potassium hydroxide (380 mg, 6.8 mmol) in water (1.5 cm^3) and the mixture was stirred at room temperature for 1 h. It was then poured into water (40 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried and concentrated to afford an oil (54 mg). The oil was dissolved in dichloromethane (12 cm^3), PCC (pyridinium chlorochromate) (150 mg, 0.7 mmol) was added and the mixture was stirred at room temperature for 3 h. After dilution with ether (40 cm^3) the solution was filtered through Celite and the filtrate was concentrated to give an oil (58 mg) which was chromatographed in dichloromethane over silica to afford *compound* **21** as a clear oil (36 mg, 62%) (Found: C, 69.9; H, 10.5. $C_{18}H_{32}O_2Si$ requires C, 70.1; H, 10.4%) and compound **22** (see below) (12 mg, 21%) as a low-melting crystalline solid. The NMR spectra of (±)-**21** and (±)-**22** agreed closely with the spectra of (±)-**21** and (±)-**22** published and kindly supplied by Professor Quinkert.

Conversion of **21** *into* **22** *by Hydrogenation*.—A mixture of **21** (30 mg) and 5% rhodium on alumina (30 mg) in 50:1 ethyl acetate–acetic acid (6 cm^3) was hydrogenated at room temperature at 66 psi for 20 h. The catalyst was filtered off and the solution was concentrated at reduced pressure to an oil (28 mg). The product in dichloromethane (10 cm^3) was treated with PCC and the mixture was stirred at room temperature for 2 h. Ether (20 cm^3) was added and solids were removed by filtration through Celite. The filtrate was concentrated to an oil which was purified by flash chromatography in dichloromethane over silica to afford **22** (14 mg, 46%) as a crystalline solid identical in all respects with the sample of **22** described above. There was also obtained from the column unchanged **21** (12 mg; yield of **22** based on recovered **21** was 78%), together with a trace of material which was presumed to be a perhydroazulene with the *cis*-geometry.

Ethyl 3-[*butylthio*(*ethoxycarbonyl*)*methyl*]-2-*hydroxy*-6-*methylbenzoate* **28**.—A solution of stannic chloride (0.214 g, 0.8 mmol) in dichloromethane (3 cm^3) was added to a solution of ethyl 2-hydroxy-6-methylbenzoate **26** (0.148 g, 0.8 mmol) in dichloromethane (1 cm^3) under nitrogen. The mixture was stirred for 15 min after which a solution of chloro sulphide **27** (0.173 g, 0.8 mmol) in carbon tetrachloride (0.5 cm^3) and dichloromethane (2 cm^3) was added dropwise with stirring. After 1 h, TLC analysis (eluent dichloromethane) revealed that two products of R_f 0.5 and 0.3 were present. The reaction mixture was treated with water (5 cm^3) and the organic phase and dichloromethane extracts (3 × 7 cm^3) of the aqueous phase were combined and washed with saturated aqueous sodium hydrogen carbonate (15 cm^3). Removal of the solvent at reduced pressure left an oil which on chromatography over silica with dichloromethane as eluent furnished *compound* **28** as a colourless oil (0.096 g, 33%) (Found: C, 60.8; H, 7.2; S, 9.2. $C_{18}H_{26}O_5S$ required C, 61.0; H, 7.3; S, 9.0%); ν_{max}(film)/cm^{-1} 3340, 1730 and 1655; $\delta_H(CDCl_3)$ 0.97 (3 H, m, CH_3 of SBu), 1.25 (3 H, t, CH_3 of Et), 1.40 (4 H, m, $2CH_2$ of SBu), 1.42 (3 H, t, CH_3 of Et), 2.56 (3 H, s, $ArCH_3$), 2.65 (2 H, m, SCH_2), 4.18 (2 H, q, CH_2 of Et), 4.43 (2 H, q, CH_2 of Et), 5.07 (1 H, s, SCHCO), 6.75 (1 H, d, *J* 8.25, ArH), 7.64 (1 H, d, *J* 8.25, ArH) and 11.91 (1 H, s, ArOH). Further elution of the column yielded a second isomer as an oil (0.116 g, 40%) to which the *para*-isomer **29** structure was assigned on spectroscopic evidence.

Preparation of Lactone **30**.—A solution of compound **28** (0.096 g, 0.3 mmol) and toluene-*p*-sulphonic acid (20 mg) in toluene (15 cm^3) was heated under reflux for 12 h. The cooled solution was diluted with ether (20 cm^3) and washed with saturated aqueous sodium hydrogen carbonate. The dried solution was concentrated at reduced pressure and the residue was purified by chromatography over silica with dichlormethane as eluent to afford lactone **30** (0.069 g, 83%) as an oil; ν_{max}(film)/cm^{-1} 1810 and 1720; $\delta_H(CDCl_3)$ 0.70–1.10 (3 H, m),

1.10–1.80 (4 H, m), 1.39 (3 H, t), 2.42 (3 H, s), 2.40–2.90 (2 H, m), 4.44 (2 H, q), 4.53 (1 H, s), 7.13 (1 H, d) and 7.42 (1 H, d).

Desulphurisation of **28**.—Freshly activated zinc powder (7 g) was added to a stirred solution of sulphide **28** (0.91 g, 2.57 mmol) in glacial acetic acid (30 cm^3) and the mixture was diluted with dichloromethane (50 cm^3) and filtered through Celite. The filtrate and dichloromethane washings of the zinc residues were combined and concentrated to an oil which was redissolved in fresh dichloromethane (50 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (2 × 15 cm^3). The dried solution was concentrated and the residue was purified by flash chromatography over silica with dichloromethane as eluent to afford the sulphur free phenolic *diester* **31** (0.63l g, 92%) as an oil (Found: C, 63.3; H, 7.1. $C_{14}H_{18}O_5$ requires C, 63.1; H, 6.8%); ν_{max}(film)/cm^{-1} 3340, 1735 and 1655; δ_H($CDCl_3$) 1.21 (3 H, t, CH_3 of Et), 1.37 (3 H, t, CH_3 of Et), 2.50 (3 H, s, $ArCH_3$), 3.55 (2 H, s, $ArCH_2CO$), 4.10 (2 H, q, CH_2 of Et), 4.37 (2 H, q, CH_2 of Et), 6.67 (1 H, d, ArH, *J* 7.5), 7.20 (1 H, d, ArH, *J* 7.5) and 11.70 (1 H, s, ArOH); δ_C($CDCl_3$) 14.21 (q), 24.04 (q), 35.54 (t), 60.75 (t), 61.66 (t), 112.34 (s), 120.98 (s), 122.41 (d), 135.28 (d), 140.41 (s), 160.94 (s), 171.79 (s) and 171.98 (s).

Sodium Borohydride Reduction of **31**.—The above phenolic diester **31** (0.481 g, 1.8 mmol) in ethyl acetate (20 cm^3) was treated with sodium borohydride (0.52 g, 13.8 mmol) in portions and the mixture was then heated under reflux for 7 h. The cooled mixture was poured slowly with stirring into 10% hydrochloric acid (20 cm^3). The organic layer and ethyl acetate extracts (2 × 15 cm^3) of the aqueous layer were combined and dried. Removal of the solvent at reduced pressure left an oil which when purified by flash chromatography on silica with dichloromethane as eluent afforded *ethyl 2-(2-hydroxy-3-hydroxymethyl-4-methylphenyl)acetate* **32** (0.329 g, 81%) which crystallised with time, m.p. 75.5–77.0 °C (from hexane–dichloromethane) (Found: C, 64.1; H, 7.1. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.1%); ν_{max}($CDCl_3$)/cm^{-1} 3580, 3320 and 1725; δ_H($CDCl_3$) 1.25 (3 H, s, CH_3 of Et), 2.15 (3 H, s, $ArCH_3$), 3.24 (1 H, br s, $ArCH_2OH$), 3.55 (2 H, s, $ArCH_2CO$), 4.14 (2 H, q, CH_2 of Et), 4.77 (2 H, s, $ArCH_2OH$), 6.62 (1 H, d, ArH, *J* 7.5), 6.99 (1 H, d, ArH, *J* 7.5) and 8.81 (1 H, brs, ArOH); δ_C($CDCl_3$) 14.03 (q), 18.91 (q), 36.32 (t), 60.36 (t), 61.27 (t) 119.29 (s), 121.76 (d), 123.71 (s), 129.69 (d), 135.54 (s), 154.77 (s) and 173.61 (s).

Phenolic Aldehyde **33**.—A stirred solution of **32** (46 mg, 0.02 mmol) in 1,4-dioxane (1 cm^3) was purged with nitrogen and DDQ (47 mg, 0.2 mmol) was added in one portion. The mixture was heated under reflux for 5 h and then cooled, diluted with dichloromethane (10 cm^3) and filtered. The filtrate was concentrated at reduced pressure and the residue was purified by flash chromatography on silica gel with dichloromethane as the eluent to afford *ethyl 2-(3-formyl-2-hydroxy-4-methylphenyl)acetate* **33** (23 mg, 50%) as an oil which solidifed with time; ν_{max}(film)/cm^{-1} 1640; δ_H($CDCl_3$) 1.26 (3 H, t, CH_3 of Et), 2.60 (3 H, s, $ArCH_3$), 3.62 (2 H, s, CH_2OH), 4.17 (2 H, q, CH_2 of Et), 6.69 (1 H, d, *J* 7, ArH), 7.33 (1 H, d, *J* 7, ArH), 10.31 (1 H, s, CHO) and 12.21 (1 H, s, OH).

Lactone Aldehyde **25**.—A solution of aldehyde **33** (10 mg) and toluene-*p*-sulphonic acid (10 mg) in toluene (3 cm^3) was heated under reflux for 13 h. The cooled solution was diluted with ether (10 cm^3) and washed with saturated aqueous sodium hydrogencarbonate (2 × 8 cm^3). The organic phase was dried and concentrated at reduced pressure to an oil which on flash chromatography over silica gel with dichloromethane as eluent afforded 2-(3′-formyl-2′-hydroxy-4′-methylphenyl)acetic acid 2,2′-lactone **25** (5 mg, 63%) as a crystalline solid; ν_{max}(KBr)/cm^{-1} 1810; δ_H($CDCl_3$) 2.65 (3 H, s, $ArCH_3$), 3.76 (2 H, s, CH_2CO), 6.99 (1 H, d, *J* 11, ArH), 7.35 (1 H, d, *J* 11, ArH) and 10.50 (1 H, s, CHO).

6-*Methylsalicylaldehyde* **34**.—Boron tribromide (0.19 cm^3) in dichloromethane (2 cm^3) was added dropwise under nitrogen to a solution of 6-methylanisaldehyde (1.1 g, 8.1 mmol) in dichloromethane (10 cm^3) at room temperature. After 1 h the mixture was poured into water (4 cm^3) and the organic layer and dichloromethane extracts of the aqueous layer were combined, dried and concentrated to an oil. The crude product was purified by flash chromatography over silica gel with dichloromethane as eluent to afford compound **34** (0.878 g, 81%) as an oil which partly crystallised with time; δ_H($CDCl_3$) 2.51 (3 H, s, $ArCH_3$), 6.57–7.00 (2 H, m, ArH), 7.25–7.60 (1 H, m, ArH), 10.54 (1 H, m, CHO) and 12.08 (1 H, s, OH).

Preparation of **34a**/**34b** *Mixture*.—A solution of chloro sulphide **27** (0.204 g, 0.97 mmol) in carbon tetrachloride–dichloromethane (1:1; 2 cm^3) was added dropwise with stirring to a solution of 6-methylsalicylaldehyde (0.132 g, 0.97 mmol) and stannic chloride (0.253 g, 0.97 mmol) in dichloromethane (4 cm^3) under nitrogen at room temperature. After 1 h the reaction mixture was poured into cold water (5 cm^3). The organic layer and dichloromethane extracts (2 × 7 cm^3) of the aqueous layer were combined, washed with saturated aqueous sodium hydrogen carbonate and dried. Removal of the solvent at reduced pressure, followed by purification of the residue by flash chromatography over silica gel with dichloromethane as eluent, furnished **34a** and **34b** in a 1:1 mixture as a pale yellow oil (0.247 g, 82%). The isomer ratio was determined from the ^1H NMR spectrum of the mixture.

3-*Bromo-6-methoxy-2-methoxybenzaldehyde* **35**.—A solution of bromine (1.61 g, 10 mmol) in carbon tetrachloride (6 cm^3) was added over 15 min to a chilled (−10 °C) solution of 2-methoxy-6-methylbenzaldehyde (1.26 g, 8.4 mmol) in carbon tetrachloride (12.5 cm^3) containing iron filings (20 mg). After 45 min the reaction was poured into ice–water (50 cm^3). The organic phase was separated, washed with aqueous sodium thiosulphate (2 × 10 cm^3) and brine (10 cm^3) and dried. Removal of the solvent at reduced pressure gave compound **35** (1.52 g, 79%) as light brown needles, m.p. 85–87 °C, after crystallisation from hexane (Found: C, 47.4; H, 4.0; Br, 34.5. $C_9H_9BrO_2$ requires C, 47.2; H, 3.9; Br, 34.0%); ν_{max}($CHCl_3$)/cm^3 1680; δ_H($CDCl_3$) 2.57 (3 H, s, $ArCH_3$), 3.84 (3 H, s, OCH_3), 6.89 (1 H, d, *J* 9, ArH), 7.79 (1 H, d, *J* 9, ArH) and 10.67 (1 H, d, CHO).

3-*Bromo-6-hydroxy-2-methylbenzaldehyde* **36**.—A solution of boron tribromide (1.65 g, 6.6 mmol) in dichloromethane (2 cm^3) was added dropwise to a solution of compound **35** (1 g, 4.4 mmol) in dichloromethane (10 cm^3) under nitrogen at 0 °C. After 1 h water (10 cm^3) was added cautiously. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (5 cm^3) and brine (5 cm^3), dried and concentrated at reduced pressure. The residue was purified by flash chromatography on silica gel with dichloromethane as the eluent to afford *phenolic aldehyde* **36** (0.85 g, 91%) as a crystalline solid, m.p. 104 °C (Found: C, 44.5; H, 3.4; Br, 36.9. $C_8H_7BrO_2$ requires C, 44.7; H, 3.3; Br, 37.2%); ν_{max}($CHCl_3$)/cm^{-1} 3060 and 1670; δ_H($CDCl_3$) 2.64 (3 H, s, $ArCH_3$), 6.82 (1 H, d, *J* 9, ArH), 7.71 (1 H, d, *J* 9, ArH), 10.56 (1 H, s, CHO) and 12.22 (1 H, s, OH).

3-*Bromo*-5-[*butylthio*(*ethoxycarbonyl*)*methyl*]-6-*hydroxy*-2-*methylbenzaldehyde*. **37**.—Stannic chloride (3.62 cm^3, 31.0 mmol) was added dropwise to a solution of **36** (6.7 g, 31 mmol)

in dichloromethane (30 cm^3) under nitrogen at room temperature. After 10 min chloro sulphide **27** (6.5 g 31 mmol) in carbon tetrachloride (40 cm^3) was added dropwise over a 40 min period. After a further 30 min dichloromethane (50 cm^3) was added and the solution was then washed with water (2 × 25 cm^3) and saturated aqueous sodium hydrogen carbonate (50 cm^3), dried and evaporated at reduced pressure. Flash chromatography of the residue over silica gel with dichloromethane as eluent, furnished *compound* **37** (10.1 g, 83%) as a viscous oil. An analytical sample was prepared by Kugelrohr distillation at 250 °C and 0.45 mmHg (Found: C, 49.3; H, 5.6; Br, 20.7; S, 8.6. $C_{16}H_{21}BrO_4S$ requires C, 49.4; H, 5.4; Br, 20.7; S, 8.2%); ν_{max}(film)/cm^{-1} 1725 and 1640; δ_H($CDCl_3$) 0.98 (3 H, m, CH_3 of Bu), 1.30 (3 H, t, CH_3 of Et), 1.10–1.87 [4 H, m, $(CH_2)_2$ of Bu], 2.61 (2 H, m, SCH_2 of Bu), 2.66 (3 H, s, $ArCH_3$), 4.15 (2 H, q, CH_2 of Et), 4.91 [1 H, s, ArCH(SR)CO], 8.00 (1 H, s, ArH), 10.29 (1 H, s, CHO) and 12.48 (1 H, s, OH).

Formation of Formyl Acid **38** *by Hydrolysis of* **37**.—A solution of sodium hydroxide (20 g, 0.5 mol) in water (30 cm^3) was added with stirring to a solution of ester **37** (11.62 g, 0.03 mol) in dioxane (30 cm^3) at room temperature. After *ca.* 15 min a buoyant yellow solid formed and stirring was continued at room temperature for 12 h. The reaction mixture was then diluted with water (500 cm^3) and THF (20 cm^3) and the aqueous layer was separated and washed once with dichloromethane. The aqueous layer was made strongly acidic by the addition of conc. hydrochloric acid and the resulting milky mixture was extracted with dichloromethane (2 × 100 + 1 × 50 cm^3). The combined organic extracts were, in turn, extracted with saturated aqueous sodium hydrogen carbonate (2 × 100 + 2 × 50 cm^3), and the latter extracts were acidified with conc. hydrochloric acid. The resulting milky mixture was extracted with dichloromethane (2 × 100 + 1 × 50 cm^3), and the combined extracts were dried and concentrated at reduced pressure to afford a viscous oil. Filtration of the crude product in ether through a bed of silica gel afforded 2-(3-*bromo*-5-*formyl*-6-*hydroxy*-4-*methylphenyl*)-1-*butylthioacetic acid.* **38** (8.41 g, 78%) as a yellow solid. An analytical sample, m.p. 110–111 °C, was obtained by crystallisation from dichloromethane–hexane (Found: C, 46.5; H, 4.7; Br, 22.0; S, 8.8. $C_{14}H_{17}BrO_4S$ requires C, 46.5; H, 4.7; Br, 22.0; S, 8.9%); ν_{max}($CHCl_3$)/cm^{-1} 3000br, 1710 and 1640; δ_H($CDCl_3$) 0.98 (3 H, m, CH_3 of Bu), 1.10–2.10 [4 H, m, $(CH_2)_2$ of Bu], 2.62 (5 H, m, $ArCH_3$ and SCH_2), 5.01 [1 H, s, ArCH(SR)CO], 8.10 (1 H, s, ArH), 10.10 (1 H, brs, CO_2H), 10.51 (1 H, s, CHO) and 12.72 (1 H, s, OH).

5-*Bromo*-3-*butylthio*-7-*formyl*-6-*methylbenzofuran*-2(3H)-*one* **39**.—Oxaloyl chloride (2 cm^3, 0.023 mol) was added to a suspension of phenolic acid **38** (8.53 g, 0.024 cm^3) in benzene (40 cm^3) under nitrogen at room temperature. The mixture was stirred and after 30 min a second quantity (2 cm^3) of oxaloyl chloride was added. After 12 h the solvent and residual oxaloyl chloride were removed at reduced pressure. The residue was taken up in fresh benzene (50 cm^3) and the solution was heated under reflux for 3 h. The cooled solution was concentrated to an oil (6.89 g, 85%) which solidified with time, m.p. 107–109 °C. An analytical sample of *compound* **39** was obtained by Kugelrohr distillation at 250 °C at 0.1 mmHg (Found: C, 49.2; H, 4.4. $C_{14}H_{15}BrO_3S$ requires C, 49.0; H, 4.4%); ν_{max}(film)/cm^{-1} 2860, 1820 and 1695; δ_H($CDCl_3$) 0.93 (3 H, m, CH_3 of butyl), 1.05–1.80 [4 H, m, $(CH_2)_2$ of SBr], 2.71 (5 H, s, $ArCH_3$ and SCH_2), 4.53 [1 H, s, ArCH(SR)CO], 7.73 (1 H, s, ArH) and 10.27 (1 H, s, CHO).

tert-*Butyl* 3-(5-*Bromo*-3-*butylthio*-2,3-*dihydro*-6-*methyl*-2-*oxobenzofuran*-7-*yl*)*prop*-2-*enoate* **41**.—A solution of ylide **40** (247 mg, 0.66 mmol) in benzene (3 cm^3) was added dropwise to a solution of aldehyde **39** (205 mg, 0.6 mmol) in benzene (1 cm^3). During the addition the reaction mixture took on a red–orange colour. After 1 h the solvent was removed at reduced pressure and the residue was purified by chromatography over silica gel with dichloromethane as eluent to afford *compound* **41** as an oil (224 mg, 85%) which solidified with time, m.p. 62–65 °C (Found: C, 54.7; H, 6.0. $C_{10}H_{25}BrO_4S$ requires C, 54.4; H, 5.7%); ν_{max}(film)/cm^{-1} 1815 and 1705; δ_H($CDCl_3$) 0.95 (3 H, m, CH_3 of SBr), 1.53 [9 H, m, $C(CH_3)_3$], 1.10–1.90 [4 H, m, $(CH_2)_2$], 2.50 (3 H, s, CH_3), 2.68 (2 H, m, SCH_2), 4.51 [1 H, s, ArCH(SR)CO], 6.71 (1 H, d, *J* 16.5, CH=CH), 7.64 (1 H, s, ArH) and 7.77 (1 H, d, *J* 16.5, CH=CH).

tert-*Butyl* 3-(2,3-*Dihydro*-6-*methyl*-2-*oxobenzofuran*-7-*yl*)-*propionate* **42**.—Freshly prepared Raney nickel (*ca.* 12 g) was added to a solution of cinnamate **41** (3.13 g, 7.1 mmol) in isopropyl alcohol (70 cm^3) and the mixture heated under reflux for 2 h. The cooled mixture was filtered through Celite and the filtrate was concentrated to an oil (1.5 g) under reduced pressure. The crude product was purified by flash chromatography over silica with dichloromethane as eluent to afford *compound* **42** (1.33 g, 68%) as a solid. An analytically pure sample was obtained by crystallisation from dichloromethane–hexane, m.p. 88.5–90.0 °C (Found: C, 69.3; H, 7.4. $C_{16}H_{20}O_4$ requires C, 69.6; H, 7.3%); ν_{max}(film)/cm^{-1} 1810 and 1725; δ_H($CDCl_3$) 1.44 [9 H, s, $C(CH_3)_3$], 2.34 (3 H, s, CH_3), 2.00–3.10 [4 H, m, $(CH_2)_2$], 3.64 (2 H, s, $ArCH_2$) and 6.90 (2 H, q, ArH).

2-*Diazo*-5-(2,3-*dihydro*-6-*methyl*-2-*oxobenzofuran*-1-*yl*)*pentan*-3-*one* **44**.—Oxaloyl chloride (0.7 cm^3, 8 mmol) was added to a suspension of acid **43** (602 mg, 2.74 mmol) in benzene (10 cm^3) and the mixture was heated under reflux under nitrogen for 1.5 h. The solution was concentrated at reduced pressure just prior to treatment with diazoethane. Ethereal diazoethane (*ca.* 50 cm^3) was prepared from *N*-ethyl-*N*-nitrosourea (3.23 g, 0.028 mol) and 50% aqueous potassium hydroxide (10 cm^3, 0.09 mol). To the ethereal solution at −15 °C was added the above acid chloride in dry ether (8 cm^3) over 25 min. After 1 h the solution was concentrated at reduced pressure to afford the *diazoketone* **44** (432 mg) as an oil. A portion purified by flash chromatography over silica gel with dichloromethane as eluent (81% recovery) solidified on prolonged storage at −10 °C, m.p. 65–67 °C (Found: C, 64.7; H, 5.7; N, 9.6. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.4; N, 10.9%); ν_{max}(film)/cm^{-1} 2080, 1810 and 1630; δ_H 1.96 [3 H, s, $C(N_2)CH_3$], 2.33 (3 H, s, $ArCH_3$), 3.66 (2 H, s, $ArCH_2$) and 6.93 (2 H, q, ArH).

Preparation of Phenolic tert-*Butyl Cinnamate* **45**.—A solution of Wittig reagent **40** (106 mg, 0.28 mmol) in benzene (5 cm^3) was added dropwise with stirring under nitrogen to a solution of aldehyde **37** (100 mg, 0.26 mol) in benzene (2 cm^3) at room temperature. The mixture was then heated under reflux for 1 h and after cooling, was concentrated to an oil which was purified by chromatography over silica. Elution with dichloromethane afforded tert-*butyl* 3-{4-*bromo*-2-[*butylthio*(*ethoxycarbonyl*)-*methyl*]-1-*hydroxy*-5-*methylphenyl*}prop-2-*enoate* **45** as an oil (92 mg, 74%) (Found: C, 54.1; H, 6.3; Br, 17.3; S, 6.9. $C_{22}H_{31}BrO_5S$ requires C, 54.2; H, 6.4; Br, 16.9; S, 6.6%) ν_{max}(film)/cm^{-1} 3300 and 1700; δ_H($CDCl_3$) 0.9 (3 H, m, Me of SBu), 1.28 (3 H, t, Me of Et), 1.55 (9 H, s, Bu^t), 1.00–1.80 [4 H, m, CH_2)$_2$ of SBu], 2.43 (3 H, s, ArMe), 2.50 (2 H, m, CH_2 of SBu), 4.19 (2 H, q, CH_2 of Et), 4.57 (2 H, s, ArCHS), 6.39 (1 H, d, CH=), 7.32 (1 H, s, ArH), 7.65 (1 H, d, CH=) and 8.14 (1 H, br s, ArOH); δ_C($CDCl_3$) 172.37 (s), 166.33 (s), 153.34 (s), 138.40 (s), 137.88 (d), 133.85 (d), 127.02 (d), 125.40 (s), 120.72 (s), 116.11 (s), 80.63 (s), 62.83 (t), 50.23 (d), 31.97, 30.93, 28.26, 21.89, 20.79, 14.03 and 13.58.

Preparation of Methyl Ether **46**.—An ethereal solution of diazomethane was prepared from Diazald (12.3 g). A solution of phenol **45** (5.1 g, 0.001 mol) in ether (30 cm^3) was added to the diazomethane solution at −20 °C. After 20 min the solvent and residual diazomethane were removed at reduced pressure and the residue was passed through a silica gel column in dichloromethane to afford compound **46** as an oil (3.24 g, 62% yield) which was used in the next stage without further purification. The new ^1H NMR signal at δ 3.67 (3 H) confirmed that methylation had occurred.

Preparation of tert-*Butyl* 3-(3-*Carboxymethyl*-2-*methoxy*-6-*methylphenyl*)*propionate* **47** *by Hydrogenation of* **46**.—A mixture of freshly prepared Raney nickel (from 4 g Ni–Al alloy) and **46** (0.615 g, 1.2 mmol) in ethanol (20 cm^3) was heated under reflux for 1.5 h. The cooled mixture was filtered through Celite and the filtrate was concentrated to an oil (0.382 g) which was shown by ^1H NMR spectroscopy to contain some unchanged cinnamate. The product was taken up in ethanol (5 cm^3) and Adams' catalyst (10 mg) was added to it; the mixture was then stirred under a balloon of hydrogen for 2 h at room temperature. The catalyst was removed by filtration through a bed of silica and the filtrate was concentrated to give *compound* **47** as an oil (0.373 g, 90%). An analytically pure sample was obtained by Kugelrohr distillation at 175 °C and 0.1 mmHg (Found: C, 67.8; H, 8.2. $C_{19}H_{28}O_5$ requires C, 67.9; H, 8.3); ν_{max}(film)/cm^{-1} 1730; δ_H($CDCl_3$) 1.22 (3 H, t, Me of Et), 1.46 (9 H, s, Bu^t), 2.28 (3 H, s, ArMe), 2.10–3.10 (4 H, m, $ArCH_2CH_2$), 3.56 (2 H, $ArCH_2$), 3.71 (3 H, s, OMe), 4.11 (2 H, q, CH_2 of Et) and 6.90 (2 H, q, ArH AB); δ_C($CDCl_3$) 172.50 (s), 171.85 (s), 157.00 (s), 137.10 (s), 132.68 (s), 128.78 (d), 126.24 (d), 125.40 (s), 80.11 (s), 61.47 (q), 60.69 (t), 35.61, 35.35, 28.13, 22.68, 19.30 and 14.23.

Reaction of tert-*Butyl Ester* **47** *with Trifluoroacetic Acid*.—Trifluoroacetic acid (4 cm^3) was added to a solution of ester **47** (0.373 g, 1.11 mmol) in dichloromethane (14 cm^3) and the solution was stirred at room temperature with a continuous purge of nitrogen for 12 h. Removal of the solvent at reduced pressure furnished a clear oil (0.317 g, 100%) which slowly crystallised with time. Recrystallisation from dichloromethane gave 3-(3-*carboxymethyl*-2-*methoxy*-6-*methylphenyl*)*propionic acid* **48** as colourless flakes, m.p. 76–77 °C (Found: C, 64.0; H, 7.0. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.1%); ν_{max}(KBr)/cm^{-1} 3000 (br), 1725 and 1710; δ_H($CDCl_3$) 1.21 (3 H, t, Me of Et), 2.30 (3 H, s, ArMe), 2.10–3.20 (4 H, m, $ArCH_2CH_2$), 3.58 (2 H, s, $ArCH_2$), 3.73 (3 H, s, OMe), 4.11 (2 H, q, CH_2 of Et), 6.93 (2 H, q, ArH AB) and 8.70 (1 H, br s, CO_2H).

Preparation of Diazoketone **49**.—A mixture of acid **48** (115 mg, 0.41 mmol) and oxalyl chloride (0.15 cm^3, 1.72 mmol) in benzene (2 cm^3) was heated under reflux under nitrogen for 1 h. The cooled solution was concentrated at reduced pressure and the resulting crude acid chloride was dissolved in dry ether (9 cm^3) and added dropwise to an ethereal solution of diazoethane (45 cm^3 from 1 g, 8.6 mmol of *N*-ethyl-*N*-nitrosourea) at −15 °C. After 30 min the solvent and residual diazoethane were removed at reduced pressure to afford the 2-[3-(4-*diazo*-3-*oxopentyl*)-2-*methoxy*-4-*methylphenyl*]*acetic acid ethyl ester* (131 mg, 100%) as a green oil which was used without further purification; ν_{max}(film)/cm^{-1} 2080, 1730 and 1635; δ_H($CDCl_3$) 1.23 (3 H, t, Me of Et), 1.94 [3 H, s, $C(N_2)Me$], 2.28 (3 H, s, ArMe), 2.40–3.20 (4 H, m, $ArCH_2CH_2$), 3.57 (2 H, s, $ArCH_2$), 3.70 (3 H, s, OMe), 4.10 (2 H, q, CH_2 of Et) and 6.95 (2 H, q, ArH).

Preparation of Diazoketone **50**.—Acid **48** (125 mg, 0.45 mmol) was converted into the acyl chloride exactly as described above and added in ether (9 cm^3) to ethereal diazomethane (40 cm^3, from 2.15 g Diazald) at −15 °C. Removal of the solvent and residual diazomethane after 45 min afforded the 2-[3-(4-diazo-3-oxobutyl)-2-methoxy-4-methylphenyl]acetic acid ethyl ester (100%) which was spectroscopically and chromatographically pure and which was used directly; ν_{max}(film)/cm^{-1} 2080, 1725 and 1635; δ_H($CDCl_3$) 1.24 (3 H, t, Me of Et), 2.28 (3 H, s, ArMe), 2.20–3.20 (4 H, m, $ArCH_2CH_2$), 3.57 (2 H, s, $ArCH_2$), 3.71 (3 H, s, ArOMe), 4.11 (2 H, q, CH_2 of Et), 5.22 [1 H, s, C(N2)H] and 6.91 (2 H, q, ArH AB).

Rhodium(II) *Catalysed Cyclisation of* **50**.—A solution of diazoketone **50** (47 mg, 0.16 mmol) in dichloromethane (9 cm^3) was added dropwise over a 30 min period to a stirred solution of rhodium(II) mandelate (1 mg) in dichloromethane (40 cm^3) at room temperature. After a further 5 min, the solution was washed with water (20 cm^3), dried and concentrated to an oil (100%) which was found by NMR spectroscopy to contain *ca.* 70% cycloheptatrienyl-type products and *ca.* 30% of an aromatic by-product. The cycloheptatrienyl-type products **51** and **52** were present in a 4:1 ratio from ^1H NMR spectroscopic investigation.

Preparation of Diazoketone **53**.—Acid **43** (466 mg, 2.12 mmol) was converted, *via* the corresponding acyl chloride, into diazoketone **53** using ethereal diazomethane (65 cm^3 from 6 g Diazald) exactly as described for diazoketone **50** above. The crude product was purified by flash chromatography in dichloromethane to afford 1-diazo-4-(2,3-dihydro-6-methyl-2-oxobenzofuran-7-yl)butan-2-one as a yellow crystalline solid (443 mg, 86%), m.p. 99–102 °C (Found: C, 63.9; H, 5.13; N, 11.0. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.9; N, 11.5%); ν_{max}($CHCl_3$)/cm^{-1} 2100, 1800 and 1635; δ_H($CDCl_3$) 2.33 (3 H, s, ArMe), 2.20–3.10 (4 H, m, $ArCH_2CH_2$), 3.64 (2 H, s, $ArCH_2$), 5.32 [1 H, s, $C(N_2)H$] and 6.92 (2 H, q, ArH AB).

Rhodium(II)-*Catalysed Cyclisation of Diazoketone* **53**.—A solution of the diazoketone (40 mg) in dichloromethane (9 cm^3) was added dropwise over 30 min to a solution of rhodium(II) mandelate (1 mg) in dichloromethane (40 cm^3) under reflux. After an additional 5 min the cooled solution was washed with water (20 cm^3), dried and concentrated at reduced pressure to afford an oil (36 mg). ^1H NMR spectroscopic analysis of the oil showed that it contained two cycloheptatrienyl components **54** and **55** (*ca.* 75%) and an aromatic component (25%); the vinylic resonance pattern was not sufficiently well resolved to permit firm assignments.

Triethylamine-catalysed rearrangement of the **54** *and* **55** *Mixture*.—A sample of diazoketone **53** (81 mg) was decomposed with rhodium(II) mandelate exactly as described above in dichloromethane. The cooled dichloromethane solution was treated with 0.1 cm^3 of a 5% solution of triethylamine in dichloromethane instantly generating a vivid red colouration. After 30 min TLC indicated the absence of cycloheptatrienes **54** and **55** and the formation of two coloured components. The solvent was removed at reduced pressure and the residue was subjected to flash chromatography in dichloromethane on silica which yielded a red powder (14 mg, 20%) followed by an orange powder (33 mg, 47%). Recrystallisation of the former gave red needles from dichloromethane–hexane, m.p. 240–242 °C; ν_{max}($CHCl_3$)/cm^{-1} 1750 and 1715; δ_H(250 MHz; $CDCl_3$) 2.74 (2 H, m), 2.75 (3 H, s), 3.26 (2 H, m), 5.79 (1 H, s), 7.06 (1 H, d, *J* 12) and 7.39 (1 H, d, *J* 12); δ_C(100 MHz; $CDCl_3$) 23.20, 23.82, 36.25, 98.65, 131.07, 132.02, 134.93, 141.00, 146.03, 149.92, 151.20, 169.32 and 206.95; in 1:1 C_6D_6:$CDCl_3$ solution the δ 2.37 singlet of the methyl substituent is well resolved from the flanking methylene multiplets at 400 MHz. In an NOE experiment irradiation of this singlet enhanced the δ 6.3 doublet;

m/z 214 [M^+ (of $C_{13}H_{10}O_3$), 100%], 186(4), 171(2), 158(23), 143(2), 129(17), 115(22), 102(3), 89(2), 77(3), 64(5), 51(6) and 39(3). The orange solid was recrystallised from dichloromethane–hexane to afford also orange–brown blocks, m.p. > 280 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1770 and 1750; δ_H(270 MHz; $CDCl_3$) 2.33 (s, 3 H), 2.75 (m, 2 H), 3.01 (m, 2 H), 5.84 (s, 1 H), 7.02 (d, 1 H, *J* 12) and 7.18 (d, 1 H, *J* 12); in an NOE experiment irradiation of the δ 2.33 singlet enhanced both the δ 7.02 doublet and the δ 3.01 multiplet; δ_C(100 MHz; $CDCl_3$) 23.23, 28.06, 36.27, 99.21, 120.28, 125.02, 128.79, 130.89, 136.39, 139.69, 148.82, 153.41, 154.91, 168.99 and 203.26; *m/z* 214 [M^+ ($C_{13}H_{10}O_3$), 100%], 199(3), 186(5), 171(2), 158(36), 149(6), 143(1), 129(19), 115(20), 102(5), 87(2), 77(5), 69(3), 57(4), 51(8) and 39(3).

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