The Intramolecular Buchner Reaction of Aryl Diazoketones. Synthesis and X-Ray Crystal Structures of Some Polyfunctional Hydroazulene Lactones

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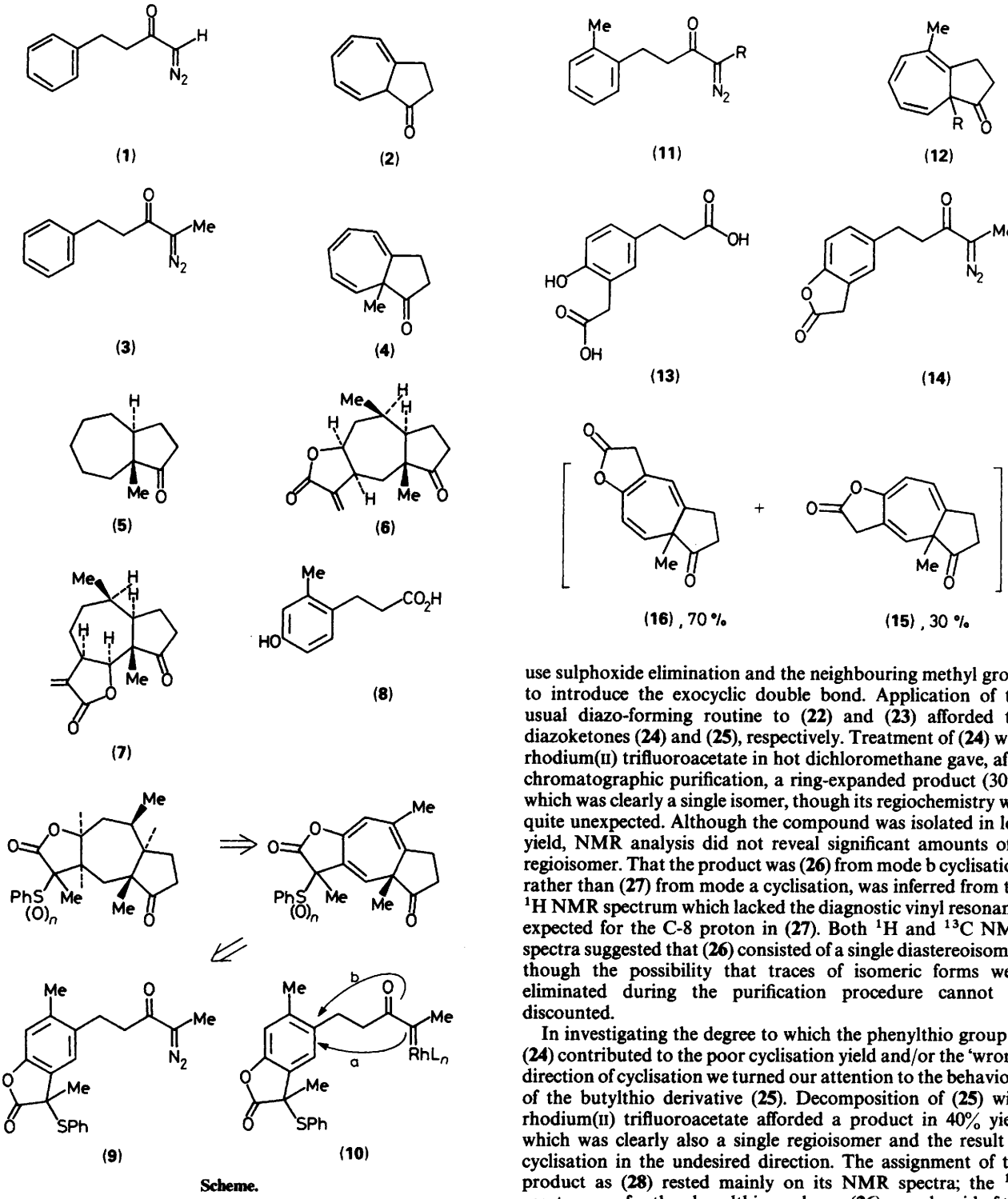
The feasibility of constructing polyfunctional hydroazulenes bearing fused lactone rings *via* rhodium(II)-catalysed cyclisation of suitably constituted diazoketones followed by catalytic hydrogenation has been examined with respect to both direction and efficiency of cyclisation. The presence of the lactone on the aromatic precursor influences the direction of cyclisation as do substituents at the α-position on the lactone ring. Sulphur-containing substituents inhibit cyclisation. Several new unnatural hydroazulene lactones have been produced. The stereochemistry of hydrogenation of the cyclisation products in two cases has been determined by X-ray diffraction and NMR analysis. Crystals of lactone (**34**) are monoclinic, space group $P2_1/a$, in a cell of dimensions $a = 8.625(2)$, $b = 12.993(4)$, $c = 12.109(2)$ Å, $\beta = 105.79(1)°$. Crystals of lactone (**42**) are monoclinic, space group $P2_1/c$, in a cell of dimensions $a = 12.885(2)$, $b = 6.115(4)$, $c = 19.417(4)$ Å, $\beta = 107.14(1)°$. The structures were solved by direct methods and refined by full-matrix least-squares calculations; for (**34**), $R = 0.047$ for 1 405 reflections with $I > 3\sigma(I)$; for (**42**), $R = 0.045$ for 1 370 reflections with $I > 3\sigma(I)$. The crystal structures establish the relative stereochemistry of hydrogenation of the unsaturated lactones and confirm the direction of cyclisation of the ketocarbenoid intermediates.

In the preceding paper[1] we showed how rhodium(II)-catalysed intramolecular Buchner reactions of aryl diazoketones derived from dihydrocinnamic acids can be used to synthesise bicyclodecane structures based on the azulene ring system with oxygenated functional groups in both rings. The conversion of (**1**) into (**2**) represents the general approach. Our interest in this type of cyclisation includes its application to the synthesis of more highly functionalised hydroazulenes of the type found in many natural products of the guaianolide and pseudoguaianolide family. With regard to the latter, more abundant subgroup we have also established that cyclisation of the methyl substituted diazoketone (**3**) proceeds so as to place the bridgehead substituent in position and, furthermore, that hydrogenation of (**4**) is highly stereoselective with respect to formation of the *trans*-hydroazulene (**5**). The *trans*-geometry is a characteristic feature of many pseudoguaianolides, *e.g.* confertin (**6**)[2] and damsin (**7**).[2] Interest in the chemistry of these molecules has been strong for more than a decade, stimulated by the realisation that many members of the series possess pronounced biological activity. Their efficient total synthesis presents a significant challenge to organic chemists.[2] Our synthetic work in this area is based on the use of simple benzenoid diazoketones as precursors to which can be attached in advance most of the additional functionality required for selected pseudoguaianolides.

Confertin (**6**) was selected as the initial target. Two broad options were considered with regard to the choice of benzenoid precursor: *viz.* to have the lactone ring in place in the diazoketone or to add the lactone at a later stage after cyclisation. Both were examined using the phenolic acid (**8**) as a common starting material. The former option is discussed in this paper and the latter in a paper to follow. γ-Lactone groups were attached to (**8**) using α-chloro sulphide esters as electrophiles, and a new procedure which we have described in detail elsewhere.[3] Retro-synthetic analysis of confertin (**6**) (Scheme) suggested that an α-sulphenylated lactone could be used to generate the exocyclic methylene group *via* sulphoxide elimination at an appropriate point in the synthesis and that a hydroazulene could be obtained by hydrogenation of an azulenone which in turn could be realised by cyclisation of a diazoketone such as (**9**). We presumed that rhodium(II)-catalysed cyclisation of the carbenoid derived from (**9**) would proceed along pathway a rather than b in (**10**), largely because of the directive effect of an *ortho*-methyl group observed earlier with the model compounds (**11**; R = H and Me) which gave (**12**; R = H and Me) exclusively.

The directive effect of the lactone ring *per se* on the direction of cyclisation also needed to be considered and to do this the phenolic diacid (**13**)[3] was transformed into the diazoketone (**14**) by sequential treatment with oxaloyl chloride and ethereal diazoethane. Decomposition of (**14**) with rhodium(II) trifluoroacetate in hot dichloromethane afforded ring-expanded products in 86% yield (by NMR analysis). The presence of two distinct methyl singlets at δ 0.99 and 1.02 (ratio 70:30) in the ^{1}H spectrum of the product mixture suggested that both mode a and mode b cyclisation of the ketocarbenoid had occurred and the product was, therefore, taken to be a mixture of (**15**) and (**16**). Because of the lability of these trienone systems, conversion to the more stable tetralones offered an expedient way of identifying the major isomer. Accordingly, the (**15**)–(**16**) mixture was exposed to trifluoroacetic acid, causing rearrangement to tetralones (**17**) and (**18**) from which (**18**) was isolated by PLC and identified on the basis of its NMR data. Although the minor tetralone (**18**) was not isolated, isomer (**17**) was clearly the major component of the mixture and we concluded on that basis that trienone (**16**) was the major product of the ketocarbenoid cyclisation. Significantly, in our model studies[1] the *meta*-methyl diazoketone (**19**) was found to cyclise with a

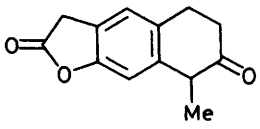


Scheme.

similar regioselectivity, producing a 70:30 mixture of tetralones (**20**) and (**21**).

Having established the feasibility of cyclising a diazoketone bearing a γ-lactone ring, we addressed the problem of preparing precursors with a substitution pattern appropriate to the production of a confertin intermediate. Two sulphenylated lactones were chosen, the phenylthio derivative (**22**) and the butylthio derivative (**23**). Both compounds were readily obtained from the phenolic acid (**8**).[3] Initially our intention was to carry the sulphide group of either (**22**) or (**23**) through to a later stage and use sulphoxide elimination and the neighbouring methyl group to introduce the exocyclic double bond. Application of the usual diazo-forming routine to (**22**) and (**23**) afforded the diazoketones (**24**) and (**25**), respectively. Treatment of (**24**) with rhodium(II) trifluoroacetate in hot dichloromethane gave, after chromatographic purification, a ring-expanded product (30%) which was clearly a single isomer, though its regiochemistry was quite unexpected. Although the compound was isolated in low yield, NMR analysis did not reveal significant amounts of a regioisomer. That the product was (**26**) from mode b cyclisation, rather than (**27**) from mode a cyclisation, was inferred from the ^{1}H NMR spectrum which lacked the diagnostic vinyl resonance expected for the C-8 proton in (**27**). Both ^{1}H and ^{13}C NMR spectra suggested that (**26**) consisted of a single diastereoisomer, though the possibility that traces of isomeric forms were eliminated during the purification procedure cannot be discounted.

In investigating the degree to which the phenylthio group in (**24**) contributed to the poor cyclisation yield and/or the 'wrong' direction of cyclisation we turned our attention to the behaviour of the butylthio derivative (**25**). Decomposition of (**25**) with rhodium(II) trifluoroacetate afforded a product in 40% yield which was clearly also a single regioisomer and the result of cyclisation in the undesired direction. The assignment of the product as (**28**) rested mainly on its NMR spectra; the ^{1}H spectrum, as for the phenylthio analogue (**26**), was devoid of the characteristic C-8 proton resonance. Furthermore, though scarcely definitive, the striking agreement between the ^{13}C δ values of 114.2/114.0 and 114.4/114.0 for the C-6/C-9 carbon atoms of (**28**) and (**26**), respectively, strongly suggested their common structure. These assignments were supported by experiments with sulphur-free precursors (*vide infra*). Although we cannot adequately interpret the regiochemical preference shown in the cyclisation of (**26**) and of (**28**), it is clear that the presence of the lactone moiety in both compounds exerts a directive effect which is more powerful than the directive effect expected for the *ortho*-methyl substituent on the basis of



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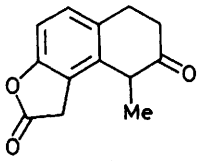

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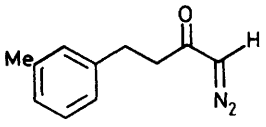

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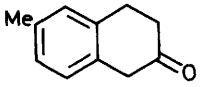

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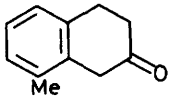

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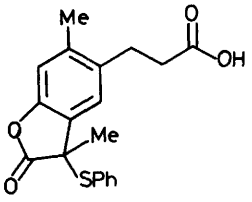

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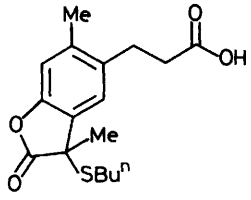

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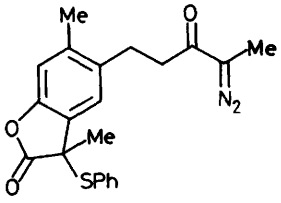

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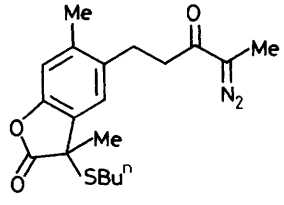

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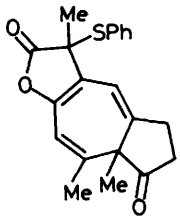

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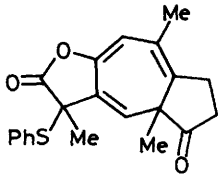

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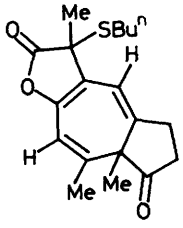

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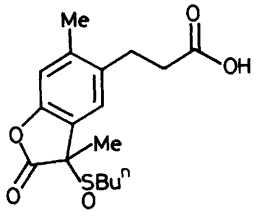

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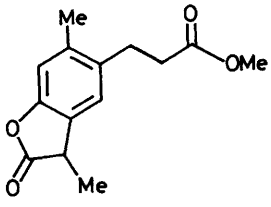

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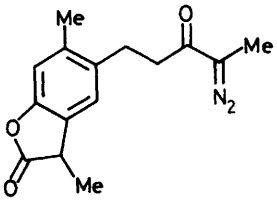

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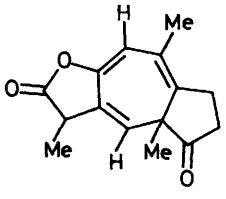

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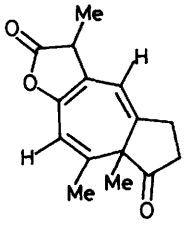

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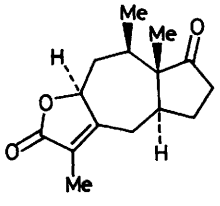


(34)

our studies with model compounds. One attempt was made to effect cyclisation of a diazoketone at the sulphoxide rather than the sulphide level. Sulphoxide (**29**) was produced when the butylthio lactone (**23**) was treated with ozone at −78 °C, but although (**29**) did form a diazoketone on sequential treatment with oxaloyl chloride and diazoethane, the product was devoid of the n-butyl group. The structure of this compound was not pursued when we discovered that it did not produce a cycloheptatriene derivative when exposed to rhodium(II) carboxylates.

Accordingly, though a successful cyclisation with a sulphenylated precursor had obvious attractions *vis-à-vis* pseudoguaianolide synthesis, we turned our attention to sulphur-free systems. The diazoketone (**31**) was prepared from ester (**30**)[3] in the usual way (60% yield), and was decomposed with rhodium(II) trifluoroacetate in dichloromethane to yield a product in *ca.* 80% yield which consisted of a 50:50 mixture of both possible cyclisation products (**32**) and (**33**). The evidence that both isomers were formed was provided by the ^{1}H NMR spectrum, which contained four vinylic resonances, the signal at δ 5.42 attributable to the C-8 proton of (**32**), and two equal intensity bridgehead methyl singlets at δ 0.89 and 0.96. Thus, although the unwanted regioisomer was still being produced, removal of the sulphur-containing substituent from the lactone ring had tilted the cyclisation regiochemistry towards the isomer needed for entry into the natural series; whether this remote substituent effect is steric or electronic in origin, or both, is unclear. Rather than attempt a lengthy separation of (**32**) and (**33**), particularly in view of the known lability of such systems to traces of acid, we decided to hydrogenate directly the mixture. Exposure to hydrogen and Adam's catalyst afforded a mixture of several products from which a crystalline tetrahydro derivative was isolated by column chromatography. X-Ray

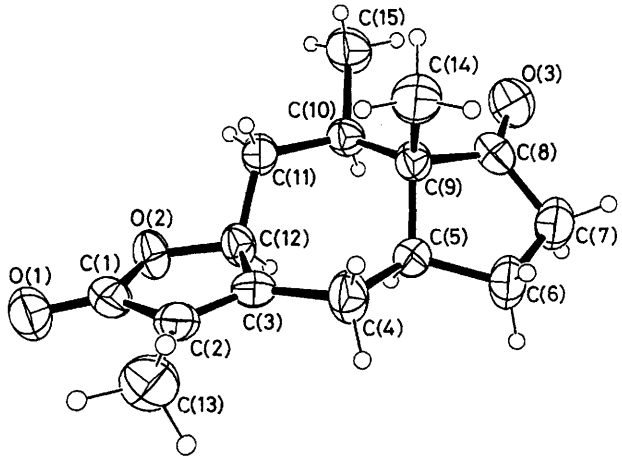


Figure 1. ORTEP[9] plot of (**34**) showing our numbering system.

diffraction was used to show that this compound possessed the structure and relative stereochemistry displayed in (**34**). Figure 1 shows the relative stereochemistry and crystallographic numbering system. The structure consists of discrete molecules separated by normal van der Waals distances. The lactone ring [C(1), C(2), C(3), C(12), O(2)] is planar. The bond lengths (Table 1) show clearly that C(2)–C(3) [1.329(3) Å] is a normal double bond. The seven-membered ring has a chair conformation, with methyl groups C(14) and C(15) in axial and equatorial positions, respectively. The conformation of this ring may be defined by the interplanar angles [C(12), C(3), C(4), C(5)]/[C(11), C(12), C(5), C(9)] of 128.1° and [C(11), C(12), C(5), C(9)]/[C(9), C(10), C(11)] of 125.1°. The cyclopentanone moiety has a C(5) envelope conformation [C(5) lies 0.556 Å out of the C(6)–C(9) plane]. The molecular dimensions (Table 1) are normal. Lactone (**34**) is thus the product of cyclisation of the diazoketone (**31**) in the unwanted direction, *i.e.* towards the methyl group, with a double bond migration into the lactone ring during the hydrogenation step. The stereochemistry of (**34**) is that expected from hydrogen addition to the α-face of the olefinic system, the angular bridgehead methyl group blocking the β-face. Although we presumed that hydrogenation products derived from the sought after isomer (**32**) were also present, no other identifiable products were isolated from the mixture.

It was now clear that both the direction and extent of intramolecular cyclisation of these diazoketone lactones were influenced by the nature of the substituents on the lactone ring, and in view of the beneficial effect of removing sulphur-containing substituents, we decided to examine a precursor from which the lactonic α-methyl group was also absent. Several of the published syntheses of confertin either include or terminate at tricycle (**35**),[2] addition of the exocyclic α-methylene group being well documented.[2] Unfortunately, the necessary lactonic acid (**36**) was available only as the minor component of a mixture with its regioisomer (**37**), and complete separation of the two proved exceedingly difficult. A pure sample of (**36**) could not be obtained but by fractional crystallisation of the mixture we did isolate (**37**) and converted it into diazoketone (**38**) with a view to probing the direction of cyclisation in this unnatural series.

In the meantime we had found that rhodium(II) mandelate[4,5] is a particularly useful catalyst for these intramolecular cyclisations.[5] It is easier to prepare than trifluoroacetate, and is very efficient in the decomposition of diazoketones in which the diazo carbon atom is disubstituted. In the case in hand, rhodium(II) mandelate-catalysed decomposition of (**38**) gave a higher yield of product (>90%) than did rhodium(II) trifluoroacetate. The NMR spectrum of the product showed immediately that it consisted of a single regioisomer, and the AB pattern for the two vinylic hydrogen atoms confirmed the direction of cyclisation as that resulting in trienone (**39**). Thus type a cyclisation had been fully restored, the ketocarbenoid

Table 1.

(a) Molecular dimensions for (**34**)

(i) Bond lengths (Å)

O(1)–C(1)	1.205(3)	C(5)–C(6)	1.529(4)
O(2)–C(1)	1.358(3)	C(5)–C(9)	1.554(4)
O(2)–C(12)	1.450(3)	C(6)–C(7)	1.508(4)
O(3)–C(8)	1.216(4)	C(7)–C(8)	1.505(5)
C(1)–C(2)	1.465(4)	C(8)–C(9)	1.533(3)
C(2)–C(3)	1.329(3)	C(9)–C(10)	1.551(4)
C(2)–C(13)	1.487(4)	C(9)–C(14)	1.546(4)
C(3)–C(4)	1.492(4)	C(10)–C(11)	1.534(3)
C(3)–C(12)	1.493(4)	C(10)–C(15)	1.523(4)
C(4)–C(5)	1.522(4)	C(11)–C(12)	1.518(4)

(ii) Bond lengths (°)

C(1)–O(2)–C(12)	109.2(2)	O(3)–C(8)–C(7)	123.5(2)
O(1)–C(1)–O(2)	121.1(3)	O(3)–C(8)–C(9)	125.7(3)
O(1)–C(1)–C(2)	129.8(3)	C(7)–C(8)–C(9)	110.8(2)
O(2)–C(1)–C(2)	109.1(2)	C(5)–C(9)–C(8)	100.4(2)
C(1)–C(2)–C(3)	107.8(2)	C(5)–C(9)–C(10)	113.6(2)
C(1)–C(2)–C(13)	122.4(2)	C(5)–C(9)–C(14)	112.0(2)
C(3)–C(2)–C(13)	129.8(3)	C(8)–C(9)–C(10)	111.7(2)
C(2)–C(3)–C(4)	128.0(3)	C(8)–C(9)–C(14)	106.5(2)
C(2)–C(3)–C(12)	110.1(2)	C(10)–C(9)–C(14)	111.9(2)
C(4)–C(3)–C(12)	121.9(2)	C(9)–C(10)–C(11)	114.5(2)
C(3)–C(4)–C(5)	115.6(3)	C(9)–C(10)–C(15)	114.3(3)
C(4)–C(5)–C(6)	111.9(2)	C(11)–C(10)–C(15)	107.2(2)
C(4)–C(5)–C(9)	117.7(2)	C(10)–C(11)–C(12)	116.8(2)
C(6)–C(5)–C(9)	105.1(2)	O(2)–C(12)–C(3)	103.8(2)
C(5)–C(6)–C(7)	105.0(3)	O(2)–C(12)–C(11)	108.7(2)
C(6)–C(7)–C(8)	105.3(2)	C(3)–C(12)–C(11)	115.3(3)

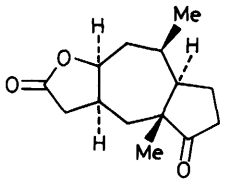
(b) Molecular dimensions for (**42**)

(i) Bond lengths (Å)

O(1)–C(1)	1.201(4)	C(4)–C(13)	1.528(5)
O(2)–C(1)	1.352(3)	C(5)–C(6)	1.533(4)
O(2)–C(12)	1.470(4)	C(5)–C(9)	1.541(3)
O(3)–C(8)	1.451(3)	C(6)–C(7)	1.538(4)
O(3)–C(15)	1.337(3)	C(7)–C(8)	1.527(4)
O(4)–C(15)	1.200(4)	C(8)–C(9)	1.533(4)
C(1)–C(2)	1.487(6)	C(9)–C(10)	1.525(4)
C(2)–C(3)	1.527(4)	C(9)–C(14)	1.529(4)
C(3)–C(4)	1.539(4)	C(10)–C(11)	1.531(4)
C(3)–C(12)	1.532(4)	C(11)–C(12)	1.514(4)
C(4)–C(5)	1.530(4)	C(15)–C(16)	1.484(4)

(ii) Bond angles (°)

C(1)–O(2)–C(12)	109.9(2)	O(3)–C(8)–C(7)	113.5(2)
C(8)–O(3)–C(15)	117.5(2)	O(3)–C(8)–C(9)	109.8(2)
O(1)–C(1)–O(2)	120.9(3)	C(7)–C(8)–C(9)	105.6(2)
O(1)–C(1)–C(2)	130.1(3)	C(5)–C(9)–C(8)	97.5(2)
O(2)–C(1)–C(2)	109.0(3)	C(5)–C(9)–C(10)	112.1(2)
C(1)–C(2)–C(3)	105.2(3)	C(5)–C(9)–C(14)	114.6(2)
C(2)–C(3)–C(4)	112.9(2)	C(8)–C(9)–C(10)	113.0(2)
C(2)–C(3)–C(12)	99.6(3)	C(8)–C(9)–C(14)	107.8(2)
C(4)–C(3)–C(12)	119.1(3)	C(10)–C(9)–C(14)	111.1(2)
C(3)–C(4)–C(5)	111.9(2)	C(9)–C(10)–C(11)	115.1(2)
C(3)–C(4)–C(13)	113.3(3)	C(10)–C(11)–C(12)	116.2(3)
C(5)–C(4)–C(13)	116.8(3)	O(2)–C(12)–C(3)	105.0(2)
C(4)–C(5)–C(6)	116.6(2)	O(2)–C(12)–C(11)	107.0(2)
C(4)–C(5)–C(9)	121.1(2)	C(3)–C(12)–C(11)	122.3(3)
C(6)–C(5)–C(9)	103.8(2)	O(3)–C(15)–O(4)	123.1(2)
C(5)–C(6)–C(7)	105.1(2)	O(3)–C(15)–C(16)	111.8(3)
C(6)–C(7)–C(8)	104.1(2)	O(4)–C(15)–C(16)	125.1(3)



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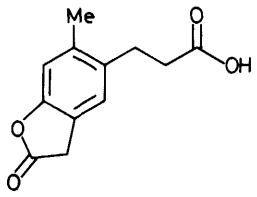

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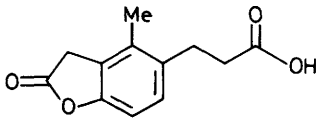

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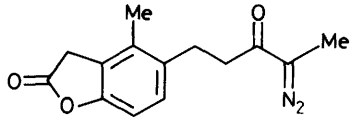

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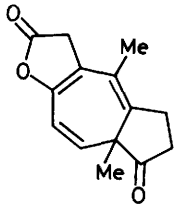
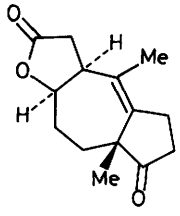
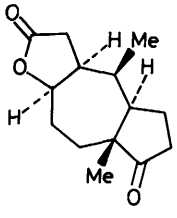


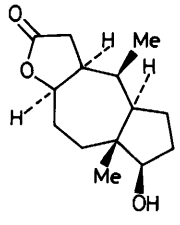
(39)



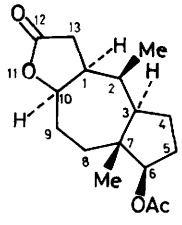
(40)



(41)



(41a)



(42)

attacking the aromatic ring at the bond away from the *ortho*-methyl group. This assignment could be confirmed as follows. Hydrogenation of (**39**) over palladium on charcoal at ambient pressure saturated two of the olefinic bonds, furnishing (**40**) in 33% yield. Exposure of (**40**) to more forcing hydrogenation conditions at 60 psi over rhodium on alumina produced a single fully saturated stereoisomer (**41**) in quantiative yield. Reduction of (**41**) with sodium borohydride furnished a lactone alcohol

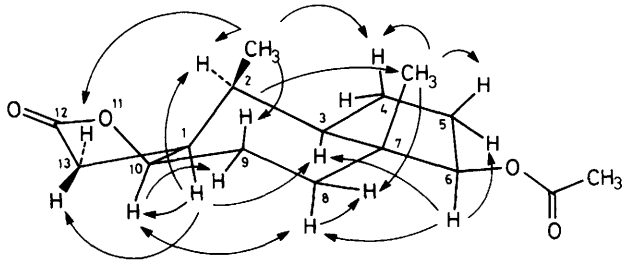


Figure 2. A representation of (**42**); arrows indicate protons showing significant NOE enhancements; weak enhancements: 8α-H–3α-H and 8α-H–1α-H.

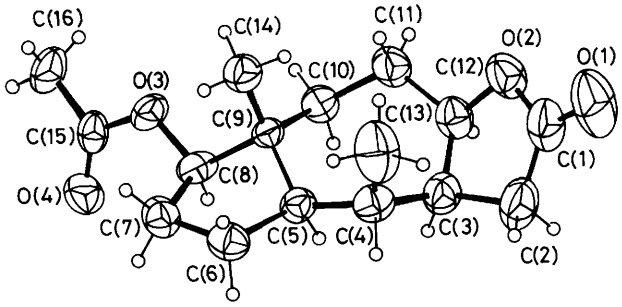


Figure 3. ORTEP[9] plot of (**42**) showing our numbering system.

(**41a**) which on acylation with acetic anhydride in pyridine produced a crystalline lactone acetate (**42**), m.p. 129–130 °C, whose structure and relative stereochemistry were elucidated by NMR analysis using two-dimensional homo (^{1}H,^{1}H) and heteronuclear (^{1}H,^{13}C) correlated spectroscopy (COSY) to determine atom connectivities. Stereochemical, structural, and signal assignments, including determination of the preferred conformation, were achieved by nuclear Overhauser enhancement (NOE) difference experiments (*cf.* Figure 2). This structure determination was later confirmed by single crystal X-ray diffraction analysis. Figure 3 shows the relative stereochemistry and crystallographic numbering system. The structure consists of discrete molecules separated by normal van der Waals distances. The lactone ring [C(1), C(2), C(3), C(12), O(2)] has a C(3) envelope conformation [C(3) 0.528 Å from the O(2), C(1), C(2), C(12) plane]. The seven-membered ring has a slightly distorted chair conformation with C(13) and C(14) methyl groups axial. The conformation of the seven-membered ring is defined by the interplanar angles [C(3), C(4), C(11), C(12)]/[C(4), C(5), C(10), C(11)] of 129.1° and [C(4), C(5), C(10), C(11)]/[C(5), C(9), C(10)] of 124.1°. The cyclopentane ring has a C(9) envelope conformation [C(9), 0.727(3) Å from the C(5)–C(8) plane]. The molecular dimensions (Table 1) are normal. This compound has, therefore, the sought after disposition of the C-5 and C-10 methyl groups, the correct stereochemistry of both lactone and cyclopentane ring systems, but the opposite regiochemistry with respect to that of a known pseudoguaianolide.

In conclusion, we have shown that the intramolecular catalysed Buchner reaction is applicable to polyfunctional hydroazulene systems including examples with fused γ-lactone rings.

Experimental

M.p.s were determined on a Thomas Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on an Hitachi Perkin-Elmer R-20 A spectrometer (60 MHz) or on a Bruker AM-400 spectrometer (400.1 MHz); ^{13}C NMR spectra were recorded on a JEOL FX-60 spectrometer (15 Mz) or on a Bruker AM-400 spectrometer (100.6 MHz) Standard Bruker

software was employed for the COSY and NOE difference experiments. Elemental analyses were performed by the Microanalytical Laboratory, University College, Cork. Merck PF_{254} silica gel was used for all forms of chromatography. Magnesium sulphate was employed as the drying agent.

Lactone Diazoketone (**14**) [*5-(4-Diazo-3-oxopentyl)benzofuran* 2(3H)-*one*].—A solution of oxaloyl chloride (5 ml) in dry ether (10 ml) was added dropwise to a solution of the phenolic diacid (**13**)[3] (1.68 g) in dry ether (50 ml). After 2 h a further quantity of oxaloyl chloride (4 ml) was added and the mixture was heated under reflux for 10 min. After 16 h at room temperature the solvent and residual reagent were removed under reduced pressure leaving the acyl chloride which was used without purification. Ethereal diazoethane was prepared from *N*-ethyl-*N*-nitrosourea (17 g). The ethereal solution was isolated by phase separation in a cold-jacketed separating funnel, dried over KOH pellets, and distilled. A solution of the acyl chloride in dry ether (24 ml) was added dropwise over 30 min to the ethereal diazoethane at −30 °C with stirring. After stirring for 7 h the solvent and residual diazoethane were removed at *ca.* 10 °C using a rotatory evaporator fitted with an acetic acid trap. Purification of the residue by chromatography over silica gel (dichloromethane) afforded (**14**) as a yellow oil (0.6 g, 33%); ν_{max} 2 065, 1 805, and 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 1.97 (3 H, s, Me), 2.83 (4 H, m, CH_2CH_2), 3.70 (2 H, s, CH_2), and 7.12 (3 H, m, ArH).

Rhodium-catalysed Decomposition of the Diazoketone (**14**).—A solution of the diazoketone (**14**) (0.2 g) in dichloromethane (15 ml) was added dropwise during 2–3 h to a stirred refluxing solution of rhodium(II) trifluoroacetate (2 mg) in dichloromethane (170 ml) containing anhydrous sodium carbonate (40 mg). Similar amounts of catalyst were added in four instalments at regular intervals throughout the addition period. Reaction was complete within about 5 min of ending the addition. The cooled mixture was filtered, washed with water (2 × 50 ml), and dried. Removal of solvent under reduced pressure left a brown oil which was estimated by NMR spectroscopy to contain 75% of a mixture of (**16**) and (**15**) in a *ca.* 70:30 ratio (from integration of the methyl singlets at δ 0.99 and 1.02). This mixture of products was used directly in the next experiments.

Formation of the Tetralones (**17**) *and* (**18**) *from the Diazoketone* (**14**).—The crude product obtained above from catalysed decomposition of (**14**) was dissolved in dry dichloromethane (50 ml) and treated with trifluoroacetic acid (0.3 ml). The mixture was stirred at room temperature for 12 h and then was shaken successively with water (50 ml), 2% aqueous sodium hydrogen carbonate (2 × 50 ml), and water (2 × 50 ml). The dried solution was concentrated to a brown oil (0.18 g), a 100 mg portion of which was purified by PLC (dichloromethane) to yield a yellow crystalline solid [0.05 g, 51% yield based on the diazoketone (**14**)]. Recrystallisation from acetone–hexane gave the *tetralone* (**17**), m.p. 128–129 °C (Found: C, 71.9; H, 5.6. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.6%); ν_{max}(film) 1 810 and 1 715 cm^{-1}; $\delta_H(CDCl_3)$ 1.50 (3 H, d, Me), 2.55 (2 H, t, CH_2), 3.09 (2 H, t, CH_2), 3.54 (1 H, q, CH), 3.74 (2 H, s, 2 H), 7.00 (1 H, s, ArH), and 7.20 (1 H, s, ArH). The minor isomer, tetralone (**18**), was not isolated.

Lactone Diazoketone (**24**) [*5-(4-Diazo-3-oxopentyl)-3,6-dimethyl-3-phenylthiobenzofuran*-2(3H)-*one*.—A solution of lactone acid (**22**)[3] (1 g) in dry ether (60 ml) was treated with oxaloyl chloride (5 ml) and the mixture was stirred under nitrogen for 18 h. The solvent and residual reagent were removed at reduced pressure to afford the crude acid chloride which was treated with ethereal diazoethane (from 10.5 g of *N*-ethyl-*N*-nitrosourea) as described above for the diazoketone (**14**). After stirring for 16 h the solvent and residual diazoethane were removed and the crude product was purified by PLC (dichloromethane) to afford diazoketone (**24**) as an oil (0.65 g, 67%); ν_{max} 2 070, 1 808, and 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 1.74 (3 H, s, Me), 1.96 (3 H, s, Me), 2.26 (3 H, s, Me), 2.84 (4 H, m, CH_2CH_2), 6.73 (1 H, s, ArH), 7.17 (1 H, s, ArH), and 7.28 (5 H, s, ArH).

Lactone Diazoketone (**25**) [*3-Butylthio-5-(4-diazo-3-oxopentyl)-3,6-dimethylbenzofuran*-2(3H)-*one*].—A solution of lactone acid (**23**)[3] (0.934 g) in dry ether (20 ml) was treated with oxaloyl chloride (6 ml) and the mixture was stirred at room temperature under nitrogen for 3.5 h. Removal of solvent and residual reagent afforded the crude acyl chloride which was treated with ethereal diazoethane (from 10.5 g of *N*-ethyl-*N*-nitrosourea) as described above. After 3 h the mixture was concentrated at 10 °C, and the residue was purified by PLC (dichloromethane) to afford the diazoketone (**25**) as an oil (0.463 g, 44%); ν_{max} 2 065, 1 803, and 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 0.88 (3 H, m, Me), 1.40 (4 H, m, CH_2CH_2), 1.73 (3 H, s, Me), 1.98 (3 H, s, Me), 2.37 (3 H, s, Me), 2.44 (2 H, m, CH_2), 2.94 (4 H, m, CH_2CH_2), 6.98 (1 H, s, ArH), and 7.15 (1 H, s, ArH).

Rhodium(II)*-catalysed Decomposition of* (**24**).—A solution of the diazoketone (**24**) (0.071 g) in dry dichloromethane (5 ml) was added during 50 min to a refluxing solution of rhodium(II) trifluoroacetate (5 mg) in dichloromethane (50 ml). The cooled reaction mixture was processed as described above for decomposition of (**14**), yielding an oil whose ^1H NMR spectrum indicated a 25% content of the target trienone with 75% of an aromatic entity. The crude product (0.25 g) from several small scale decompositions of (**24**) was purified by PLC (30% ethyl acetate in hexane) to afford a clear oil (0.092 g) which was estimated by NMR spectroscopy to contain *ca.* 35% of the trienone. TLC analysis (using the above solvent system) indicated that this oil contained two components of R_F 0.30 and 0.25. The minor component of R_F 0.30 was isolated following a second PLC separation, affording trienone (**26**) as an oil (0.019 g); ν_{max}(film) 1 790, 1 740, and 1 620 cm^{-1}; $\delta_H(CDCl_3)$ 0.88 (3 H, s, Me), 1.59 (3 H, s, Me), 1.83 (3 H, s, Me), 3.10–2.20 (4 H, m, CH_2CH_2), 5.82br (1 H, s, vinyl), 6.58br (1 H, s, vinyl), and 7.37 (5 H, m, ArH); $\delta_C(CDCl_3)$ 218.50 (CO), 176.59 (OCO), 148.33, 138.26, 138.00, 136.38, 130.01, 129.49, 128.84, 119.87, 114.35, 114.03, 56.20, 53.86, 37.94, 27.16, 22.03, 21.38, and 15.66

Rhodium(II)*-catalysed Decomposition of* (**25**).—A solution of diazoketone (**25**) (0.08 g) in dichloromethane (15 ml) was added during 1 h to dichloromethane (150 ml) containing rhodium(II) trifluoroacetate (0.003 g × 3) under reflux. The cooled reaction mixture was processed as described above for decomposition of (**14**), yielding an oil whose ^1H NMR spectrum indicated a 40% content of trienone (**28**) with about 60% of an aromatic entity. A portion of the crude product was purified by chromatography (PLC, silica) to afford (**28**) as a yellow oil (50% recovery); ν_{max}(film) 1 798 and 1 748 cm^{-1}; $\delta_H(CDCl_3)$ 0.94 (s, 3 H), 0.75–1.10 (m, 3 H), 1.57 (s, 3 H), 1.20–1.80 (m, 4 H), 1.95 (s, 3 H), 3.10–2.30 (m, 6 H), 6.25 (s, 1 H), and 6.41 (s, 1 H); $\delta_C(CDCl_3)$ 218.50, 177.77, 148.14, 138.39, 138.14, 120.39, 114.22 (d), 114.03 (d), 53.99, 51.72, 37.94, 30.93, 30.00, 29.37, 27.16, 22.22, 22.09, 15.72, and 13.58; *m/z* (%) 276.1 (1), 259.1 (3), 143.1 (100), 228.1 (17), 215.1 (73), 201.1 (41), 173.1 (6), 144.1 (4), 115.1 (7), 105.1 (3), 91.1 (6), 77.0 (3), 57.1 (6), and 47.0 (3).

Lactone Diazoketone (**31**) [*5-(4-Diazo-3-oxopentyl)-3,6-dimethylbenzofuran*-2(3H)-*one*].—Ester lactone (**30**)[3] (1.68 g) was saponified with aqueous sodium hydroxide and an ethereal solution of the resulting diacid phenol was treated with oxaloyl chloride (5 ml) following which the mixture was stirred at room temperature for 3.5 h. The solvent and residual reagent were

removed and the residue treated with ethereal diazoethane (from 17 g of *N*-ethyl-*N*-nitrosourea) as described above. After 4 h the mixture was concentrated at 10 °C and the residue was purified by chromatography (dichloromethane) to afford diazoketone (**31**) as a yellow solid (81%); ν_{max} 2 070, 1 805, and 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 1.54 (3 H, d, Me), 1.97 (3 H, s, Me), 2.34 (3 H, s, Me), 2.90 (4 H, m, CH_2CH_2), 3.65 (1 H, q, CH), 6.94 (1 H, s, ArH), and 7.07 (1 H, s, ArH).

Rhodium(II)*-catalysed Decomposition of the Diazoketone* (**31**).—A solution of the diazoketone (**31**) (0.63 g) in dichloromethane (20 ml) was added during 1 h to a stirred mixture of rhodium(II) trifluoroacetate (3 × 7 mg) and sodium carbonate (0.08 g) in dichloromethane (500 ml) under reflux under nitrogen. The cooled reaction mixture was filtered and concentrated to an oil whose NMR spectrum indicated the presence of *ca.* 60% of the trienones (**32**) and (**33**). The experiment was repeated on a 0.45 g sample of the diazoketone and the crude products of both runs were combined and hydrogenated as described below.

Hydrogenation of the Trienones (**32**) *and* (**33**).—The crude mixture of (**32**) and (**33**) from the previous experiment was hydrogenated in ethanol (60 ml) over Adam's catalyst (0.08 g) at 25 psi for 15 h. Removal of the catalyst followed by concentration of the filtrate yielded a product whose NMR spectrum indicated the presence of vinylic hydrogen resonances. The hydrogenation was repeated at 30 psi for 20 h after which time the NMR spectrum showed no remaining vinylic hydrogen signals. Tlc analysis (30% ethyl acetate in hexane) revealed the presence of four components of R_F 0.05 (major), 0.15, 0.25, and 0.45. A portion of the crude product (0.850 g) was chromatographed using the above solvent system as eluant, revealing that the fraction of R_F 0.05 was in fact two components of R_F 0.03 (0.13 g, 15%) and 0.07 (0.16 g, 19%) (both yields are based on the diazoketone precursor). A portion of the R_F 0.03 component (0.105 g) was further purified by PLC using 30% ethyl acetate in hexane to yield a clear oil which rapidly crystallised on standing at room temperature. Recrystallisation from acetone–hexane gave crystals of (**34**) (0.025 g), m.p. 160–164 °C; *m/z* 248.1 (M^+); ν_{max}(KBr) 1 746 and 1 732 cm^{-1}; $\delta_H(CDCl_3)$ 0.79 (s, 3 H, Me), 1.23 (d, 1 H, *J* 7 Hz, Me), 1.36 (dt, 1 H, *J* 14, 12 Hz), 1.58 (m, 1 H), 1.80br (s, 3 H, CH_3), 1.86 (m, 1 H), 2.05 (m, 1 H), 2.15–2.78 (m, 6 H), and 4.92 (dq, 1 H, *J* 12, 1.5 Hz); $\delta_C(CDCl_3)$ 220.80, 162.53, 122.29, 81.48, 51.63, 43.97, 39.34, 37.98, 27.95, 26.01, 16.72, 9.36, and 8.53.

Lactone Diazoketone (**38**) [*5-(4-Diazo-3-oxopentyl)-4-methylbenzofuran-2*(3H)*-one*].—A mixture of lactone acid (**37**)[3] (0.513 g) and thionyl chloride (2 ml) was heated under reflux for 10 min under nitrogen. A further amount of thionyl chloride (2 ml) and dichloromethane (2 ml) were added and heating was continued for 1 h. The reaction solution was then allowed to stand at room temperature until immediately prior to reaction of the acyl chloride with diazoethane. Ethereal diazoethane was prepared as described above from *N*-ethyl-*N*-nitrosourea (5.6 g). A solution of the acyl chloride (obtained as an oil upon removal of residual thionyl chloride and solvent) in ether (6 ml) was added dropwise over 10 min under nitrogen to the diazoethane solution at −10 °C. After 1–5 h the solvent and residual diazoethane were removed under reduced pressure and the residue was purified by chromatography using dichloromethane to afford the diazoketone (**38**) as a yellow solid (0.473 g, 79%), m.p. 94–95 °C; $\delta_H(CDCl_3)$, 1.97 (3 H, s, Me), 2.25 (3 H, s, Me), 2.40–3.15 (4 H, m, CH_2CH_2), 3.57 (2 H, s, CH_2), and 6.90 (2 H, q, ArH).

Rhodium(II)*-catalysed Decomposition of the Diazoketone* (**38**).—A solution of the diazoketone (**38**) (45 mg) in dichloromethane (20 ml) was added dropwise with stirring to a solution of rhodium(II) mandelate (1.5 mg) in dichloromethane (90 ml) over 25 min under reflux. The cooled solution was concentrated to an oil whose ^1H NMR spectrum indicated the presence of *ca.* 95% of trienone (**39**); $\delta_H(CDCl_3)$ 0.90 (3 H, s, Me), 1.92 (3 H, s, Me), 2.00–3.00 (4 H, m, CH_2CH_2), 3.48 (2 H, s, CH_2), 5.05 (1 H, d, *J* 11 Hz, vinylic), and 6.11 (1 H, d, *J* 11 Hz, vinylic). The cyclisation was repeated on a 133 mg sample of (**38**), and the products of both reactions were combined and hydrogenated as described below.

Hydrogenation of the Trienone (**39**).—The crude sample of (**39**) was hydrogenated in 50:50 ethanol–ethyl acetate (8 ml) over 10% palladium on carbon at ambient pressure for 18 h. After removal of the catalyst and concentration of the solution, an oil (186 mg) was obtained which was taken up in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate to afford a product (145 mg). Column chromatography using dichloromethane as the eluant afforded *2,7-dimethyl-11-oxatricyclo*[8.3.0.$0^{3,7}$]*tridec-2-en-6,12-dione* (**40**) as a colourless solid (53 mg, 33%), m.p. 130–131 °C (Found: C, 71.4; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); $\nu_{max.}$(film) 1 775 and 1 734 cm^{-1}; $\delta_H(CDCl_3)$ 0.81 (s, 3 H, Me), 1.72br (s, 3 H, Me), 1.30–3.00 (m, 9 H), 3.27 (m, 2 H, Me), and 5.06 (m, 1 H); $\delta_C(CDCl_3)$ 221.17, 174.91, 130.08, 129.36, 84.01, 49.12, 47.11, 36.32, 33.98, 32.88, 26.83, 22.09, 18.65, and 14.10.

The unsaturated lactone (**40**) (50 mg) in ethyl acetate (4 ml) containing 5% rhodium on alumina (20 mg) was subjected to further hydrogenation for 12 h. Removal of the catalyst and solvent afforded (**41**) as an oil which slowly crystallised on standing at room temperature. The ^1H NMR spectrum of (**41**) contained a 3-proton doublet at δ 1.10, indicating the removal of the remaining double bond in (**40**). The crude product was dissolved in benzene (3 ml) containing methanol (1 ml) and sodium borohydride (2 equiv.) was added portionwise with stirring during 15 min. After an additional 1 h at room temperature, the solution was poured into aqueous ammonium chloride. The organic layer and ethyl acetate extracts of the aqueous layer were washed with brine, then dried and concentrated. Chromatography of the residue with 30% ether in hexane as the eluant gave the desired alcohol (**41a**) (35 mg) as colourless crystals, m.p. 135–136 °C; ν_{max}(KBr) 2 430 and 1 775 cm^{-1}; $\delta_H(CDCl_3)$ 0.94 (s, 3 H), 1.06 (d, 3 H, *J* 8 Hz), 1.23–1.88 (m, 8 H), 1.92–2.18 (m, 2 H), 2.27 (m, 1 H), 2.35 (dd, 1 H, *J* 17, 2 Hz), 2.66 (m, 1 H), 2.81 (dd, 1 H, *J* 17 and 10 Hz), 3.59 (t, 1 H, *J* 9 Hz), 4.72 (dt, 1 H, *J* 11, 7 Hz); $\delta_C(CDCl_3)$ 11.56, 11.95, 24.82, 26.12, 29.63, 32.88, 35.35, 38.59, 44.12, 51.98, 81.80, and 84.21 (quaternary C atoms omitted). A portion of the product (14 mg) was dissolved in pyridine (2 ml) and acetic anhydride (2 ml) was added under nitrogen. After 12 h at room temperature the reaction mixture was poured on ice and the product was extracted into ethyl acetate. The extract was washed with brine, then dried and concentrated. Crystallisation of the residue from ether–hexane afforded the *lactone acetate* (**42**) as large chunky crystals, m.p. 129–130 °C. The structural assignment was made on the basis of the 400 MHz NMR analysis (see Discussion) and confirmed by X-ray diffraction (Found: C, 68.9; H, 8.7. $C_{16}H_{24}O_4$ requires C, 68.6; H, 8.6%); ν_{max}(KBr) 1 772 and 1 725 cm^{-1}; $\delta_H(CDCl_3)$ 0.98 (s, 3 H, 7-Me), 1.05 (d, 3 H, 2-Me, *J* 7.7 Hz), 1.14 (t, 1 H, 8α-H, *J* 14 Hz), 1.48 (m, 5β-H), 1.50 (m, 4α-H), 1.52 (m, 3α-H), 1.70 (dd, 8β-H, *J* 14, 8 Hz), 1.77 (m, 4β-H), 1.83 (m, 2α-H), 1.97 (m, 9β-H), 2.02 (s, 3 H, Ac), 2.17 (m, 5α-H), 2.23 (m, 9α-H), 2.33 (dd, 13β-H, *J* 17.7, 2 Hz), 2.64 (m, 1α-H), 2.80 (dd, 13α-H, *J* 17.7, 9.8 Hz), 4.57 (t, 6α-H, *J* 9 Hz), and 4.70 (dt, 10α-H, *J* 10.8, 7 Hz); $\delta_C(CDCl_3)$ 11.4 (C-2- *Me*), 13.0 (C-7-*Me*), 21.1 (Ac), 25.0 (C-4), 25.9 (C-9), 26.6 (C-5), 32.7 (C-8), 35.3 (C-13), 38.4 (C-2), 44.0 (C-1), 46.1 (C-7), 51.7 (C-3), 82.1 (C-6), 83.9 (C-10), 171.0 (Ac), and 176.7 (C-12).

Table 2. Fractional atomic co-ordinates for the non-hydrogen atoms, with e.s.d.s in parentheses.

(a) Compound (**34**)

Atom	*x/a*	*y/b*	*z/c*
O(1)	−0.671 2(2)	0.087 7(2)	0.547 5(2)
O(2)	−0.487 8(2)	0.028 4(2)	0.702 0(2)
O(3)	0.273 6(3)	−0.093 0(2)	0.964 2(2)
C(1)	−0.532 3(3)	0.083 3(2)	0.603 0(2)
C(2)	−0.389 1(3)	0.130 8(2)	0.581 7(2)
C(3)	−0.263 0(3)	0.105 4(2)	0.668 0(2)
C(4)	−0.091 1(4)	0.135 6(2)	0.685 6(3)
C(5)	0.025 5(3)	0.097 0(2)	0.796 0(2)
C(6)	0.191 3(4)	0.147 2(3)	0.817 4(3)
C(7)	0.301 5(4)	0.082 0(3)	0.908 8(3)
C(8)	0.219 6(3)	−0.021 0(2)	0.901 2(2)
C(9)	0.059 2(3)	−0.020 5(2)	0.807 4(2)
C(10)	−0.072 6(3)	−0.082 4(2)	0.843 8(2)
C(11)	−0.242 7(3)	−0.070 7(2)	0.762 9(2)
C(12)	−0.314 9(3)	0.036 7(2)	0.750 2(2)
C(13)	−0.396 8(4)	0.194 3(2)	0.478 2(3)
C(14)	0.094 2(4)	−0.065 8(2)	0.698 6(2)
C(15)	−0.038 5(4)	−0.197 3(3)	0.859 3(3)

(b) Compound (**42**)

Atom	*x/a*	*y/b*	*z/c*
O(1)	0.541 6(2)	0.670 7(5)	0.589 5(1)
O(2)	0.367 6(2)	0.580 3(4)	0.544 7(1)
O(3)	−0.054 1(1)	0.139 3(3)	0.626 4(1)
O(4)	−0.120 2(2)	−0.196 5(4)	0.629 9(1)
C(1)	0.472 7(2)	0.531 9(6)	0.578 4(2)
C(2)	0.482 1(2)	0.294 2(7)	0.595 2(2)
C(3)	0.367 4(2)	0.221 1(5)	0.592 0(2)
C(4)	0.348 3(2)	0.216 1(5)	0.666 6(1)
C(5)	0.239 3(2)	0.110 9(5)	0.663 7(1)
C(6)	0.226 6(2)	0.028 3(5)	0.735 3(2)
C(7)	0.104 5(2)	−0.017 0(5)	0.720 0(1)
C(8)	0.055 1(2)	0.052 6(5)	0.641 6(1)
C(9)	0.131 2(2)	0.229 1(4)	0.628 0(1)
C(10)	0.114 4(2)	0.271 8(5)	0.548 1(1)
C(11)	0.187 3(2)	0.449 5(5)	0.531 5(2)
C(12)	0.301 5(2)	0.380 4(5)	0.534 9(1)
C(13)	0.375 7(2)	0.432 0(6)	0.707 6(2)
C(14)	0.113 5(2)	0.437 4(5)	0.666 6(2)
C(15)	−0.134 3(2)	−0.002 8(5)	0.623 0(1)
C(16)	−0.240 8(2)	0.108 6(6)	0.609 4(2)

X-Ray Diffraction Analysis.—Crystal data. (**34**), $C_{15}H_{20}O_3$, M = 248.3. Monoclinic, a = 8.625(2), b = 12.993(4), c = 12.109(2) Å, β = 105.79(1)°, U = 1 305.9(9) Å^3, Z = 4, D_c = 1.26 g cm^{-3}, $F(000)$ = 536. Mo-K_α radiation, λ = 0.710 73 Å, μ(Mo-K_α) = 0.8 cm^{-1}. Space group $P2_1/a$ uniquely from the systematic absences ($h0l$ absent if $h = 2n + 1$, $0k0$ absent if $k = 2n + 1$). A colourless prism of dimensions 0.13 × 0.38 × 0.58 mm was used for the analysis.

Crystal data. (**42**), $C_{16}H_{24}O_4$, M = 280.4. Monoclinic, a = 12.885(2), b = 6.115(4), c = 19.417(4) Å, β = 107.14(1)°, U = 1 462(1) Å^3, Z = 4, D_c = 1.27 g cm^{-3}, $F(000)$ = 608. Mo-K_α radiation, λ = 0.710 73 Å, μ(Mo-K_α) = 0.8 cm^{-1}. Space group $P2_1/c$ uniquely from the systematic absences ($h0l$ absent if $l = 2n + 1$, $0k0$ absent if $k = 2n + 1$). A colourless small block crystal of dimensions 0.2 × 0.2 × 0.2 mm was used for the analysis.

* Hydrogen atom co-ordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. For details, see section 5.6.3. Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

Data collection, analysis, and refinement. Structures (**34**) and (**42**) were analysed in a similar fashion. In what follows, data for (**34**) are given first with those for (**42**) in parentheses. Accurate cell data and crystal orientation matrix were determined on a CAD-4 diffractometer by a least-squares treatment of the setting angles of 25(25) reflections in the range $9 < \theta < 15°$ ($8 < \theta < 12°$). Intensities of reflections with $2 < 2\theta < 52°$ ($2 < 2\theta < 50°$) were measured by the $\omega/2\theta$ scan technique [ω scan width (0.70 × 0.35 tanθ)] using graphite monochromatized Mo-K_α radiation. There was no evidence of crystal decay during the course of the data collection. 2 450 (2 403) Unique reflections were measured; 1 405 (1 370) reflections with $I > 3\sigma(I)$ were labelled 'observed', and used in structure solution and refinement after correction for Lorentz and polarisation factors.

The structures were solved with the aid of MULTAN-82[6] which revealed all non-hydrogen atoms. Refinement was by full-matrix least-squares calculations, initially with isotropic and then with anisotropic thermal parameters. At an intermediate stage of the refinement, difference maps showed maxima in positions consistent with the expected locations of the hydrogen atoms; in the final round of calculations the hydrogen atoms were positioned on geometrical grounds (C–H 0.95 Å), and included (as riding atoms) in the structure factor calculations with an overall B(iso) of 5.0 Å^2. At convergence, the maximum shift/error ratio was <0.005 (0.005) with R = 0.047 (0.045) and R_w = 0.062 (0.056). Weights were derived from the counting statistics [$w = 1/\sigma^2F_o + 0.040(F_o)^2$], and scattering factors were taken from International Tables for X-ray Crystallography.[7] All calculations were performed on a PDP11/73 computer using SDP-Plus.[8] Details of molecular geometry are in Tables 1(a) and 1(b), and atomic co-ordinates are in Tables 2(a) and 2(b).* Final difference maps had maxima ±0.23 (0.23) e Å^{-3}, and were devoid of chemically significant features.

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