Tetrahedron. Vol. 29, pp. 403 to 412. Pergamon Press 1973. Printed in Great Britain

STRUCTURE AND STEREOCHEMISTRY OF BERTYADIONOL

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(*Received in the UK* 11 *September* 1972; *Accepted for publication* 29 *September* 1972)

Abstract—The structure of bertyadionol, a member of a new class of diterpenes, has been elucidated by chemical and physical methods. The absolute configuration of the cyclopropane ring was determined by degradation of bertyadionol to (−)-*cis*-homocaronic acid dimethyl ester. Application of Nuclear Magnetic Double Resonance techniques, INDOR and NOE measurements, allowed the determination of the absolute stereochemistry of two of its derivatives.

INTRODUCTION

In recent years a number of novel diterpenes have been isolated from members of the plant family Euphorbiaceae and the closely related Thymelaeaceae. These diterpenes can be conveniently divided into two classes: the phorbols, containing phorbol (**1**)[1] and related diterpenes;[2] and a macrocyclic group which includes epoxylathyrol (**2**),[3] bertyadionol (**3**),[4] and jatrophone (**4**).[5] In considering these diterpenes some features are noteworthy: bertyadionol (**3**) and epoxylathyrol (**2**) can formally be related to the phorbols by assuming intraannular cyclization between C-8 and the CO of the α,β-unsaturated ketone. The isolation[6] of the macrocyclic diterpene hydrocarbon casbene (**5**) provides some indication for the possible biosynthesis of these diterpenes.

Casbene (**5**) arises as a cyclization product of geranylgeranyl pyrophosphate with an enzyme preparation from *Ricinus communis* (Euphorbiaceae). Although the structure and stereochemistry of casbene remains to be fully defined it is tempting to imply **5** as the possible precursor of both the phorbols and the macrocyclic group of diterpenes. The naturally occurring esters of epoxylathyrol (**2**) and lathyrol are not physiologically active, unlike their counterparts in the phorbol series which show co-carcinogenic and irritant properties.[7] Jatrophone (**4**) however has been shown to have significant tumor inhibiting activity.[5] Finally, the novel structure of these diterpenes is reflected in the fact that the majority of these structures were initially resolved by X-ray crystallography. One exception is bertyadionol (**3**) and in this communication we report results of the structural elucidation of **3** and the determination of the absolute stereochemistry of two of its derivatives. A preliminary report on its structure has appeared elsewhere.[4*] The occurrence of bertyadionol (**3**) in *Bertya cuppressoidea*† represents the first diterpene of its kind to be isolated from the Euphorbiaceae sub-family Ricinocarpoideae. Only one other *Bertya* species, *B. dimerostigma*, has previously been examined, affording a flavone.[8]

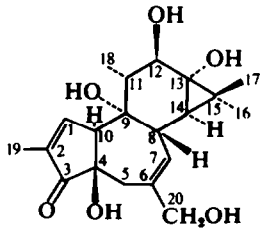
RESULTS AND DISCUSSION

An ethereal solution of the neutral residues of *Bertya cuppressoidea* deposited crystals of a diterpene for which the name bertyadionol is proposed. Bertyadionol (**3**), $C_{20}H_{26}O_3$, m.p. 159–160° was characterised as a monoacetate (**6**) and a dioxime, thus identifying the oxygen functions as an alcohol and two CO groups. The IR spectrum of **3** showed OH absorption at 3610 cm^{-1}, and CO bands at 1710 and 1665 cm^{-1}, the latter indicating extensive conjugation. The presence of a conjugated system was also evidenced by the UV spectrum with maxima at 220 nm (ϵ 10,600), 263 nm (9,200) and 332 nm (3,400).

From the NMR spectrum ($CDCl_3$) of **3** it was evident that bertyadionol contained two tertiary Me's (singlets at δ 1·11 and 1·18), a secondary Me (δ 1·22, d, J = 6·5 Hz), two vinyl Me's (δ 1·47 and 1·81, each a d., $J \sim$ 1·5, 1·2 Hz) and two vinyl protons which appeared as a broad singlet (δ 5·95) superimposed upon a broadened doublet (J = 10 Hz). A four line signal at δ 4·25 was indicative of

*In the previous communication[4] the numbering system used for bertyadionol was the same as that for epoxylathyrol. In turn this was adopted from the numbering system used for phorbol, reflecting the probable biogenetic relationship between the two. Whilst accepting this approach we feel that, in view of the increasing number of diterpenes belonging to this class a more logical and independent numbering system is required. In the present communication we have therefore adopted and extended for bertyadionol that used for jatrophone (See structures **3** and **4**).

†Previously[4] referred to as *Bertya sp. nov.* This species has now been classified: H. K. Airy Shaw, *Kew Bulletin* **20**, 67 1971 (No. 1), Royal Botanic Gardens, Kew, London.



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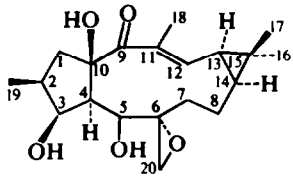

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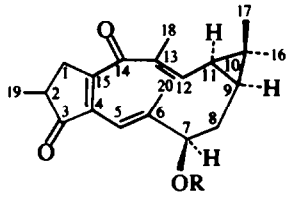

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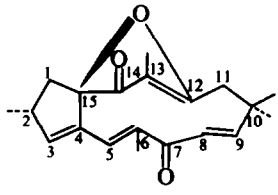

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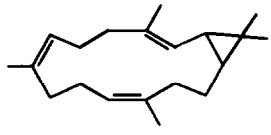

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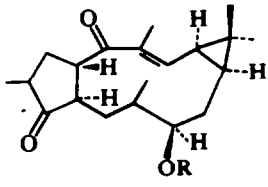

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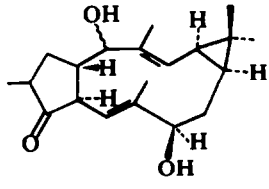

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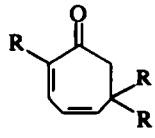

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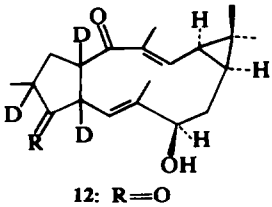

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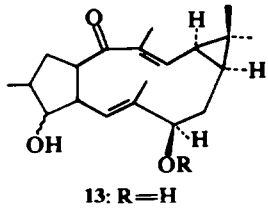
15: R= 



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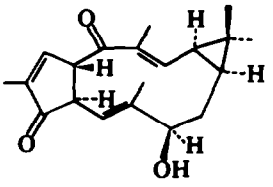

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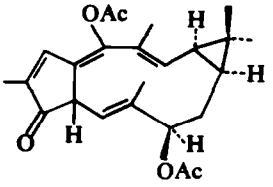

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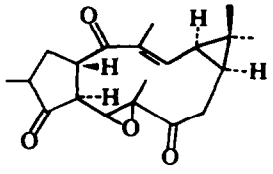

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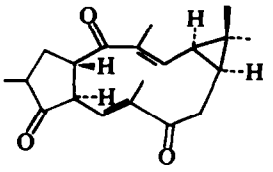

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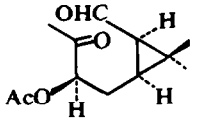

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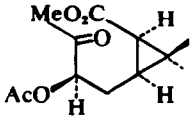

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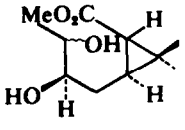

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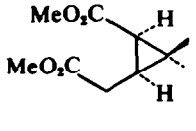
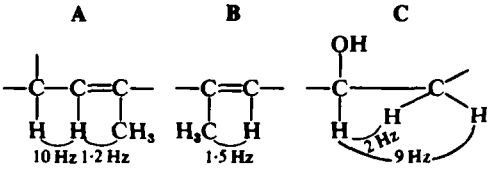


23

a secondary carbinol methine proton and confirmation was obtained from the spectrum of the acetate (**6**), where the signal appeared at δ 5·20.

On the basis of double irradiation experiments on bertyadionol (**3**) in pyridine solution the partial structures *A*, *B* and *C* were proposed.



δ(C_5D_5N):	1·6*	6·15	1·89	1·68	6·20	4·48	2·4*	2·0*
δ($CDCl_3$):		5·98	1·81	1·47	5·95	4·25		

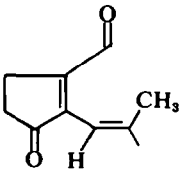
Zinc reduction of bertyadionol (**3**) gave products which were dependent on the reaction conditions. With zinc dust and sodium acetate in acetic anhydride at 100°, smooth conversion to the dihydrodiketo acetate (**7**) occurred, while with zinc dust in acetic acid at room temperature the corresponding alcohol (**8**) was the major product; co-occurring with approximately 25% of the isomeric diol (**9**). The IR spectrum of the dihydrodiketo alcohol (**8**) showed OH absorption at 3600 cm^{-1}, while bands at 1735 and 1650 cm^{-1} were indicative of a cyclopentanone and a doubly conjugated ketone respectively. The presence of a cyclopentanone inferred a cyclopentenone as part of the structure of bertyadionol. Reduction of the enedione system results in only one major chromophore in **7** (λ_{max} 275 nm; ε 15,800), assigned to the cyclopropyl vinyl ketone system. Although the 332 nm absorption in the UV spectrum of bertyadionol (**3**) is in the right region for a CO $n \rightarrow \pi^*$ transition it has an extremely high intensity for this type of transition, and it seems likely that the band is due to an electron transfer transition of an extensively conjugated ketone. Since this absorption disappears on reduction to **7** the UV spectrum of **3** is best interpreted as resulting from the homo-annular dienone system (C-14 carbonyl + 4,15- and 5,6-double bonds). Eucarvone (**10**) and the cyclopheptadienone (**11**) exhibit UV maxima at 303 nm (ε 6,300) and 292 nm (ε 6,200) respectively.[9] Addition of the required alkylation increments to these systems

*Values obtained from decoupling; approximate only.

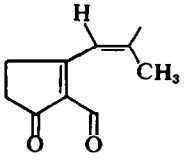
results in an approximate calculated value for bertyadionol of 333 nm, while the low extinction coefficient of the lowest energy UV band in the diterpene may be caused by twisting of the 5,6-double bond away from planarity with the α,β-unsaturated ketone. The 263 nm maximum of bertyadionol may be due to a displaced absorption from either the cross-conjugated 1,4-enedione system, the cross-conjugated cyclopropyl-vinyl-ketone or a contribution from the $\Delta^{4(15)}$-14-carbonyl chromophore.

The NMR spectrum (90 MHz, $CDCl_3$) of the dihydrodiketo acetate (**7**) indicated that both tertiary Me and both vinyl Me groups had been retained, with substantially the same chemical shifts as in **3**, while the acetate Me and its associated methine proton gave rise to signals at δ 2·01 and 4·87 respectively. Two vinyl resonances occurred, both as doublets of quartets at δ 6·09 ($J = 1{\cdot}2$ and 11·3 Hz) and 5·40 ($J = 1{\cdot}5$ and 10·2 Hz). A triplet at δ 2·66 ($J = 10{\cdot}4$ Hz) was shown by decoupling to be associated with the δ 5·40 signal. The more deshielded vinyl proton of **7** was coupled to a high field proton ($\delta \sim 1{\cdot}4$) and also to the more deshielded (δ 1·87, $J = 1{\cdot}2$ Hz) of the two vinyl Me signals indicating that it corresponded to the vinyl doublet of bertyadionol. Thus the other vinyl proton of bertyadionol was present in **7** at δ 5·40 with a large coupling to the triplet at δ 2·66 (4-H), suggesting that the vinyl proton was now coupled to a proton introduced by reduction of a tetrasubstituted double bond. The shielding (0·55 ppm) relative to bertyadionol of the newly coupled vinyl proton was consistent with the loss of a double bond which was conjugated with the 5,6-double bond of bertyadionol.

Taking into account the spectral data of **3**, **7** and **8**, it is possible, starting from a conjugated ketone, to include this ketone in a 5-membered ring, and to infer the relationship of this cyclopentenone with partial structure **A**. The two possible resultant structures, **D** and **E**, may be distinguished by consideration of the reduction of bertyadionol **3** to **8**.



D



E

Whereas reduction of α,β-unsaturated ketones and dienones require[10] excess zinc and long reaction time at elevated temperatures 1,4-enediones are known[11] to reduce rapidly under mild conditions. Bertyadionol is reduced in less than ten minutes and this is good evidence for the enedione system shown in partial structure **D**. Under these conditions it is unlikely that either the homo- or heteroannular dienone components in the alternative **E** would reduce.[12]

Rather unexpectedly, chromous acetate/acetic acid reduction of bertyadionol (**3**) resulted in a 90% yield of the previously obtained diol (**9**), together with the dihydrodiketo alcohol (**8**, 10%). IR CO absorption at 1705 cm^{-1}, as well as a UV max at 250 nm (ϵ 5,500) in **9**, indicated retention of the cyclopentenone and reduction of the conjugated C-14 CO function. The NMR spectrum ($CDCl_3$) showed the new C-14 methine proton as a singlet at δ 5·02. The shielding of the C-12 proton (0·88 ppm) and the C-13 Me (0·28 ppm) relative to their position in bertyadionol (**3**) was as expected following reduction at C-14, and served to establish the relationship between partial structure **B** and the more extensively conjugated CO of the enedione moiety. Additional evidence for the multi-allylic position of 14-H in **9** was obtained from the mass spectrum whose most intense ion occurred at $M^+ - 17$. In this case the cross conjugated system may be brought into conjugation by the loss of ·OH. In terms of a partial structure, the information obtained from chromous acetate reduction enables **B** to be added to the non-cyclopentenoid carbonyl of the previously established structure **E**, resulting in the cross conjugated species **F**.

The formation of the diol (**9**) of the major product on reduction of **3** with chromous acetate/acetic acid is unexpected since chromous ion type reductions of enediones are known[13,14] to lead to the corresponding diones. The reduction of CO groups with chromous reagents is not common although some cases have been reported.[15] However bertyadionol has a cross conjugating system attached to the enedione at C-14, and an intermediate which retains delocalisation through both unsaturated systems is expected. Protonation of such an intermediate at C-14 would lead to the product (**9**) from chromous acetate reduction. It is still possible, however, to protonate via a C-4 anion which is equivalent to a C-14 anion in terms of extended delocalisation. Alternatively, the reduction may be the result of a combination of solvation effects, steric effects or the differences in reduction potentials of the various systems involved.

To explore the environment of the cyclopentanone CO, deuterium exchange was carried out on the dihydrodiketo acetate (**7**) with 2N DCl, resulting in a 70% yield of a d_3 product. The positions of deuteration were determined from the NMR spectrum of the resultant tri-deutero compound (**12**). The large coupling between 12-H and 11-H was retained, but the 5-H signal appeared as a broad singlet instead of a doublet, and the triplet (4-H) shown to be coupled to 5-H had disappeared. So too had a broad signal centred at δ 3·33 in **7**, and thought to be due to 15-H. An additional singlet appeared in the Me region at δ 1·16, replacing the

doublet previously observed for the secondary Me. Thus in terms of the partial structure F for bertyadionol, the secondary Me must be located at C-2.

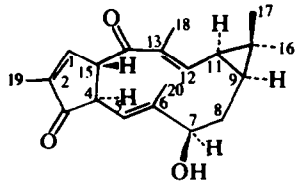
That the cyclopentanone was flanked on either side by one proton was demonstrated by sodium borohydride reduction of **8**, **7** and its d_3-derivative (**12**). Reduction proceeded smoothly and selectively at C-3, affording a mixture of epimers, from which the major product was obtained by chromatography. Verification that the reduction occurred at C-3 was obtained from the IR spectrum of **13** which showed CO absorption at 1650 cm^{-1} only. The NMR spectrum of the corresponding hydroxy-keto acetate (**14**) showed the C-3 proton as a broad triplet, $W_{1/2}$ = 12 Hz, centred at δ 3·87. The signal for 4-H had changed from a triplet (J = 10 Hz) to a broadened quartet, $W_{1/2} \sim 20-25$ Hz, consistent with an additional coupling of 5–6 Hz. The mass spectrum of the d_3-reduction product (**15**), revealed that little back exchange had occurred, and the NMR spectrum showed the C-3 methine proton as a singlet. Hence two of the deuterium atoms must be at positions 2 and 4. At this stage the substitution pattern of the cyclopentane ring could be inferred, but final definition was obtained by base catalysed isomerisation of bertyadionol (**3**) to the 1,5-enedione isomer (**16**). Because of the marked instability of bertyadionol, which gave complex mixtures when treated with strong base or acid, the isomerisation was carried out in pyridine/H_2O at 100°, and the conversion was monitored by NMR spectroscopy.

Consistent with the loss of the 4,15-double bond, the UV spectrum of **16** had a maximum (λ_{max}; 275 nm, ε 7,700) characteristic of the conjugated cyclopropyl-vinyl-ketone chromophore. Addition of sodium hydroxide to the UV solution resulted in the formation of a sodium salt and a bathochromic shift of the maximum to 435 nm (ε 9,700), indicating extensive conjugation in the enolate anion. Ready formation of the enol acetate (**17**) was additional evidence of an acidic proton expected for the vinylogous β-diketone in **16**. Although the 1,4-enedione had disappeared the IR spectrum of **16** indicated that a cyclopentenone may still be present (ν_{max} 1725 and 1660 cm^{-1}).

The NMR spectrum (C_6D_6; 90 MHz) contained a new vinyl Me signal (δ 1·69, $W_{1/2}$ = 3 Hz) and a broadened low field singlet (δ 7·30), indicating that the tetrasubstituted double bond of bertyadionol had migrated to the 1,2-position. Double irradiation experiments allowed the assignments shown in Table 1 to be made. The chemical shifts and coupling constants of the cyclopentenone moiety of **16** were similar to those of phorbol (**1**) and its derivatives with a similar unsaturated system.[1]

Support for these decoupling results was obtained from a series of deuterated derivatives of **16**. The 15-d_1-derivative was obtained by heating **16** in pyridine/D_2O at 100°. Its NMR spectrum showed the 4-H signal simplified from a quartet to a doublet (J = 11 Hz) and the 19-methyl as a doublet (J = 2 Hz). Isomerisation of bertyadionol in C_5D_5N/D_2O afforded a mixture (1:1) of d_2- and d_3-compounds. In both cases exchange at C-4 and C-15 was almost complete and integration of the NMR spectrum indicated that the d_3-compound had also exchanged 1-H. The signal for 5-H now appeared as a broad singlet at δ 5·65 while the 19-methyl signal, a combination of a singlet from the d_3-compound superimposed on a doublet from the d_2-compound, appeared as a broad singlet. The low field 1-H proton of the d_2-compound was a doublet (J = 2 Hz) and decoupling demonstrated that it was coupled to the 19-Me.

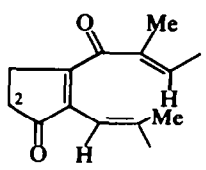
Table 1. Decoupling experiments on the pyridine isomerisation product (**16**)



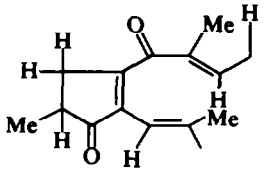
Proton(s)	Chemical shift (δ, C_6D_6)	Coupling constants (Hz)
1-H	7·30	J_{1-15} = 1·5; J_{1-19} = 2
2-Me	1·69	J_{1-19} = 2; $J_{15-19} \sim$ 1·5
4-H	2·79	J_{4-15} = 4·9; J_{4-5} = 11·2
5-H	5·58	J_{4-5} = 11·2; $J_{5-20} \sim$ 1
6-Me	1·43	
7-H	4·07	$J_{7-8a} \sim$ 9; $J_{7-8b} \sim$ 2
8-Ha, 8-Hb	~ 2·5, 1·1	$J_{8a-8b} \sim$ 14
12-H	6·05	J_{11-12} = 11; $J_{12-18} \sim$ 1
13-Me	1·89	
15-H	3·58	J_{1-15} = 1·5; $J_{15-19} \sim$ 1·5; J_{4-5} = 4·9

The third deuterated derivative was obtained by treating the above d_2-d_3 mixture briefly with dilute sodium hydroxide solution, effecting exchange at C-15. The NMR spectrum of the resultant d_1-d_2 mixture showed a decrease in relative height and an increase in width of the signal due to the 19-Me group. Similarly, the 1-H signal was now a broad singlet ($W_{1/2} \sim$ 4 Hz), indicating that it, too, had picked up a further coupling from 15-H. These results clearly show that C-1 of bertyadionol is a methylene group, and in addition they define the substitution pattern of the cyclopentane ring and provide supporting evidence for the 1,4-enedione system. Thus the partial structure of bertyadionol may be extended to **G**.

The formation of **16** may be considered as enolisation of bertyadionol at C-2, abstraction of the doubly allylic 1-H, followed by protonation at C-4, the relative rates of C-1 and C-4 protonation determining the extent of deuterium exchange at C-1.



F



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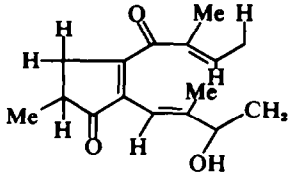


H

The resultant enol of the vinylogous β-diketone is related to **16** through a common enolate ion and isomerisation can occur by protonation at C-15.

The NMR spectrum (CCl_4) of the enol acetate (**17**) shows the 1-H signal as a doublet ($J = 2$ Hz) while the 4-H, also a doublet ($J = 10$ Hz) appears with a chemical shift (δ 3·58) consistent with the introduction of a further double bond to which 4-H is allylic. Enol acetylation at C-14 is supported by the IR spectrum of **17** in which carbonyl bands appear at 1765 cm^{-1} (enol acetate), 1740 cm^{-1} (acetate) and 1710 cm^{-1} (cyclopentenone).

Integration of the secondary OH function into the proposed structure was sought by oxidation. However, in the case of bertyadionol (**3**) the OH was unexpectedly resistant to oxidation, the instability of **3** precluding the use of acidic reagents. The oxidation was therefore carried out on the dihydrodiketo alcohol (**8**) which on Jones' oxidation afforded a mixture of two major products, separable by preparative TLC.

The mass spectrum of the lower R_F component indicated the addition of one atom of oxygen (which was lost as a primary fragmentation from the molecular ion) and the loss of two H atoms. The IR spectrum showed the presence of three ketone groups; a cyclopentanone (1750 cm^{-1}), the cyclopropylvinyl-ketone (1655 cm^{-1}) and an additional band at 1705 cm^{-1}. The NMR spectrum ($CDCl_3$) contained only one vinyl proton doublet (δ 6·58, $J = 11$ Hz), with a further 10 Hz doublet at δ 3·43. Also lacking was a vinyl Me group, which appeared as a tertiary Me (s, δ 1·08). On the basis of this evidence the compound was assigned the epoxide structure **18**.

The second product from Jones' oxidation of **8** was the trione (**19**), also obtained from Sarrett oxidation of **8**. The introduction of a new conjugated CO group was apparent from the IR spectrum of **19** which showed absorption bands at 1680 cm^{-1} (C-7 CO), 1740 and 1660 cm^{-1} (C-3 and C-14 CO's respectively). The NMR spectrum of the trione (**19**) showed the C-5 and C-12 vinyl protons as broad doublets ($J = 10$ Hz) at δ 6·22 and 6·08. The similarity of their chemical shifts attests to the fact that both double bonds are conjugated, while the deshielding of 5-H by 0·66 ppm in the trione (**19**) relative to **8** is consistent with the introduction of a CO group β- to the 5-position. Formation of the epoxide (**18**) is not unexpected, as epoxidation of conjugated ketones with Jones' reagent has been reported.[16] Extension of the partial structure of bertyadionol to **H** follows from the association of the secondary OH (and by inference the C-8 methylene) with the 5,6-double bond.

Completion of the structure involved the incorporation of two tertiary Me groups, two C atoms and one H atom. The only way in which this could be achieved was by formation of a cyclopropane ring extending conjugation of the α,β-unsaturated CO system (C-14 to C-12). This was consistent with the spectral data obtained for **3** and its derivatives. Confirmation of the presence of such a moiety was obtained by degradation of bertyadionyl acetate (**6**). Reaction with $OsO_4/NaIO_4$ afforded a compound whose NMR spectrum indicated two tertiary Me signals (δ 1·22 and 1·27), an acetate and Me ketone (singlets at δ 2·13 and 2·18), an acetate methine proton (doublet of doublets, $J_1 = 8$ Hz, $J_2 = 5$ Hz) at δ 4·96 and an aldehyde proton (doublet, $J = 4$ Hz) at δ 9·63, all of which was consistent with the expected aldehyde (**20**). Jones' oxidation of this aldehyde, followed by diazomethane methylation, afforded the keto-methyl ester-acetate (**21**), whose NMR spectrum was similar to that of **20**, with the inclusion of a OMe signal (δ 3·63) and the occurrence of a doublet, $J = 9$ Hz, at δ 1·43, attributed to the previously obscured 11-H. The IR spectrum of **21** (CS_2) exhibited CO absorption at 1745 cm^{-1} (acetate), 1725 cm^{-1} (methyl ester) and 1720 cm^{-1} (methyl ketone), and the structure was further supported by the mass spectrum which showed the expected fragmentations.

Conversion of **21** into a mixture of diol epimers (**22**) was effected by treatment with excess $NaBH_4$ in 0·1% NaOH solution. The crude diol mixture was cleaved with $NaIO_4$ in dioxan, and the resultant aldehyde was oxidized and methylated, yielding the diester (**23**) whose NMR, MS and GLC behaviour were identical with those of (±)-*cis*-homocaronic acid dimethyl ester prepared by methylation (CH_2N_2) of the authentic diacid. The specific rotation of the derived diester (−37·45°) is that expected for (−)-*cis*-homocaronic acid dimethyl ester, the (+)-enantiomer having reported values[17] of +37·5° and +42·8°. Thus the relative and absolute stereochemistry of carbons 9, and 11 was established, and the skeletal structure **3** for bertyadionol was completely elucidated.

Stereochemistry of bertyadionol and derivatives

The results presented above define the structure of bertyadionol (**3**) and the absolute stereochemistry

at C-9 and C-11. Four other points of stereochemistry require elucidation: the configuration of (a) the 5-double bond (b) the 12-double bond (c) the allylic secondary OH at C-7 and (d) the secondary Me at C-2. Although it has not yet been possible to resolve all these points, some progress has been made by application of NMDR techniques to two derivatives of bertyadionol resulting in the elucidation of the absolute stereochemistry of the pyridine isomerisation product (**16**) and, with the exception of the configuration at C-2, that of the reductive acetylation product (**7**).

The measurement of intramolecular NOE has proved useful in the determination of the structure and stereochemistry of many compounds.[18] Interestingly it provides an effective method for determining the configuration of double bonds.[19] To this end the pyridine isomerisation product (**16**) was chosen for NOE measurements. Unfortunately the technique cannot readily be applied to bertyadionol as the resonance signals for the two vinyl protons coincide. Saturation of the signal for 15-H in the NMR spectrum of **16** results in an increase in the intensity of the signals due to 1-H, 12-H and 5-H (Table 2), indicating that these protons are on the same side of the molecule and contiguous. An NOE

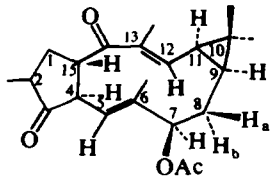
Table 2. Nuclear Overhauser effect (%) obtained for the pyridine isomerisation product (**16**) in [$^2H_6$]-benzene

Proton signals saturated	% increase in proton signals observed				
	1-H	4-H	5-H	15-H	12-H
15-H	11		9		11
C6-Me	1	11	2	−1	2·5
H-12	−1		−2	6	
C2-Me	8				2

effect between 15-H and 12-H is only possible for a *trans*- or E configuration of the 12-olefinic linkage. Saturation of the C-6 Me resonance signal increases the intensity of the signals for 4-H but not for 5-H requiring the *trans*- or **E** configuration for the 5-double bond. Since no effect was observed between the C-6 Me and either 15-H or 12-H, the C-6-Me and 4-H must be on the opposite side of the molecule to 15-H, 12-H and 5-H. This is only possible if the cyclopentenone ring fusion is *trans*. Results which allow determination of the configuration of the C-7 OH and a choice to be made between the two possible *trans*-ring fusion were obtained by application of the INDOR technique[18] to the reductive acetylation product (**7**).

In the NMR spectrum (90 MHz) of **7** resonances for 7-H, 12-H and 5-H are well resolved and separated from each other. The 7-H resonance appears as a 4 line signal at (445·5, 442·4, 434·4, 431·3 Hz) and INDOR experiments monitoring each line in

Table 3. Summary of coupling constants from INDOR measurements on



J_{7-8a}	11 Hz	$J_{12-13Me}$	1·5 Hz
J_{7-8b}	3 Hz	J_{11-12}	11·5 Hz
J_{8a-8b}	13·5 Hz	J_{9-11}	8·0 Hz
J_{8a-9}	12·5 Hz	J_{5-6Me}	1·5 Hz
J_{8b-9}	4 Hz	J_{4-5}	10 Hz
		J_{4-15}	11 Hz

turn allowed the detection of the hidden C-8 methylene protons. Each proton yields 8 lines (AB part of an ABMX spin system) and the chemical shifts and the coupling constants could be obtained by first order analysis (Table 3). Whereas the more deshielded C-8 hydrogen shows small coupling ($J = 4$ and 3 Hz) to the two adjoining protons (7-H and 9-H), the other C-8 hydrogen shows large coupling to both these protons ($J = 11$ and 12·5 Hz). Similar experiments monitoring the lines due to 12-H resonances allowed the detection of the 11-H (4 lines) and from this $J_{9-11} = 8$ Hz could be calculated. This value is consistent for the *cis*-ring fusion of the cyclopropane ring. INDOR experiments on the 5-H resonance lines showed that 4-H is coupled to 15-H with $J = 11$ Hz. Combination of these results with those obtained from NOE experiments lead to the relative and absolute stereochemistry for **16**. (Although it can be argued that a combination of the results of the INDOR and NOE experiments may not be valid, our justification relies on the fact that INDOR measurements on **6**, **7** and **16** have yielded comparable and self-consistent results. However those obtained for **7** were more readily interpretable by first order analysis and in the interest of clarity and brevity these are reported).

An examination of the molecular models indicates that, of the two *trans*-ring fusions possible for the cyclopentenone ring, only the one represented (Fig 1) will accommodate the dihedral angles required by the coupling constants observed for the 4 proton system 7-H, 8-H_2, 9-H. The configuration of the C-7 OH follows directly from the need to meet these requirements and is assigned the **7R**-configuration. For the alternative *trans*-ring fusion (4β, 15α) these requirements cannot be accommodated irrespective of the configuration of the 7-OH group.

From these results the following conclusions can be stated: (a) the absolute stereochemistry of the pyridine isomerisation product is as shown in Fig 1,

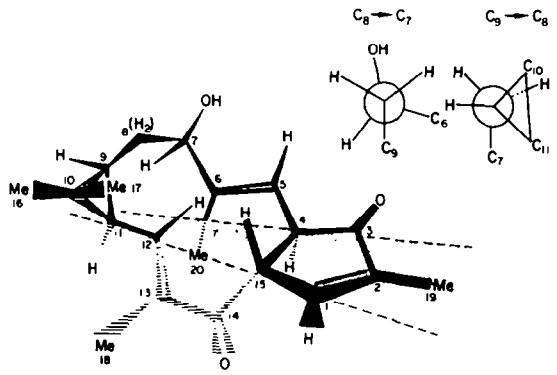


Fig. 1.

(b) the reductive acetylation product has the same stereochemistry (Table 3) with the configuration of the secondary methyl undetermined, (c) extrapolation of these results to bertyadionol is possible only if the assumption is made that *cis* ⇌ *trans* isomerisation of one or both the double bonds does not occur in the formation of **7** and **16**. Clearly further work is required before the absolute stereochemistry of bertyadionol can be unambiguously assigned and work toward this end is now in progress.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. Analyses were carried out by the Australian Microanalytical Service, Melbourne. IR spectra were recorded with a Perkin-Elmer Infracord model 337. UV spectra were determined as EtOH solutions on a Perkin-Elmer 137 UV Spectrophotometer. NMR spectra were recorded with a Varian HA-60 spectrometer (60 MHz) and a Bruker Spectrospin High Resolution NMR spectrometer (90 MHz). INDOR and NOE measurements were taken on the Brucker spectrometer. Mass spectra were obtained with a Varian MAT CH7 Mass spectrometer. Rotations were measured in $CHCl_3$ solns at room temp with a Hilger and Watts manual polarimeter.

Isolation of bertyadionol (**3**). *Bertya cuppressoidea* was collected 40 miles east of Norseman, W.A. and the dried, milled leaves and stems (9·5 Kg) were extracted with EtOH for 3 days. The soln was concentrated, diluted with H_2O and extracted with ether, which was washed with 8% $NaHCO_3$ aq. The remaining ethereal soln was washed with H_2O, dried and evaporated. After standing for a week, a concentrated ether soln of the "neutral" material deposited crystals (15·1 g) of bertyadionol. The mother liquors were defatted by boiling with aqueous MeOH and decanting the hot supernatant soln. The concentration of H_2O was gradually increased, and the amount of diterpene present in the ppt was estimated from the NMR spectra. Chromatography of the diterpene-rich material afforded a further 7 g of bertyadionol. Recrystallization from C_6H_6-light petroleum gave needles of *bertyadionol* (**3**), m.p. 159–160°, $[\alpha]_D$ −389°. (Found: C, 75·89; H, 8·27. $C_{20}H_{26}O_3$ requires: C, 76·40; H, 8·34%); $\nu_{max}^{CCl_4}$ 3610, 1710, 1665 cm^{-1}; λ_{max} 220 (ε 10,600), 263 (9,200), 332 (3,400); MS: M^+ obsd 314·188618, ($C_{20}H_{26}O_3$ requires: 314·188183), M–CO 286·193695 ($C_{19}H_{26}O_2$ 286·193269), M–H_2O–C_3H_7 253·122572 ($C_{17}H_{17}O_2$ 253·122846), M–H_2O–CO–CH_3 253·158983 ($C_{18}H_{21}O$ 253·159232), M–C_5H_9 245·117551 ($C_{15}H_{17}O_3$ 245·117762), M–C_6H_6O 244·145564 ($C_{16}H_{20}O_2$ 244·146321). NMR ($CDCl_3$) δ: 5·95 (5-H, br.s), 5·98 (12-H, br.d, J_{11-12} = 10 Hz), 4·25 (7-H,d of d), 1·81 (18-Me, d, J_{12-18} ~ 1·2 Hz), 1·47 (20-Me, d, J_{5-20} ~ 1·5 Hz), 1·22 (19-Me, d, J_{2-19} = 6·5 Hz), 1·11 (16-, 17-Me, s).

Acetylation of bertyadionol. Bertyadionol (**3**, 100 mg) was acetylated with pyridine (5 ml) Ac_2O (2 ml) at room temp. After work up the *acetate* (**6**; 110 mg) crystallised from C_6H_6–light petroleum as needles, m.p. 166–167°. (Found: C, 74·31; H, 7·87. $C_{22}H_{28}O_7$ requires: C, 74·13; H, 7·92%); $\nu_{max}^{CS_2}$ 1745, 1715, 1220, 1020, 755 cm^{-1}; MS: *m/e* 356 (M^+); NMR ($CDCl_3$; 90 MHz) δ: 6·09 (5-H, 12-H, br), 5·17 (7-H, d of d), 2·04 (acetate), 1·86 (18-Me, d, J_{12-18} = 1·2 Hz), 1·67 (20-Me, d, J_{5-20} = 1·5 Hz), 1·24 (19-Me, d, J_{2-19} = 7·0 Hz), 1·18 and 1·11 (16-, 17-Me, s).

Bertyadionol dioxime. Bertyadionol (**3**; 100 mg) in pyridine (5 ml) was allowed to react with hydroxylamine hydrochloride (400 mg) at room temp overnight. The neutral product recovered on crystallisation from $CHCl_3$–C_6H_6 gave the *dioxime*, m.p. 181°, MS: M^+ observed: 344·2099 ($C_{20}H_{28}O_3N_2$ requires: 344·2099). NMR (C_5D_5N) δ: 6·15 (5H, br.s), 5·43 (12-H, m), 4·45 (7-H, m), 1·95 (18-Me, br.s), 1·8 (20-Me, br.s), 1·05 (16-, 17-Me).

Reductive acetylation of bertyadionol

(a) Bertyadionol (**3**, 200 mg) was dissolved in Ac_2O (10 ml) and anhyd NaOAc (500 mg) was added. After soln was effected Zn dust (200 mg) was added and the mixture heated on a steam bath for 15 min. The Zn was filtered off and the filtrate worked up to give almost quantitative yield of the *dihydrodiketo acetate* (**7**) which recrystallized from ether-*n*-pentane as prisms, m.p. 153–155°, $[\alpha]_D$ −41·8° ($CHCl_3$). (Found: C, 73·41; H, 8·54. $C_{22}H_{30}O_4$ requires: C, 73·71; H, 8·44%); $\nu_{max}^{CS_2}$ 1735, 1220, 1030, 1010, 750; λ_{max} 275 (ε 15,800); MS: *m/e* 358 (M^+), 175 (100%), 159 (65), 148 (54); NMR ($CDCl_3$; 90 MHz) δ: 6·09 (12-H, d of q, J_{11-12} = 11·3 Hz, J_{12-18} = 1·2 Hz), 5·40 (5-H, d of q, J_{4-5} = 10·4 Hz, J_{5-19} = 1·5 Hz) 4·87 (7-H, d of d), 3·33 (15-H, m), 2·66 (4-H, t, J_{4-5} = 10·4 Hz), 2·01 (acetate), 1·87 (18-Me, d, J_{12-18} = 1·2 Hz), 1·52 (20-Me, d, J_{5-20} = 1·5 Hz), 1·21 and 1·13 (16-, 17-Me, s).

(b) Bertyadionol (**3**, 400 mg) was dissolved in AcOH (15 ml) and Zn dust (400 mg) was added. After 10 min at room temp the reaction was worked up. The resulting two component mixture was chromatographed on alumina (Neutral, Act I); elution with 50% $CHCl_3$–light petroleum afforded **8** (300 mg), which could not be crystallised; $\nu_{max}^{CCl_4}$ 3600, 1735, 1650, 1145, 1040, 675; λ_{max} 275 (ε 15,800). MS: *m/e* (%) 316 (M^+), 175 (75), 159 (35), 148 (100); NMR ($CHCl_3$) δ: 6·13 (12-H, br. d, J_{11-12} = 11 Hz), 5·56 (5-H, br. d, J_{4-5} = 10·5 Hz), 4·0 (7-H, m, $W_{1/2}$ ~ 13 Hz), 2·63 (4-H, t, J_{4-5} = J_{5-10} = 10 Hz), 1·87 (18-Me, d, J_{12-18} = 1 Hz), 1·48 (20-Me, d, J_{5-20} = 1 Hz), 1·2 and 1·1 (16-, 17-Me, s). Acetylation of **8** with pyridine/Ac_2O afforded the acetate, m.p. and mixed m.p. 152–153°, and identical with **7**.

Continued elution of the column ($CHCl_3$) afforded a compound (90 mg), identical (NMR, MS) with **9** obtained from chromous acetate reduction of bertyadionol.

Chromous acetate reduction of bertyadionol. Bertyadionol (**3**, 650 mg) was dissolved in glacial AcOH (45 ml) and CO_2 was bubbled through the soln for 10 min. Excess chromous acetate (prepared by the method of Barton[20]), was added and the reaction mixture stirred for a further

10 min under a CO_2 atmosphere. Work up by the same method as for reductive acetylation afforded a product (700 mg) estimated by NMR to be a 90:10 mixture of two compounds. Crystallisation from C_6H_6–light petroleum enabled the *diol* (**9**, 530 mg) to be separated as prisms, m.p. 198–201°, $[\alpha]_D$ −372·5° ($CHCl_3$). (Found: C, 75·91; H, 8·84. $C_{20}H_{28}O_3$ requires: C, 75·91; H, 8·92%); $\nu_{max}^{CCl_4}$ 3610, 3475 (br), 1705. λ_{max} 250 (ε 5,500) MS: M^+ obsd 316·2039 ($C_{20}H_{28}O_3$ requires: 316·2038). NMR ($CDCl_3$) δ: 5·6 (5–H, br.s), 5·1 (12–H, br. d, J_{11-12} = 11 Hz), 5·02 (14–H, br. s), 4·05 (7–H, d of d, J_{7-8} ~ 10 Hz), 1·53 and 1·42 (18–Me, 20–Me, br. s), 1·19 (19–Me, d, J_{2-19} = 7·5 Hz), 1·1 and 1·07 (16–, 17–Me, s).

Deuteration of the dihydroketo acetate (**7**). An approximately 2N soln of DCl was prepared by adding D_2O (0·5 ml) to a mixture of acetyl chloride (1·5 g) in dioxan (4 ml). Ac_2O (1·5 g) was added to prevent acetate hydrolysis, and **7** (50 mg) was added to the soln. After 3 hr at room temp the mixture was diluted with ether and washed several times with H_2O. Evaporation of the ethereal soln afforded the 2,4,15-d_3 compound (**12**, 51 mg); MS: *m/e* 361 (29%, d_3), 360 (14%, d_2), 359 (3%, d_1), 358 (2%, d_0); NMR ($CHCl_3$) δ: 6·07 (12–H, br.d, J_{11-12} = 11 Hz), 5·39 (5–H, br.s), 4·85 (7–H, d of d), 2·01 (acetate), 1·78 (18–Me, d, J_{12-18} = 1 Hz), 1·52 (20–Me, d, J_{5-20} = 1·5 Hz), 1·22 (19–Me, s), 1·16 and 1·12 (16–, 17–Me, s).

Sodium borohydride reductions of the dihydrodiketo acetate and derivatives

(a) The acetate **7** (123 mg) was dissolved in MeOH (12 ml), and $NaBH_4$ (120 mg) was added. After stirring at −60° for 1·5 hr, the soln was poured into H_2O and extracted with ether. Evaporation of the ethereal soln afforded an epimeric mixture (125 mg). Chromatography on alumina and elution with 50% $CHCl_3$–light petroleum gave a fraction which consisted of both epimers, as judged by NMR and TLC. Further elution gave fractions of *one epimer* (**14**, 57 mg) in a pure, non-crystalline state; $\nu_{max}^{CCl_4}$ 3620, 1740, 1655 cm^{-1}; MS: M^+ observed: 360·2327 ($C_{22}H_{32}O_4$ requires: 360·2300); 159 (72%), 150 (70), 149 (45); NMR($CHCl_3$) δ: 5·97 (12–H, br.d, J_{11-12} = 11 Hz), 5·42 (5–H, br. d, J_{4-5} = 11 Hz), 4·85 (7–H, d of d), 3·87 (3–H, br. t, $W_{1/2}$ = 12 Hz), 2·03 (acetate), 1·85 (18–Me, d, J_{12-18} = 1 Hz), 1·57 (20–Me, d, J_{5-20} = 1 Hz), 1·2 and 1·08 (16–, 17–Me, s), 1·04 (19–Me, d, J = 7 Hz).

(b) Similar reduction of **8** (100 mg) followed by chromatography yielded **13** (31 mg); NMR ($CHCl_3$) δ: 5·98 (12–H, br.d, J_{11-12} = 11 Hz), 5·57 (5–H, br.d, J_{4-5} = 11 Hz), 3·7–4·2 (7–H, 3–H, m), 1·85 (18–Me, d, J_{12-18} = 1 Hz), 1·49 (20–Me, d, J_{5-20} = 1 Hz), 1·18 and 1·08 (16–, 17–Me, s).

(c) Identical reduction of the d_3-compound **12** (190 mg) afforded the d_3-cyclopentanol **15** (74 mg); MS: *m/e* 363 (18%, d_3), 362 (6%, d_2), 361 (2%, d_1), 360 (3%, d_0); NMR ($CDCl_3$) δ: 5·97 (12–H, br. d, J_{11-12} = 11 Hz), 5·42 (5–H, br. s), 4·85 (7–H, d of d), 3·87 (3–H, s), 2·03 (acetate), 1·86 (18–Me, d, J_{12-18} = 1 Hz), 1·57 (20–Me, d, J_{5-20} = 1·5 Hz), 1·2 and 1·08 (16–, 17–Me, s), 1·03 (19–Me, s).

Pyridine isomerisation of bertyadionol. Bertyadionol (**3**, 300 mg) was dissolved in pyridine (4 ml) containing 0·5 ml of H_2O and heated at 100° under N_2 until NMR spectroscopy indicated the disappearance of reactant (3 hr). The solvent was evaporated and the residue chromatographed on alumina (Act III). Elution with 30% $CHCl_3$–light petroleum afforded the *isomerised product* (**16**, 280 mg) which crystallised as the ether solvate, m.p. 82–102°, $[\alpha]_D$ −61·9° ($CHCl_3$); $\nu_{max}^{CCl_4}$ 3600, 3450, 1725, 1660 cm^{-1}; λ_{max} 214 (ε 10,200), 275 (7,700); (+NaOH) 227 (7,800), 265 (5,500), 435 (9,700); MS: M^+ observed 314·1885 ($C_{20}H_{26}O_3$ requires: 314·1882); 164 (100%), 151 (30%); NMR (C_6D_6: 90 MHz) δ: 7·30 (1–H, br.s), 6·05 (12–H, br. d, J_{11-12} = 11 Hz), 5·58 (5–H, br.d, J_{4-5} = 11·2 Hz), 4·07 (7–H, d of d), 3·58 (15–H, m), 2·79 (4–H, q, J_{4-5} = 11·2 Hz; J_{4-15} = 4·9 Hz), 1·89 (18–Me, br.s), 1·69 (19–Me, br.s), 1·43 (20–Me, d, J_{5-20} = 1 Hz), 0·99 (16–, 17–Me,s).

Enol acetate of the pyridine isomer (**16**). Isomerised product **16** (100 mg) was dissolved in pyridine (2 ml) and Ac_2O (1 ml) was added. After heating at 100° for 1 hr, the mixture was worked up in the normal way. Filtration of the residue through alumina in 10% $CHCl_3$–light petroleum afforded the *enol acetate* (**17**); $\nu_{max}^{CS_2}$ 1765, 1740, 1710, 1220, 1190, 1040. MS: *m/e* 398 (M^+); NMR (CCl_4) δ: 7·45 (1–H, d, J_{1-19} = 2 Hz), 5·25 (12–H, 5–H, br. d), 4·86 (7–H, d of d), 3·58 (4–H, d, J_{4-5} = 10 Hz), 2·16 and 1·93 (acetates), 1·8 (18–, 19–, 20–Me, m), 1·13 and 1·03 (16–, 17–Me, s).

Deuteration of the pyridine isomer (**16**)

(a) Warming **16** in pyridine containing D_2O (10 min at 100°) yielded 15-d_1–**16**; MS: *m/e* 315 (17%, d_1), 314 (3%, d_0), 165, 151. NMR (C_6H_6) δ: as for **16**, 1–H obscured, 15–H absent, 4–H a doublet with J_{4-5} = 10 Hz, 19–Me, d, J_{1-19} ~ 1·5 Hz.

(b) Treatment of bertyadionol with C_5D_5N/D_2O under the same conditions as for the preparation of **16** afforded a mixture of 1,4,15-d_3–**16** and 4,10-d_2–**16**; MS: *m/e* 317 (10%, d_3), 316 (10%, d_2), 315 (1%, d_1), 314 (1%, d_0), 167, 166, 151. NMR ($CDCl_3$) δ: 7·43 (residual 1–H), 5·59 (5–H, br.s), 1·83 (19–Me). Except for lack of signals for 4–H and 15–H remainder of spectrum as for **16**.

(c) The d_2, d_3-mixture was dissolved in NaOH (2% aq) for 10 min. Acidification and extraction into ether afforded a mixture of 1,4-d_2–**16** and 4-d_1–**16**; MS: *m/e* 316 (5%, d_2), 315 (14%, d_1), 314 (2%, d_0), 165, 164, 151; NMR ($CDCl_3$) δ: As for d_2, d_3-mixture above, 10–H signal reintroduced.

Oxidation of the dihydrodiketo alcohol (**8**)

(a) *Jones' oxidation.* The alcohol **8** (120 mg) was dissolved in acetone (50 ml) and Jones' reagent was added dropwise until a pale yellow colour persisted. After 5 min EtOH (1 ml), and H_2O were added and the soln extracted with ether. Preparative TLC of the mixture recovered afforded **19** (18 mg) (see below) and the *epoxide* (**18**, 15 mg); $\nu_{max}^{CCl_4}$ 1750, 1705, 1655 cm^{-1}; MS: *m/e* 330, 314, 287, 163, 152, 109 (100%); NMR ($CDCl_3$) δ: 6·58 (12–H, br. d, J_{11-12} = 11 Hz), 3·43 (5–H, d, J_{4-5} = 10 Hz), 1·92 (18–Me, d, J_{12-18} = 1 Hz), 1·25 (16–, 17–Me, s), 1·19 (19–Me, d, J_{2-19} = 7 Hz), 1·08 (20–Me, s).

(b) *Sarett oxidation.* The alcohol **8** (130 mg) was stirred in a soln of pyridine (12 ml) containing CrO_3 (150 mg). After 18 hr at room temp the mixture was poured into ether and the ethereal soln washed with $NaHCO_3$aq and H_2O. Evaporation of the ethereal soln afforded a mixture of starting material and trione from which the *trione* (**19**, 45 mg) could be separated by preparative TLC as an unstable oil, $\nu_{max}^{CCl_4}$ 1740, 1680, 1660 cm^{-1}; λ_{max} 215 (ε 2,500), 245 (3,200), 275 (3,400). MS: M^+ observed 314·1888, ($C_{20}H_{26}O_3$ requires: 314·1882); 271, 163 (100%), 151; NMR ($CDCl_3$) δ: 6·08 and 6·22 (12–H and 5–H, each br. d), 1·84 (18–Me, d, J_{12-18} = 1 Hz), 1·52 (20–Me, d, J_{5-20} = 1 Hz), 1·23 (16–, 17– 19–Me, m).

Isolation of (−)-cis-*homocaronic acid dimethyl ester* (**23**). Bertyadionyl acetate (**6**, 600 mg) was dissolved in

dioxan (80 ml) and H_2O (20 ml). OsO_4 (10 mg) was added and the soln stirred at room temp until a dark colour developed. After 15 min $NaIO_4$ (2 g) was added and the stirring continued for a further 5·5 hr. The mixture was poured into H_2O and extracted with several portions of ether. Evaporation of the ethereal soln afforded **20** (520 mg); NMR ($CHCl_3$) δ: 9·63 (CHO, d, $J = 4$ Hz), 4·96 (acetate methine, d of d, $J_1 = 8$ Hz, $J_2 = 5$ Hz), 2·18 and 2·13 (acetate and methyl ketone), 1·27 and 1·22 (*gem*-dimethyl group). The crude **20** was dissolved in acetone and oxidized with Jones' reagent for 5 min at room temp. The resultant acid was methylated with ethereal CH_2N_2. Preparative TLC afforded the *methyl ester acetate* (**21**, 170 mg), $\nu_{max}^{CS_2}$ 1745, 1725, 1720 cm^{-1}; MS: M^+ observed 256·1327 ($C_{13}H_{20}O_5$ requires: 256·1310), M–15 241·1074 ($C_{12}H_{17}O_5$ requires: 241·1075), *m/e*: 228 (M–CO), 225 (M–OCH_3), 214 (M–CH_2CO), 197 (M–CO_2Me), 196 (M–CH_3CO_2H), 183 (M–CH_2CO–OCH_3), 182 (M–OCH_3–CH_3CO), 181 (M–CH_3CO_2H–CH_3), 171 (M–CH_2CO–$COCH_3$), 153, 140, 139. NMR (CCl_4) δ: 4·78 (acetate methine, d of d, $J_1 = 9$ Hz, $J_2 = 4$ Hz), 3·63 (OMe), 2·1 (acetate + methyl ketone), 1·43 (d; $J = 9$ Hz) 1·17 (*gem*-dimethyl). The acetate **21** (650 mg) was dissolved in 50% EtOH–H_2O (100 ml) containing NaOH (0·1%). $NaBH_4$ (800 mg) was added and the soln was stirred at room temp for 1·5 hr. Work-up in the usual manner afforded the epimeric diol mixture (**22**, 605 mg) $\nu_{max}^{CCl_4}$ 3600–3350, 1730, 1155, 1120; NMR ($CDCl_3$)δ: 4·27 (2 × OH, exchanged by D_2O), 3·57 (OMe), 1·18 and 1·13 (*gem*-dimethyl + secondary Me). The crude diol (**22**, 600 mg) was dissolved in dioxan (100 ml) and H_2O (25 ml), and $NaIO_4$ (2 g) was added. The mixture was stirred at room temp for 3 hr, then worked up to afford an aldehyde (269 mg) which was oxidised to the acid with Jones' reagent. Methylation with CH_2N_2, followed by preparative TLC, yielded (−)-cis-*homocaronic acid dimethyl ester* (**23**, 18 mg) $[\alpha]_D$ −37·45 (values quoted[17] for the (+)-enantiomer + 37·5, + 42·8°). The diester was identical with an authentic sample with respect to mobility and retention time on a 5 ft GLC column of diethyleneglycolsuccinate (5% on Chrom. W80/100) at 70°–110°. The same column was capable of separating clearly the *cis*- and *trans*-diesters, and also the *cis*-diester from an open chain analogue, adipic acid dimethyl ester. The natural and authentic diester samples also exhibited identical NMR and MS.

Retention times of esters. (DEGS 5 ft 100°).

Compound	Time (min)
cis-Homocaronic diester	4·3
trans-Homocaronic diester	6·25
Adipic diester	5·0

Acknowledgements—We thank Professor L. Crombie for samples of (±)-*cis*- and *trans*-homocaronic acid and Professor M. Matsui for a sample of (±)-*cis*-homocaronic acid. We gratefully acknowledge Dr. J. MacLeod of the Australian National University for high resolution mass spectra measurements. This work was supported by a grant from the Australian Research Grants Committee.

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