

ment was carried out by full matrix least squares with anisotropic thermal parameters for all atoms except the hydrogens which have isotropic temperature factors. The final unweighted R index is 0.041 for the 1091 observed reflections. A difference *Fourier* based on the final parameters has no features greater than $0.2 \text{ e } \text{\AA}^{-3}$ in magnitude.

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69. The Structure of Arteannuin B and its Acid Hydrolysis Product

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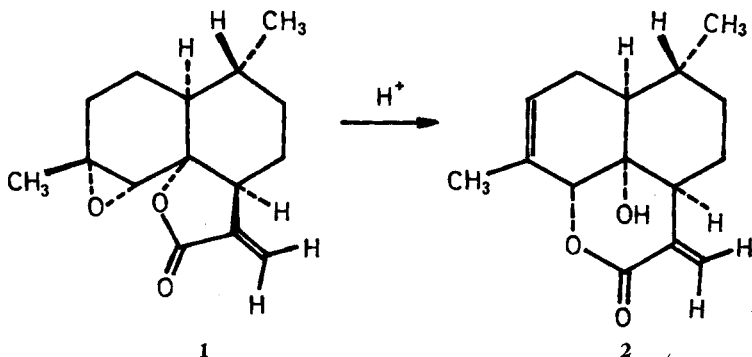
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Zusammenfassung. Die Struktur des Sesquiterpen- γ -Laktons Arteannuin B (**1**) wurde röntgenographisch und diejenige seines Hydrolyseproduktes (**2**) durch eine vollständige Analyse des NMR.-Spektrums ermittelt.

1. Introduction. – The isolation of the sesquiterpene lactone arteannuin B from *Artemisia Annuua* L. and several conversions including the formation of an acid hydrolysis product have recently been reported by *Stefanović et al.* [1]. Certain arguments were presented there in preliminary form which led to a proposal of structures **1** and **2** for arteannuin B and its hydrolysis product. We report here our own investigation of these two compounds²⁾, which confirm these structure proposals. First a detailed argument will be presented for the structure of the acid hydrolysis product **2**, based



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²⁾ We thank Prof. *Stefanović* for the samples of Arteannuin B and its hydrolysis product.

largely on its NMR.-spectrum, after some of the signals were separated by $\text{Eu}(\text{fod})_3$ reagent. Arteannuin B (**1**) itself did not complex sufficiently with the shift reagent, so that its crowded NMR.-spectrum could not be interpreted. Its structure was, therefore, obtained from an X-ray analysis.

2. The acid hydrolysis product (2). – 2.1. *Our observations.* – Elemental analysis (C 72.6%, H 8.3%) and the mass spectrum ($M^+ = 248\text{ m/e}$) correspond to the molecular formula $\text{C}_{15}\text{H}_{20}\text{O}_3$. The IR.-spectrum contains bands at 3570, 1715 and 1625 cm^{-1} and the UV.-spectrum a maximum at 213 $\text{m}\mu$ ($\epsilon = 7700$). The 220 MHz ^1H -NMR.-spectrum (CDCl_3) of **2** is reproduced in fig. 1. It contains signals for 20 protons, namely 14 distinct one-proton signals and 2 three-proton signals. The hydrogens which give rise to these signals are labeled in Fig. 1 and listed in Table 1 as Ha to Ho and as Me(a) and Me(b).

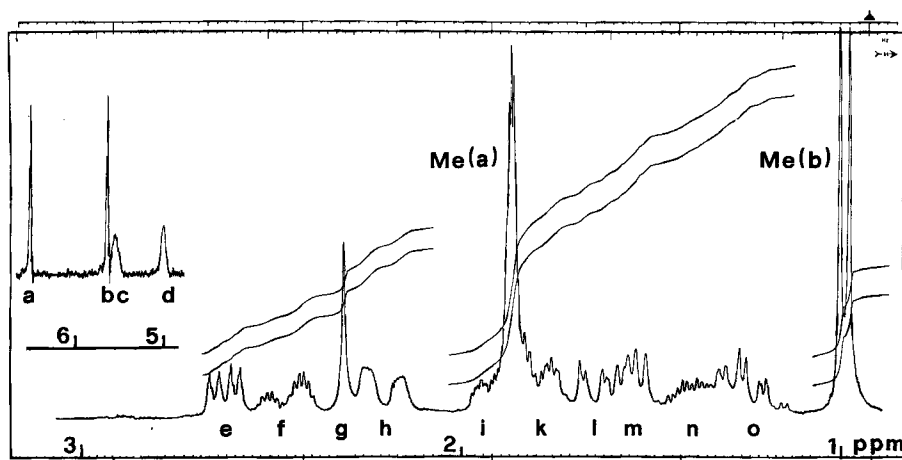


Fig. 1. 220-MHz- ^1H -NMR.-spectrum of hydrolysis product (**2**)

The coupling constants, obtained either directly from the 220-MHz-spectrum (Fig. 1) or from the 100-MHz-“europium-shifted”-spectrum, are also presented in Table 1, together with the europium-induced shift ($\Delta\delta_{\text{Eu}}$) for each hydrogen. About half of the coupling partners could be identified by spin decoupling experiments and these are given in brackets after the corresponding coupling constants in Table 1.

In Table 2 the coupling constants are grouped in ten classes. In each class the hydrogens which produce signals with one or more coupling constants in that range are listed a corresponding number of times. This procedure is followed because the spectrum does not warrant reliance on a greater precision than that range in the matching of coupling constants. All classes contain an even number of hydrogen atoms, except the $J = 12\text{--}13\text{ Hz}$ class. Thus one $12\text{--}13\text{ Hz}$ coupling has been missed. An examination of the spectrum shows that no coupling of this order could have been missed in any signal except that of Hn. The signal of Hn shows a high multiplicity and partly overlaps with the signal of Ho; moreover its width in a “europium-shifted” (but less resolved) spectrum is greater ($\sim 50\text{ Hz}$) than would be expected ($\sim 38\text{ Hz}$) without this additional coupling.

From an inspection of Table 2 it can be seen that there are four pairs of protons which are not assigned to each other by spin decoupling but must be coupling partners, because they are the only pair left in a class. These are Hf/Hh ($J = \sim 19$ Hz); Hm/Hn ($J = \sim 11$ Hz); He/Hi ($J = 5-6$ Hz); Hi/Hk ($J = \sim 2$ Hz). To make the ensuing arguments easier to follow all the known coupling partners are re-presented

Table 1. Chemical shifts (ppm), coupling constants (Hz) and europium-induced shifts (ppm) for the hydrogens of **2**

| Hydrogen atom | Chemical shift δ | Coupling constants | $\Delta\delta_{Eu}^a$ |
|---------------|-------------------------|--|-----------------------|
| Ha | 6.54 | $J = 1.3$ (Hb); 1.3 (He) | 4.2 |
| Hb | 5.66 | $J = 1.3$ (Ha); 1.3 (He) | 1.8 |
| Hc | 5.57 | $J = 2.0$ (Me(a)); 2-3 (Hf); ~ 4 (Hh) | 0.9 |
| Hd | 5.02 | $J = 1.5$ (Me(a)); 2-3 (Hf) | 2.9 |
| He | 2.64 | $J = 12-12.5$; 5.5; 1.3 (Ha); 1.3 (Hb) | 4.4 |
| Hf | 2.47 | $J = \sim 19$; 5-6 (Hm); 2-3 (Hc); 2-3 (Hd) | 2.0 |
| Hg | 2.31 | singlet | 16.7 |
| Hh | 2.20 | $J = \sim 19$; ~ 4 (Hc); 1 (Me(a)) | 1.1 |
| Hi | 1.92 | $J = 12$; 5.5; 3-4; ~ 2 | 1.6 |
| | | | or 0.7 |
| Me(a) | 1.86 | various small couplings | 0.4 |
| Hk | 1.78 | $J = 12$; 3.5; 3-4; ~ 2 | 0.7 |
| | | | or 1.6 |
| Hi | 1.63 | $J = 12$; 12; 12; 3.5 | 2.3 |
| Hm | 1.55 | $J = \sim 11$; 5-6 (Hf) | 2.7 |
| Hn | 1.32 | $J = \sim 11$; 5.6 (Me(b)); 3-4 | 1.6 |
| Ho | 1.19 | $J = 12$; 12; 12; 3.5-4 | 0.8 |
| Me(b) | 0.95 | $J = 5.6$ (Hn) | 0.5 |

a) Molar ratio $Eu(fod)_3$ to **2** = 0.4.

Table 2. Classification of the hydrogens of compound **2** according to coupling constants (Hz)^{a)}

| | | |
|---------------|---|------------------------------------|
| $J = \sim 19$ | : | Hf; Hh |
| $J = 12-13$ | : | He; Hi; Hk; Hl; Hl; Hl; Ho; Ho; Ho |
| $J = \sim 11$ | : | Hm; Hn |
| $J = 5-6$ | : | Hf/Hm; Hn/Me(b); He; Hi |
| $J = 3-4$ | : | Hc/Hh; Hi; Hk; Hk; Hl; Hn; Ho |
| $J = 2-3$ | : | Hc/Hf; Hd/Hf |
| $J = \sim 2$ | : | Hc/Me(a); Hi; Hk |
| $J = 1.5$ | : | Hd/Me(a) |
| $J = 1.3$ | : | Ha/Hb; Ha/He; Hb/He |
| $J = \sim 1$ | : | Hh/Me(a) |

a) The proton pairs known to be coupled to each other by spin decoupling are connected by a diagonal line.

in Table 3 and the protons which have unknown partners are given in Table 4 together with their unassigned coupling constants. The above mentioned 12-13 Hz coupling which has been read into the signal of Hn is also included in Table 4.

From the data presented in this section it was possible to derive unambiguously the structure of **2**. In the following sections a deductive argument will be presented

for the stepwise building up of a carbon and oxygen skeleton based solely on spectral evidence, foremost vicinal, geminal and allylic coupling relationships among protons of specific chemical shifts. The following procedure is used: Evident information is taken as the starting point for a sequence of arguments to find the ligands of atoms

Table 3. *Assigned coupling partners in the NMR.-spectrum of 2*

| Coupling partners ^{a)} | Coupling constants (Hz) | Coupling partners ^{a)} | Coupling constants (Hz) |
|---------------------------------|-------------------------|---------------------------------|-------------------------|
| Hf/Hh* | ~19 | Hc/Me (a) | ~2 |
| Hm/Hn* | ~11 | Hi/Hk* | ~2 |
| Hf/Hm | 5–6 | Hd/Me (a) | 1.5 |
| He/Hi* | 5–6 | Ha/Hb | 1.3 |
| Hn/Me (b) | 5.6 | Ha/He | 1.3 |
| Hc/Hh | 3–4 | Hb/He | 1.3 |
| Hc/Hf | 2–3 | Hh/Me (a) | ~1 |
| Hd/Hf | 2–3 | | |

^{a)} The proton pairs marked * are assigned to each other by the exclusion argument, the others by spin decoupling.

Table 4. *Unassigned coupling constants in the NMR.-spectrum of 2*

| Hydrogen atom | Coupling constants (Hz) |
|---------------|--------------------------|
| He | 12–13 |
| Hi | 12–13; 3–4 |
| Hk | 12–13; 3–4; 3–4 |
| Hl | 12–13; 12–13; 12–13; 3–4 |
| Hn | 12–13; 3–4 |
| Ho | 12–13; 12–13; 12–13; 3–4 |

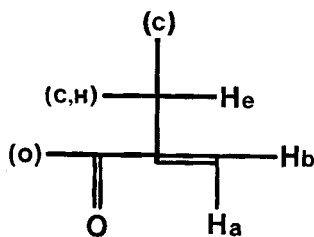
and hence to connect atoms to each other until the available evidence does not permit continuation. A 'partial structure' results, which has open ends. These open ends are to be called ligand positions. Usually the nature of the atom(s) in a ligand position can be identified by exclusion arguments; its symbol is then attached to the partial structure in brackets (*e.g.* (c), (o)). When there are two atoms left possible for a ligand position, both are shown in the bracket (*e.g.* (c, h)). In this way three partial structures (**A**, **B** and **C**) are built up from separate starting points.

Since these partial structures overlap at certain positions they can be connected to give partial structure **D**. Further evidence becomes apparent throughout the derivation from exclusion arguments, so that partial structure **D** can be completed and cyclised to give the constitution of hydrolysis product **2** of arteannuin B. Conformational considerations then lead to the full structure (configuration and conformation). No claim is made that this particular sequence of arguments is the only or even the best one possible. It is of interest that this complex system with 16 different hydrogen atoms showed an NMR.-spectrum which lent itself to a first order analysis.

2.2. Derivation of the partial structure A. The carbonyl band in the IR.-spectrum (1715 cm^{-1}) corresponds to a conjugated ester or lactone or to an open-chain or six-

membered ring ketone. A terminal double-bond of the type (C) (C) C = CH₂ is indicated by the two NMR.-signals (Ha and Hb) in the vinyl region (δ = 6.54 and 5.66 ppm), particularly by their small (1.3 Hz) mutual coupling and by the absence of any large (vicinal) coupling. That this double bond is in conjugation with the carbonyl group follows from the large deshielding of Ha and Hb (δ -value calculated [2] [3] for a non-conjugated terminal double bond: 4.72 ppm) and from the high intensity of the IR.-band at 1625 cm⁻¹. The UV.-absorption maximum (213 nm, ϵ = 7700) shows that the carbonyl group belongs to a conjugated ester or lactone, and not to a conjugated ketone or aldehyde function. The large difference in chemical shifts of Ha and Hb ($\Delta\delta$ = 0.88 ppm) must be due to a *s-cis* conformation of C=O and C=C (see [3]) but the δ -values themselves (6.54 and 5.66 ppm) are significantly higher than those in α -methylidene-cyclanones (found δ = 5.7–5.8 and 5.0–5.25 ppm [3]), so that a *s-cis* arranged H₂C=C-COOR system is indicated.

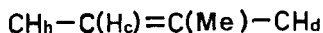
Both Ha and Hb show an additional coupling of 1.3 Hz (apart from the above mentioned mutual coupling). This coupling is in both cases with He and its value corresponds to an allylic type. Indeed the chemical shift of He (δ = 2.64 ppm) corresponds to a hydrogen atom in an allylic position. Since He is not a methyl hydrogen we get partial structure A.



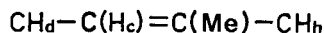
Partial structure A

2.3. Derivation of the partial structure B. A second double bond is made evident from the NMR.-spectrum in which a methyl signal (δ = 1.86 ppm, Me(a)) and a vinyl hydrogen signal (δ = 5.57 ppm, Hc) are coupled together with J = \sim 2 Hz. The protons of the vinylic methyl group (Me(a)) are also coupled, albeit very weakly, with Hd (J = 1.5 Hz) and also with Hh (J = \sim 1 Hz). Hd and Hh are therefore present in structures of the type MeC=C-CH and C=C(Me)-CH. Because Hd and Hh are not coupled to each other (all the couplings of both hydrogens have been assigned otherwise) they cannot be geminal and must therefore bear a 1,4-relationship across the double-bond as in CH-C=C-CH.

At this point it is impossible to decide whether the methyl group is geminal to C(Hd) or to C(Hh). The two possibilities will be called variants **a** and **b**. At the end of this section an argument will be made in favour of variant **a** and for this reason only variant **a** will be shown in the following diagrams.



variant **a**



variant **b**

It can be seen immediately from the large coupling (J = \sim 19 Hz) between Hh and Hf that these hydrogens are geminal neighbours. This is confirmed by their

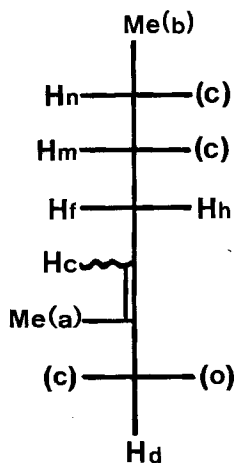
similar chemical shifts (Hf: $\delta = 2.47$; Hh: 2.20 ppm), which are typical for allylic hydrogen atoms. Hd and Hf must, therefore, also bear a 1,4-relationship (as Hd and Hh) across the double bond. The fact that Hd and Hf show a coupling of 2–3 Hz, whereas Hd and Hh do not, may be explainable by a more favourable arrangement for long distance coupling of the former hydrogen pair than of the latter.

Of interest is the low chemical shift ($\delta = 5.02$ ppm) of Hd. That this hydrogen atom is in a vinylic position is considered unlikely because the calculated [2] δ -value for a hydrogen atom in such an environment is ~ 5.7 ppm. Also the UV.-spectrum does not exhibit an absorption characteristic for a diene which would have to be highly substituted (all vinylic hydrogen signals assigned). The chemical shift of Hd however, also fits for a position, which – aside from being allylic – is geminal to a single oxygen (see also section 2.4.). Therefore, and because Hd has no hydrogen as geminal neighbour (all couplings of Hd accounted for otherwise), C(Hd) must carry a carbon which bears no hydrogen (or none in a conformation to couple with Hd).

The only coupling still to be considered for Hf is with Hm. Its value (5–6 Hz) proves that these hydrogens are vicinal (geminal would make a methyl group). It is of interest that Hm does not couple with its other vicinal neighbour Hh (all couplings of Hh allocated otherwise) and this will be discussed later in a conformational argument.

Hm cannot have a geminal neighbour because it would be unthinkable that such a hydrogen would have zero coupling with both its vicinal neighbours Hf and Hh (all the couplings of Hf and Hh are accounted for). Because of its chemical shift Hm cannot be geminal to an oxygen. Two carbon atoms must, therefore, be attached to C(Hm). One of these carbon atoms must carry Hn ($J = \sim 11$ Hz for Hm/Hn) as well as Me(b) ($J = 5.6$ Hz for Hn/Me(b)), but no other hydrogenatom (Me(b) signal is doublet).

This gives partial structure **B**.



Partial structure **B**

At this point an argument can be made favouring variant **a**, in which Hc is vicinal to Hf and Hh, but allylic to Hd: The observations are: 1) Hc does not couple with

Hd (all coupling partners of both these protons have already been found) and 2) Hc couples with Hf ($J = 2-3$ Hz) as well as with Hh ($J = 3-4$ Hz). It is more reasonable to accept that an allylic coupling is zero and two vicinal couplings lie in the range of 2 to 4 Hz (variant **a**) rather than that both allylic couplings exhibit 2 to 4 Hz values and the vicinal coupling vanishes (variant **b**).

2.4. *Derivation of partial structure C.* Up to now we have placed thirteen hydrogen atoms (Ha, Hb, Hc, Hd, Hf, Hh, Hm, Me(a) and Me(b)) by making use of all their couplings. A fourteenth hydrogen atom can be placed on this list: We know that there must be a hydroxyl group in compound **2** because its IR.-spectrum in chloroform has a band at 3570 cm^{-1} and its NMR.-spectrum shows a signal ($\delta = 2.31$ ppm, for Hg) which is shifted very strongly ($\Delta\delta = 16$ ppm) by 0.4 mol equivalents of europium reagent.

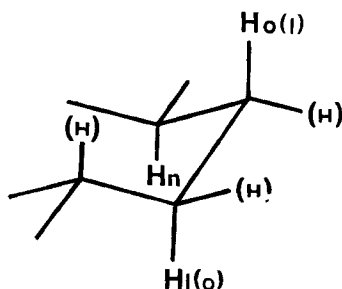
Two more hydrogen atoms (He and Hn) have been placed, but not all of their couplings have been assigned. Four hydrogen atoms therefore remain to be placed. These are Hi, Hk, Hl and Ho. All the coupling constants which have not, as yet, been used in the argument are presented in Table 5, to which the reader should refer for the remaining discussion in this section.

Table 5. *Coupling constants which have, as yet, not been used in the argument*

| Hydrogen atom | Coupling constants (Hz) ^{a)} |
|---------------|---------------------------------------|
| He | 12-13; 5-6 (Hi) |
| Hi | 12-13; 5-6 (He); 3-4; ~ 2 (Hk) |
| Hk | 12-13; 3-4; 3-4; ~ 2 (Hi) |
| Hl | 12-13; 12-13; 12-13; 3-4 |
| Hn | 12-13; 3-4 |
| Ho | 12-13; 12-13; 12-13; 3-4 |

a) Identified coupling partners given in brackets

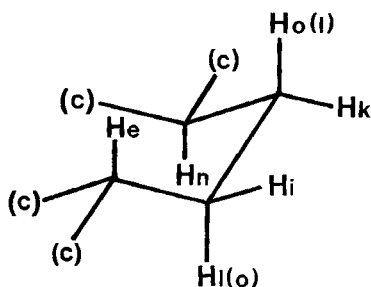
There are two hydrogen atoms (Hl and Ho, $\delta = 1.63$ and 1.19 ppm) each possessing three large couplings ($J = 12-13$ Hz). The only possible structural units which allow this are $-\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CHCH}_2\text{CH}_2\text{CH}-$ and these must be present in a suitable conformation. Since these units may carry only unplaced hydrogens, they must include He and Hn. Hn, however, cannot belong to a CH_2 group (see partial structure **B**), so that $-\text{CH}_2\text{CH}_2\text{CH}_2-$ can be eliminated. The structural unit which carries the six unplaced hydrogen atoms must therefore be:



The conformation shown accounts for the three large couplings of Hl and Ho (one geminal and two antiperiplanar vicinal for each) but leaves open alternative assignments for these two hydrogen atoms (Ho(l) and Hl(o)) as to their neighbourhood with Hn. As expected from this unit, Hn exhibits a large ($J = 12-13$, antiperiplanar) and a smaller (3-4 Hz, synclinal) coupling.

The geminal neighbours of Ho and of Hl should possess four couplings each: one geminal (12-13 Hz) and three synclinal vicinal (3-4 Hz). According to Table 5, this fits only for Hi and Hk and, in agreement with this, Hl and Ho each show a synclinal vicinal coupling (3-4 Hz), one with Hi and the other with Hk. Furthermore, it is known that Hi and Hk are coupled together ($J = \sim 2$ Hz).

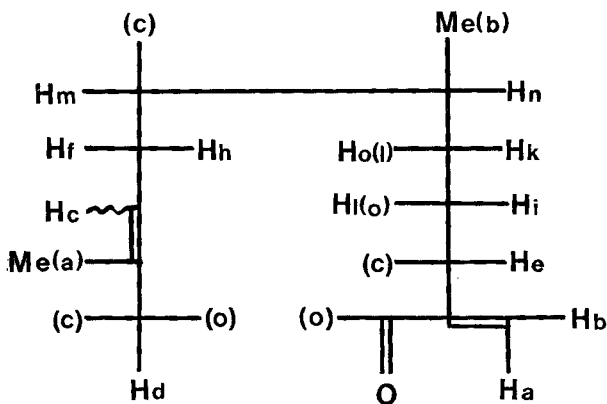
Since Hi is known to be coupled ($J = 5-6$ Hz) with He and since both He and Hl(o) have only one unassigned coupling ($J = 12-13$ Hz each), it is possible to draw partial structure C.



Partial structure C

The ligand atoms at C(He) and C(Hn) must be reserved for carbon as shown since Hn and He have no geminal neighbours (all couplings of He and Hn have now been assigned).

2.5. Derivation of partial structures D and E. Inspection of partial structures A, B and C shows that both A and C contain C(He) and both B and C contain C(Hn). The three partial structures can therefore be combined to give partial structure D,

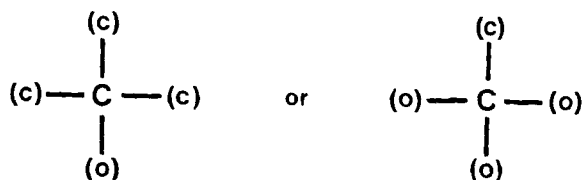


Partial structure D

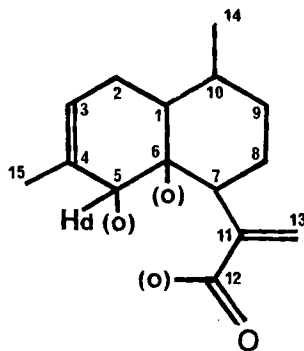
in which the conformational aspects connected with the derivation of partial structure **C** are omitted (see, however, section 2.7.).

Partial structure **D** contains fourteen carbon atoms with all ligands identified. Only one carbon atom, therefore, remains to be placed.

Since all twenty hydrogen attachments have been accounted for, either in partial structure **D** or as the hydroxyl group (Hg), the remaining carbon atom cannot carry a hydrogen. It can only carry an odd number of carbon atoms because the total number of ligand positions reserved for carbon atoms must be even, now that no more carbon atoms are available for addition and since partial structure **D** has an odd number of such positions. Thus there are two possible units containing this extra carbon, namely



but since one oxygen has already been assigned (as carbonyl oxygen atom) only the unit containing one oxygen atom remains. This unit must therefore be attached to partial structure **D** at the three carbon ligand positions. This gives partial structure **E**.



Partial structure **E**

In partial structure **E** all the hydrogen atoms, except Hd, have been omitted and the carbon atoms are numbered 1 to 15.

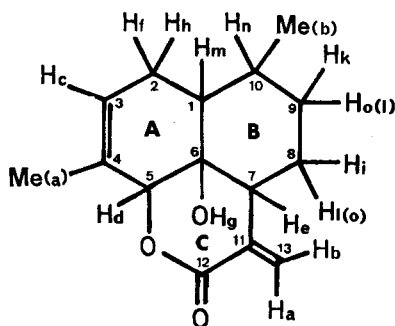
2.6. *The constitution of the hydrolysis product 2.* We now turn to the placement of the three oxygen atoms which are present in **2**. One of them, the carbonyl oxygen atom, has been fully characterized. Of the other two, one belongs to a hydroxyl group and thus to the unit (c)-O-Hg. The remaining oxygen atom must be part of the unit (c)-O-(c) since there are no more candidates for a hydroxyl hydrogen atom. There are three possibilities, a), b) and c), for the incorporation of these two oxygen units into partial structure **E**. They correspond to the incorporation of the hydroxyl unit ((c)-O-Hg) to any of the three ligand positions reserved for oxygen atom, namely

at C(12), at C(5) and at C(6). In each case the (c)-O-(c) unit is then attached to the remaining two oxygen ligand positions of partial structure E.

a) If the hydroxyl unit were at C(12) then compound **2** would have a carboxyl group and an epoxide ring. A carboxyl group is excluded by the sharpness of the band at 3570 cm^{-1} and by the absence of a broad band at $3300\text{--}2500\text{ cm}^{-1}$ in the IR.-spectrum.

b) If the hydroxyl unit were attached to C(5), then compound **2** would contain a five-membered lactone ring with an exocyclic double bond. This is excluded by the IR.-band at 1715 cm^{-1} (expected $\sim 1760\text{ cm}^{-1}$). Furthermore Hd would be in an environment of the type $\text{C}=\text{C}-\text{CH}(\text{OH})-\text{R}$, for which its chemical shift is calculated (Shoolery rule [4]) to be $\delta = 4.58\text{ ppm}$. This is not in good agreement with the found value ($\delta = 5.02\text{ ppm}$).

c) There remains only the third possibility, which is to attach the hydroxyl unit to C(6) as shown in the constitutional formula below. The ring closure *via* oxygen atom between C(5) and C(12) leads to a six membered lactone with an exocyclic double bond, which is in good agreement with the IR.-band at 1715 cm^{-1} . Here, the hydrogen atom Hd finds itself in an environment of the type $\text{C}=\text{C}-\text{CH}(\text{OCOR})-\text{R}$, for which the calculated [4] chemical shift ($\delta = 5.15\text{ ppm}$) fits well with the observed one ($\delta = 5.02\text{ ppm}$).



Constitution of the hydrolysis product **2**

This constitution is in accord with the isoprene rule and shows compound **2** to belong to the *cadinane* sesquiterpene series.

2.7. Configuration of the hydrolysis product 2. The constitution which was derived in the preceding section has five centres of chirality (C(1), C(5), C(6), C(7) and C(10)) so that 16 pairs of enantiomers are possible. In the following discussion we arbitrarily choose an absolute configuration and call the diastereomers simply isomers. The isomers due to the configuration of the methyl group at C(10) will be treated later. There remain 8 ring fusion isomers, namely all combinations of A/B *cis* or *trans*, B/C *cis* or *trans* and A/C *cis* or *trans*.

Strain-free models, with all three rings in the chair or semi-chair (ring A) form, can be built for four of these isomers. In the other four isomers, ring A and/or ring C must be built in the semi-boat or boat form. In the following considerations models

with as many chair forms as possible are chosen. The ring system is numbered as in cadinane and the side of H-C(1) is called the α -side.

Inspection of the models shows that the conformation at the C(1)-C(2) bond is sensitive to the configurational problem at hand. C(2) carries two hydrogens, Hf and Hh, and C(1) carries one, Hm. The pertinent fact is that Hm does not couple (or only extremely weakly) with Hh, but does show a coupling ($J = 5-6$ Hz) with Hf. This fact eliminates 6 of the 8 ring fusion isomers, namely all except the A/B, B/C,

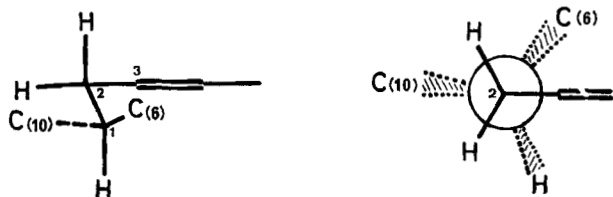


Fig. 2. Partial conformation of the A ring in the six eliminated isomers

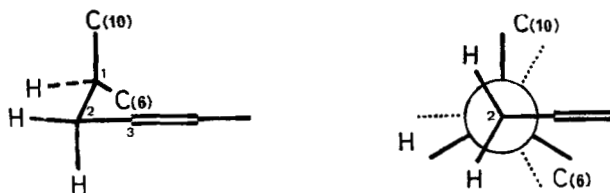


Fig. 3. Partial conformation of the ring A in the isomers I and II

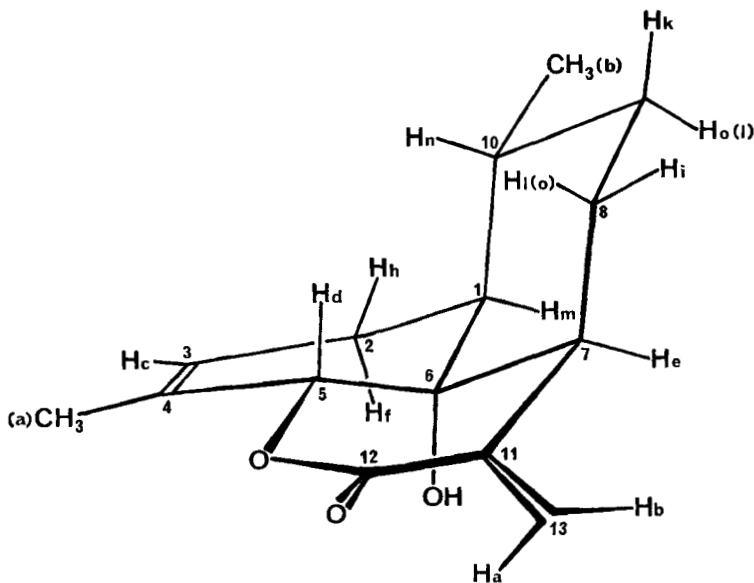


Fig. 4. Stereoformula of the acid hydrolysis product (2) of arteannuin B

A/C *cis, cis, cis*-(I) and the *cis, cis, trans*-(II) isomers, for the following reason: In the six eliminated isomers, ring A must take up a conformation (semi-chair or boat) relative to the C(1)–C(2) axis as shown in Fig. 2. The observed coupling of the two proton pairs (5–6 and ~ 0 Hz) is not consistent with this arrangement where H–C(1) in the projection lies outside the angle between the two H–C(2)'s.

In the remaining two isomers the conformation of ring A is such that the C(1)–C(2) environment appears as shown in Fig. 3. Here, H–C(1) projects between the two H–C(2)'s. The strained semi-boat form of ring A in isomer I forces the substituents at C(1) and C(2) into a perfect staggered conformation (as shown by the dotted lines on C(1) in Fig. 3), so that the two torsional angles of H–C(1) with both H–C(2)'s are approximately 60° . This arrangement is hardly likely to give rise to the observed couplings of 5–6 and ~ 0 Hz.

In isomer II ring A exists in a semi-chair form. The corresponding local conformation is shown by the heavy lines on C(2) in the right hand diagram of Fig. 3. H–C(1) has then a torsional angle with one H–C(2) of $35\text{--}45^\circ$ and with the other of $75\text{--}85^\circ$. These angles fit well with the observed couplings of 5–6 and ~ 0 Hz in compound **2**. We conclude that compound **2** possesses the A/B *cis*-, B/C *cis*-, A/C *trans*-configuration as shown in Fig. 4.

The above argument involving the Hf/Hm and Hh/Hm coupling constants ($J = 5\text{--}6$ and ~ 0 Hz, resp.) did not make use of any specific assignment of Hf and Hh to the α - or β -hydrogen atom at C(2). This assignment can now be made using the same two couplings; for it is H α -C(2) which has the smaller torsional angle with H–C(1) while this angle of H β -C(2) is closer to 90° . Therefore, Hf (J with Hm = 5–6 Hz) is H α -C(2), and Hh ($J = \sim 0$ Hz) is H β -C(2) (see Fig. 4). The model shows that Hf is a little closer to the hydroxyl group than Hh and, accordingly, Hf is about twice as sensitive to europium shift reagent as Hh (see Table 1).

The conformation of the carbon chain C(7), C(8), C(9), C(10) which emanated from the derivation of partial structure **C** (see section 2.4.) clearly supports the chair form of ring B. Since Hm and Hn have a large vicinal coupling ($J = \sim 11$ Hz) they must both be axial, meaning that the methyl group at C(10) is equatorial and therefore in an α -configuration.

3. Structure of arteannuin B (1). – Since the natural product lactone **1** did not lend itself to a structural analysis, such as was applied to the hydrolysis product **2**, an X-ray structure determination was performed³⁾.

Compound **1** crystallises in the non-centrosymmetric space group $P2_12_12_1$ with the lattice constants $a = 9.016 (\pm 0.004)$ Å, $b = 12.245 (\pm 0.006)$ Å and $c = 12.252 (\pm 0.006)$ Å. The density of the crystals determined chemically is 1.21 g/cc.; from X-ray data it was calculated to be 1.22 g/cc. There are 4 molecules in the unit cell.

1251 reflections were measured with a 4-circle-single-crystal diffractometer (Picker & Co.) using Mo-K α radiation. Of these reflections, 601 had an intensity less than three times the standard deviation.

³⁾ After this work was completed we became aware of the fact that an X-ray structure determination of arteannuin B had also been performed by M. R. Uskoković, T. H. Williams & J. F. Blount of Hoffmann-La Roche, Inc. Nutley, N. J. We are grateful to Dr. Uskoković for his agreement to publish the results side by side.

The presumed structure was calculated using the direct method⁴). The R-value after anisotropic refinement and introduction of the calculated H-atoms was 0.065 (further refinement is still in progress).

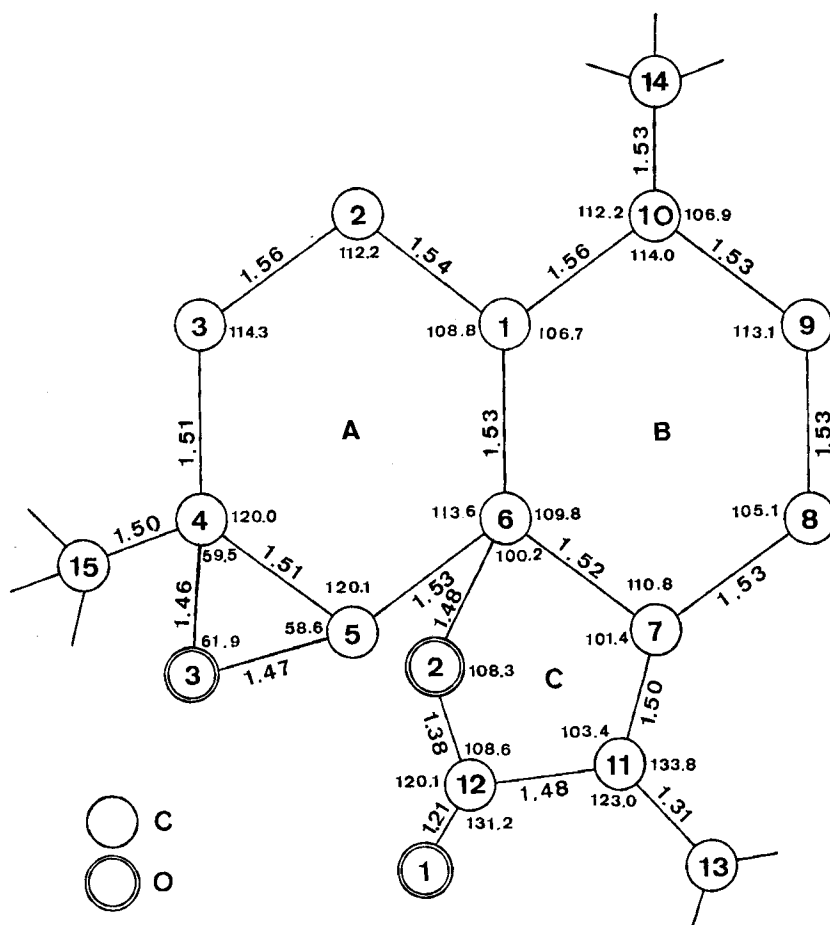


Fig. 5. Bond lengths and bond angles of arteannuin B (1)
(σ of the bonds: 0.01_5 Å, σ of the angles: 0.9 – 1.2°)

The bond distances and bond angles of arteannuin B are shown in Fig. 5. Ring B exists in a chair form; this is not the case for ring A inasmuch as C(3), C(4), C(5) and C(6) are in a plane and the six-membered ring angles at C(4) and C(5) are 120° . The medium planes of the two six-membered rings (rings A and B) enclose an angle of about 100° and those of rings B and C 169° . The angle between the oxirane ring and the medium plane of ring A is about 102° . Fig. 6 shows the structure of arteannuin B (1) and Fig. 7 depicts it in a stereoscopic plot with the thermal ellipsoids of carbons and oxygens.

⁴) Calculations were carried out in the computer centre of the ETH, Zürich on a CDC 6500/6400.

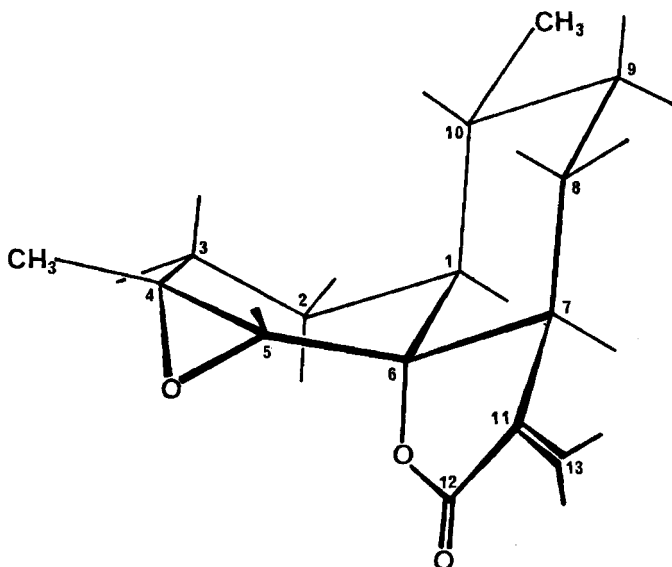


Fig. 6. Stereoformula of arteannuin B (1)

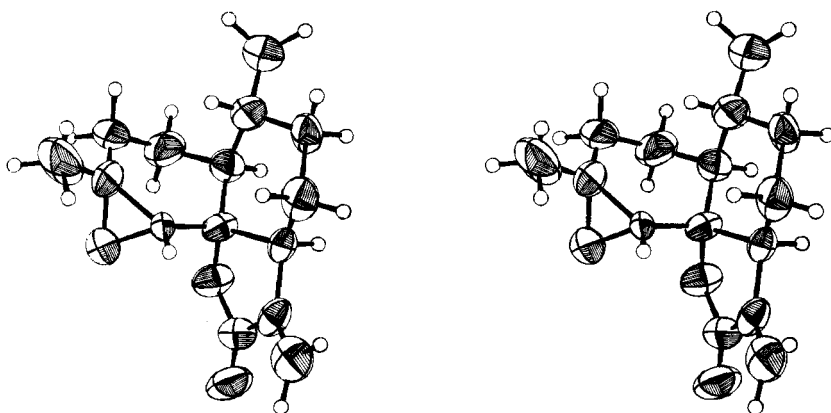


Fig. 7. Stereoscopic plot of arteannuin B (1)

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