Pergamon

*Tetrahedron* Vol. 50, No. 47, pp. 13553-13566, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00886-8

# Some Remarkable Reactions of the Diterpene Eriocephalin: *Neo*-Clerodane Derivatives with Insect Antifeedant Activity§

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***Abstract***- Base-catalyzed reaction of the *neo*-clerodane diterpenoid eriocephalin (**1**) gave the derivatives **3** and **4**. The formation of these compounds implies an elimination of the C-19 carbon atom of **1** as formaldehyde by a retroaldol reaction and, in the case of **4**, subsequent reaction of this formaldehyde with the 18-alkoxide intermediate followed by an intramolecular and stereoselective 1,4-addition of the resulting C-18-oxa-methylene alkoxide. Treatment of the derivative of eriocephalin **9** with base yielded transacetylation and hydrolysis products (**10-14**), with inversion of the configuration at the C-20 asymmetric centre. Mechanistic aspects of these transformations and the results achieved in the biological assay as insect antifeedants of these *neo*-clerodane derivatives are also reported.

A large number of *neo*-clerodane[1] and 19-nor-*neo*-clerodane diterpenoids have been isolated from plants in the last few years[2]. Interest in these compounds has been stimulated by their biological activity as antifeedants against some economically important lepidopterous pests[2a]. The species belonging to the genus *Teucrium* (family Labiatae) have afforded a great number of these compounds[2], some of them having been assessed for antifeedant activity against larvae of polyphagous species of Lepidoptera[2a,3]. However, the *neo*-clerodanes isolated from *Teucrium* are less active as insect antifeedants than other natural *neo*-clerodanes biosynthesized by species of the genera *Ajuga*[3c] and *Scutellaria*[4].

As a part of our studies on *neo*-clerodane diterpenes from *Teucrium* species (see references cited in 2), we were interested in obtaining synthetic derivatives of the more abundant natural compounds in order to investigate how the changes in the structure influence the antifeedant activity of these substances[5]. In this communication, we wish to report some unexpected chemical transformations of the *neo*-clerodane diterpene eriocephalin[6] (**1**), together with the results on the antifeedant activity of the natural compound (**1**) and several hemisynthetic derivatives, which were assessed against larvae of the lepidopteran *Spodoptera littoralis*.

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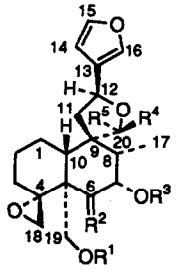
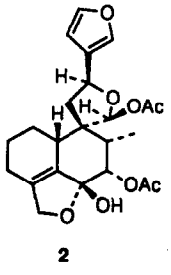
## RESULTS AND DISCUSSION

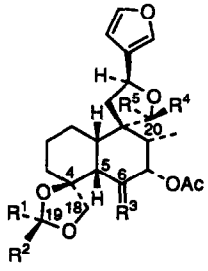
Recently[7], we investigated some reactions of the diterpene eriocephalin (**1**) establishing a likely mechanism for the transformation of *neo*-clerodanes into their 19-nor derivatives. This transformation, which involves the loss of the C-19 carbon atom as formaldehyde, was achieved by reaction of eriocephalin (**1**) with an excess of potassium *tert*-butoxide (1:2.5 molar ratio) in dry THF at 0 °C for 20 minutes, obtaining the unstable 19-nor-*neo*-clerodane derivative **2**, which in turn, under very mild conditions[7], undergoes a dehydration reaction yielding compound **3**.

We have now observed that when the above reaction was carried out with less than one equivalent of potassium *tert*-butoxide (1:0.9 molar ratio) for three days compound **3** was also obtained besides minor quantities of a new substance (50% and 15% yield on isolated compounds, respectively), the structure of which (**4**) was established on the basis of the following results.

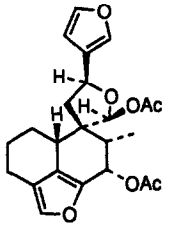




**2**



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| **1** | Ac | O | H | OAc | H |
| **9** | Ac | αOH,βH | Ac | OAc | H |
| **10** | Ac | αOAc,βH | Ac | H | OAc |
| **11** | Ac | αOAc,βH | Ac | H | OH |
| **12** | Ac | αOH,βH | Ac | H | OH |
| **13** | Ac | αOAc,βH | H | H | OH |
| **14** | H | αOH,βH | H | H | OH |
| **15** | Ac | αOAc,βH | Ac | OAc | H |



**3**

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| **4** | H | H | O | OAc | H |
| **5** | H | H | αOH,βH | OAc | H |
| **6** | H | H | αOH,βH | H | OBz |
| **7** | Me | H | O | OAc | H |
| **8** | H | Me | O | OAc | H |

Compound **4** had a molecular formula $C_{24}H_{30}O_9$ and its IR spectrum was devoid of hydroxyl absorptions. Comparison of the $^1H$ and $^{13}C$ NMR spectra of **4** (Tables 1 and 2, respectively) with those of eriocephalin[6] (**1**) and some of its derivatives[6] revealed that **4** maintained the β-substituted furan, the (12*S*,20*S*)-20-*O*-acetyl-20,12-hemiacetal and the C-6 keto groups of the starting material (**1**). In addition, compound **4** possessed an acetoxyl group at the C-7α position (which must be originated by a 1,3-diaxial transacetylation from the C-19 acetoxyl group to the C-7α hydroxyl function of eriocephalin[7]), a 4,18-methylenedioxy group [C-18 and C-19 protons as two AB systems at δ 3.54 and 3.90 ($J_{gem}$=9.1 Hz), and δ 4.91 and 4.92 ($J_{gem}$=7.1 Hz), respectively; $\delta_C$ 78.9 s (C-4), 75.1 t (C-18) and 93.5 t (C-19)] replacing the 4α,18-oxirane of **1**, and a methine

Table 1. $^1$H NMR Spectroscopic Data of Compounds 4-8[a]

| H | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|
| 1α | 1.32 qd | *b* | *b* | *b* | 1.31 qd |
| 1β | 1.94 dq | *b* | *b* | 1.93 m | 1.91 dq |
| 2β | *b* | *b* | *b* | 1.47 qt | 1.54 m |
| 5β | 3.09 dd | *b* | *b* | 3.03 dd | 3.09 dd |
| 6β | - | 4.06 t | 4.09 t | - | - |
| 7β | 5.26 dd | 4.80 dd | 5.07 dd | 5.25 dd | 5.24 dd |
| 8β | 2.70 ddq | 2.28 dq | *b* | 2.67 ddq | 2.68 ddq |
| 10β | 2.47 dddd | *b* | *b* | 2.45 dddd | 2.45 dddd |
| 11A[c] | 2.20 dd | *b* | 2.38 d | 2.18 dd | 2.18 dd |
| 11B[c] | 2.93 dd | 2.50 dd | 2.38 d | 2.90 dd | 2.92 dd |
| 12 | 5.37 dd | 5.23 dd | 5.33 t | 5.36 dd | 5.34 dd |
| 14 | 6.40 t | 6.35 dd | 6.46 dd | 6.39 dd | 6.39 dd |
| 15 | 7.41[b] | 7.37[b] | 7.39 t | 7.39 t | 7.40[b] |
| 16 | 7.41[b] | 7.37[b] | 7.52 m | 7.40 m | 7.40[b] |
| Me-17 | 0.99 d | 1.19 d | 1.32 d | 0.96 d | 0.97 d |
| 18A[c] | 3.54 d | 3.71 d | 3.68 d | 3.41 d | 3.72 d |
| 18B[c] | 3.90 d | 3.81 d | 3.83 d | 4.09 d | 3.74 d |
| 19A | 4.91 d | 4.99 d | 5.01 d | 5.01 q | 5.02 q |
| 19B | 4.92 d | 5.02 d | 5.05 d | - | - |
| 20 | 6.50 s | 6.54 s | 6.79 s | 6.49 s | 6.48 s |
| Me-C(19) | - | - | - | 1.36 d | 1.34 d |
| OAc | 2.16 s | 2.15 s | 2.15 s | 2.14 s | 2.14 s |
| | 2.07 s | 2.04 s | *d* | 2.05 s | 2.05 s |
| *J* (Hz) | | | | | |
| 1α,1β | 13.2 | *b* | *b* | *b* | 13.0 |
| 1α,2α | 3.3 | *b* | *b* | *b* | 3.8 |
| 1α,2β | 13.2 | *b* | *b* | 12.0 | 13.0 |
| 1α,10β | 13.2 | *b* | *b* | 13.1 | 13.0 |
| 1β,2α | 2.6 | *b* | *b* | *b* | 3.6 |
| 1β,2β | 2.6 | *b* | *b* | 3.9 | 3.6 |
| 1β,10β | 2.6 | *b* | *b* | 2.7 | 3.2 |
| 2α,2β | *b* | *b* | *b* | 12.0 | *b* |
| 2β,3α | *b* | *b* | *b* | 12.0 | *b* |
| 2β,3β | *b* | *b* | *b* | 3.9 | *b* |
| 5β,6β, | - | 3.1 | 3.2 | - | - |
| 5β,7β | 1.1 | 0 | 0 | 1.0 | 1.0 |
| 5β,10β | 5.9 | *b* | *b* | 6.0 | 6.1 |
| 6β,7β | - | 3.1 | 3.3 | - | - |
| 7β,8β | 6.7 | 5.9 | 6.0 | 6.6 | 6.7 |
| 8β,10β | 2.2 | 0 | *b* | 2.0 | 2.0 |
| 8β,17 | 7.2 | 7.5 | 7.5 | 7.2 | 7.2 |
| 11A,11B | 12.4 | 12.4 | 0 | 12.5 | 12.7 |
| 11A,12 | 9.5 | 9.5 | 7.1 | 9.5 | 9.7 |
| 11B,12 | 6.8 | 6.9 | 7.1 | 7.0 | 7.1 |
| 14,15 | 1.3 | 1.7 | 1.7 | 1.6 | 1.6 |
| 14,16 | 1.3 | 0.8 | 0.9 | 1.0 | 1.1 |
| 15,16 | *b* | *b* | 1.7 | 1.6 | *b* |
| 18A,18B | 9.1 | 8.2 | 8.2 | 9.3 | 9.1 |
| 19A,19B | 7.1 | 6.8 | 8.2 | - | - |
| 19,Me-C(19) | - | - | - | 4.8 | 4.8 |

[a] At 300 MHz, all in $CDCl_3$ solution. Chemical shifts are relative to residual $CHCl_3$ (δ 7.25). All these assignments were confirmed by double resonance experiments. [b] Overlapped signal. [c] The hydrogens (pro-*R* and pro-*S*) of the C-11 and C-18 methylene groups were distinguished by NOE experiments (see Table 3). [d] Benzoate group: δ 8.09 dd, 2H (H-2', H-6'), 7.48 m, 2H (H-3', H-5'), 7.61 br t, 1H (H-4'), $J_{2',3'}$=7.0 Hz, $J_{2',4'}$=1.4 Hz, $J_{3',4'}$=7.6 Hz.

carbon at C-5 ( $\delta_{H\text{-}5\beta}$ 3.09 dd, $J_{5\beta,10\beta}$=5.9 Hz, $J_{5\beta,7\beta}$=1.1 Hz; $\delta_{C\text{-}5}$ 53.7 d) instead of the quaternary C-5 carbon of eriocephalin (**1**), whereas the rest of the hydrocarbon framework of compounds **1** and **4** was identical, except for the absence in the latter of the 5α-acetoxymethylene substituent of the former (see Tables 1 and 2 and refs 6).

Table 2. $^{13}C$ NMR Data of Compounds **4**, **5**, **7** and **8**[a]

| C | 4 | 5 | 7 | 8 | C | 4 | 5 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 25.3 t | 25.0 t | 25.5 t | 25.2 t | 14 | 108.6 d | 108.8 d | 108.7 d | 108.7 d |
| 2 | 21.8 t | 22.1 t | 21.6 t | 22.0 t | 15 | 143.6 d | 143.4 d | 143.7 d | 143.7 d |
| 3 | 30.9 t | 31.4 t | 33.6 t | 30.5 t | 16 | 139.8 d | 139.7 d | 139.8 d | 139.8 d |
| 4 | 78.9 s | 82.1 s | 79.1 s | 79.6 s | 17 | 13.4 q | 13.2 q | 13.4 q | 13.5 q |
| 5 | 53.7 d | 42.4 d | 53.7 d | 54.8 d | 18 | 75.1 t | 72.8 t | 76.3 t | 75.1 t |
| 6 | 204.2 s | 70.3 d | 204.2 s | 204.4 s | 19 | 93.5 t | 94.0 t | 100.8 d | 99.6 d |
| 7 | 77.3 d | 74.6 d | 77.4 d | 77.4 d | 20 | 98.4 d | 99.2 d | 98.5 d | 98.5 d |
| 8 | 43.0 d[b] | 35.9 d[b] | 43.1d[b] | 43.1 d[b] | OAc | 169.8 s | 170.3 s | 169.9 s | 169.9 s |
| 9 | 54.0 s | 54.2 s | 54.0 s | 54.0 s | | 169.8 s | 169.7 s | 169.8 s | 169.8 s |
| 10 | 42.8 d[b] | 37.0 d[b] | 43.0 d[b] | 42.5 d[b] | | 21.2 q | 21.4 q | 21.2 q | 21.3 q |
| 11 | 42.3 t | 41.8 t | 42.4 t | 42.3 t | | 20.5 q | 21.1 q | 20.5 q | 20.4 q |
| 12 | 74.1 d | 74.1 d | 74.2 d | 74.2 d | Me-C(19) | - | - | 20.6 q | 20.5 q |
| 13 | 126.6 s | 126.9 s | 126.7 s | 126.7 s | | | | | |

[a]All in $CDCl_3$ solution, at 50.3 MHz, except for **8** (125.7 MHz). Chemical shifts are relative to the solvent ($\delta_{CDCl3}$ 77.00). Multiplicities were determined by the DEPT pulse sequence and HMQC spectra. [b]These assignments may be reversed, but those given here are considered to be the most likely.

In accordance with the observed coupling value between the C-5 and C-10 methine protons ($J$=5.9 Hz) compound **4** had a *cis*-decalin part and the β-configuration of these hydrogens was in agreement with NOE experiments. Irradiation at δ 3.09 (H-5β) caused, among others (see Table 3), positive NOE enhancement in the signals of the H-7β, H-10β and $H_B$-11 protons, thus establishing that the C-5 hydrogen possessed a β-configuration like the H-7 and H-10 axial β-protons.

All the above data established that, except for the stereochemistry of the C-4 asymmetric centre[8], the new derivative of eriocephalin had the structure depicted in **4**.

Reduction of compound **4** with sodium borohydride yielded the 6α-hydroxy derivative **5** by a stereoselective *exo*-attack of the reagent from the less hindered β-face. Irradiation at the signal of the H-6β equatorial proton of **5** (δ 4.06 t, $J_{6\beta,5\beta}$=$J_{6\beta,7\beta}$=3.1 Hz) under NOE conditions caused strong positive NOE enhancement in the signals of the H-5β, H-7β and $H_B$-18 protons (Table 3), thus suggesting that the C-18 methylene group had an *endo* 4α-configuration (see the molecular model of **5**) and consequently, that the stereochemistry of the C-4 spirocarbon was *S*.

In order to confirm rigorously all the above deductions on the structures of compounds **4** and **5**, we decided to undertake an X-ray diffraction analysis of one of these substances. Unfortunately, compounds **4** and **5** were not suitable for this purpose[9], but treatment of **5** with benzoyl chloride in pyridine solution yielded a substance

(**6**) whose crystallization from methanol gave single crystals. Figure 1 shows the X-ray molecular model of compound **6** confirming the above deductions on the structures of the derivatives **4** and **5** and establishing that reaction of **5** with benzoyl chloride only caused the substitution of the 20-acetoxyl group by a benzoyloxy group with inversion of the configuration at C-20. (For more details on the crystalline structure of **6** see Experimental).

Table 3. NOE Experiments on Compounds **4**, **5**, **7**, **8** and **10-15**[a]

| Compound | Irradiated proton (δ) | Observed NOE enhancement[b] |
|---|---|---|
| **4** | H-5β (3.09) | H-7β [+++], H-10β [+++], $H_B$-11 (pro-*S*)[c] [+++], $H_A$-18 (pro-*R*)[c] [+++] |
| **5** | H-6β (4.06) | H-5β [+++], H-7β [+++], $H_B$-18 (pro-*R*)[c] [+++] |
| **7** | H-5β (3.03) | H-7β [+++], H-10β [+++], $H_B$-11 (pro-*S*)[c] [++], $H_A$-18 (pro-*R*)[c] [++] |
| | $H_A$-18 (3.41) | H-5β [+++], $H_B$-18 [+++], H-19 [+++] |
| | $H_B$-18 (4.04) | $H_A$-18 [+++], H-19 [-] |
| | H-19 (5.01) | H-5β [+], $H_A$-18 [++], Me-C(19) [++] |
| **8** | H-5β (3.09) | H-7β [+++], H-10β [+++], $H_A$-11 (pro-*R*)[c] [-], $H_B$-11 (pro-*S*)[c] [+++], $H_B$-18 (pro-*R*)[c] [++], Me-C(19) [+] |
| | H-19 (5.02) | $H_A$-18 [++], Me-C(19) [++] |
| **10** | Me-17 (1.07) | H-7β [++], H-8β [+], $H_B$-11 (pro-*R*)[c] [++], H-14 [+], H-16 [+], H-20 [++] |
| | H-20 (6.74) | $H_B$-11 [++], H-16 [+], Me-17 [++], $H_B$-19 [++] |
| **11** | Me-17 (0.98) | H-7β [++], H-8β [++], $H_B$-11 (pro-*R*)[c] [+], H-14 [+], H-16 [+], H-20 [++] |
| | H-20 (5.83) | H-16 [+], Me-17 [++], $H_B$-19 [++] |
| **12** | Me-17 (1.00) | H-7β [+], H-8β [++], $H_B$-11 (pro-*R*)[c] [+], H-14 [+], H-16 [+], H-20 [+] |
| | H-20 (5.77) | $H_B$-11[++], H-14[+], H-16 [+], Me-17 [++], $H_B$-19 [++] |
| **13** | Me-17 (1.17) | H-7β [+], H-8β [++], $H_B$-11 (pro-*R*)[c] [++], H-14 [+], H-16 [+], H-20 [+] |
| **14** | Me-17 (1.19) | H-7β [+], H-8β [++], $H_B$-11 (pro-*R*)[c] [++], H-14 [+], H-16 [+], H-20 [++] |
| **15**[d] | Me-17 (1.25) | H-7β [+], H-8β [+], $H_B$-11 (pro-*R*)[c] [+], H-14 [+], H-16 [+], $H_A$-19 [++], $H_B$-19 [+] |

[a]Measured at 300 MHz by the FT difference method. [b]The signs [+], [++] and [+++] denote weak (0.5-2%), medium (3-5%) and strong (>8%) positive NOE enhancement, respectively. The sign [-] means a weak negative NOE enhancement. [c]These NOE experiments allowed the assignment of both (pro-*R* and pro-*S*) protons of the C-11 and C-18 methylene groups. [d]The NOE experiment with this previously known compound[6b] has been made for comparative purposes: **15** possesses ring B in a distorted chair conformation, in which Me-17 is a pseodoaxial substituent (observed NOE with C-19 methylene protons) close to the C-20 carbon (no NOE with H-20, which is placed in opposite side of the plane defined by the 20,12-lactol).

The behaviour of compound **5** under the conditions of the benzoylation reaction (see Experimental) is not surprising, because the *endo* 6α-hydroxyl group must be resistant to the esterification reaction due to steric hindrance and nucleophilic substitutions on C-20 with inversion of the configuration have previously been observed in other (20*S*)-20-*O*-acetyl-20,12-hemiacetal-*neo*-clerodane derivatives[10]. Although the mechanism of the transformation of **5** into **6** was not investigated, we suppose that it involves the formation of an oxonium ion

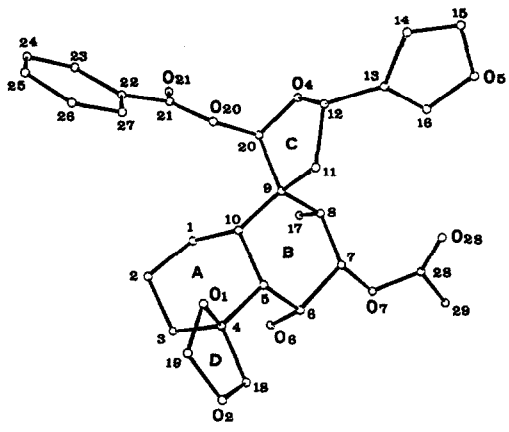



Figure 1. X-Ray molecular model of compound **6**, showing the atomic-numbering scheme (hydrogens are omitted for clarity).

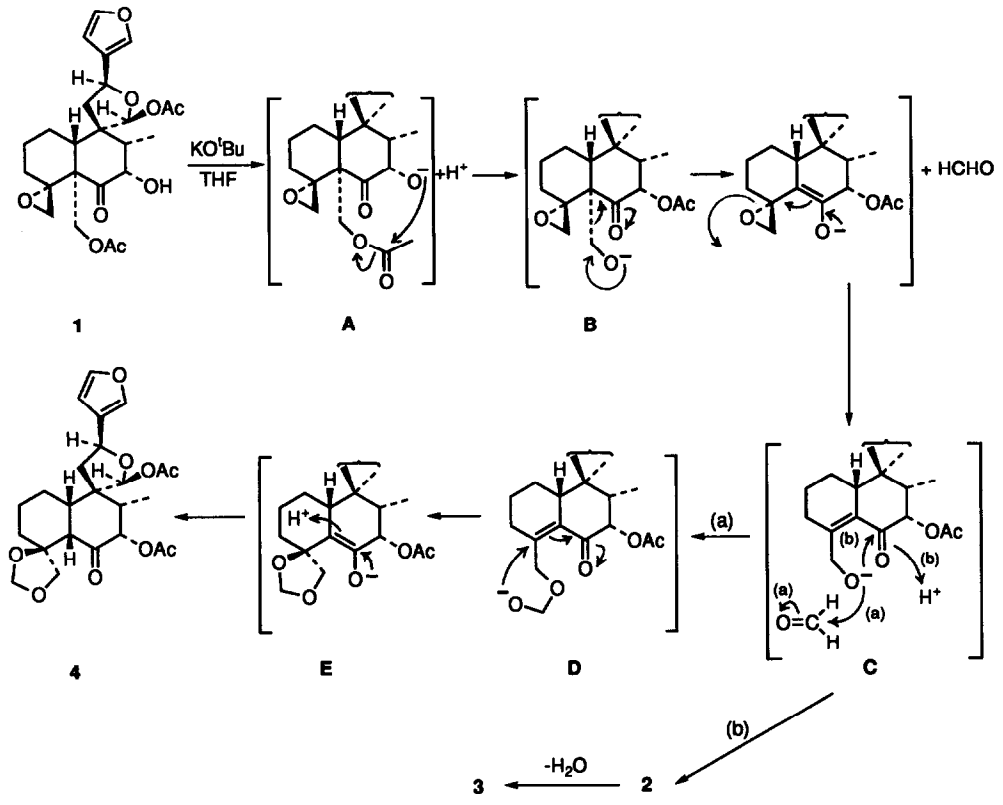
at C-20 and subsequent stereoselective attack of a benzoate anion[11] from the less hindered *Re* face. A less probable alternative mechanism could be an initial hydrolysis[11,12] of the C-20 acetate of **5** followed by inversion of the configuration at the lactol centre (as a result of ring opening and reclosure to the thermodynamically and sterically most favoured arrangement) and finally, esterification of the epimeric hemiacetal. In any case, the stereoselectivity of this reaction must be attributed to the steric effects of the axial C-17 methyl and 12-furan neighbouring groups, both placed on the same side of the plane defined by the 20,12-lactol.

The formation of the derivative **4** from eriocephalin (**1**) could be rationalized considering that the 4β,18-methylenedioxy group of **4** arises from formaldehyde, which is generated in the retroaldol reaction that causes the transformation of the *neo*-clerodane diterpenes into their 19-nor derivatives[7] such as **2** and **3**. This hypothesis was rigorously corroborated by reaction of **1** with sodium *tert*-butoxide in presence of an excess of acetaldehyde (1:0.9:8 molar ratio, respectively; see Experimental). Under these conditions, eriocephalin (**1**) gave the derivatives **3** and **4** (50% and 7.5% yield, respectively) and a new substance (8% yield, $C_{25}H_{32}O_9$) whose structure **7** differed from **4** only in the existence of a 4β,18-ethylidenedioxy group [$\delta_H$ 5.01 q, 1H, $J$=4.8 Hz (H-19) and 1.36 d, 3H, $J$=4.8 Hz (Me attached to C-19); $\delta_C$ 100.8 d (C-19) and 20.6 q (Me attached to C-19); Tables 1 and 2] instead of the 4β,18-methylenedioxy moiety of **4**. Moreover, when the above reaction was carried out in presence of a large excess (100:1) of acetaldehyde, compounds **3** and **7** (48% and 7% yield, respectively) were obtained together with minor quantities (6%) of another substance (**8**) whose spectroscopic data revealed that it was the C-19 epimer of **7** (Tables 1 and 2). The stereochemistry at the C-19 asymmetric centre of compounds **7** and **8** was established by NOE experiments (Table 3), which were in agreement with a 19*S* configuration in **7** (*exo*-stereoisomer) and a 19*R* stereochemistry for the C-19 epimer **8** (*endo*-stereoisomer).

The structure of compound **4** is compatible with the mechanistic pathway shown in Scheme 1. This mechanism is initiated by the formation of an alkoxide (**A**) in the C-7α hydroxyl group of eriocephalin (**1**) followed by a transacetylation of the C-19 acetyl substituent. The resulting C-19 alkoxide (**B**) is transformed into the 19-nor-18-alkoxide (**C**) by loss of the C-19 alkoxymethylene substituent as formaldehyde in a retroaldol reaction in which the C-6 ketone takes part[7]. In presence of an excess of base, the alkoxide intermediate **C** produces the unstable derivative **2** (or its stable dehydration product **3**) by an intramolecular attack on the carbonyl C-6 carbon[7], whereas with less than one equivalent of base this alkoxide (**C**) can also react by another competitive way, namely, by an intermolecular reaction with formaldehyde generated in the process giving the C-18-oxa-methylene alkoxide **D**, which by an intramolecular attack on the C-4 olefinic carbon (1,4-addition reaction) from the less hindered *exo*-face of the decalin moiety (intermediate **E**), followed by protonation at the

C-5β position, produces the derivative **4**. Obviously, compounds **7** and **8** are obtained when acetaldehyde is added to the reaction as a competitive reagent.

Scheme 1




(a) With a defect of base both routes [(a) and (b)] are competitive. (b) With an excess of base only this route occurs.

Regarding the mechanism shown in Scheme 1, it is important to remark that compound **4** was obtained only in the reaction of eriocephalin (**1**) with less than one equivalent of base, whereas with an excess of potassium *tert*-butoxide compound **1** was almost quantitatively transformed into the derivative **2** (96% yield)[7]. Presumably, this different behaviour is due to the stability of formaldehyde in the reaction mixture.

We next turned our attention to compound **9**[6b] as a suitable derivative for obtaining 19-nor-*neo*-clerodanes by a fragmentation reaction[13] of 4α,18-epoxy-19-alkoxides, without participation of the C-6 ketone, and for synthesizing 5,6-seco-*neo*-clerodanes via fragmentation of 4α,18-epoxy-6α-alkoxides. Although previous assays[7] for achieving these fragmentations were unsuccessful, we decided to try the reaction under more drastic conditions.Treatment of **9** with sodium *tert*-butoxide (1:1.5 molar ratio, respectively) in THF at room temperature for 24 hours yielded compounds **10** (9% yield), **11** (6%), **12** (16%), **13** (51%) and **14** (11.5%), as a consequence of intra- and intermolecular transacetylation reactions (**10**, **11**, **13**) and partial (**12**, **13**) or total (**14**) hydrolysis of the acetates of **9**. Attemps at obtaining products of fragmentation of **9** by this reaction

Table 4. $^1$H NMR Spectroscopic Data of Compounds **10-15**[a]

| H | 10 | 11 | 12 | 13 | 14 | 15[b] |
|---|---|---|---|---|---|---|
| 1α | 2.46 qd | 2.63 qd | 2.58 qd | 2.65 qd | *c* | *c* |
| 2β | 1.43 qt | 1.34 qt | 1.33 qt | 1.35 qt | *c* | *c* |
| 3α | *c* | *c* | *c* | 2.31 dddd | *c* | *c* |
| 3β | *c* | 1.05 dt | 1.08 dt | 1.04 dt | *c* | *c* |
| 6β | 4.77 br d | 4.77 br d | 3.65 br d | 4.69 br d | 4.10[c] | 4.75 dd |
| 7β | 5.21 dd | 5.20 dd | 5.35 t | 3.80 t | 4.10[c] | 5.25 dd |
| 8β | 1.77 qd | 1.68 qd | 1.62 qd | 1.53 qd | *c* | *c* |
| 10β | *c* | *c* | 1.70 dd | 1.74 dd | *c* | *c* |
| 11A | 1.97 dd | 1.76 dd | 1.75 dd | 1.82 dd | *c* | *c* |
| 11B | 2.30 dd | 2.29 dd | 2.29 dd | 2.24 dd | 2.92 dd | 2.53 dd |
| 12 | 4.99 dd | 5.10 dd | 5.09 dd | 5.08 dd | 5.30 dd | 5.19 dd |
| 14 | 6.37 dd | 6.37 dd | 6.37 dd | 6.41 dd | 6.77 dd | 6.42 m |
| 15 | 7.37 t | 7.38 t | 7.37 t | 7.39 t | 7.65 t | 7.35 m[c] |
| 16 | 7.40 m | 7.39 m | 7.38 m | 7.41 m | 7.80 m | 7.35 m[c] |
| Me-17 | 1.07 d | 0.98 d | 1.00 d | 1.17 d | 1.19 d | 1.25 d |
| 18A[d] | 2.20 d | 2.18 d | 2.41 d | 2.18 d | 2.53 d | 2.21 d |
| 18B[e] | 2.94 dd | 2.93 dd | 3.18 dd | 2.94 dd | 3.59 dd | 2.95 dd |
| 19A | 4.60 br d | 4.66 br d | 4.83 br d | 4.67 br d | 3.92 br d | 4.53 dd |
| 19B | 4.98 d | 5.40 d | 5.17 d | 5.72 d | 4.77 d | 5.72 d |
| 20 | 6.74 s | 5.83 d[f] | 5.77 d[f] | 6.09 d[f] | 5.38 s | 6.40 s |
| OAc | 2.26 s | 2.16 s | 2.10 s | 2.11 s | - | 2.13 s |
| | 2.14 s | 2.07 s | 2.07 s | 2.03 s | - | 2.10 s |
| | 2.06 s | 1.90 s | - | - | - | 1.92 s |
| | 1.92 s | - | - | - | - | 1.90 s |
| OH-6[g] | - | - | 3.61 s | - | *h* | - |
| OH-7[g] | - | - | - | 2.94 s | *h* | - |
| OH-20[g] | - | 3.40 d | 3.46 d | 2.79 d | *h* | - |
| *J* (Hz) | | | | | | |
| 1α,1β | 13.6 | 13.4 | 12.8 | 12.7 | *c* | *c* |
| 1α,2α | 3.3 | 2.5 | 3.1 | 3.4 | *c* | *c* |
| 1α,2β | 13.6 | 13.4 | 12.8 | 12.7 | *c* | *c* |
| 1α,10β | 13.6 | 13.4 | 12.8 | 12.7 | *c* | *c* |
| 1β,2β | 2.9 | 3.6 | 3.9 | 4.1 | *c* | *c* |
| 1β,10β | *c* | *c* | 2.5 | 2.4 | *c* | *c* |
| 2α,2β | 13.6 | 13.3 | 13.4 | 13.2 | *c* | *c* |
| 2α,3α | *c* | *c* | *c* | 2.9 | *c* | *c* |
| 2α,3β | *c* | 3.6 | 3.1 | 3.4 | *c* | *c* |
| 2β,3α | 13.6 | 13.3 | 13.4 | 13.2 | *c* | *c* |
| 2β,3β | 2.9 | 3.6 | 3.1 | 3.4 | *c* | *c* |
| 3α,3β | *c* | 13.0 | 13.1 | 13.0 | *c* | *c* |
| 6β,7β | 3.8 | 4.1 | 3.3 | 3.4 | *c* | 4.0 |
| 7β,8β | 2.5 | 2.9 | 3.3 | 3.4 | *c* | 2.1 |
| 8β,17 | 7.0 | 7.1 | 7.1 | 7.1 | 7.2 | 7.0 |
| 11A,11B | 13.2 | 13.2 | 13.2 | 13.2 | 15.6 | 13.5 |
| 11A,12 | 10.6 | 10.4 | 10.3 | 10.5 | 9.2 | 9.0 |
| 11B,12 | 6.6 | 6.6 | 6.8 | 6.6 | 7.4 | 6.6 |
| 14,15 | 1.8 | 1.8 | 1.8 | 1.7 | 1.9 | *h* |
| 14,16 | 0.9 | 0.9 | 0.9 | 0.9 | 1.1 | *h* |
| 15,16 | 1.8 | 1.8 | 1.8 | 1.7 | 1.9 | *c* |
| 18A,18B | 3.7 | 3.7 | 3.4 | 3.8 | 4.5 | 3.6 |
| 18B,3α | 2.4 | 2.6 | 2.8 | 3.4 | 3.0 | 2.4 |
| 19A,19B | 12.4 | 12.8 | 12.5 | 13.0 | 12.8 | 12.0 |
| 19A,6β | <0.4 | <0.4 | <0.4 | <0.4 | <0.4 | 1.0 |
| 20,20(OH) | - | 3.3 | 3.4 | 3.4 | *h* | - |

[a]At 300 MHz, in $CDCl_3$ solution except for **14** (pyridine-$d_5$). Chemical shifts are relative to residual $CHCl_3$ (δ 7.25). All these assignments were confirmed by double resonance experiments. The hydrogens (pro-*R* and pro-*S*) of the C-11 methylene were distinguished by NOE experiments (see Table 3). [b]Taken from ref. 6b (at 90 MHz) and included for comparative purposes. [c]Overlapped signal. [d]*Exo*-hydrogen with respect to ring B. [e]*Endo*-hydrogen with respect to ring B, long-range coupled with H-3α. [f]Collapsed into a singlet after addition of $D_2O$. [g]Disappeared after addition of $D_2O$. [h]Not observed.

were unsuccessful and under other conditions of reaction (larger amounts of base or time of reaction) only compound **14** was produced.

The structures of the derivatives **10-14** were supported by their $^1$H NMR spectra (Table 4) and other spectroscopic data (see Experimental). In particular, the inversion of the configuration at the C-20 carbon atom in **10-14** was rigorously established by NOE experiments (Table 3) and, in the case of the peracetyl derivative **10**, by comparison with the $^1$H NMR spectroscopic data of compound **15** (Tables 3 and 4), a substance previously obtained[6b] from eriocephalin (**1**).

Table 5. Effect of Eriocephalin (**1**) and its Derivatives (**7-14**) on the Feeding Behaviour of Larvae of *Spodoptera littoralis*

| Compound | Antifeedant Index[a] mean±S.E.M. | AI 50[b] Conc. ppm |
|---|---|---|
| **1**[c] | 5.5±8.95 | >1000 |
| **7** | -5.4±12.00 | >1000 |
| **8** | 34.1±13.71* | 390 |
| **9** | -21.1±13.86 | >1000 |
| **10** | 26.7±11.23 | >1000 |
| **11** | -14.3±12.18 | >1000 |
| **12** | 5.4±9.29 | >1000 |
| **13** | 54.0±9.72* | 39 |
| **14** | 30.4±13.95* | 300 |

[a]Antifeedant Index [(C-T)/(C+T)]x100 obtained when larvae were exposed to discs treated with 100 ppm of the test compounds; 10 replications per compound. [b]Probit analysis was used to calculate the concentration (ppm) required to give an Antifeedant Index of 50%. [c]Results from previous bioassays indicate some variation in the response of different generations of *S. littoralis* to this compound, for which a value of 48.9±5.98 was recorded in ref. 3c. *Significant difference in the amount of treatment and control discs eaten (Wilcoxon signed rank test, P<0.05).

The inversion of the configuration at C-20 in these compounds (**10-14**) can be rationalized considering that compound **9** undergoes an initial hydrolysis of its 20-acetate and a base-catalyzed hydrolysis[14] of the resulting 20,12-hemiacetal, which originates the epimeric 20,12-lactol by reclosure. This epimerization is sterically favoured by the disappearance of the strong interactions between the acetoxyl groups at the C-7α and C-20 positions when they are on the same side of the plane defined by the 20,12-lactol (compound **9**)[15].

Finally, several of the non-natural *neo*-clerodane derivatives described above were tested for antifeedant activity against larvae of *Spodoptera littoralis*. The results of these biossays are shown in Table 5, along with the activity of eriocephalin (**1**) and its derivative **9**, which have been included for comparative purposes. The results show that changes in the position of the acetates and the stereochemistry at C-20 alter the activity of the compound (compare **9**, a phagostimulant, with its derivatives **10**, **12**, **14** and particularly **13**, which was the most potent antifeedant in the present study). Major structural changes in the molecule of eriocephalin (**1**) result in a noticeable increase (**8**) or a decrease (**7**) in antifeedant activity. These results, and particularly those corresponding to compounds **8**, **13** and **14** (Table 5), demonstrate the interest of the chemical transformations of natural *neo*-clerodanes in the search for substances with potent antifeedant activity[5c,d].

## EXPERIMENTAL

Mps are uncorrected. Starting materials, eriocephalin (**1**) and its derivative **9**, were available from previous work[6b].

*(12S,20S)-7α-Acetoxy-20-O-acetyl-6,18;15,16-diepoxy-19-nor*-neo-*cleroda-4(18),5,13(16),14-tetraene-20,12-hemiacetal* (**3**) *and (5S,12S,20S)-7α-acetoxy-20-O-acetyl-15,16-epoxy-4β,18-methylenedioxy-6-oxo-19-nor*-neo-*cleroda-13(16),14-diene-20,12-hemiacetal* (**4**) *from eriocephalin* (**1**). A solution of **1** (100 mg, 0.215 mmol) and KO$^t$Bu (22 mg, 0.194 mmol) in dry THF (10 ml) was stirred at 0 °C for 72 h under Ar. Then, 4 ml of an aqueous $NH_4Cl$ saturated solution was added to the reaction and the mixture was extracted with EtOAc (3x10 ml). The EtOAc extract was dried over $MgSO_4$, filtered and evaporated to dryness giving a residue (72 mg) that was subjected to column chromatography (silica gel Merck No. 7734, deactivated with 15% (w/v) $H_2O$, *n*-hexane - EtOAc 4:1 as eluent) yielding compounds **3** (45 mg, 50% yield) and **4** (15 mg, 15% yield). Compound **3** was identical in all respects (mp, $[\alpha]_D$, IR, $^1H$ NMR, MS) with the previously described compound[7] and direct comparison (mmp, TLC) with an authentic sample confirmed this identity. Compound **4**: mp 160-161 °C (EtOAc - *n*-hexane); $[\alpha]_D^{21}$ -39.4° ($CHCl_3$; *c* 0.663). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3140, 1600, 1508, 880 (furan), 1750, 1740, 1240 (OAc), 1730 (ketone), 2950, 2920, 2870, 1460, 1435, 1380, 1370, 1170, 1160, 1115, 1075, 1030, 1020, 1005, 955, 945, 910, 800, 750. $^1H$ NMR: Table 1. $^{13}C$ NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 420 $[M\text{-ketene}]^+$ (0.4), 403 (3), 374 (5), 373 (5), 360 (2), 330 (2), 314 (10), 153 (31), 111 (40), 95 (24), 94 (34), 91 (10), 81 (23), 55 (11), 43 (100). (Anal. Found: C, 62.05; H, 6.64. $C_{24}H_{30}O_9$ requires: C, 62.32; H, 6.54%.)

*Sodium borohydride reduction of compound* **4** *to give (5R,12S,20S)-7α-acetoxy-20-O-acetyl-15,16-epoxy-6α-hydroxy-4β,18-methylenedioxy-19-nor*-neo-*cleroda-13(16),14-diene-20,12-hemiacetal* (**5**). Treatment of **4** (89 mg) with an excess of $NaBH_4$ (40 mg) in MeOH solution (10 ml), at room temperature for 2 h in the usual manner gave **5** (59 mg, after chromatographic purification; 66% yield) as an amorphous solid, mp 101-110 °C; $[\alpha]_D^{18}$ -14.0° ($CHCl_3$; *c* 0.157). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3480 (OH), 3140, 3120, 1600, 1505, 875 (furan), 1735, 1240 (OAc), 2930, 2860, 1450, 1375, 1160, 1080, 1020, 960, 890, 810, 730. $^1H$ NMR: Table 1. $^{13}C$ NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 404 $[M\text{-HOAc}]^+$ (16), 376 (9), 323 (8), 316 (19), 286 (11), 239 (15), 205 (31), 153 (55), 111 (93), 99 (84), 95 (87), 94 (100), 91 (41), 81 (56), 43 (10). (Anal. Found: C, 61.87; H, 6.89. $C_{24}H_{32}O_9$ requires: C, 62.05; H, 6.94%.)

*(5R,12S,20R)-7α-Acetoxy-20-O-benzoyl-15,16-epoxy-6α-hydroxy-4β,18-methylenedioxy-19-nor*-neo-*cleroda-13(16),14-diene-20,12-hemiacetal* (**6**) *from compound* **5**. A solution of **5** (25 mg) in pyridine (5 ml) was treated with an excess of BzCl at 80 °C for 5 h. Work-up in the usual manner yielded **6** (20 mg, 76% yield; after crystallization from MeOH): mp 241-243 °C; $[\alpha]_D^{18}$ +44.0° ($CHCl_3$; *c* 0.116). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3460 (OH), 3150, 3120, 1600, 1505, 875 (furan), 3060, 1720, 1580, 710 (OBz), 1730, 1260 (OAc), 2960, 2870, 1450, 1370, 1090, 1050, 890, 805. $^1H$ NMR: Table 1. EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 404 $[M\text{-HOBz}]^+$ (24), 344 (3), 233 (18), 162 (23), 105 (100), 95 (21), 94 (20), 91 (9), 81 (19), 77 (22), 55 (13), 43 (18). (Anal. Found: C, 66.21; H, 6.29. $C_{29}H_{34}O_9$ requires: C, 66.14; H, 6.51%.)

*X-Ray structure determination of compound* **6**. A suitable crystal of **6** (0.20x0.10x0.15 mm) was selected for data collection. $C_{29}H_{34}O_9$; $M_r$=526.583 g mol$^{-1}$. The lattice parameters were determined from 2θ values of 26 reflections with 10°<θ<40°: $a$=23.974(5), $b$=9.204(1), $c$=12.229(2) Å, $V$=2698.5(4) Å$^3$; space group $P2_12_12_1$ from systematic absences: h00 with h odd, 0k0 with k odd and 00l with l odd; Z=4. The data were collected on a diffractometer Philips PW 1100 with CuKα, graphite monochromator, bisecting geometry, ω/2θ scan mode. Two standard reflections were measured every 90 measurements during the data collection and no crystal decay was observed. From 2647 independent reflections up to θ=65° (hkl range: h≤28, k≤10, l≤14) only 1692 were considered observed with $I$>2σ($I$) and were used for structure determination and refinement. The data were corrected for Lorentz and polarization effects, but not for absorption.

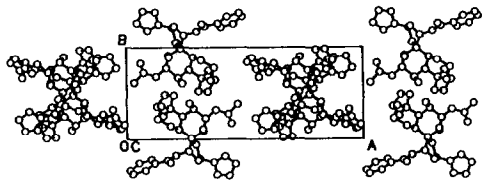



Figure 2. Stereoscopic drawing (PLUTO[20]) of the molecular packing of compound **6**.

The structure was solved by direct methods (SIR88)[16] and first refined by full-matrix least-squares with isotropic temperature factors and then by full-matrix least-squares with anisotropic temperature factors for all non-hydrogen atoms. The hydrogen atoms were located from difference Fourier maps. In the final refinement the H atoms were included isotropically as fixed contributors.

The weighting scheme used is empirical no to give trends in <wΔ$^2F$> vs. <$F_o$> and <sin θ/λ>. The final $R$ and $R_w$ values are 9.4 and 10.0%, respectively. The final difference synthesis shows the residual electron density no greater than 0.61 eÅ$^{-3}$. The number of variables is 337, degrees of freedom 1355 and ratio of freedom 5.02. The low precision of the structure and the high level of some thermal parameters [O(5), C(14), C(16)] are due to the poor crystal quality, yielding a weak diffraction pattern. Scattering factors were taken from the literature[17]. All calculations were performed on a VAX 6410 computer using the *X-Ray 76 System*[18] and several local programs. Lists of atomic coordinates, thermal parameters, structure factors, bond lengths, bond angles and torsion angles corresponding to compound **6** have been deposited at the Cambridge Crystallographic Data Centre.

In the crystalline state, rings A and B of the decalin moiety of compound **6** (Fig. 1) show chair conformation[19] and the A/B junction is *cis*; the two five-membered rings C (20,12-hemiacetal) and D (4β,18-methylenedioxy) show envelop conformation and they are almost perpendicular to the decalin plane (dihedral angles of 83°). Figure 2 shows the molecular packing of **6** into the unit cell[20]. There is one intermolecular hydrogen bond between the 6α-hydroxyl group and the O(2) oxygen atom [C(18)-O-C(19), see Fig. 1], where O(6)-H=1.09 Å, O(6)...O(2)=2.92 Å, H(6)...O(2)=1.91Å and the angle at HO(6) is 152° (1.5-x, 2-y, 1/2+z). In the packing there are also several intermolecular contacts less than the sum of the van der Waals radii [e.g. O(2)...O(7)=3.20 Å (i); O(5)...O(28)=3.13 Å (ii); O(4)...H(19)2=2.21 Å (iii); O(21)...H(7)=2.67 Å (iii); O(21)...H(5)=2.51 Å (iv); O(5)...H(24)=2.62 Å (v); C(16)...H(24)=2.55 Å (v); C(23)...H(15)=2.62 Å (vi); (i) 1.5-x, 2-y, 1/2+z; (ii) 1-x, y-1/2, 1/2-z; (iii) 1.5-x, 1-y, z-1/2; (iv) 1.5-x, 1-y, 1/2+z; (v) x-1/2, 1/2-y, -z; (vi) 1.5-x, -y, z-1/2].

*(5S,12S,20S)-7α-Acetoxy-20-O-acetyl-15,16-epoxy-6-oxo-19-nor*-neo-*cleroda-13(16),14-diene-20,12-hemiacetal-4β,18-(S)- and (R)-ethylidenedioxy derivatives* (**7** *and* **8**, *respectively*) *from eriocephalin* (**1**). A solution of **1** (104 mg, 0.23 mmol) and NaO$^t$Bu (19.5 mg, 0.20 mmol) in dry THF (15 ml) was stirred at 0 °C for 15 min under Ar. Then, MeCHO (78 mg, 1.76 mmol) was added and the reaction mixture stirred for a further 48 h. Work-up as described above for compound **4** yielded [after column chromatography (silica gel deactivated with 15% $H_2O$, *n*-hexane-EtOAc 4:1 as eluent)] compounds **3** (46 mg, 50% yield), **4** (8 mg, 7.5%) and **7** (9 mg, 8%).

A solution of **1** (560 mg, 1.2 mmol), NaO$^t$Bu (100 mg, 1.04 mmol) and MeCHO (5.3 g, 120 mmol) in dry THF (30 ml) was left at 0 °C for 3 days. Work-up as above gave compounds **3** (241 mg, 48% yield), **7** (40 mg, 7%) and **8** (35 mg, 6%) after column chromatography (see above).

*Compound* **7**: mp 228-230 °C (decomp.; from EtOAc - *n*-hexane); $[\alpha]_D^{20}$ -48.8° ($CHCl_3$; *c* 0.381). IR (KBr) $\nu_{max}$ cm$^{-1}$: 3150, 3120, 1510, 875 (furan), 1745, 1730 (OAc and ketone), 1254 (OAc), 2990, 2940, 2860, 1450, 1390, 1375, 1150, 1130, 1120, 1090, 1010, 960, 900, 800. $^1$H NMR: Table 1. $^{13}$C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 448 $[M-CO]^+$ (0.01), 417 $[M-OAc]^+$ (0.4), 416 $[M-HOAc]^+$ (0.1), 374 (0.3), 314 (1), 220 (2), 187 (2), 173 (3), 163 (4), 153 (7), 111 (27), 95 (21), 94 (29), 93 (15), 91 (12), 81 (27), 79 (15), 69 (13), 55 (13), 43 (100). (Anal. Found: C, 63.19; H, 6.87. $C_{25}H_{32}O_9$ requires: C, 63.01; H, 6.77%.)

*Compound* **8**: mp 223-225 °C (EtOAc - *n*-hexane); $[\alpha]_D^{19}$ -29.0° ($CHCl_3$; *c* 0.131). IR (KBr) $\nu_{max}$ cm$^{-1}$: 3140, 3120, 1505, 875 (furan), 1745, 1740, 1730 (OAc and ketone), 1240 (OAc), 2950, 2860, 1460, 1390, 1380, 1150, 1110, 1080, 1020, 940, 900, 880, 870, 810. $^1$H NMR: Table 1. $^{13}$C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 417 $[M-OAc]^+$ (0.04), 374 (0.1), 313 (0.3), 220 (0.1), 199 (0.2), 163 (0.4), 157 (0.3), 133 (0.5), 119 (0.5), 105 (1), 95 (1), 94 (3), 93 (2), 91 (3), 79 (2), 58 (9), 55 (2), 43 (100). (Anal. Found: C, 62.76; H, 6.93. $C_{25}H_{32}O_9$ requires: C, 63.01; H, 6.77%.)

*Derivatives* **10-14** *from compound* **9**. A solution of **9** (1.5 g, 2.96 mmol) and NaO$^t$Bu (370 mg, 3.85 mmol) in dry THF (50 ml) was stirred at 0 °C for 15 min and then at room temperature for 24 h. Work-up in the usual manner yielded a crude of reaction (1.4 g) which was subjected to column chromatography (silica gel, $CHCl_3$-MeOH 49:1 as eluent) giving the following compounds in order of increasing chromatographic polariry: **10** (146 mg, 9% yield), **11** (130 mg, 6%), **12** (220 mg, 16%), **13** (700 mg, 51%) and **14** (130 mg, 11.5%).

*(12S,20R)-6α,7α,19-Triacetoxy-20-O-acetyl-4α,18;15,16-diepoxy*-neo-*cleroda-13(16),14-diene-20,12-hemiacetal* (**10**). Amorphous solid, mp 95-105 °C; $[\alpha]_D^{22}$ +20.1° ($CHCl_3$; *c* 0.716). IR (KBr) $\nu_{max}$ cm$^{-1}$ 3140, 3120, 1505, 875 (furan), 3040 (oxirane), 1740 br, 1260 br, 1230 br (OAc), 2950, 2880, 1370, 1160, 1095, 1030, 945, 890, 800. $^1$H NMR: Table 4. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 549 $[M+H]^+$ (1.2), 548 $[M]^+$ (0.2), 488$[M-HOAc]^+$ (37), 458 (19), 445 (21), 428 (4), 387 (97), 327 (16), 297 (28), 233 (13), 216 (51), 186 (32), 159 (27), 145 (37), 117 (22), 105 (36), 95 (72), 94 (56), 91 (44), 81 (59), 79 (44), 55 (30), 43 (100). (Anal. Found: C, 61.48; H, 6.47. $C_{28}H_{36}O_{11}$ requires: C, 61.30; H, 6.61%.)

*(12S,20S)-6α,7α,19-Triacetoxy-4α,18;15,16-diepoxy*-neo-*cleroda-13(16),14-diene-20,12-hemiacetal*[21] (**11**). Amorphous solid, mp 100-110 °C; $[\alpha]_D^{22}$ -5.6° ($CHCl_3$; *c* 0.248). IR (KBr) $\nu_{max}$ cm$^{-1}$: 3460 (OH), 3140, 3120, 1505, 875 (furan), 3040 (oxirane), 1740 br, 1260 br, 1230 br (OAc), 2950, 2880, 1370, 1160, 1090, 1030, 800. $^1$H NMR: Table 4. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 506 $[M]^+$ (0.02), 488 $[M-H_2O]^+$

(0.1), 446 [M-HOAc]$^+$ (0.04), 391 (0.2), 201 (2), 171 (3), 159 (3), 145 (4), 105 (4), 97 (9), 95 (5), 91 (4), 69 (4), 43 (100). (Anal. Found: C, 61.48; H, 6.84. $C_{26}H_{34}O_{10}$ requires: C, 61.65; H, 6.77%.)

*(12S,20S)-7α,19-Diacetoxy-4α,18;15,16-diepoxy-6α-hydroxy-*neo*-cleroda-13(16),14-diene-20,12-hemiacetal* (**12**). Mp 219-222 °C (EtOAc - *n*-hexane); $[\alpha]_D^{21}$ +7.2° ($CHCl_3$; *c* 0.483). IR (KBr) $\nu_{max}$ cm$^{-1}$: 3500, 3420 (OH), 3140, 3120, 1505, 875 (furan), 3040 (oxirane), 1735, 1250 (OAc), 2930, 2880, 1480, 1370, 1160, 1150, 1090, 1030, 980, 915, 840, 790, 780. $^1$H NMR: Table 4. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 464 [M]$^+$ (5), 404 [M-HOAc]$^+$ (0.6), 387 (12), 345 (13), 339 (19), 327 (20), 279 (17), 219 (22), 201 (20), 173 (25), 95 (21), 91 (18), 81 (11), 43 (100). (Anal. Found: C, 62.18; H, 6.76. $C_{24}H_{32}O_9$ requires: C, 62.05; H, 6.94%.)

*(12S,20S)-6α,19-Diacetoxy-4α,18;15,16-diepoxy-7α-hydroxy-*neo*-cleroda-13(16),14-diene-20,12-hemiacetal* (**13**). Mp 158-160 °C (EtOAc - *n*-hexane); $[\alpha]_D^{21}$ -3.3° ($CHCl_3$; *c* 0.694). IR (KBr) $\nu_{max}$ cm$^{-1}$: 3540, 3380 (OH), 3130, 3110, 1505, 875 (furan), 3050 (oxirane), 1740, 1700, 1280, 1250 (OAc), 2940, 1460, 1390, 1210, 1160, 1110, 1090, 1020, 1000, 970, 920, 800, 780, 760, 690. $^1$H NMR: Table 4. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 464 [M]$^+$ (32), 446 [M-$H_2O$]$^+$ (37), 404 [M-HOAc]$^+$ (12), 387 (100), 357 (15), 345 (22), 327 (52), 297 (26), 281 (14), 251 (5), 239 (3), 43 (7). (Anal. Found: C, 61.83; H, 7.03. $C_{24}H_{32}O_9$ requires: C, 62.05; H, 6.94%.)

*(12S,20S)-4α,18;15,16-Diepoxy-6α,7α,19-trihydroxy-*neo*-cleroda-13(16),14-diene-20,12-hemiacetal* (**14**). Mp 205-208 °C (EtOAc); $[\alpha]_D^{21}$ -56.3° ($CHCl_3$-MeOH 1:1; *c* 0.263). IR (KBr) $\nu_{max}$ cm$^{-1}$: 3530, 3440, 3320 (OH), 3140, 1505, 875 (furan), 3030 (oxirane), 2950, 1440, 1360, 1270, 1160, 1150, 1120, 1060, 1040, 1020, 1000, 940, 920, 900, 800. $^1$H NMR: Table 4. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 380 [M]$^+$ (0.1), 362 [M-$H_2O$]$^+$ (0.1), 344 [M-2$H_2O$]$^+$ (0.1), 245 (1), 227 (3), 175 (5), 161 (5), 131 (8), 105 (15), 97 (53), 95 (22), 94 (11), 91 (25), 79 (27), 69 (49), 55 (38), 53 (21), 41 (100). (Anal. Found: C, 63.31; H, 7.36. $C_{20}H_{28}O_7$ requires: C, 63.14; H, 7.42%.)

*Insect bioassays.* A two-choice bioassay was used to assess the antifeedant activity of the compounds against larvae of *Spodoptera littoralis* (Boisduval). The compounds were presented to final stadium larvae on glass-fibre discs (Whatman GF/A 2.1 cm diam.), made palatable by the addition of 100 µl of 50 mM sucrose solution and subsequently air-dried. Discs receiveing sucrose only were used as controls. Treatment discs were made by adding a further 100 µl of a solution containing one of the test compounds at one of four concentrations (10, 100, 500 and 1000 ppm). These discs were then redried and all the discs were weighed. Larvae 24-36 h into the final stadium that had been deprived of food for 4 h were placed singly in Petri dishes along with a control disc and treatment disc. The larvae remained in the Petri dishes for 18 h or until approximately 50% of either disc had been consumed. The discs were re-weighed and the Antifeedant Index [(C-T)/(C+T)]x100 calculated, where C and T represent the amount of control and treatment disc eaten, respectively. Each concentration of the test compounds was tested against 10 different larvae.

***Acknowledgements.*** This work was supported by the DGICYT (grant PB90-0078, Spain) and "Consejería de Educación y Cultura de la Comunidad de Madrid" (grant No. 276/92, Spain). The authors thank Paul Green for his help in culturing the insects. The insect bioassays were carried out under MAFF licence No. PHF 1020/10 issued under Import and Export (Plant Health Great Britain) Order 1980 and Plant Pests (Great Britain) Order 1980.

## REFERENCES AND NOTES


1. Although the hydrocarbon skeleton of these diterpenes is biogenetically derived from an *ent*-labdane and they should be named *ent*-clerodanes, we prefer to use the term *neo*-clerodane proposed by Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc., Chem. Commun.* **1979**, 97-99, because it is the nomenclature used in the great part of the articles published on this subject since 1979.
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8. The results of the NOE experiment on compound 4 (Table 3) were not reliable for assigning the stereochemistry of the C-4 carbon atom, because the observed NOE between the H-5β proton and one of the C-18 methylene protons ($H_A$-18, Table 3) must be expected for both configurations at C-4 (see the molecular model of 4). Obviously, exhaustive NOE experiments could allow the unambiguous assignment of this stereochemistry in 4, but we preferred to establish more easily and securely this structural feature by other ways.
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(*Received in UK* 20 *September* 1994; *accepted* 7 *October* 1994)