# Chemical Transformations of the Neoclerodane Diterpenes Eriocephalin and Capitatin: An Access to 4,5-*seco*-Neoclerod-5(19)-ene Derivatives[1]

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Treatment of the 7-*O*-acetyl derivative (**2**) of eriocephalin (**1**) with HCl yielded minor quantities of the 4,5-*seco*-neoclerod-5(19)-ene derivatives **3** and **4**. Under the same treatment, capitatin (**6**) underwent an identical fragmentation reaction giving **9** in good yield, via the unstable chlorohydrin intermediate **8**. Sodium cyanoborohydride reduction of **9** yielded compounds **10** and **11** by a stereoselective 1,4-reduction process. The mechanistic aspects of these transformations are discussed. The 4,5-seco derivatives **9**, **10**, and **11** can be useful intermediates for the synthesis of natural and synthetic neoclerodane diterpenoids, which are of interest on account of their activity as insect antifeedants and other important biological properties.

A large number of diterpenoids belonging to the neoclerodane[3] type have been isolated from plants and microorganisms in the past few years.[4] These compounds have attracted interest because of their biological activities, especially as insect antifeedants and as antifungal, antitumor, antimicrobial, and molluscicidal agents.[4] The species of the genus *Teucrium* (family Labiatae) are the most abundant natural source of this kind of diterpenoids.[4−8]

In our studies on neoclerodane diterpenoids from *Teucrium* species, we were interested in establishing chemical correlations between some of these compounds[9,10] and also in obtaining synthetic derivatives in order to test their biological activities.[11−13] In this paper we wish to report the transformation of 19-acetoxy-4α,18-epoxy-6-oxo-neoclerodane diterpenes (such as **2** and **6**) into their corresponding 4,5-*seco*-neoclerod-5(19)-ene derivatives **3**, **4**, and **9**, and the stereoselective reduction of the enone structural moiety of **9**, providing data on the mechanistic pathway of these reactions. The 4,5-*seco*-neoclerodanes, such as **3**, **4**, and **9**−**11**, can be useful intermediates for the synthesis of other neoclerodane diterpenoids.

## Results and Discussion

The starting material for all the reactions reported below was eriocephalin (**1**), a naturally occurring compound isolated for the first time from *Teucrium eriocephalum* in minute amounts (0.0033% on dry plant material)[14] and subsequently found in large quantities (1.1−1.3%) in the aerial parts of *Teucrium lanigerum*.[15] In order to avoid the isomerization of eriocephalin (**1**) into 20,7α-lactols[15] under basic or acid conditions, we decided to carry out the chemical transformations with the 7-*O*-acetyl derivative **2**[14,15] of the natural diterpenoid **1**.

Treatment of **2** with HCl gave a complex mixture of products and minor quantities of two pure substances (**3**, 7% yield, and **4**, 6% yield). Elemental analysis and LRMS confirmed the $C_{24}H_{29}O_8Cl$ molecular formula for **3**, and its UV spectrum revealed the existence of an α,β-unsaturated carbonyl function (λ max 240 nm, log ε 3.92). The $^1$H- and $^{13}$C-NMR spectra of this compound (Tables 1 and 2, respectively) were in agreement with the proposed structure of **3**, showing characteristic signals for an α-chloromethylene ketone grouping [$\delta_H$ 4.05, 2H, s (2H-18); $\delta_C$ 48.0 t (C-18) and 202.0 s (C-4)], two acetates [$\delta_H$ 2.18 and 2.07, both 3H, s; $\delta_C$ 169.9 s, 169.8 s, 21.2 q, and 20.6 q (OAc at C-7α and C-20)] and an exocyclic methylene group conjugated with a ketone [$\delta_H$ 5.25, 1H, dd, and 5.78, 1H, d, $J_{gem}$ = 1.2 Hz, $J_{allyl}$ = 0.7 Hz (C-19 protons); $\delta_C$ 146.1 s (C-5), 197.2 s (C-6), and 123.1 t (C-19)], instead of the signals corresponding to the 4α,18-oxirane and the C-19 acetoxymethylene group of the starting material **2**.[14,15]

Compound **4** ($C_{22}H_{27}O_7Cl$), the 20-deacetyl derivative of **3**, was confirmed by the $^1$H-NMR spectrum (Table 1) [$\delta_{H\text{-}20}$ 5.58 (at $\delta$ 6.52 in **3**); only one OAc group at C-7α: $\delta$ 2.17, 3H, s, geminal H-7$\beta$ at $\delta$ 5.39 (at $\delta$ 5.40 in **3**)]. The stereochemistry of **4** at its C-20 asymmetric center was not ascertained. We suppose, however, that it possesses a 20*S* configuration because it is known[12] that in eriocephalin (**1**) and related compounds (such as **2**) the hydrolysis of the C-20-acetate produces an epimerization at C-20, via hydrolysis of the resulting 20,12-hemiacetal and reclosure to the epimeric 20,12-lactol. This epimerization is sterically favored by the disappearance of the strong interactions between the oxygenated substituents at the C-7α and C-20 positions.

Several attempts at improving the yield of compounds **3** and/or **4** were unsuccessful, inasmuch as very complex reaction mixtures were always obtained. Only in one of these reactions (see Experimental Section) a minor compound (**5**, 9% yield, $C_{22}H_{29}O_8Cl$) was isolated. This substance was formed from **2** by an attack of the nucleophile on the primary center of the epoxide (C-18), originating the corresponding chlorohydrin,[11] and an additional hydrolysis of both C-7α and C-20 acetates, with inversion of the configuration at this last asymmetric carbon. This structural feature of **5** was established by NOE experiments. The irradiation at $\delta$ 1.09 (Me-17) caused NOE enhancement in the signal of the H-20 proton ($\delta$ 5.36, 3%) and the irradiation at $\delta$ 5.36 (H-20) produced NOE enhancement (9%) on the Me-17 protons ($\delta$ 1.09), thus establishing that the Me-17 and C-20 protons are on the same side of the plane defined by the 20,12-lactol.[12]

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**Table 1.** $^1$H-NMR Spectral Data of Compounds **3**−**5** and **7**−**14**

| proton(s) | **3** | **4** | **5** | **7** | **8** | **9** | **10**[a] | **11**[b] | **12** | **13** | **14** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H-4 | | | | | | | | 3.75 (m) | | | |
| H-5$\beta$ | | | | | | | 3.03 (qdd)[c] | 3.02 (br qd)[d] | | | |
| H-6$\beta$ | | | | | | | | | 3.65 (dd) | 4.00 (br d) | 4.11 (dd) |
| H-7$\beta$ | 5.40 (d) | 5.39 (d) | 3.68 (d) | 5.77 (d) | 5.39 (d) | 5.46 (d) | 5.24 (dd)[c] | 5.23 (br d)[d] | 5.36 (t) | 5.24 (dd) | 5.37 (t) |
| H-8$\beta$ | *e* | *e* | *e* | *e* | 2.25 (qd) | *e* | *e* | *e* | 1.82 (qd) | ~1.92[e] | *e* |
| $H_A$-11 | *e* | *e* | 2.19 (dd) | 3.15 (d) | 2.58 (dd) | 2.44 (dd) | 2.46 (dd) | 2.44 (dd) | 2.33 (dd) | 2.38 (dd) | 2.44 (d) |
| $H_B$-11 | *e* | *e* | 2.30 (dd) | 3.80 (d) | 2.82 (dd) | 2.84 (dd) | 3.12 (dd) | 3.12 (dd) | 2.45 (dd) | 2.47 (dd) | 2.44 (d) |
| H-12 | 5.26 (dd) | 5.18 (dd) | 5.15 (br t) | | 5.61 (dt)[f] | 5.52 (dd) | 5.51 (dd) | 5.51 (dd) | 5.31 (br t) | 5.34 (t) | 5.32 (t) |
| H-14 | 6.36 (dd) | 6.49 (dd) | 6.35 (dd) | 6.72 (dd) | 6.34 (dd) | 6.39 (dd) | 6.43 (dd) | 6.42 (dd) | 6.33 (t) | 6.34 (t) | 6.35 (t) |
| H-15 | 7.38 (m)[e] | 7.39 (t) | 7.42 (t) | 7.45 (t) | 7.44 (t) | 7.44 (t) | 7.46 (t) | 7.44 (t) | 7.40 (m)[e] | 7.42 (m)[e] | 7.43 (m)[e] |
| H-16 | 7.38 (m)[e] | 7.42 (m) | 7.41 (m) | 8.07 (dd) | 7.41 (m) | 7.46 (m) | 7.52 (m) | 7.51 (m) | 7.40 (m)[e] | 7.42 (m)[e] | 7.43 (m)[e] |
| Me-17 | 1.01 (3H, d) | 1.11 (3H, d) | 1.09 (3H, d) | 1.46 (3H, d) | 0.93 (3H, d) | 1.17 (3H, d) | 1.25 (3H, d) | 1.25 (3H, d) | 1.00 (3H, d) | 1.05 (3H, d) | 1.09 (3H, d) |
| $H_A$-18 | 4.05 (s) | 4.04 (s) | 3.80 (dd) | 2.45 (d)[g] | 3.45 (dd) | 4.04 (s) | 4.05 (s) | 3.41 (dd) | 2.43 (d)[g] | 3.92 (dd) | 3.91 (d) |
| $H_B$-18 | 4.05 (s) | 4.04 (s) | 3.86 (d) | 3.06 (dd)[h] | 3.85 (d) | 4.04 (s) | 4.05 (s) | 3.55 (dd) | 3.14 (dd)[h] | 4.00 (d) | 4.02 (dd) |
| $H_A$-19 | 5.25 (dd) | 5.20 (dd) | 3.98 (dd) | 4.47 (d) | 5.03 (s) | 5.44 (t) | | | 4.75 (dd) | 5.34 (br d) | 4.14 (dd) |
| $H_B$-19 | 5.78 (d) | 5.74 (d) | 4.63 (d) | 4.66 (d) | 5.03 (s) | 6.10 (t) | | | 5.85 (d) | 5.43 (d) | 5.74 (d) |
| Me-19 | | | | | | | 1.18 (3H, d) | 1.14 (3H, d) | | | |
| H-20 | 6.52 (s) | 5.58 (d)[i] | 5.36 (s) | 10.04 (s) | | | | | | | |
| OAc | 2.18 (3H, s) | 2.17 (3H, s) | 2.14 (3H, s) | 2.13 (3H, s) | 2.13 (3H, s) | 2.16 (3H, s) | 2.14 (3H, s) | 2.13 (3H, s) | 2.13 (3H, s) | 2.15 (3H, s) | 2.17 (3H, s) |
| | 2.07 (3H, s) | | | 2.04 (3H, s) | 2.00 (3H, s) | | | | 2.04 (3H, s) | 2.00 (3H, s) | 1.41 (3H, s)[j] |
| OH-4 | | | *k* | | 3.42 (s)[l] | | | | | 3.49 (s)[l] | |
| OH-6 | | | | | | | | | 3.45 (s)[l] | 4.08 (s)[l] | |

| $J_{H,H}$ (Hz) | **3** | **4** | **5** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4,18A | | | | | | | | 6.7[m] | | | |
| 4,18B | | | | | | | | 4.3[m] | | | |
| 5$\beta$,10$\beta$ | | | | | | | 6.7 | 6.7 | | | |
| 5$\beta$,19 | | | | | | | 6.7 | 6.7 | | | |
| 6$\beta$,7$\beta$ | | | | | | | | | 3.9 | 3.2 | 3.8 |
| 7$\beta$,8$\beta$ | 6.5 | 6.5 | 0.5 | 6.8 | 5.5 | 5.5 | 5.9 | 5.9 | 3.9 | 3.9 | 3.8 |
| 8$\beta$,17 | 7.3 | 7.3 | 6.7 | 7.5 | 7.5 | 7.2 | 7.3 | 7.3 | 7.0 | 7.0 | 7.0 |
| 11A,11B | *e* | *e* | 13.6 | 17.6 | 13.2 | 13.0 | 13.1 | 13.1 | 14.1 | 14.2 | 0 |
| 11A,12 | 6.9 | 7.0 | 8.2 | | 1.7 | 7.1 | 9.6 | 9.8 | 8.8 | 8.7 | 8.6 |
| 11B,12 | 9.3 | 9.4 | 7.8 | | 9.1 | 7.2 | 6.3 | 6.2 | 8.6 | 8.7 | 8.6 |
| 14,15 | 1.9 | 1.8 | 1.9 | 1.9 | 1.8 | 1.9 | 1.8 | 1.8 | 1.5 | 1.4 | 1.5 |
| 14,16 | 0.9 | 0.8 | 1.0 | 0.8 | 0.9 | 0.9 | 0.9 | 0.8 | 1.5 | 1.4 | 1.5 |
| 15,16 | *e* | 1.8 | 1.7 | 1.4 | 1.8 | 1.9 | 1.8 | 1.8 | *e* | *e* | *e* |
| 18A,18B | 0 | 0 | 12.3 | 3.7 | 11.6 | 0 | 0 | 11.1 | 3.5 | 11.5 | 11.2 |
| 18A,3$\alpha$ | 0 | 0 | 1.4 | 0 | 1.3 | 0 | 0 | 0 | 0 | 0.7 | 0 |
| 18B,3$\alpha$ | 0 | 0 | 0 | 1.9 | 0 | 0 | 0 | 0 | 2.4 | 0 | 1.2 |
| 19A,19B | 1.2 | 1.3 | 12.0 | 11.9 | 0 | 1.0 | | | 12.8 | 12.9 | 10.0 |
| 19A,6$\beta$ | | | | | | | | | 1.3 | <0.5 | 2.8 |
| 19A,10$\beta$ | 0.7 | 0.7 | 1.1 | 0 | 0 | 1.0 | | | 0 | 0 | 0 |
| 19B,10$\beta$ | 0 | 0 | 0 | 0 | 0 | 1.0 | | | 0 | 0 | 0 |

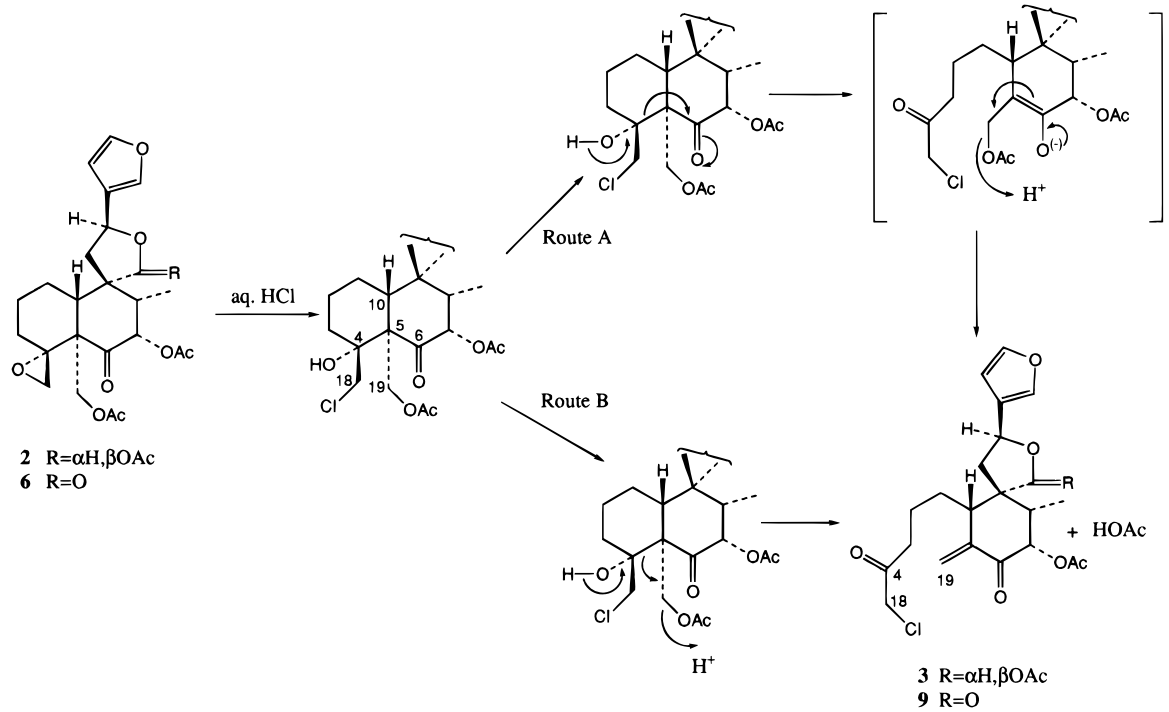
[a] These are C-3 methylene protons at $\delta$ 2.56 (2H, t, $J_{vic}$ = 7.0 Hz). [b] Some proton(s) signals of **11** appeared as double signals: Me-17 and Me-19 at $\delta$ 1.26 (d, $J_{vic}$ = 7.3 Hz) and 1.13 (d, $J_{vic}$ = 6.7 Hz), respectively, inasmuch as **11** is an epimeric mixture at C-4 (see footnote *m*). [c] $J5\beta,7\beta$ = 0.8 Hz. [d] $J5\beta,7\beta$ < 0.3 Hz. [e] This is an overlapped signal. [f] This is allylic, $J_{12,16}$ = 1.5 Hz. [g] This is exo hydrogen with respect to ring B. [h] This is endo hydrogen with respect to ring B. [i] This collapsed into a singlet after addition of $D_2O$; $\delta_{OH(20)}$ 2.89 (d, $J_{H,OH}$ = 2.2 Hz). [j] This is an orthoacetate signal. [k] Value was not observed. [l] Signal disappeared after addition of $D_2O$. [m] The other C-4 epimer showed $J_{4,18A}$ = 0 Hz, $J_{4,18B}$ = 3.4 Hz, and $J_{18A,18B}$ = 11.1 Hz.

**Table 2.** $^{13}$C-NMR Spectral Data of Compounds **3**, **5**, **7**−**9**, and **11**−**14**

| carbon | **3** | **5** | **7** | **8** | **9** | **11**[a] | **12** | **13** | **14** |
|---|---|---|---|---|---|---|---|---|---|
| C-1 | 22.3 (t) | 24.2 (t) | 22.0 (t) | 21.9 (t)[b] | 22.2 (t) | 25.4 (t) | 22.4 (t) | 22.5 (t)[b] | 22.0 (t)[b] |
| C-2 | 30.7 (t) | 21.0 (t) | 25.0 (t) | 22.0 (t)[b] | 29.0 (t) | 28.1 (t) | 24.9 (t) | 22.9 (t)[b] | 22.4 (t)[b] |
| C-3 | 39.0 (t) | 29.2 (t) | 30.7 (t) | 29.0 (t) | 39.1 (t) | 33.6 (t) | 30.8 (t) | 29.8 (t) | 27.4 (t) |
| C-4 | 202.0 (s) | 75.7 (s) | 60.8 (s) | 77.8 (s) | 202.1 (s) | 70.7 (d) | 66.4 (s) | 77.5 (s) | 77.0 (s) |
| C-5 | 146.1 (s) | 55.9 (s) | 54.2 (s) | 55.6 (s) | 143.0 (s) | 44.4 (d) | 44.1 (s) | 47.7 (s) | 37.4 (s) |
| C-6 | 197.2 (s) | 211.3 (s) | 199.6 (s) | 206.5 (s) | 194.2 (s) | 203.6 (s) | 71.6 (d) | 75.9 (d)[c] | 69.9 (d) |
| C-7 | 77.1 (d) | 80.2 (d) | 75.2 (d) | 75.6 (d) | 75.5 (d) | 76.7 (d) | 74.3 (d) | 74.4 (d)[c] | 73.8 (d) |
| C-8 | 40.2 (d) | 40.0 (d) | 40.1 (d) | 39.7 (d) | 41.7 (d) | 45.7 (d) | 41.2 (d) | 41.7 (d) | 40.1 (d) |
| C-9 | 53.8 (s) | 45.5 (s) | 49.4 (s) | 49.5 (s) | 49.3 (s) | 50.0 (s) | 51.2 (s) | 51.9 (s) | 51.1 (s) |
| C-10 | 48.7 (d) | 42.1 (d) | 46.1 (d) | 43.6 (d) | 45.9 (d) | 47.3 (d) | 52.7 (d) | 51.6 (d) | 47.7 (d) |
| C-11 | 42.9 (t) | 37.3 (t) | 50.3 (t) | 44.9 (t) | 44.2 (t) | 44.6 (t) | 46.0 (t) | 47.4 (t) | 46.7 (t) |
| C-12 | 74.1 (d) | 70.3 (d) | 191.9 (s) | 71.8 (d) | 71.0 (d) | 70.5 (d) | 71.0 (d) | 71.1 (d) | 71.2 (d) |
| C-13 | 126.5 (s) | 127.9 (s) | 127.0 (s) | 126.0 (s) | 124.4 (s) | 123.4 (s) | 124.7 (s) | 125.1 (s) | 125.0 (s) |
| C-14 | 108.6 (d) | 108.3 (d) | 108.3 (d) | 107.6 (d) | 108.0 (d) | 108.3 (d) | 107.8 (d) | 107.8 (d) | 107.7 (d) |
| C-15 | 143.7 (d) | 144.0 (d) | 144.4 (d) | 144.4 (d) | 144.3 (d) | 144.3 (d) | 144.3 (d) | 144.3 (d) | 144.4 (d) |
| C-16 | 139.7 (d) | 138.8 (d) | 147.4 (d) | 138.3 (d) | 139.5 (d) | 140.3 (d) | 139.4 (d) | 139.4 (d) | 139.5 (d) |
| C-17 | 13.6 (q) | 13.2 (q) | 11.3 (q) | 12.9 (q) | 11.8 (q) | 10.5 (q) | 12.4 (q) | 12.5 (q) | 12.4 (q) |
| C-18 | 48.0 (t) | 48.2 (t) | 51.9 (t) | 47.9 (t) | 48.0 (t) | 50.4 (t) | 48.4 (t) | 49.6 (t) | 47.9 (t) |
| C-19 | 123.1 (t) | 62.4 (t) | 62.3 (t) | 61.8 (t) | 124.0 (t) | 11.1 (q) | 62.8 (t) | 63.2 (t) | 61.4 (t) |
| C-20 | 97.9 (d) | 99.9 (d) | 203.1 (d) | 174.7 (s) | 174.9 (s) | 175.7 (s) | 174.3 (s) | 174.5 (s) | 174.5 (s) |
| OAc | 169.9 (s) | 170.1 (s) | 170.3 (s) | 169.8 (s) | 170.0 (s) | 170.3 (s) | 171.2 (s) | 172.7 (s) | 171.1 (s) |
| | 169.8 (s) | 20.5 (q) | 169.5 (s) | 169.6 (s) | 20.6 (q) | 20.6 (q) | 170.5 (s) | 169.8 (s) | 21.0 (q) |
| | 21.2 (q) | | 20.6 (q) | 20.8 (q) | | | 21.1 (q) | 21.3 (q) | 109.5 (s)[d] |
| | 20.6 (q) | | 20.5 (q) | 20.4 (q) | | | 20.8 (q) | 20.9 (q) | 23.9 (q)[d] |

[a] The carbon atoms of **11** appeared as double signals ($\Delta\delta$ 0.1−0.3 ppm), except for those corresponding to the C-8, C-11, C-13 - C-17, C-19, and the OAc group, as a consequence of the mixture of epimers at the C-4 asymmetric center. [b,c] These assignments may be reversed. [d] Signals correspond to the orthoacetate group.

**Scheme 1**




The poor yields for compounds **3** and **4** are probably due to side reactions caused by the lability of the 20-*O*-acetyl 20,12-lactol of **2**, which is unstable even under very mild acidic or basic conditions.[9,12,15] For this reason, we decided to transform the 20-*O*-acetyl 20,12-hemiacetal of **2** into the corresponding 20,12-lactone.

Oxidation of **2** with Jones' reagent gave capitatin (**6**, 49% yield, a neoclerodane diterpene previously isolated from *Teucrium capitatum*[16]) and the keto aldehyde **7** (11%). The structure of **7** was confirmed by its spectroscopic data (see Tables 1 and 2, and Experimental Section) and those of other related neoclerodane derivatives.[17−20] The formation of compounds **6** and **7** from **2** can be rationalized by an initial acid catalyzed hydrolysis of the 20-*O*-acetyl group[9,15] and the subsequent oxidation of both closed and opened forms of the 20,12-hemiacetal. The C-20 aldehyde of **7** was not oxidized to carboxylic acid, probably because of steric hindrance.

Treatment of capitatin (**6**) with HCl[11] gave the highly unstable chlorohydrin **8** (98%), which was converted to the 4,5-seco derivative **9** (80%) under mild acidic conditions. The structure of **9** was in agreement with its $^1$H- and $^{13}$C-NMR spectra (Tables 1 and 2) and IR and UV data (see Experimental Section).

The reduction of **9** with sodium cyanoborohydride yielded compound **11**(63%), as a mixture of epimers at C-4, and compound **10** (10%). In both substances, the reducing reagent produced a stereoselective 1,4-reduction of the α,β-unsaturated keto grouping and, in the case of **11**, an additional reduction of the C-4 ketone. The α-configuration of the Me-19 group in **10** was evident by its $^1$H-NMR spectrum (Table 1) in which a long-range W-type coupling ($J$ = 0.8 Hz) between the H-7β ($\delta$ 5.24 dd, $J_{7\beta8\beta}$ = 5.9 Hz) and the C-5 methine ($\delta$ 3.03 quintet of doublets, $J_{5,\text{Me-19}} = J_{5,10\beta}$ = 6.7 Hz) protons was observed. These results clearly established that the H-5 proton is in the β and cis position with respect to H-10β ($J_{5\beta,10\beta}$ = 6.7 Hz) and H-5β and H-7β are equatorially oriented ($J_{5\beta,7\beta}$ = 0.8 Hz). Consequently, the Me-19 group of **10** is in the α and axial position. The stereoselectivity of this 1,4-reduction can be rationalized by considering the protonation of the enolate intermediate which occurs at the C-5 carbon from the β-face, trans with respect to the side chain attached to the C-10α contiguous position.

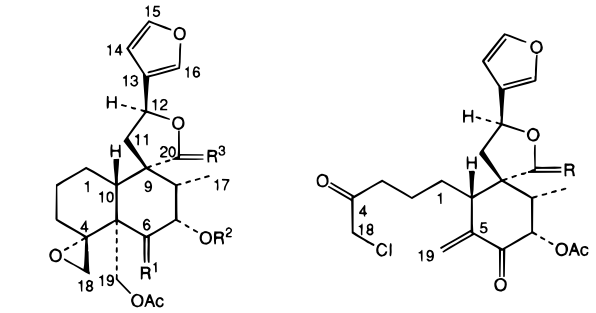
The structures of the 4,5-*seco*-neoclerod-5(19)-ene derivatives **3**, **4**, and **9** are reasonable with the two mechanistic pathways shown in Scheme 1. Both mechanisms are initiated by the formation of the corresponding chlorohydrins by ring opening of the 4α,18-epoxide in **2** and **6**. The unstable chlorohydrins could produce compounds **3** and **9** by loss of the C-19 acetoxyl group via a retroaldol reaction (route A, Scheme 1). Alternatively, a β-fragmentation reaction[21] in which there are 4α-hydroxyl and C-19 acetoxyl groups also could be involved (route B, Scheme 1).

In order to clarify the mechanism of the transformation of **2** or **6** into the corresponding 4,5-seco compounds (**3** and **9**), we prepared the 6α-hydroxy derivative **12** in quantitative yield by reduction of capitatin (**6**) with sodium borohydride. Treatment of the chlorohydrin **8** with sodium cyanoborohydride also afforded **12** in 60% yield, and minor quantities of the 4,5-seco derivatives **10** and **11.** This may be attributed to the instability of the starting material (**8**). The $^1$H-NMR spectrum of **12** revealed that the reduction of the C-6 ketone occurred from the less hindered β-face ($\delta_{\text{H-6}\beta}$ 3.65 dd, $J_{6\beta,7\beta}$ = 3.9 Hz, $J_{6\beta,19A}$ = 1.3 Hz).[6,11,15,16,19]

When compound **12** was treated with HCl under identical experimental conditions as those for **2** and **6**, only compounds **13** (65%) and **14** (14%) were isolated; thus, indicating that route A of Scheme 1 is probably the mechanism for the transformation of 19-acetoxy-18-chloro-4α-hydroxy-6-oxo-neoclerodanes to their corresponding 18-chloro-4,6-dioxo-4,5-*seco*-neoclerod-5(19)-ene derivatives.

The structures of the derivatives **13** and **14** are supported by their spectral data (Tables 1 and 2, and Experimental Section) and by those of the closely related compounds whose mechanism of formation from 19-acetoxy-4α,18-epoxy-6α-hydroxy-neoclerodanes has already been reported.[11] As before,[11] the chlorohydrin **13** was quantitatively transformed into the orthoacetate **14** in 1 h.

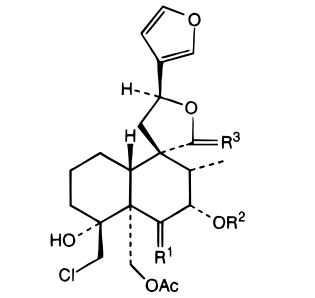
The easy entry to 4,5-*seco*-neoclerodanes reported above may be of interest for obtaining other natural and synthetic neoclerodane diterpenoids. Studies on this possibility are in progress.



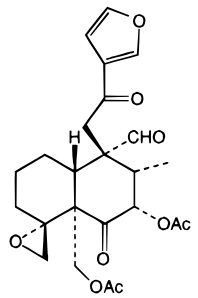
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1** | O | H | αH,βOAc |
| **2** | O | Ac | αH,βOAc |
| **6** | O | Ac | O |
| **12** | αOH,βH | Ac | O |



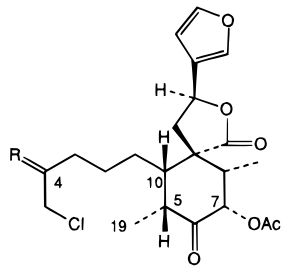
**3** R=αH,βOAc
**4** R=H,OH
**9** R=O



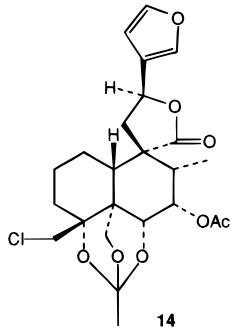
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **5** | O | H | αOH,βH |
| **8** | O | Ac | O |
| **13** | αOH,βH | Ac | O |



**7**



**10** R=O
**11** R=H,OH



**14**

## Experimental Section

**General Experimental Procedures.** Mps were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. IR spectra (KBr) were obtained on a Perkin-Elmer 681 spectrophotometer. $^1$H-NMR spectra were recorded using a Bruker AM200 apparatus at 200 MHz in $CDCl_3$ solution, and chemical shifts are reported with respect to residual $CHCl_3$ ($\delta$ 7.25). $^{13}$C-NMR spectra were recorded at 50.3 MHz in $CDCl_3$, and chemical shifts are reported with respect to solvent signals ($\delta_{CDCl_3}$ 77.0). $^{13}$C-NMR assignments were determined by DEPT and, in some cases (**3**, **11**, and **14**) by HMQC spectra. MS were recorded in the EI mode on a VG 12−250 instrument (70 eV, direct inlet). Elemental analyses were made with a Carlo Erba EA1108 apparatus. The purity of the compounds was checked by TLC on precoated plates (Merck, Si gel 60 $F_{254}$). Merck Si gel No. 7734 (70−230 mesh) deactivated with 10% $H_2O$, w/v, was used for column chromatography.

The starting material, eriocephalin (**1**), was extracted and isolated from *T. lanigerum* as described previously,[15] and its 7-*O*-acetyl derivative (**2**) was obtained by $Ac_2O$-pyridine treatment.[14,15]

**Preparation of (12*S*,20*S*)-7α-Acetoxy-18-chloro-15,16-epoxy-4,6-dioxo-4,5-*seco*-neocleroda-5(19),13(16),14-triene 20-*O*-Acetyl 20,12-Hemiacetal (3) and (12*S*,20ξ)-7α-Acetoxy-18-chloro-15,16-epoxy-4,6-dioxo-4,5-*seco*-neocleroda-5(19),13(16),14-triene 20,12-Hemiacetal (4) from 2.** A solution of **2** (500 mg) in $CHCl_3$ (50 mL) at 0 °C was treated with aqueous concd HCl (1 mL) for 40 min with stirring. The reaction mixture was diluted with $H_2O$ (100 mL) and extracted with $CHCl_3$ (4 × 25 mL). The extract was dried over $Na_2SO_4$, filtered, and evaporated to dryness giving a complex residue (TLC) from which only **3** (32 mg, 7%) and **4** (28 mg, 6%) were isolated by column chromatography (petroleum ether/EtOAc 4:1 as eluent).

**Compound 3:** mp 68−73 °C, amorphous solid ; $[\alpha]^{19}_D$ −22.1° (*c* 0.149, $CHCl_3$); UV λ max (EtOH) 240 nm (log ϵ 3.91); IR (KBr) ν max 3140, 1505, 875 (furan), 1740, 1230 (OAc), 1715 (ketones), 3080, 1625 (exocyclic methylene), 2940, 1450, 1375, 1100, 1075, 1035, 1020, 950, 800 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M]^+$ 482 (0.1) and 480 (0.3), 438 (0.8), 422 (0.9), 420 (1.6), 396 (1), 269 (3), 233 (5), 163 (9), 153 (9), 145 (7), 121 (7), 111 (20), 95 (20), 94 (33), 91 (10), 81 (17), 69 (5), 55 (10), 43 (100). Anal. Found C 60.21, H 6.12, Cl 7.13; $C_{24}H_{29}O_8Cl$ requires C 59.98, H 6.09, Cl 7.28.

**Compound 4:** mp 75−85 °C, amorphous solid; $[\alpha]^{19}_D$ −6.3° (*c* 0.111, $CHCl_3$); IR (KBr) ν max 3460 (OH), 3140, 1505, 875 (furan), 3080, 1620, 910 (exocyclic methylene), 1740, 1720, 1710 (ketones and OAc), 1240 (OAc), 2950, 1450, 1375, 1160, 1100, 1030, 970 $cm^{-1}$; $^1H$ NMR, see Table 1; EIMS (70 eV) *m*/*z* $[M]^+$ 440 (0.2) and 438 (0.6), 422 (0.1), 420 (0.3), 332 (4), 269 (2), 227 (6), 213 (12), 163 (10), 147 (11), 145 (11), 119 (10), 95 (23), 94 (39), 91 (11), 81 (23), 79 (13), 77 (15), 69 (10), 55 (15), 53 (12), 43 (100). Anal. Found C 60.31, H 6.08, Cl 7.39; $C_{22}H_{27}O_7Cl$ requires C 60.25, H 6.21, Cl 7.98.

**Preparation of (12*S*,20*S*)-19-Acetoxy-18-chloro-15,16-epoxy-4α,7α-dihydroxy-6-oxoneocleroda-13(16),14-diene 20,12-Hemiacetal (5) from 2.** A solution of **2** (300 mg) in $CCl_4$ (100 mL) at 0 °C was treated with aqueous concd HCl (0.1 mL) for 1 h with stirring. Workup as above yielded a residue (240 mg) of a complex mixture of products, from which only **5** (25 mg, 9%) could be isolated after repeated column chromatography (petroleum ether/EtOAc mixtures as eluents). Compound **5**: mp 75−85 °C, amorphous solid; $[\alpha]^{19}_D$ −17.2° (*c* 0.267, $CHCl_3$); IR (KBr) ν max 3500, 3500−3200 (OH), 3140, 1500, 875 (furan), 1740, 1230 (OAc), 1705 (ketone), 2960, 2920, 1460, 1375, 1140, 1050, 1025, 935, 800 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M - H_2O]^+$ 440 (0.1) and 438 (0.5), $[M - HCl]^+$ 420 (1), 403 (2), 402 (5), 360 (45), 219 (12), 195 (37), 134 (10), 121 (10), 105 (13), 95 (22), 94 (50), 91 (20), 81 (25), 77 (14), 69 (17), 57 (21), 55 (24), 43 (100), 41 (23). Anal. Found C 57.61, H 6.62, Cl 7.60; $C_{22}H_{29}O_8Cl$ requires C 57.88, H 6.41, Cl 7.67.

**Reaction of 2 with Jones' Reagent: Capitatin (6) and (12*S*)-7α,19-Diacetoxy-4α,18;15,16-diepoxy-6,12-dioxoneocleroda-13(16),14-dien-20-al (7).** A solution of **2** (600 mg) in $Me_2CO$ (120 mL) at 0 °C was treated with Jones' reagent (1 mL) for 20 min with stirring. The reaction mixture was diluted with $H_2O$ (150 mL) and extracted with $CHCl_3$ (4 × 50 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and evaporated to dryness giving a residue (400 mg). Chromatography (column, petroleum ether/EtOAc 3:1 as eluent) yielded **7** (61 mg, 11%) and capitatin (**6**, 270 mg, 49%).

**Capitatin (6):** mp 167−168 °C (EtOAc/petroleum ether) (lit.[16] 165−166 °C); $[\alpha]^{21}_D$ +137.2° (*c* 0.352, $CHCl_3$); IR, $^1H$ NMR, $^{13}C$ NMR, and MS were identical to those previously reported[16] for capitatin; comparison (mmp, TLC) with an authentic sample confirmed the identity.

**Compound 7:** mp 90−100 °C, amorphous solid; $[\alpha]^{21}_D$ +162.2° (*c* 0.296, $CHCl_3$); UV λ max (EtOH) 254.5 nm (log ϵ 3.40); IR (KBr) ν max 3140, 1560, 1515, 875 (furan), 3050 (oxirane), 1750 br, 1230 br (OAc), 1730 (ketone at C-6), 1710 (aldehyde), 1675 (ketone at C-12), 2950, 2880, 1450, 1375, 1160, 1080, 1050, 1020, 920, 830, 820 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M]^+$ 460 (4), 442 (1), 400 (5), 351 (49), 333 (20), 291 (19), 249 (27), 231 (26), 203 (28), 189 (20), 173 (23), 110 (100), 95 (74), 43 (18). Anal. Found C 62.71, H 6.06; $C_{24}H_{28}O_9$ requires C 62.59, H 6.13.

**Preparation of (12*S*)-7α,19-Diacetoxy-18-chloro-15,16-epoxy-4α-hydroxy-6-oxoneocleroda-13(16),14-dien-20,12-olide (8) and (12*S*)-7α-acetoxy-18-chloro-15,16-epoxy-4,6-dioxo-4,5-*seco*-neocleroda-5(19),13(16),14-trien-20,12-olide (9) from Capitatin (6).** A solution of **6** (306 mg) in $CHCl_3$ (50 mL) at room temperature was treated with aqueous concd HCl (1 mL) for 10 min with stirring. Workup in the usual manner yielded **8** (310 mg, 94%), an unstable substance that was transformed into the 4,5-seco derivative **9** by slow chromatography through Si gel with $CHCl_3$ as eluent. The same result was achieved when a solution of **8** in $CHCl_3$ or EtOAc was kept at room temperature for 12 h in the presence of Si gel. Treatment of **6** with HCl for 30 min gave a mixture (TLC) of **8** and **9** (less polar constituent), together with several decomposition products.

**Compound 8:** mp 85−95 °C, amorphous solid; $[\alpha]^{21}_D$ +126.6° (*c* 0.713, $CHCl_3$); IR (KBr) ν max 3500 (OH), 3140, 1505, 875 (furan), 1760 (γ-lactone), 1745, 1230 (OAc), 1720 (ketone), 2960, 2880, 1450, 1370, 1150, 1090, 1040, 930, 810, 780, 750 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M - H_2O]^+$ 480 (0.4) and 478 (1.5), $[M - HCl]^+$ 460 (2.5), 436 (1), 311 (32), 217 (10), 133 (10), 105 (10), 95 (25), 94 (28), 91 (15), 81 (25), 69 (10), 65 (6), 43 (100). Anal. Found C 57.82, H 5.92, Cl 7.11; $C_{24}H_{29}O_9Cl$ requires C 58.05, H 5.89, Cl 7.05.

**Compound 9:** mp 70−80 °C, amorphous solid; $[\alpha]^{19}_D$ +46.2° (*c* 0.162, $CHCl_3$); UV λ max (EtOH) 238 nm (log ϵ 3.70); IR (KBr) ν max 3150, 3130, 1510, 880 (furan), 3090, 1630, 930 (exocyclic methylene), 1760 (γ-lactone), 1750, 1740, 1725, 1720 (ketones and OAc), 1240 (OAc), 2940, 1450, 1375, 1180, 1160, 1040, 1025, 810, 780, 740 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M]^+$ 438 (2) and 436 (5), 394 (13), 378 (2), 359 (7), 312 (10), 300 (11), 282 (31), 254 (17), 236 (17), 217 (58), 199 (20), 161 (25), 133 (24), 121 (21),

105 (21), 95 (59), 94 (100), 91 (18), 81 (31), 79 (15), 77 (17), 43 (59). Anal. Found C 60.41, H 6.01, Cl 7.96; $C_{22}H_{25}O_7Cl$ requires C 60.53, H 5.78, Cl 8.02.

**Sodium Cyanoborohydride Reduction of 9: Compounds 10 [(12*S*)-7α-Acetoxy-18-chloro-15,16-epoxy-4,6-dioxo-4,5-*seco*-neocleroda-13(16),14-dien-20,12-olide] and 11 [(12*S*,4*R*)- and (12*S*,4*S*)-7α-acetoxy-18-chloro-15,16-epoxy-4-hydroxy-6-oxo-4,5-*seco*-neocleroda-13(16),14-dien-20,12-olide].** A solution of **9** (150 mg) in $CH_2Cl_2$ (20 mL) at room temperature was treated with an excess of $NaBH_3CN$ (50 mg) for 15 min. Workup as usual and column chromatography (petroleum ether/EtOAc 1:1 as eluent) of the crude of reaction yielded **10** (15 mg, 10%) and **11** (96 mg, 63%, a mixture of epimers at C-4).

**Compound 10:** mp 55−65 °C, amorphous solid; $[\alpha]^{20}_D$ +36.8° (*c* 0.144, $CHCl_3$); IR (KBr) *ν* max 3140, 1600, 1505, 875 (furan), 1765 (γ-lactone), 1740−1720 br (ketones and OAc), 1260 (OAc), 2960, 2930, 1460, 1375, 1180, 1160, 1100, 1020, 800 $cm^{-1}$; $^1H$ NMR, see Table 1; EIMS (70 eV) *m*/*z* $[M]^+$ 440 (1.5) and 438 (3), 396 (9), 380 (2), 378 (5), 338 (21), 265 (14), 218 (15), 190 (18), 179 (25), 173 (23), 133 (16), 105 (16), 95 (36), 94 (42), 91 (14), 81 (26), 57 (20), 55 (31), 43 (100). Anal. Found C 60.40, H 6.12, Cl 7.66; $C_{22}H_{27}O_7Cl$ requires C 60.25, H 6.21, Cl 7.98.

**Compound 11:** thick oil; IR (NaCl) *ν* max 3480 (OH), 3140, 1600, 1505, 875 (furan), 1760 (γ-lactone), 1750, 1730 br (ketone and OAc), 1240 (OAc), 2980, 2940, 1460, 1375, 1185, 1155, 1025, 910, $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M]^+$ 442 (0.2) and 440 (0.5), $[M - HCl]^+$ 404 (0.1), 398 (1), 391 (1), 349 (4), 267 (5), 201 (6), 192 (10), 190 (9), 179 (14), 133 (11), 95 (28), 94 (29), 91 (12), 83 (27), 81 (21), 55 (20), 43 (100); molecular ions for $C_{22}H_{29}O_7Cl$ at *m*/*z* 442 ($^{37}Cl$) and 440 ($^{35}Cl$).

**Preparation of (12*S*)-7α,19-Diacetoxy-4α,18;15,16-diepoxy-6α-hydroxy-neocleroda-13(16),14-dien-20,12-olide (12) from Capitatin (6) and Compound 8.** Treatment of a solution of **6** (220 mg) in MeOH (50 mL) with an excess of $NaBH_4$ (100 mg) at room temperature for 10 min quantitatively yielded **12**. Reaction of **8** (250 mg), in $CH_2Cl_2$ solution (20 mL), with an excess of $NaBH_3CN$ (100 mg) as described above for obtaining **10** and **11**, also gave **12** (120 mg, 60%) and minor quantities of **10** and **11** (TLC).

**Compound 12:** mp 275−278 °C (EtOAc); $[\alpha]^{21}_D$ +19.8° (*c* 0.121, $CHCl_3$/MeOH 1:1); IR (KBr) *ν* max 3500 (OH), 3150, 3120, 1505, 875 (furan), 3060 (epoxide), 1770 (γ-lactone), 1745, 1730, 1265, 1250 (OAc), 2960, 1430, 1375, 1150, 1120, 1030, 995, 820 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M]^+$ 462 (0.4), 444 (0.2), 402 (0.6), 371 (3), 314 (13), 269 (17), 218 (16), 187 (13), 179 (15), 175 (12), 161 (10), 145 (12), 133 (13), 121 (12), 105 (13), 96 (24), 95 (36), 94 (18), 91 (17), 81 (22), 55 (14), 43 (100). Anal. Found C 62.12, H 6.59; $C_{24}H_{30}O_9$ requires C 62.31, H 6.54.

**Compounds 13 [(12*S*)-7α,19-Diacetoxy-18-chloro-15,16-epoxy-4α,6α-dihydroxyneocleroda-13(16),14-dien-20,12-olide] and 14 [(12*S*)-7α-Acetoxy-18-chloro-15,16-epoxyneocleroda-13(16),14-dien-20,12-olide 4α,6α,19-Orthoacetate] from 12.** Treatment of **12** (100 mg) in $CHCl_3$ solution (20 mL) with aqueous concd HCl (1 mL) at room temperature for 10 min gave a mixture of two compounds, easily separated by column chromatography (petroleum ether/EtOAc 1:1 as eluent) obtaining **14** (less polar constituent, 15 mg, 14%) and **13** (70 mg, 65%).

After 1 h of reaction, only compound **14** was obtained. Moreover, treatment of **13** for 1 h under the reaction conditions quantitatively yielded **14**.

**Compound 13:** mp 90−100 °C, amorphous solid; $[\alpha]^{18}D$ +18.8° (*c* 0.325, $CHCl_3$); IR (KBr) *ν* max 3460 br (OH), 3150, 1600, 1505, 875 (furan), 1760 (γ-lactone), 1735 br, 1250 (OAc), 2950, 1455, 1370, 1160, 1130, 1020, 925, 800, 750, 730 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M]^+$ 500 (1) and 498 (3), $[M - H_2O]^+$ 482 (21) and 480 (44), $[M - HCl]^+$ 462 (100), 445 (23), 438 (45), 385 (35), 361 (34), 343 (43), 325 (45), 314 (59), 269 (56), 266 (47), 218 (46), 179 (56), 161 (23), 145 (17), 95 (4), 43 (8). Anal. Found C 57.62, H 6.31, Cl 6.88; $C_{24}H_{31}O_9Cl$ requires C 57.81, H 6.27, Cl 7.02.

**Compound 14:** mp 85−100 °C, amorphous solid; $[\alpha]^{19}_D$ −13.1° (*c* 0.221, $CHCl_3$); IR (KBr) *ν* max 3120, 1600, 1505, 875 (furan), 1765 (γ-lactone), 1740, 1250 (OAc), 2960, 2930, 1455, 1400, 1370, 1155, 1130, 1050, 1025, 930, 920, 885, 840, 800, 750 $cm^{-1}$; $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2; EIMS (70 eV) *m*/*z* $[M]^+$ 482 (1) and 480 (3), 430 (2), 391 (12), 385 (14), 179 (19), 143 (13), 141 (25), 105 (13), 96 (16), 95 (11), 94 (26), 91 (5), 81 (14), 57 (13), 55 (15), 43 (100). Anal. Found C 60.12, H 6.00, Cl 7.06; $C_{24}H_{29}O_8Cl$ requires C 59.98, H 6.09, Cl 7.28.

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## References and Notes

(1) Dedicated to the memory of the late Prof. Félix Serratosa, C. S. I. C.-University of Barcelona.
(2) Postgraduate from the Fakultät für Chemie, Universität Karlsruhe (T. H.), Germany.
(3) Although the hydrocarbon skeleton of these diterpenoids is biogenetically derived from an *ent*-labdane and they should be named *ent*-clerodanes, we prefer to use the term neoclerodane 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 majority of the articles published on this subject since 1979.
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