Pergamon 0031-9422(95)00521-8 Phytochemistry, Vol. 41, No. 1, pp. 247–253, 1996

0031-9422/96 $15.00 + 0.00

# *NEO*-CLERODANE DITERPENOIDS FROM *SCUTELLARIA GALERICULATA*

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(*Received* 15 *May* 1995)

**Key Word Index**—*Scutellaria galericulata*; Labiatae; *neo*-clerodane diterpenes; scutegalins C and D.

**Abstract**—Two new *neo*-clerodane diterpenoids, scutegalin C and D, have been isolated from the acetone extract of the aerial parts of *Scutellaria galericulata*. The structures of the new compounds were established by chemical and spectroscopic means as (13*S*,19*R*)-6α-acetoxy-4α,18-epoxy-7β-tigloyloxy-*neo*-cleroda-(19-*O*-tigloyl)-19,2α; 16,15-dihemiacetal (scutegalin C) and (13*S*,19*R*)-6α-acetoxy-4α,18-epoxy-*neo*-cleroda-(19-*O*-tigloyl)-19,2α, 16,15-dihemiacetal (scutegalin D). The absolute stereochemistry of scutegallin C was determined by chemical correlation with the already known *neo*-clerodane scutegalin B.

## INTRODUCTION

In a previous communication [1], we described the isolation of four *neo*-clerodane diterpenoids from the aerial parts of *Scutellaria galericulata*. Two of them were the already known [2] jodrellin T and 14,15-dihydrojodrellin T, the other two, scutegalins A and B, being new substances. In our search for new *neo*-clerodane diterpenoids [3–6], we have re-investigated the acetone extract of *S. galericulata*. We report here on the identification of the new compounds scutegalins C (**1**) and D (**2**).

## RESULTS AND DISCUSSION

The residue of a chromatographic fraction eluted with ethyl acetate–*n*-hexane (9:1) of the acetone extract of *S. galericulata* was homogeneous on TLC. However, its $^1$H NMR spectrum was very complex, revealing the presence of four structurally very similar clerodane diterpenoids. Signals for Me-20 and Me-17 protons were easily distinguished (four singlets at δ1.04, 1.03, 0.91 and 0.90 for Me-20, and two doublets at δ0.81 and 0.80 for Me-17), as well as four singlets attributable to the H-19 proton ($\delta_{H-19}$ 6.77, 6.76, 6.69 and 6.68) when the C-19 carbon is involved in an esterified 19,2α-hemiacetal function [3,6–8]. Moreover, four doublet signals, two of them at δ 5.30 and the other two at δ 5.12, were assigned to the two C-16 epimeric forms of a 16,15-hemiacetal group [1]. These data were compatible with a mixture of two different *neo*-clerodanes, each of which was present as a C-16 epimeric mixture (compounds **1** and **2**). In fact, chromium trioxide–pyridine oxidation of this mixture afforded two compounds indistinguishable by TLC (**3** and **4**), the $^1$H NMR of which was devoid of signals attributable to the H-16 hemiacetal protons. Chromatography of these compounds (**3** and **4**) by HPLC (see Experimental) allowed the isolation of the major component of the mixture (**3**).

Derivative **3** had the molecular formula $C_{32}H_{44}O_{10}$ and its $^1$H and $^{13}$C NMR spectra (Tables 1 and 2, respectively) showed signals for an acetate ($\delta_H$ 1.69, 3H, *s*; $\delta_C$ 169.5 *s* and 20.6 *q*) and two tigloyloxyl groups (Tables 1 and 2), as well as characteristic signals for a *neo*-clerodane structure (Me-17 at δ 0.83 *d*, $J_{17,8\beta}$ = 6.7 Hz, and Me-20 at δ 1.06 *s*) with a 4α,18-oxirane ring ($\delta_{HA-18}$ 2.44 and $\delta_{HB-18}$ 3.07, $J_{gem}$ = 4.3 Hz) and a 19.2α-hemiacetal function ($\delta_{H-19\alpha}$ 6.69 *s*, $\delta_{H-2\beta}$ 4.22 *m*; $\delta_{C-19}$ 91.8 *d*, $\delta_{C-2}$ 66.9 *d*). The $^1$H and $^{13}$C NMR spectra of **3** also showed signals for a 16,15-γ-lactone ($\delta_{HA-15}$ 4.20 *ddd*, $\delta_{HB-15}$ 4.34 *td*, $J_{gem}$ = 8.9 Hz, $J_{15A,14A}$ = 9.4 Hz, $J_{15A,14B}$ = 6.4 Hz, $J_{15B,14A}$ = 8.9 Hz, $J_{15B,14B}$ = 2.2 Hz; $\delta_{C-15}$ 66.4 *t*, $\delta_{C-16}$ 178.9 *s*) identical to **6** ($\delta_{HA-15}$ 4.14 *ddd*, $\delta_{HB-15}$ 4.30 *td*, $J_{gem}$ = 8.7 Hz, $J_{15A,14A}$ = 10.0 Hz, $J_{15A,14B}$ = 6.5 Hz, $J_{15B,14A}$ = 8.7 Hz, $J_{15B,14B}$ = 2.2 Hz; $\delta_{C-15}$ 66.3 *t*, $\delta_{C-16}$ 178.8), a derivative previously obtained from scutegalin B (**5**) [1]. In addition to these groups, **3** possessed two esterified equatorial alcohols at C-6α ($\delta_{H-6\beta}$ 4.68 *d*, $J_{6\beta,7\alpha}$ = 10.2 Hz) and C-7β ($\delta_{H-7\alpha}$ 5.18 *dd*, $J_{7\alpha,6\beta}$ = 10.2 Hz, $J_{7\alpha,8\beta}$ = 10.8 Hz). The location of the two tigloyloxyl groups [9] at C-19 and C-7β, and the acetate ester at C-6α, was based on the spectroscopic data described for related *neo*-clerodane diterpenoids [1]. Nevertheless, the preparation of **11**, **15** and **16** further supported this point (see below).

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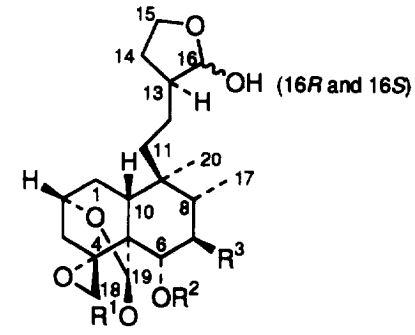
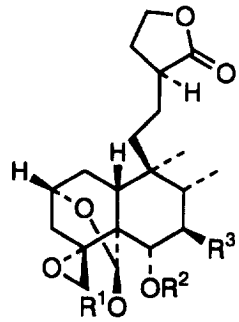
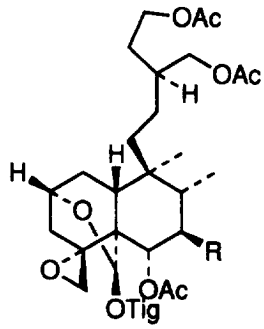



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1** | Tig | Ac | OTig |
| **2** | Tig | Ac | H |
| **5** | Tig | Ac | OH |
| **17** | H | H | OAc |
| **18** | Tig | H | OAc |

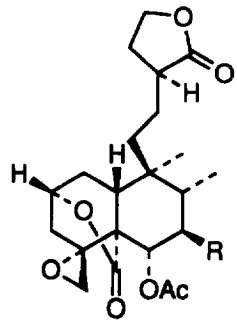



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **3** | Tig | Ac | OTig |
| **4** | Tig | Ac | H |
| **6** | Tig | Ac | OAc |
| **9** | H | Ac | OTig |
| **10** | H | Ac | H |
| **11** | H | Ac | OPyr |
| **12** | H | H | OAc |
| **19** | Tig | H | OAc |



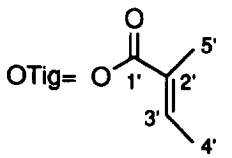

R

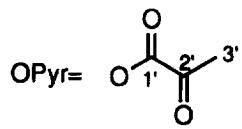
**7** OTig
**8** H




R

**13** H
**14** OTig
**15** OPyr
**16** OH




As it proved to be impossible to isolate **4**, the minor constituent of the mixture **3** and **4**, we prepared a mixture of the peracetyl derivatives **7** and **8** by sodium borohydride reduction of the natural mixture **1** and **2**, followed by acetic anhydride treatment of the resulting diols. HPLC of the mixture of **7** and **8**, again homogeneous on TLC, provided exclusively pure **7**. The $^1$H NMR spectrum of this derivative showed an additional ABX system ($\delta_H$ 4.04 *dd* and 4.15 *dd*, $J_{gem} = 6.5$ Hz, $J_{16A,13} = J_{16B,13} = 4.4$ Hz, part X overlapped) attributable to the acetylated hydroxymethylene at C-16.

In order to isolate a derivative from the minor component (**2**) of the natural diterpenoids (**1** and **2**), we carried out a selective hydrolysis of the tigloyloxyl group placed at the C-19 hemiacetal carbon by acid treatment of the mixture of **3** and **4**. The $^1$H NMR of **9** and **10**, obtained again as an inseparable mixture, showed the disappearance of the signals corresponding to the tigloyl group at C-19 and the shielding of the H-19α proton ($\delta_{H-19}$ 5.74 *s* and 5.70 *s*) with respect to the mixture **3** and **4** ($\delta_{H-19}$ 6.75 *s* and 6.68 *s*). Ozonolysis of the mixture **9** and **10** (see Experimental) gave, after work-up, the

Table 1. $^1$H NMR spectral data for compounds **3**, **7**, **10**–**13**, **15**, **16** and **19**

| H | 3 | 7 | 10 | 11 | 12 | 13 | 15 | 16 | 19 |
|---|---|---|---|---|---|---|---|---|---|
| 2$\beta$ | 4.22 *m* * | 4.23 *m*† | 4.21 *m** | 4.23 *m** | 4.21 *m** | 4.72 *m*† | 4.32 *m*† | 4.78 *m*† | 4.24 *m** |
| 3$\alpha$ | 2.51 *dt* | 2.55 *dt* | 2.58 *dt* | * | 2.69 *dt* | * | * | * | 2.58 *dt* |
| 6$\beta$ | 4.68 *d* | 4.72 *d* | 4.66 *dd* | 4.83 *d* | 3.30 *d* | 4.69 *dd* | 4.87 *d* | 4.61 *d* | 3.34 *d* |
| 7$\alpha$ | 5.18 *dd* | 5.19 *dd* | * | 5.16 *dd* | 5.03 *dd* | * | 5.59 *dd* | 4.00 *t* | 5.05 *dd* |
| 13$\alpha$ | 2.35 *m* | * | * | * | * | * | * | * | * |
| 15A | 4.20 *ddd* | 4.00 *brd* | 4.16 *ddd* | 4.20 *ddd* | 4.20* | 4.16 *ddd* | 4.19 *ddd* | 4.18 *ddd* | 4.19 *ddd* |
| 15B | 4.34 *td* | | 4.30 *td* | 4.35 *td* | 4.35 *td* | 4.32 *td* | 4.36 *td* | 4.34 *td* | 4.36 *td* |
| 16A | — | 4.04 *dd* | — | — | — | — | — | — | — |
| 16B | — | 4.15 *dd* | — | — | — | — | — | — | — |
| Me-17 | 0.83 *d* | 0.80 *d* | 0.84 *d* | 0.87 *d* | 0.83 *d* | 0.83 *d* | 0.87 *d* | 0.99 *d* | 0.85 *d* |
| 18A‡ | 2.44 *d* | 2.47 *d* | 2.41 *d* | 2.45 *d* | 2.33 *d* | 2.57 *d* | 2.62 *d* | 2.60 *d* | 2.66 *d* |
| 18B§ | 3.07 *d* | 3.09 *d* | 2.94 *d* | 3.00 *d* | 3.08 *d* | 3.18 *d* | 3.28 *d* | 3.30 *d* | 3.22 *d* |
| 19$\alpha$ | 6.69 *s* | 6.70 *s* | 5.69 *d*‖ | 5.73 *d*‖ | 5.69 *s* | — | — | — | 6.57 *s* |
| Me-20 | 1.06 *s* | 1.05 *s* | 0.85 *s* | 0.99 *s* | 0.94 *s* | 0.76 *s* | 0.90 *s* | 0.81 *s* | 1.03 *s* |
| 3′ | 7.18 *qq* | 7.07 *qq* | — | — | | — | — | — | 7.00 *qq* |
| Me-4′ | 1.77 *dq* | 1.75 *dq* | — | — | | — | — | — | 1.77 *dq* |
| Me-5′ | 1.86 *dq* | 1.85 *dq* | — | — | | — | — | — | 1.83 *dq* |
| 3″** | 6.80 *qq* | 6.73 *qq* | — | — | | — | — | — | — |
| Me-4″ | 1.74 *dq* | 1.75 *dq* | — | — | | — | — | — | — |
| Me-5″ | 1.86 *dq* | 1.85 *dq* | — | — | | — | — | — | — |
| OAc | 1.69 *s* | 2.04 *s*<br>2.03 *s*<br>1.75 *s* | 2.02 *s* | 1.99 *s* | 2.09 *s* | 2.01 *s* | 2.00 *s* | 2.10 *s* | 2.06 *s* |
| OPyr | — | — | — | 2.39 *s* | — | — | 2.40 *s* | — | — |
| OH†† | — | — | 3.44 *d* | 3.30 *d* | 3.89 *s*<br>3.22 *s* | — | — | — | 2.77 *d* |
| *J* (Hz) | | | | | | | | | |
| 1$\alpha$, 3$\alpha$ | 2.1 | 1.5 | 2.4 | * | 2.5 | * | * | * | 2.5 |
| 2$\beta$, 3$\alpha$ | 2.1 | 1.5 | 2.4 | * | 2.5 | * | * | * | 2.5 |
| 3$\alpha$,3$\beta$ | 13.9 | 15.2 | 15.2 | * | 15.1 | * | * | * | 14.5 |
| 6$\beta$,7$\alpha$ | 10.2 | 10.1 | 9.6 | 10.0 | 9.9 | 11.8 | 9.8 | 9.5 | 9.7 |
| 6$\beta$,7$\beta$ | — | — | 7.0 | — | | 4.7 | — | — | — |
| 7$\alpha$,8$\beta$ | 10.8 | 10.9 | * | 11.1 | 10.4 | * | 11.1 | 9.5 | 11.0 |
| 8$\beta$,17 | 6.7 | 6.7 | 5.9 | 6.6 | 6.7 | 6.6 | 6.7 | 6.7 | 6.7 |
| 15A,15B | 8.9 | | 8.8 | 8.9 | 8.8 | 8.9 | 9.0 | 8.9 | 8.9 |
| 15A,14A | 9.4 | | 10.0 | 10.0 | * | * | 10.1 | 9.9 | * |
| 15A,14B | 6.4 | | 6.2 | 6.4 | * | * | 6.1 | 6.5 | * |
| 15B,14A | 8.9 | | 8.8 | 8.9 | 8.8 | 8.9 | 9.0 | 8.9 | 8.9 |
| 15B,14B | 2.2 | | 2.5 | 2.2 | 1.8 | 2.3 | 2.2 | 2.4 | 2.4 |
| 16A,16B | — | 6.5 | — | — | | — | — | — | — |
| 16A,13 | — | 4.4 | — | — | | — | — | — | — |
| 16B,13 | — | 4.4 | — | — | | — | — | — | — |
| 18A, 18B | 4.3 | 4.2 | 4.1 | 3.9 | 3.8 | 4.1 | 3.9 | 4.0 | 3.7 |
| 19,OH | — | — | 3.4 | 2.0 | | | — | — | — |
| 3′,4′ | 7.1 | 7.0 | — | — | — | — | — | — | 7.0 |
| 3′,5′ | 1.5 | 1.4 | — | — | | — | — | — | 1.5 |
| 4′,5′ | 1.3 | 1.2 | — | — | | — | — | — | 1.0 |
| 3″,4″ | 7.3 | 7.4 | | — | — | — | — | — | — |
| 3″,5″ | 1.8 | 1.8 | — | — | — | — | — | — | — |
| 4″,5″ | 1.3 | 1.2 | — | — | — | — | — | — | — |

At 200 MHz. Chemical shifts are relative to residual $CHCl_3$ ($\delta$ 7.25). Spectral parameters were obtained by first order approximation.

*Overlapped signal.

†$W_{1/2}$; **7** = 9.1 Hz; **13** = 8.2 Hz; **15** = 8.3 Hz; **16** = 7.9 Hz.

‡*Exo* hydrogen with respect to ring B.

§*Endo* hydrogen with respect to ring B.

‖Collapsed into *s* after addition of $D_2O$.

′Tiglate at C-19.

**Tiglate at C-7.

††Disappeared after addition of $D_2O$.

Table 2. $^{13}$C NMR spectral data for compounds **3**, **7**, **10**–**13**, **15**, **16** and **19** (50.3 MHz, $CDCl_3$)*

| C | 3 | 7 | 10 | 11 | 12 | 13 | 15 | 16 | 19 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 28.1 *t* | 30.6 *t* | 28.2 *t* | 28.1 *t* | 28.3 *t* | 27.6 *t* | 27.5 *t* | 27.4 *t* | 28.2 *t* |
| 2 | 66.9 *d* | 66.9 *d* | 66.7 *d* | 66.6 *d* | 66.8 *d* | 67.3 *d* | 68.6 *d* | 70.3 *d* | 66.9 *d* |
| 3 | 36.9 *t* | 36.9 *t* | 36.7 *t* | 36.7 *t* | 36.6 *t* | 36.4 *t* | 36.5 *t* | 36.6 *t* | 36.5 *t* |
| 4 | 60.7 *s* | 60.7 *s* | 60.8 *s* | 60.7 *s* | 61.8 *s* | 61.3 *s* | 61.3 *s* | 61.4 *s* | 62.2 *s* |
| 5 | 42.1 *s* | 42.1 *s* | 42.5 *s* | 43.4 *s* | 43.4 *s* | 46.8 *s* | 47.4 *s* | 47.6 *s* | 41.8 *s* |
| 6 | 72.5 *d*† | 72.5 *d*† | 69.9 *d* | 75.8 *d*† | 74.3 *d*† | 72.4 *d* | 75.3 *d*† | 72.6 *d*† | 74.2 *d*† |
| 7 | 70.3 *d*† | 70.1 *d*† | 32.5 *t* | 70.8 *d*† | 72.1 *d*† | 32.1 *t* | 72.6 *d*† | 71.9 *d*† | 71.6 *d*† |
| 8 | 40.6 *d*‡ | 40.5 *d* | 34.6 *d* | 39.0 *d*‡ | 39.3 *d*‡ | 34.8 *d* | 40.3 *d*‡ | 41.2 *d*‡ | 39.7 *d*‡ |
| 9 | 40.5 *s* | 39.8 *s* | 38.9 *s* | 43.4 *s* | 39.8 *s* | 40.0 *s* | 40.5 *s* | 40.2 *s* | 39.8 *s* |
| 10 | 39.2 *d*‡ | 40.5 *d* | 40.6 *d* | 40.2 *d*‡ | 39.6 *d*‡ | 41.7 *d* | 42.0 *d*‡ | 41.9 *d*‡ | 39.2 *d*‡ |
| 11 | 34.7 *t* | 34.6 *t* | 34.5 *t* | 30.7 *t* | 35.1 *t* | 33.6 *t* | 33.8 *t* | 34.0 *t* | 34.8 *t* |
| 12 | 23.3 *t* | 24.1 *t* | 23.4 *t* | 23.2 *t* | 23.5 *t* | 22.2 *t* | 22.0 *t* | 22.0 *t* | 23.3 *t* |
| 13 | 39.9 *d*‡ | 34.9 *d* | 39.4 *d* | 39.9 *d*‡ | 39.5 *d*‡ | 39.4 *d* | 38.9 *d* | 39.0 *d* | 39.3 *d*‡ |
| 14 | 26.7 *t* | 26.7 *t* | 26.7 *t* | 26.9 *t* | 26.8 *t* | 26.5 *t* | 26.6 *t* | 26.7 *t* | 26.5 *t* |
| 15 | 66.4 *t* | 66.3 *t* | 66.3 *t* | 66.3 *t* | 66.4 *t* | 66.3 *t* | 66.4 *t* | 66.4 *t* | 66.5 *t* |
| 16 | 178.9 *s* | 62.2 *t* | 178.9 *s* | 178.7 *s* | 179.0 *s* | 178.9 *s* | 178.8 *s* | 178.9 *s* | 179.5 *s* |
| 17 | 10.7 *q* | 10.6 *q* | 15.2 *q* | 10.6 *q* | 10.5 *q* | 15.1 *q* | 10.7 *q* | 14.0 *q* | 10.6 *q* |
| 18 | 49.9 *t* | 49.9 *t* | 49.6 *t* | 49.4 *t* | 50.0 *t* | 50.1 *t* | 50.2 *t* | 50.3 *t* | 50.8 *t* |
| 19 | 91.8 *d* | 91.8 *d* | 93.1 *d* | 93.2 *d* | 93.6 *d* | 171.0 *s* | 170.2 *s* | 175.2 *s* | 92.6 *d* |
| 20 | 18.1 *q* | 18.2 *q* | 16.8 *q* | 18.0 *q* | 18.1 *q* | 14.5 *q* | 15.7 *q* | 15.8 *q* | 18.1 *q* |
| 1′ | 167.1 *s* | 167.1 *s* | — | — | — | — | — | — | 165.9 *s* |
| 2′ | 128.9 *s* | 128.9 *s* | — | — | — | — | — | — | 128.9 *s* |
| 3′ | 138.0 *d* | 138.3 *d* | — | — | — | — | — | — | 138.4 *d* |
| 4′ | 14.5 *q* | 14.4 *q* | — | — | — | — | — | — | 14.6 *q* |
| 5′ | 11.9 *q* | 11.9 *q* | — | — | — | — | — | — | 12.0 *q* |
| 1″ | 165.8 *s* | 165.8 *s* | — | — | — | — | — | — | — |
| 2″ | 127.9 *s* | 128.0 *s* | — | — | — | — | — | — | — |
| 3″ | 138.3 *d* | 137.9 *d* | — | — | — | — | — | — | — |
| 4″ | 14.4 *q* | 14.4 *q* | — | — | — | — | — | — | — |
| 5″ | 12.0 *q* | 12.0 *q* | — | — | — | — | — | — | — |
| 1′ | — | — | — | 160.4 *s* | — | — | 160.3 *s* | — | — |
| 2′ | — | — | — | 192.5 *s* | — | — | 191.4 *s* | — | — |
| 3′ | — | — | — | 26.9 *q* | — | — | 26.8 *q* | — | — |
| OAc | 20.6 *q* | 20.9 *q* | 21.3 *q* | 20.8 *q* | 20.9 *q* | 21.1 *q* | 20.9 *q* | 21.3 *q* | 20.9 *q* |
| | — | 20.9 *q* | — | — | — | — | — | — | — |
| | — | 20.6 *q* | — | — | — | — | — | — | — |
| | 169.5 *s* | 170.9 *s* | 169.1 *s* | 168.7 *s* | 171.0 *s* | 170.7 *s* | 170.5 *s* | 171.5 *s* | 170.3 *s* |
| | — | 170.9 *s* | — | — | — | — | — | — | — |
| | | 169.6 *s* | — | — | — | — | — | — | — |

*Chemical shifts are relative to the solvent signal ($CDCl_3$, $\delta$ 75.0). Multiplicities were determined by the DEPT pulse sequence.
†‡These assignments may be reversed.

derivative **11**, together with unchanged **10**, now easily separated by column chromatography.

Compound **11** had the molecular formula $C_{25}H_{34}O_{10}$ and its $^{13}$C NMR spectrum revealed the presence of a pyruvate group [$\delta_C$ 160.4 *s* (C-1′), 192.5 *s* (C-2′) and 26.9 *q* (C-3′)], which had to be placed at the equatorial C-7$\beta$ position ($\delta_{H-7\alpha}$ 5.16 *dd*, $J_{7\alpha,6\beta}$ = 10.0 Hz, $J_{7\alpha,8\beta}$ = 11.1 Hz). Sodium bicarbonate treatment of **11** [10] gave **12**, brought about not only by hydrolysis of the pyruvate ester, but also by a transacetylation from C-6$\alpha$ to the sterically less congested C-7$\beta$ position, as indicated by the modification of the chemical shifts of the H-6$\beta$ and H-7$\alpha$ protons in the $^1$H NMR spectrum of **12** ($\delta_{H-6\beta}$ 3.30 *d*, $J_{6\beta,7\alpha}$ = 9.9 Hz; $\delta_{H-7\alpha}$ 5.03 *dd*, $J_{7\alpha,6\beta}$ = 9.9 Hz, $J_{7\alpha,8\beta}$ = 10.4 Hz) compared to **11** ($\delta_{H-6\beta}$ 4.83 *d*, $J_{6\beta,7\alpha}$ = 10.0 Hz; $\delta_{H-7\alpha}$ 5.16 *dd*, $J_{7\alpha,6\beta}$ = 10.0 Hz, $J_{7\alpha,8\beta}$ = 11.1 Hz). To check this point, ozonolysis of the mixure of **13** and **14** (obtained by chromium trioxide–pyridine oxidation of the mixture **9** and **10**) was undertaken. In this case, **15** and unchanged derivative **13** were obtained, and basic hydrolysis [10] of the derivative **15** yielded **16**, where only hydrolysis of the pyruvate ester at C-7$\beta$ position had taken place, the acetate group remaining at the C-6$\alpha$ position (Table 1). It was obvious that the equatorial C-6$\alpha$ position was less sterically congested in **15** (possessing a carboxylic lactone carbon at C-19) than in **11**, possessing a C-19 hemiacetal group. Accordingly, the acetate group of **1** could be placed unambiguously at the C-6$\alpha$ position, and the structure shown in the formula for **1** could be attributed to this compound, except for the configuration at the C-13 centre and its absolute stereochemistry. These two structural features were established

by chemical correlation with scutegalin B (**5**), the structure and absolute configuration of which have been unequivocally established by an X-ray diffraction analysis of its 16,15-lactone derivative [1]. Treatment of **5** with potassium *tert*-butoxide caused transacetylation from the C-6$\alpha$ position to the C-7$\beta$ carbon and partial hydrolysis of the tiglate ester at carbon C-19, to give **17** and **18**, each as a mixture of C-16 epimers. Chromium trioxide–pyridine oxidation of pure **18** yielded derivative **19**, whose structure was in complete agreement with its spectroscopic data (Tables 1 and 2). Acid treatment of **19** afforded a substance identical in all respects to **12** [obtained from **1** (see above)], thus establishing a 13*S* configuration and a *neo*-clerodane absolute stereochemistry for **1**.

The structure of the second diterpenoid, **2**, was established by analysis of its derivatives **10** and **13** (see above). Compound **10** had a molecular formula $C_{22}H_{32}O_7$ and its $^{13}C$ NMR spectrum was almost identical to that of **11** except for the signals corresponding to carbons C-7, C-8, C-9 and Me-17 [**10**: $\delta_C$ 32.5 *t* (C-7), 34.6 *d* (C-8), 38.9 *s* (C-9), 15.2 *q* (C-17); **11**: $\delta_C$ 70.8 *d* (C-7), 39.0 *d* (C-8), 43.4 *s* (C-9), 10.6 *q* (C-17)] as a consequence of the presence of the pyruvate ester at the C-7$\beta$ position in **11** instead of the methylene group found in **10**. The $^1H$ NMR spectrum was also consistent with the structure proposed for **10**, since H-6$\beta$ appeared at $\delta$4.66 as a double doublet ($J_{6\beta,7\alpha}$ = 9.6 Hz, $J_{6\beta,7\beta}$ = 7.0 Hz). On the other hand, **13** (obtained by oxidation of **10**, see above) showed $^1H$ and $^{13}C$ NMR spectra differing from those of **10** only in the signal corresponding to C-19 (**13**: $\delta_C$ 171.0 *s*; **10**: $\delta_C$ 93.1 *d*). All the above data allowed us to assign the structure depicted in **2** for scutegalin D. The configuration at the C-13 carbon and the absolute stereochemistry of **2** could not be rigorously established. However, on biogenetic grounds, it seems probable that it has a 13*S* and a *neo*-clerodane absolute configuration identical with those established for **5** and **1** [1, and this work].

It is of interest to note that the mixture of teutrifidin and 4$\alpha$,18-epoxytafricanin A (two *neo*-clerodanes whose structures differ only in the existence of a 7$\beta$-hydroxyl substituent and a C-7 methylene group, respectively) could not be separated by normal adsorption chromatography, but they were easily resolved by HPLC [11], as in the case of some derivatives of **1** and **2** (see above).

## EXPERIMENTAL

Mps: uncorr. Plant material was collected in July 1993 at Perales river, Madrid, Spain. For more details see ref. [1].

*Extraction and isolation of scutegalins C* (**1**) *and D* (**2**). Aerial parts (1.3 kg) of *S. galericulata* L., dried and finely powdered, were extracted with $Me_2CO$ (3 × 6 l) at room temp. The extract (36.5 g) was subjected to CC on silica gel (500 g, Merck 7734, deactivated with 15% $H_2O$, w/v) [1]. The fr. eluted with EtOAc–*n*-hexane (9:1) (5.9 g) was dissolved in EtOAc and decolorized by filtration through a mixt. of activated charcoal and celite (1:1), yielding an inseparable mixt. of **1** and **2** (4.7 g).

*Scutegalins C* (**1**) *and D* (**2**). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$7.09, 7.05 both *qq* (H-3′, tiglate at C-19), 6.71 *qq* (H-3′, tiglate at C-7$\beta$ in **1**), 6.79, 6.78, 6.71, 6.70 all of them *s* (H-19), 5.31, 5.15 both *d* (H-16), 3.10, 3.08 both *d* ($H_B$-18), 2.43, 2.46 both *d* ($H_A$-18), 1.06, 0.92 both *s* (Me-20), 0.84, 0.81 both *d* (Me-17).

*Derivatives* **3** *and* **4** *from* **1** *and* **2**. Oxidation ($CrO_3$–pyridine, 980 mg, 9.8 ml) of the mixt. of **1** and **2** (293 mg, in 9.8 ml pyridine) for 24 hr at room temp. gave a mixt. of **3** and **4** (250 mg). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.07 *qq* (H-3′, tiglate at C-19), 6.75 *qq* (H-3′, tiglate at C-7$\beta$ in **3**), 6.75, 6.68 both *s* (H-19), 5.17 *t* (H-7$\alpha$ in **3**), 4.67 *d* (H-6$\beta$ in **3**), 4.60 *dd* (H-6$\beta$ in **4**), 3.07, 2.98 both *d* ($H_B$-18), 2.45, 2.42 both *d* ($H_A$-18), 1.05, 0.92 both *s* (Me-20), 0.83, 0.82 both *d* (Me-17). From this mixt. only pure **3** could be isolated by HPLC using a semiprep. Hypersil $C_{18}$ column (25 cm × 0.5 mm, 5 $\mu$m). MeOH–$H_2O$ (3:2) at 1 ml min$^{-1}$ was used as mobile phase.

*Compound* **3**. Amorphous solid, mp 85–95°; $[\alpha]_D^{27}$ + 28.2° ($CHCl_3$, *c* 0.482). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 2930, 2920, 1770, 1750, 1710, 1650, 1450, 1380, 1270, 1230, 1140, 1070, 1020, 970; $^1H$ NMR: Table 1; $^{13}C$ NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 588 $[M]^+$ (absent), 505 $[M\text{-tigloyl}]^+$ (1), 489 (9), 347 (1), 300 (2), 269 (2), 187 (10), 169 (4), 112 (11), 83 (100), 55 (46), 43 (12), $C_{32}H_{44}O_{10}$ $M_r$ 588.

*Compounds* **7** *and* **8** *from* **1** *and* **2**. Treatment of the mixt. of **1** and **2** (500 mg) with $NaBH_4$ (excess) in $CH_2Cl_2$–EtOH (1:1, 50 ml) soln for 1 hr at room temp. gave, after usual work-up, a mixt. (490 mg) which was treated with $Ac_2O$–pyridine (1:1, 50 ml) for 24 hr at room temp. The reaction mixt. was evapd to dryness *in vacuo* and the residue was filtered through silica gel in EtOAc soln. to give a mixt. of **7** and **8** (480 mg). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.1 *qq* (H-3′, tiglate at C-19), 6.76 *qq* (H-3′, tiglate at C-7$\beta$ in **7**); 6.74, 6.67 both *s* (H-19); 5.17 *t* ($J_{7\alpha,6\beta} = J_{7\alpha,8\beta}$ = 10.1 Hz, H-7$\alpha$ in **7**); 4.71 *d* ($J_{6\beta,7\alpha}$ = 10.1 Hz, H-6$\beta$ in **7**); 4.59 *dd* ($J_{6\beta,7\alpha}$ = 10.1 Hz, $J_{6\beta,7\beta}$ = 6.1 Hz, H-6$\beta$ in **8**); 4.22 *m* (H-2$\beta$); 3.1, 2.9 both *d* ($J_{gem}$ = 4.2 Hz, $H_B$-18); 2.04, 2.02 both *s* (OAc); 1.03, 0.9 both *s* (Me-20); 0.77 *d* (Me-17). From this mixt. only pure **7** could be isolated by HPLC using a semiprep. Hypersil $C_{18}$ column (25 cm × 0.7 mm, 5 $\mu$m). MeOH–$H_2O$ (3:2) at 1 ml min$^{-1}$ was used as mobile phase.

*Compound* **7**. Amorphous solid, mp 70–80°; $[\alpha]_D^{22}$ + 17.4° ($CHCl_3$; *c* 1.26). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3020, 2980, 1745 (*br*), 1650, 1450, 1370, 1260, 1140, 1100, 1070, 1030, 870; $^1H$ NMR: Table 1; $^{13}C$ NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 676 $[M]^+$ (absent), 577 $[M - \text{tigloyloxy}]^+$ (0.8), 446 (1), 405 (0.3), 315 (0.3), 258 (0.3), 231 (0.7), 215 (3), 187 (6), 159 (5), 107 (10), 91 (12), 83 (79), 69 (13), 55 (58), 43 (100). $C_{36}H_{52}O_{12}$ $M_r$ 676.

*Selective hydrolysis of the tiglate ester of* **3** *and* **4** *to give* **9** *and* **10**. To a soln of the mixt. of **3** and **4** (250 mg) in THF (25 ml) 1 N $H_2SO_4$ was added dropwise until pH *ca* 2. The reaction mixt. was stirred at room temp. for 50 min. Dilution with $H_2O$ and extraction with $CH_2Cl_2$ gave, after drying the organic phase and removal of solvents, a residue which on CC using *n*-hexane–EtOAc (1:1) as eluent yielded 55 mg unreacted **3** and **4** and

100 mg of the mixt of **9** and **10**. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.77 *qq* (H-3′, tiglate at C-7$\beta$ in **9**); 5.7, 5.6 both *s* (H-19); 5.14 *t* ($J_{7\alpha,6\beta} = J_{7\alpha,8\beta} = 10.9$ Hz, H-7$\alpha$ in **9**); 4.70 *d* ($J_{6\beta,7\alpha} = 10.9$ Hz, H-6$\beta$ in **9**); 4.60 *dd* ($J_{6\beta,7\alpha} = 10.9$ Hz, H-6$\beta$ in **10**); 3.0, 2.9 both *d* ($H_B$-18); 1.99, 1.88 both *s* (OAc).

*Ozonolysis of the mixt. of* **9** *and* **10**. A soln. of **9** and **10** (400 mg) in $CH_2Cl_2$ (30 ml) at $-78°$, was bubbled with $O_3$ for 15 min, then $Ph_3P$ in excess was added and the reaction mixt. was allowed to warm up to room temp. The residue (370 mg) obtained after removal of solvent was subjected to CC [silica gel, $CHCl_3$–MeOH (19:1) as eluent] yielding unchanged **10** (110 mg) and **11** (160 mg).

*Compound* **10**. Mp 174–175° (EtOAc–*n*-hexane); $[\alpha]_D^{19}$ + 11.8° ($CHCl_3$; *c* 0.221); IR $\nu_{max}^{KBr}$ cm$^{-1}$ 3480, 2960, 2940, 1765, 1710, 1500, 1460, 1440, 1370, 1280, 1150, 1100, 1070, 1030, 900, 830; $^1$H NMR: Table 1; $^{13}$C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 408 $[M]^+$ (0.2), 390 (5), 337 (2), 302 (3), 290 (7), 207 (5), 189 (69), 171 (71), 159 (28), 134 (37), 121 (35), 107 (22), 99 (15), 95 (15), 91 (28), 86 (33), 81 (18), 67 (19), 55 (50), 43 (100), 41 (35). (Found: C, 64.85; H, 7.91; $C_{22}H_{32}O_7$ requires: C, 64.68; H, 7.90%).

*Compound* **11**. Mp 191–193° (EtOAc–*n*-hexane); $[\alpha]_D^{19}$ + 24.4° ($CHCl_3$, *c* 0.447); IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3480, 2980, 2940, 1770, 1755, 1725, 1450, 1430, 1375, 1350, 1275, 1250, 1180, 1130, 1030, 930, 890; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 494 $[M]^+$ (absent), 476 $[M-18]^+$ (0.3), 407 (0.8), 197 (7), 187 (42), 175 (11), 169 (12), 159 (17), 113 (34), 91 (15), 86 (13), 69 (21), 55 (32), 43 (100), 41 (24). (Found: C, 60.89; H, 6.97. $C_{25}H_{34}O_{10}$ requires: C, 60.72; H, 6.93%).

*Hydrolysis of the pyruvate ester of* **11** *to give* **12**. To a soln. of **11** (120 mg) in THF (15 ml) at 0°, a satd soln. of $NaHCO_3$ (15 ml) was added, and the reaction mixt. stirred for 30 min. Dilution with $H_2O$ (20 ml) and extraction with $CHCl_3$ (4 × 15 ml) gave a residue which, after CC [silica gel, EtOAc–*n*-hexane (2:3) as eluent] gave **12** (90 mg): mp 110–120° (amorphous solid); $[\alpha]_D^{18}$ + 11.1° ($CHCl_3$; *c* 0.234); IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3450, 2960, 2930, 1770, 1740, 1380, 1250, 1070, 1025, 925, 880; $^1$H NMR: Table 1; $^{13}$C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 424 $[M]^+$ (absent), 249 (46), 187 (52), 175 (23), 157 (21), 149 (41), 135 (97), 105 (41), 91 (56), 81 (51), 79 (36), 71 (41), 67 (41), 57 (73), 55 (81), 43 (100). The $^1$H and $^{13}$C NMR spectra agreed with a $C_{22}H_{32}O_8$ molecular formula.

*Chromium trioxide–pyridine oxidation of the mixt.* **9** *and* **10**: *Derivatives* **13** *and* **14**. $CrO_3$ (155 mg) in pyridine (1.5 ml) was added to a pyridine (1.5 ml) soln of **9** and **10** (47 mg) at room temp. and the mixt left for 24 hr. Work-up in the usual manner yielded, after purification by chromatography, a mixt. of **13** and **14** (26 mg). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.8 *qq* (H-3′, tiglate at C-7$\beta$ in **14**), 5.5 *t* ($J_{7\alpha,6\beta} = J_{7\alpha,8\beta} = 10.5$ Hz, H-7$\alpha$ in **14**); 4.7 *m* (H-2$\beta$, H-6$\beta$ in **14**), 3.3, 3.1 both *d* ($J_{gem} = 3.9$ Hz, $H_B$-18); 0.8, 0.7 both *s* (Me-20); 0.79, 0.76 both *d* (Me-17).

*Ozonolysis of the mixture of* **13** *and* **14**. This was carried out as described above for **9** and **10**. Unchanged **13** (40 mg) and **15** (73 mg) were obtained after CC [silica gel, $CHCl_3$-MeOH (4:1) as eluent].

*Compound* **13**. Mp 187–190° (EtOAc); $[\alpha]_D^{18}$ + 5.0° ($CHCl_3$; *c* 1.068); IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3080, 2960, 2940, 2880, 1760 (broad), 1725, 1460, 1370, 1250, 1170, 1080, 1030, 975, 885; $^1$H NMR: Table 1; $^{13}$C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 406 $[M]^+$ (0.1), 363 (1), 346 (0.6), 319 (1), 189 (7), 171 (14), 149 (10), 119 (10), 91 (9), 86 (16), 81 (8), 69 (14), 57 (12), 55 (20), 43 (100). (Found: C, 63.50; H, 7.58. $C_{22}H_{30}O_7$. 1EtOAc requires: C, 63.14; H 7.75%).

*Compound* **15**. Mp 214–216° (EtOAc–*n*-hexane); $[\alpha]_D^{18}$ + 22.2° ($CHCl_3$; *c* 0.280); IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3080, 2980, 2950, 1750 (broad), 1375, 1230, 1140, 1020, 975, 930, 870; $^1$H NMR: Table 1; $^{13}$C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 492 $[M]^+$ (0.2), 404 (1), 345 (3), 309 (3), 269 (6), 249 (17), 187 (12), 135 (17), 119 (14), 113 (41), 105 (19), 91 (20), 86 (12), 81 (12), 79 (13), 69 (24), 55 (36), 43 (100), 41 (26). (Found: C, 60.79; H, 6.74. $C_{25}H_{32}O_{10}$ requires: C, 60.96; H, 6.55%).

*Sodium bicarbonate treatment of* **15**. To a soln. of **15** (220 mg) in THF (20 ml), satd $NaHCO_3$ soln. (30 ml) was added at room temp., and reaction mixt. kept at 40° for 45 min. Extraction with EtOAc (4 × 15 ml) yielded, after evapn of the solvents, a residue which was subjected to CC [silica gel, EtOAc–*n*-hexane (3:2) as eluent] to give pure **16** (150 mg): mp 237–239° (EtOAc–*n*-hexane); $[\alpha]_D^{18}$ + 15.4° ($CHCl_3$; *c* 0.188); IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3420, 2980, 2940, 1760, 1745, 1370, 1240, 1180, 1120, 1030, 980, 920, 880; $^1$H NMR: Table 1; $^{13}$C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 422 $[M]^+$ (0.8), 404 (0.3), 362 (0.6), 334 (1), 300 (1), 249 (100), 205 (9), 187 (30), 149 (12), 135 (55), 91 (15), 86 (16), 79 (11), 69 (13), 55 (28), 43 (73). (Found: C, 64.24; H, 6.93. $C_{22}H_{30}O_8$ requires: C, 62.14; H, 7.16%).

*Base treatment of scutegalin B* (**5**) [1]. To a soln of **5** (1.02 g) in THF (77 ml), KO$^t$Bu (225 mg) was added at room temp., and the reaction mixt. stirred for 30 min, then satd $NH_4Cl$ soln. (40 ml) was added and the reaction mixt. extracted with EtOAc (4 × 20 ml). After evapn to dryness, the residue was subjected to CC with EtOAc–*n*-hexane (1:1) as eluent, yielding starting material (**5**, 400 mg), **17** (250 mg) and **18** (250 mg). **17**: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 5.7 *s* (H-19), 5.3, 5.1 both *br s* (H-16), 5.0 *t* (H-7$\alpha$), 4.2 *m* (H-2$\beta$), 2.1 *s* (OAc), 0.9 **s** (Me-20), 0.8 *d* (Me-17). **18**: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.9 *qq* (H-3′), 6.5, 6.6 both *s* (H-19), 5.3, 5.1 both *d* (H-16), 5.0 *t* (H-7$\alpha$), 4.2 *m* (H-2$\beta$), 3.4, 3.3 both *d* (H-6$\beta$), 2.04, 2.03 both *s* (OAc), 1.8 *dq* (Me-5′), 1.7 *dq* (Me-4′), 1.0 *s* (Me-20), 0.8 *d* (Me-17).

*Chromium trioxide–pyridine oxidation of* **18**. A soln of **18** (380 mg) in pyridine (4 ml) was treated with $CrO_3$ (400 mg) in pyridine (4 ml) as described above, yielding **19** [180 mg, after CC (silica gel, EtOAc–*n*-hexane, 1:1, as eluent)]: mp 90–110° (amorphous solid); $[\alpha]_D^{22}$ + 45.2° ($CHCl_3$; *c* 0.361); IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3540, 2970, 2930, 1770, 1740, 1715, 1650, 1380, 1240, 1060, 965, 930, 870, 820; $^1$H NMR: Table 1; $^{13}$C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 506 $[M]^+$ (absent), 216 (26), 200 (100), 185 (24), 172 (22), 154 (13), 115 (25), 91 (21), 77 (55),

69 (30), 45 (66), 43 (89). The $^1H$ and $^{13}C$ NMR spectra agreed with a molecular formula of $C_{27}H_{38}O_9$.

*Hydrolysis of the tiglate ester of* **19**. To a soln. of **19** (166 mg) in THF (16 ml) 1 N $H_2SO_4$ was added to pH *ca* 2 with stirring at 0°. After 4 hr, satd $NaHCO_3$ soln (16 ml) was added. Extraction with EtOAc (4 × 15 ml) and chromatography of the residue obtained after evapn of the solvents gave a compound (90 mg) identical in all respects (mp, $[\alpha]_D$, IR, $^1H$ NMR, MS and TLC behaviour) with the **12** described above and obtained from **1**.

*Acknowledgements*—This work was subsidized by the Spanish 'Dirección General de Investigación Científica y Técnica' (Grant PB 93-0154) and 'Consejería de Educación y Cultura de la Comunidad de Madrid' (Grant 276/92).

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