From a Phagostimulant Natural Product to Semisynthetic Antifeedants Against *Spodoptera littoralis* Larvae: Chemical Transformations of the Neoclerodane Diterpenoid Scutegalin B†

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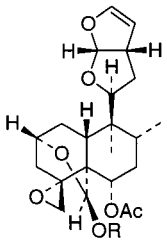
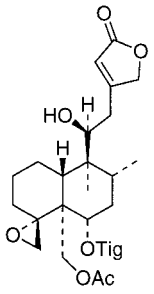
Scutegalin B (**4**), a natural neoclerodane diterpenoid possessing phagostimulant activity against larvae of the lepidopteran *Spodoptera littoralis*, has been subjected to a series of chemical transformations obtaining several derivatives. The activity of some of these changes to antifeedant (**10**, **12**, **16**, and **17**), although other derivatives are inactive (**6**, **7**, and **15**) or maintain phagostimulant activity (**8** and **9**) of the starting material (**4**). The most potent antifeedant was **16**, which possesses 16,15-lactone and a (19*S*)-19,2α-hemiacetal groups instead of the 16,15-lactol and (19*R*)-(19-*O*-tigloyl)19,2α-hemiacetal of the phagostimulant precursor **4**. These and other structure−activity relationships are discussed, establishing that the biological action is strongly modulated by minimal structural variations.

Clerodanes are a large group of naturally occurring diterpenoids isolated mainly from Compositae and Labiatae plants.[1] These compounds have attracted interest because of their challenging structures and their antifeedant properties against some economically important insect pests.[2] Among these substances, jodrellins A (**1**) and B (**2**)[3] and scutalpin C (**3**)[4] are the most potent neoclerodane[5] antifeedants known against larvae of *Spodoptera littoralis*. We are concerned with the search for new natural neoclerodane diterpenoids,[6] and with studies of their chemical reactivity.[7]

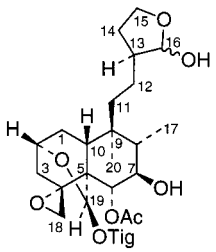
Scutegalin B (**4**)[8] is the major diterpene constituent of the acetone extract of the aerial parts of *Scutellaria galericulata* L. This neoclerodane shares some structural features with **1** and **2**, though it does not behave as an insect antifeedant but as a phagostimulant agent against larvae of the Egyptian cotton leafworm (*S. littoralis*). The different biological action of **1** and **2**[3] with respect to **4**,[8] together with the uncertain knowledge available on the structure−activity relationships of these compounds,[2−4,8] prompted us to undertake some chemical transformations of **4** in order to establish how the nature of the C-9 side chain and the functionality of the decalin part modulate feeding behavior of *S. littoralis* larvae. Furthermore, **4** is a suitable substrate for obtaining analogues of some intermediates involved in an approach to the total synthesis of **1** and **2**,[9,10] and knowledge of its chemical reactivity would be useful for the synthesis of these and other structurally related compounds.



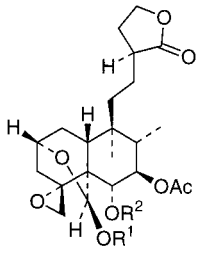
1 R=Ac
2 R=CO^{i}Pr



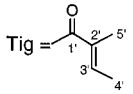
3



4
(16*R* and *S* forms)



18 R^1=Me, R^2=Ac
19 R^1=Tig, R^2=H



Results and Discussion

Scutegalin B (**4**) is a mixture of two epimeric hemiacetal forms of its 16,15-lactol, which is in equilibrium with the 15-hydroxy-16-aldehyde open form;[8] therefore, this grouping is prone to reduction with sodium borohydride. Nevertheless, reduction of the 16,15-lactol of **4** was performed on the previously synthesized[8] 7*β*-*O*-acetyl derivative **5** (Scheme 1) in order to avoid side reactions of transacetylation from C-6α to the sterically less congested C-7*β* position.[11] Treatment of **5** with $NaBH_4$ yielded the 15,16-diol **6**, which, in turn, was transformed into **7** by acetylation. Ester groups at the C-19 hemiacetal position are selectively hydrolyzed under acid conditions,[8,11] thus **7** was converted into the 19,2α-lactol **8** by treatment with dilute H_2SO_4. Oxidation of **8** with Jones' reagent [12] afforded the neoclerodan-19,2α-olide derivative **9**. All the derivatives of

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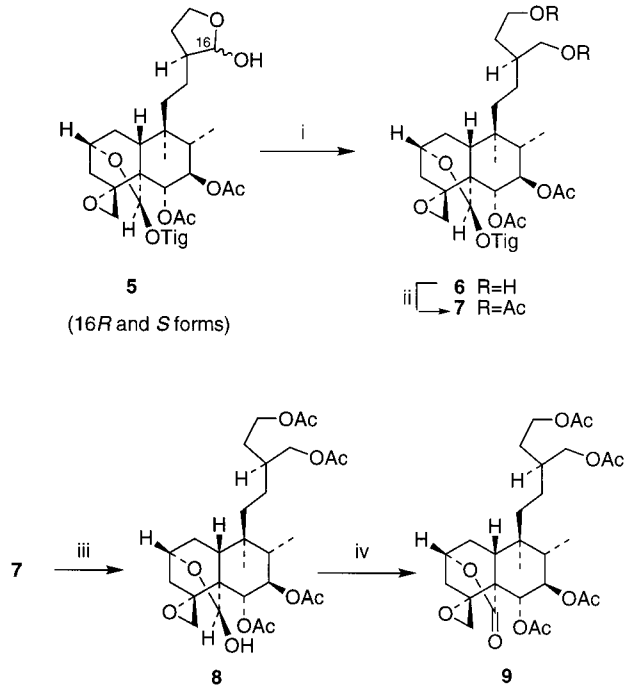
Scheme 1[a]



[a] Key: (i) $NaBH_4$, CH_2Cl_2−EtOH (1:1), room temperature, 5 min. (ii) Ac_2O−pyridine (1:1) room temperature, 3 days. (iii) H^+, THF, room temperature, 4.5 h. (iv) Jones' reagent, 0 °C, 5 min.

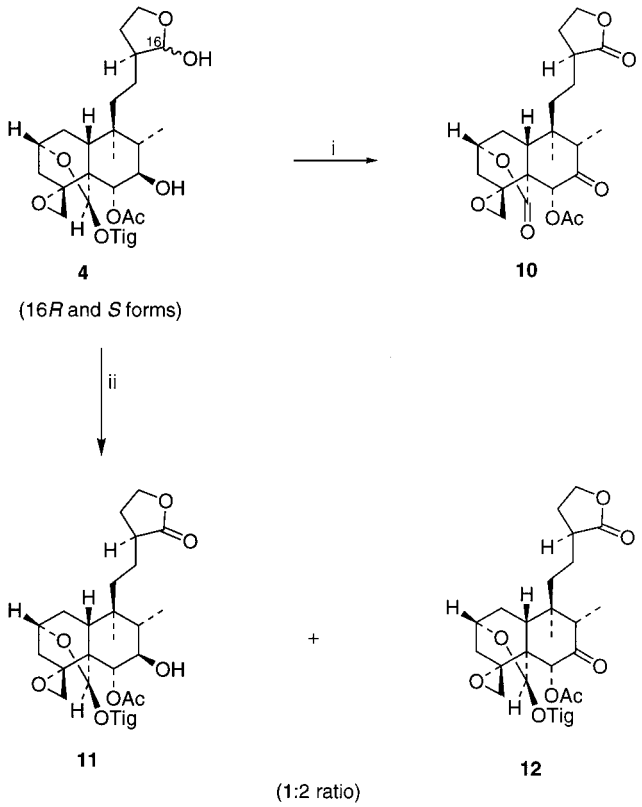
5 obtained by this sequence of reactions possess a 15,16-diol (**6**) or its corresponding diacetate (**7**−**9**) and different functionality at the C-19 position: 19-*O*-tigloyl-19,2α-hemiacetal (**6** and **7**), 19,2α-hemiacetal (**8**), or 19,2α-lactone (**9**) groupings.

Next, we obtained another set of derivatives of **4** having a 16,15-lactone. Jones' oxidation of **4** (Scheme 2) produced the 7-keto-16,15;19,2α-dilactone **10**. Hydrolysis of the tiglate ester at C-19 took place prior to oxidation of the 19,2α-hemiacetal group.[8,11] Selective oxidation of the 16,-15-lactol of **4** may be achieved by using the chromium trioxide−dipyridine complex.[13] Treatment of **4** with this reagent for 24 h at room temperature gave the 16,15-lactone derivative **11** together with the 7-oxoneoclerodan-16,15-olide derivative **12**, in a 1:2 ratio (Scheme 2).

Compounds **6**−**12** were tested as antifeedants against larvae of *S. littoralis*. In accordance with the antifeedant index values shown in Table 1,[14] the activity of these compounds is largely dependent on the functionality of the C-9 side chain. Thus, derivatives **6**−**9**, possessing a 15,16-diol (**6**) or diacetate (**7**−**9**), have no activity (**6** and **7**) or behave as phagostimulants (**8** and **9**) like scutegalin B (**4**). The 16,15-lactone derivatives **10**−**12** showed a moderate activity as antifeedants. Compounds **1** and **2**, which exhibit strong antifeedant action, possess a tetrahydrofurofuran side chain at C-9, while functionality of the decalin part is very close to that of **6**−**8**, **11**, and **12**, except for oxidation at C-7 and the acyl substituent of the C-19 hemiacetal group. Therefore, we prepared derivatives possessing a 16,-15-lactone and acetate or isobutyrate esters at C-19.

Acylation of neoclerodane-19,2α-hemiacetals is not an easy transformation. Treatment of **13**[8] with acetic anhydride−pyridine gave the 2α-acetoxyneoclerodan-19-al derivative **14** (Scheme 3). The same behavior was also observed when **13** was treated with isobutyric anhydride−pyridine or isobutyryl chloride-triethylamine, yielding **15**. This opening of a 19,2α-hemiacetal under esterification conditions has been reported for other neoclerodane derivatives.[15]

Scheme 2[a]



[a] Key: (i) Jones' reagent, 0 °C, 15 min. (ii) CrO_3·2Py, pyridine, room temperature, 16 h.

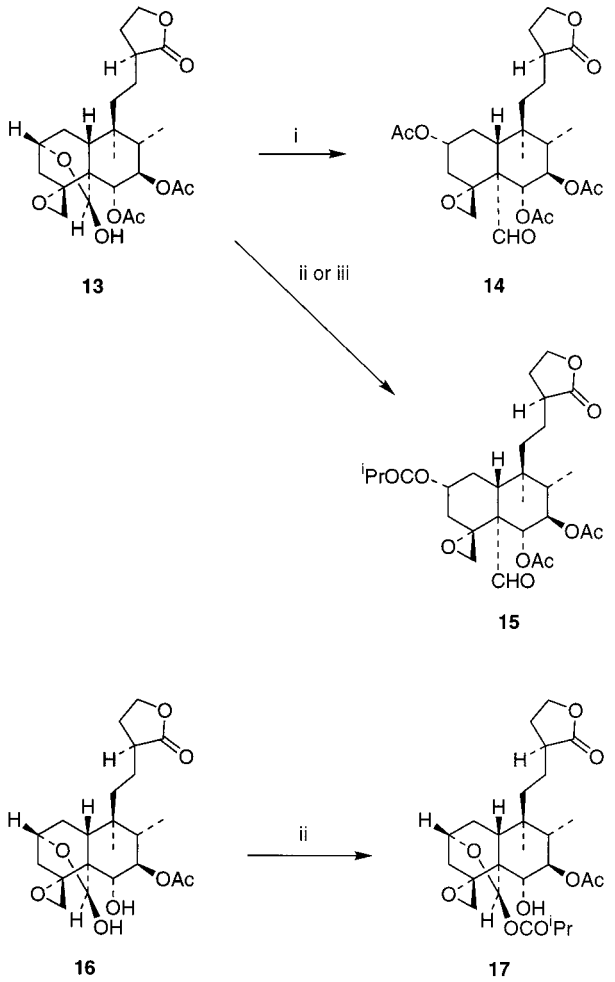
Table 1. Effect of Some Natural (**1**−**4**) and Semisynthetic (**6**−**19**) Neoclerodanes on the Feeding Behavior of Larvae of *Spodoptera littoralis*

	antifeedant activity	
compound	choice bioassay (antifeedant index mean ± SEM)[a]	no-choice bioassay (EC_{50}, ppm)[b]
1[c]	92.0 ± 7.6[d]	*e*
2[c]	100 ± 0.0[d]	*e*
3[f]	96.8 ± 1.2[d]	<1
4[g]	−27.0 ± 12.0	870
6	18.8 ± 19.3	*e*
7	−0.4 ± 5.0	*e*
8	−38.8 ± 10.1	*e*
9	−27.4 ± 7.1	*e*
10	44.1 ± 10.4[d]	>1000
11	29.3 ± 15.2	>1000
12	36.5 ± 9.9[d]	350
13	34.0 ± 16.3	>1000
14	17.2 ± 9.9	*e*
15	−10.0 ± 8.5	*e*
16	67.0 ± 5.5[d]	51
17	37.5 ± 6.0[d]	>1000
18	−29.5 ± 7.8	*e*
19	18.6 ± 7.9	>1000

[a] Antifeedant index [(C−T)/(C+T)] × 100 of compounds tested at 100 ppm, 10 replications per compound. A negative value indicates a phagostimulant activity. [b] EC_{50} is the effective concentration required to decrease by 50% the amount eaten in 16 h of a treated disk, relative to the sucrose control; 10 replications per concentration per compound. [c] Taken from Anderson et al.[3] [d] Significant difference in the amount of treatment and control disk eaten (Wilcoxon signed ranks test, $P<0.05$). [e] Not determined. [f] Taken from Muñoz et al.[4] [g] Taken from Rodríguez et al.[8]

Esterification of the hemiacetal hydroxyl group at C-19 was only achieved on **16** (Scheme 3), a 19,2α-hemiacetal-neoclerodan-16,15-olide derivative possessing a hydroxyl

Scheme 3[a]

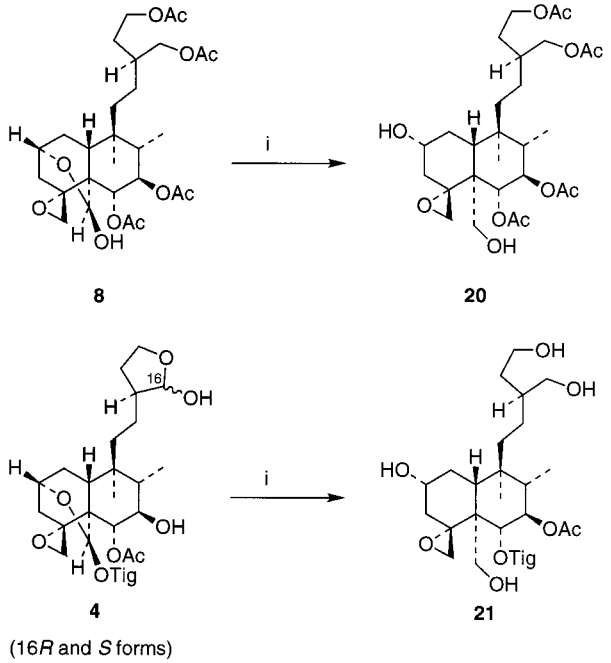


[a] Key: (i) Ac_2O−pyridine (1:1), room temperature, 24 h. (ii) $(^iPrCO)_2O$−pyridine (1:1), room temperature, 24 h. (iii) ^iPrCOCl−Et_3N, CH_2Cl_2, 0 °C, 2 h.

group at the C-6α position instead of the 6α-acetoxyl substituent of **13**. Treatment of **16**[11] with isobutyric anhydride−pyridine gave the 19-isobutyrate ester **17**, in which only esterification of the 19,2α-lactol occurred (Scheme 3).

The most active compound tested was **16** (antifeedant index 67.0 ± 5.5), which possesses a hydroxyl group at C-6α and a nonesterified 19,2α-hemiacetal. The high antifeedant activity of **16** against larvae of *S. littoralis* could be attributed in part to its 19,2α-hemiacetal function because 16,15-lactone derivatives possessing 19-*O*-acyl (**11**, **12**, and **17**) or 19,2α-lactone groups (**10**) were less active than **16**. Moreover, the change of the 19,2α-lactol of **16** by a 2α-acyloxy-19-aldehyde arrangement resulted in a drastic decrease of the antifeedant action (**14** and **15**, see Table 1). Additionally, when the 19,2α-hemiacetal of **16** was transformed into a 19-*O*-methyl-19,2α-acetal[16] (**18**, see Experimental Section), this derivative was a phagostimulant, and the presence of a free alcohol at C-6α, together with an esterified 19,2α-lactol (**19**, a derivative of scutegalin B obtained previously[11]), also caused a noticeable decrease of the antifeedant activity with respect to **16** (Table 1). The presence of a 16,15-lactone in these neoclerodanes also seems to play an important role in their biological action. This was supported by comparing the data shown in Table 1 for **8** (a phagostimulant substance without that functionality but having a 19,2α-lactol) and **16** (in which both 16,-15-lactone and 19,2α-lactol groups are present).

Scheme 4[a]



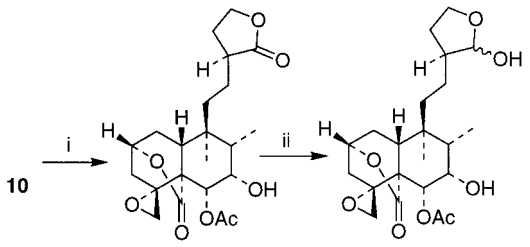
[a] Key: (i) $NaBH_4$, CH_2Cl_2−EtOH (1:1), room temperature, 5 min.

We performed a series of chemical transformations in order to explain the different behavior of compounds **13** and **16** (Scheme 3) under standard esterification reaction conditions. The results shown in Scheme 3 suggest that the C-19 position in **13** is sterically congested due to the presence of the 6α-acetoxyl group and that the 19,2α-hemiacetal is in equilibrium with its 2α-hydroxy-19-aldehyde form, which is prone to esterification giving **14** or **15**, both possessing ring A in a chair conformation[15] instead of the boat conformation of **13**. On the contrary, esterification of **16**, in which the 6α-*O*-acetyl group of **13** is absent, yielded the 19-*O*-acyl derivative **17**, maintaining the boat conformation of ring A and the free hydroxyl at the C-6α position of the precursor (**16**).[17]

In agreement with the above results (Scheme 3), treatment of **8**, having a bulky substituent at C-6α, with sodium borohydride yielded the 2α,19-dihydroxy derivative **20** (Scheme 4) via reduction of the 2α-hydroxy-19-aldehyde form of **8**. Reaction of scutegalin B (**4**) with the same reagent afforded the tetraol **21** (Scheme 4), but in this case a double transesterification occurred (from the C-6α to the C-7*β* and from the C-19*β* to the C-6α positions) prior to reduction of the resulting 19,2α-hemiacetal.

The behavior of **4**, **8**, **13**, and **16** under reduction or esterification reactions (Schemes 3 and 4) may be a consequence of the steric hindrance around the C-6α and C-19*β* positions, and this was corroborated by reactions such as the reduction of some neoclerodan-19,2α-olides. Although these derivatives have not been isolated from *Scutellaria* plants,[1] synthetic analogues have been used as model intermediates in an approach to the total synthesis of **1**,[9,10] where diisobutylaluminum hydride (DIBAH) reduction of 19,2α-lactone derivatives without substituents at C-9 gives rise to the corresponding 19,2α-lactol group. For this reason, we treated the 19,2α-lactones **9** and **10** (Schemes 1 and 2, respectively) with DIBAH in toluene. Under standard conditions,[10] reduction of **9** was unsuccessful recovering the unreacted material, whereas only deacetyl derivatives at C-15 and/or at C-16 were detected when the reaction was carried out at 50 °C. On the other hand, reduction of the 7-keto-16,15;19,2α-dilactone **10** with

Scheme 5[a]



[a] Key: (i) $NaBH_4$, CH_2Cl_2−MeOH (9:1), 0 °C, 1.5 h. (ii) DIBAH, toluene, −20 °C, 8 h.

DIBAH yielded very complex reaction mixtures. Furthermore, after reduction of the 7α-hydroxy-16,15;19,2α-dilactone **22** (Scheme 5) with DIBAH, we were able to isolate the 16,15-lactol **23** as a mixture of epimers at C-16, but no reaction of the 19,2α-lactone of **22** was observed. The unreactivity of the 19,2α-lactone moiety of these compounds may be explained on steric and stereoelectronic grounds. The *si* face of the C-19 carboxyl group is sterically blocked by the neighboring C-20 methyl group attached to the C-9 axial position, whereas the electronegativity of the oxygen atom of the 4α,18-oxirane along with both steric and electronic effects of the 6α-acetoxyl group, preclude attack of the reducing reagent from the *re* face.

In summary, starting from a phagostimulant natural diterpene (**4**), we obtained a potent antifeedant (**16**).

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin−Elmer 241 MC polarimeter. IR spectra were obtained on a Perkin−Elmer 681 spectrophotometer. ^{1}H NMR spectra were recorded using a Bruker AM 200 apparatus at 200 MHz, or a Varian INOVA-300 spectrometer at 300 MHz, in $CDCl_3$ solution, and chemical shifts are reported with respect to residual $CHCl_3$ (δ 7.25). ^{13}C NMR spectra were recorded at 50.3 MHz in $CDCl_3$ solution, and chemical shifts are reported with respect to solvent signals (δ_{CDCl_3} 77.00). ^{13}C NMR assignments were determined by the DEPT pulse sequence method and, for some compounds (**11**, **12**, **15**, and **18**), also by HMQC spectra. MS were recorded in the positive EI mode on a VG 12−250 instrument (70 eV, direct inlet). Elemental analyses were made with a Carlo Erba EA 1108 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 15% H_2O, w/v, or Si gel SDS 60 Å (230−400 mesh) were used for column chromatography. Starting material [scutegalin B (**4**)] was extracted and isolated from *S. galericulata* as described previously,[8] and its already described derivatives (**5**, **13**, **16**, and **19**) were available from previous studies[8,11] or were prepared from **4** by known methods.[8,11]

Antifeedant Bioassay. Compounds **6**−**19** (Table 1) were assayed for antifeedant activity by presenting them on glass-fiber disks (Whatman GF/A, 2.1 cm diameter), made palatable by application of 100 μL of sucrose (0.05 M). In the choice bioassay, sixth stadium larvae of *S. littoralis* (Boisduval) were deprived of food for 4 h, then placed individually in a Petri dish with two glass-fiber disks. One disk acted as the control; the other disk, the treatment disk, was treated additionally with 100 μL of a solution (100 ppm) containing one of the test compounds. The dried disks were weighed before being presented to the larvae. The larvae were removed when they had eaten approximately 50% of one of the disks. In the no-choice bioassay, larvae were presented with treatment disks, which had been treated with 100 μL of a solution containing a test compound at one of four concentrations (1, 10, 100, or 1000 ppm). This bioassay was terminated after 16 h, the time taken to consume 50% of the control disks.

After terminating the bioassays, the disks were reweighed. In the choice bioassay the antifeedant index $[(C-T)/(C+T)] \times 100$ was calculated, where C and T are the weights of control and treatment disks consumed, respectively. The index identifies both phagostimulants (negative values) and antifeedants (positive values). In the no-choice bioassay the amount eaten of the disks treated with different concentrations was calculated and used to estimate the concentration required to decrease feeding by 50% (EC_{50}), relative to the sucrose control.

Preparation of (13*S*,19*R*)-6α,7*β*-Diacetoxy-4α,18-epoxy-15,16-dihydroxyneoclerodane 19,2α-(19-*O*-tigloyl)hemiacetal (6) from 7-*O*-Acetylscutegalin B (5). A solution of **5**[8] (1.1 g, 2 mmol) in CH_2Cl_2−EtOH (1:1, 20 mL) was treated with an excess of $NaBH_4$ (100 mg, 2.6 mmol) at room temperature for 5 min with stirring. After addition of Et_2O (30 mL) the reaction mixture was filtered through a Si gel pad. Evaporation of the solvents gave a residue that was chromatographed (Si gel column, EtOAc as eluent) to yield pure **6** (1.05 g, 1.9 mmol, 95% yield): colorless needles (EtOAc−*n*-hexane), mp 195−197 °C; $[\alpha]^{19}_D$ +57.7° (*c* 0.473, $CHCl_3$); IR (KBr) ν_{max} 3360, 2970, 1750, 1705, 1440, 1385, 1270, 1250, 1145, 1085, 1030, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.05 (1H, qq, J = 7.0, 1.4 Hz, H-3′), 6.67 (1H, s, H-19), 5.07 (1H, t, J = 10.1 Hz, H-7α), 4.63 (1H, d, J = 10.1 Hz, H-6*β*), 4.20 (1H, m, $W_{1/2}$ = 8 Hz, H-2*β*), 3.67, 3.55 (each 1H, dd, J = 6.1, 4.3 Hz, 2H-16), 3.48 (2H, br d, J = 9.1 Hz, 2H-15), 3.04, 2.45 (each 1H, d, J = 4.1 Hz, 2H-18), 2.60 (1H, dt, J = 14.4, 2.1 Hz, equatorial H-3α), 1.85, 1.77 (each 3H, s, OAc), 1.85 (3H, br d, J = 1.4 Hz, Me-5′), 1.77 (3H, dq, J = 7.0, 0.5 Hz, Me-4′), 0.97 (3H, s, Me-20), 0.80 (3H, d, J = 6.6 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.9, 169.6 (each s, O*C*OCH$_3$), 165.8 (s, C-1′), 139.4 (d, C-3′), 128.6 (s, C-2′), 91.7 (d, C-19), 73.1 (d, C-7), 70.1 (d, C-6), 66.9 (d, C-2), 65.8 (t, C-16), 60.6 (t, C-15), 60.6 (s, C-4), 49.8 (t, C-18), 42.0 (s, C-5), 40.4 (d, C-10), 40.0 (d, C-8), 39.7 (s, C-9), 39.3 (d, C-13), 36.6 (t, C-3), 35.2 (t, C-11), 30.9 (t, C-1), 26.6 (t, C-14), 24.4 (t, C-12), 20.5 (2C, q, OCO*C*H$_3$), 18.0 (q, C-20), 14.4 (q, C-4′), 11.8 (q, C-5′), 10.6 (q, C-17); EIMS m/z [M]$^+$ absent, 453 (74) [M − OTig]$^+$, 393 (2), 229 (18), 187 (56), 169 (33), 159 (36), 143 (30), 119 (25), 105 (25), 91 (29), 83 (82), 69 (44), 55 (100), 43 (99), 41 (38); *anal.* C 62.73%, H 8.10%, calcd for $C_{29}H_{44}O_{10}$, C 63.02%, H 8.03%.

Preparation of (13*S*,19*R*)-6α,7*β*,15,16-Tetraacetoxy-4α,-18-epoxyneoclerodane 19,2α-(19-*O*-tigloyl)hemiacetal (7) from Compound 6. Treatment of **6** (1.05 g, 1.9 mmol) with Ac_2O−pyridine (1:1, 50 mL) at room temperature for 3 days gave **7** (1 g, 1.57 mmol, 82.5%, after crystallization from MeOH): colorless needles; mp 146−148 °C; $[\alpha]^{19}_D$ +50.7° (*c* 0.562, $CHCl_3$); IR (KBr) ν_{max} 2990, 2960, 1745 br, 1380, 1250, 1070, 1030, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.10 (1H, qq, J = 7.0, 1.4 Hz, H-3′), 6.71 (1H, s, H-19), 5.12 (1H, dd, J = 10.8, 10.0 Hz, H-7α), 4.68 (1H, d, J = 10.0 Hz, H-6*β*), 4.25 (1H, m, $W_{1/2}$ = 8 Hz, H-2*β*), 4.10, 4.04 (each 1H, dd, J = 6.7, 4.4 Hz, 2H-16), 3.98 (2H, br d, J = 9.0 Hz, 2H-15), 3.08, 2.50 (each 1H, d, J = 4.1 Hz, 2H-18), 2.61 (1H, ddd, J = 14.5, 2.1, 1.4 Hz, equatorial H-3α), 2.07, 2.05, 1.97, 1.81 (each 3H, s, OAc), 1.89 (3H, br d, J = 1.4 Hz, Me-5′), 1.79 (3H, dq, J = 7.0, 1.1 Hz, Me-4′), 1.05 (3H, s, Me-20), 0.84 (3H, d, J = 6.7 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.7 (2C), 169.7, 169.5 (each s, O*C*OCH$_3$), 165.6 (s, C-1′), 138.2 (d, C-3′), 128.7 (s, C-2′), 91.5 (d, C-19), 72.9 (d, C-7), 69.9 (d, C-6), 66.8 (d, C-2), 66.1 (t, C-16), 62.0 (t, C-15), 60.5 (s, C-4), 49.7 (t, C-18), 41.9 (s, C-5), 40.3 (d, C-10), 40.0 (d, C-8), 39.6 (s, C-9), 36.8 (t, C-3), 34.8 (d, C-13), 34.5 (t, C-11), 30.5 (t, C-1), 26.6 (t, C-14), 24.0 (t, C-12), 20.7, 20.4 (each 2C, q, OCO*C*H$_3$), 17.9 (q, C-20), 14.3 (q, C-4′), 11.7 (q, C-5′), 10.4 (q, C-17); EIMS m/z [M]$^+$ absent, 553 (17), 537 (99) [M − OTig]$^+$, 435 (7), 388 (11), 229 (9), 187 (41), 169 (25), 159 (28), 145 (14), 119 (15), 105 (18), 91 (17), 83 (93), 55 (60), 43 (100), 41 (16); *anal.* C 62.29%, H 7.90%, calcd for $C_{33}H_{48}O_{12}$, C 62.25%, H 7.60%.

Selective Hydrolysis of the Tiglate Ester of 7 to Give Compound 8 [(13*S*,19*S*)-6α,7*β*,15,16-Tetraacetoxy-4α,18-epoxyneoclerodane 19,2α-hemiacetal]. To a solution of **7** (1 g, 1.57 mmol) in THF (100 mL) was added dropwise a 0.1 N aqueous solution of H_2SO_4 until a pH of about 2 was reached. Then, the reaction mixture was stirred at room temperature for 4.5 h. Workup [dilution with H_2O (100 mL), extraction with CH_2Cl_2 (3 × 50 mL), drying (Na_2SO_4), filtration, and evaporation of the solvents] gave a residue that was subjected to column chromatography [Si gel, EtOAc−petroleum ether (1:1) as eluent], yielding 482 mg (0.75 mmol, 48%) of unreacted **7** (less polar constituent) and 446 mg of **8** (0.80 mmol, 51%): amorphous white solid, mp 64−68 °C; $[\alpha]^{19}_D$ +18.3° (*c* 0.518, $CHCl_3$); IR (KBr) ν_{max} 3480, 2960, 2940, 1740, 1430, 1370, 1100, 1030, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.75 (1H, s, H-19), 5.11 (1H, t, J = 10.2 Hz, H-7α), 4.73 (1H, d, J = 10.2 Hz, H-6*β*), 4.22 (1H, m, $W_{1/2}$ = 8 Hz, H-2*β*), 4.10, 4.06 (each 1H, dd, J = 6.5, 4.1 Hz, 2H-16), 3.98 (2H, br d, J = 8.9 Hz, 2H-15), 3.02, 2.47 (each 1H, d, J = 4.0 Hz, 2H-18), 2.60 (1H, br dd, J = 13.8, 2.2 Hz, equatorial H-3α), 2.07, 2.06, 2.05, 2.01 (each 3H, s, OAc), 0.97 (3H, s, Me-20), 0.83 (3H, d, J = 6.7 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.8 (2C), 170.1, 169.8 (each s, O*C*OCH$_3$), 93.3 (d, C-19), 72.7 (d, C-7), 71.3 (d, C-6), 66.5 (d, C-2), 66.1 (t, C-16), 62.1 (t, C-15), 60.7 (s, C-4), 49.4 (t, C-18), 42.3 (s, C-5), 40.2 (d, C-10), 40.0 (d, C-8), 39.7 (s, C-9), 36.7 (t, C-3), 34.9 (d, C-13), 34.7 (t, C-11), 30.5 (t, C-1), 26.9 (t, C-14), 24.0 (t, C-12), 20.9, 20.5 (each 2C, q, OCO*C*H$_3$), 18.1 (q, C-20), 10.4 (q, C-17); EIMS *m*/*z* [M]$^+$ absent, 537 (16) [M − OH]$^+$, 406 (20), 388 (12), 233 (8), 205 (26), 187 (55), 175 (28), 159 (39), 150 (23), 119 (21), 91 (23), 69 (24), 55 (27), 43 (100), 41 (19); *anal.* C 60.31%, H 7.49%, calcd for $C_{28}H_{42}O_{11}$, C 60.63%, H 7.63%.

Preparation of (13*S*)-6α,7*β*,15,16-Triacetoxy-4α,18-epoxyneoclerodan-19,2α-olide (9) from Compound 8. To a solution of **8** (450 mg, 0.81 mmol) in Me_2CO (20 mL) was added an excess of Jones' reagent[12] at 0 °C with stirring. After 5 min, the excess of Jones' reagent was destroyed by addition of EtOH, and then the reaction mixture was diluted with H_2O (60 mL). Extraction with $CHCl_3$ (4 × 20 mL), and workup as usual gave a residue (420 mg) from which pure **9** (401 mg, 0.72 mmol, 89%) was obtained after chromatography (Si gel column, EtOAc as eluent): colorless needles (EtOAc−*n*-hexane), mp 159−161 °C; $[\alpha]^{19}_D$ +13.8° (*c* 0.621, $CHCl_3$); IR (KBr) ν_{max} 2980, 2940, 1770, 1730, 1480, 1370, 1250, 1100, 1090, 970 cm^{-1};^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.44 (1H, t, J = 10.2 Hz, H-7α), 4.75 (1H, m, $W_{1/2}$ = 8 Hz, H-2*β*), 4.69 (1H, d, J = 10.2 Hz, H-6*β*), 4.09, 4.02 (each 1H, dd, J = 6.3, 4.7 Hz, 2H-16), 3.95 (2H, br d, J = 9.1 Hz, 2H-15), 3.24, 2.59 (each 1H, d, J = 3.8 Hz, 2H-18), 2.21 (1H, dt, J = 15.0, 2.9 Hz, equatorial H-3α), 2.02, 1.99, 1.97, 1.95 (each 3H, s, OAc), 0.81 (3H, s, Me-20), 0.75 (3H, d, J = 6.6 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.8 (s, C-19), 170.7 (2C), 170.0, 169.7 (each s, O*C*OCH$_3$), 72.3 (2C, d, C-6, C-7), 69.0 (d, C-2), 66.0 (t, C-16), 61.9 (t, C-15), 61.3 (s, C-4), 50.1 (t, C-18), 47.5 (s, C-5), 41.0 (d, C-10), 40.4 (d, C-8), 40.3 (s, C-9), 36.4 (t, C-3), 34.8 (t, C-11), 34.4 (d, C-13), 30.5 (t, C-1), 26.5 (t, C-14), 23.3 (t, C-12), 20.8 (2C), 20.7, 20.5 (each q, OCO*C*H$_3$), 15.8 (q, C-20), 10.4 (q, C-17); EIMS *m*/*z* 552 (11) [M]$^+$, 387 (11), 249 (42), 205 (32), 187 (62), 159 (33), 135 (39), 91 (21), 81 (24), 43 (100), 41 (15); *anal.* C 61.10%, H 7.60%, calcd for $C_{28}H_{40}O_{11}$, C 60.85%, H 7.30%.

Preparation of (13*S*)-6α-Acetoxy-4α,18-epoxy-7-oxoneoclerodane-16,15;19,2α-diolide (10) from Scutegalin B (4). A solution of **4**[8] (128 mg, 0.25 mmol) in Me_2CO (10 mL) was treated with an excess of Jones' reagent[12] at 0 °C for 15 min. Workup in the usual manner yielded a residue that was subjected to column chromatography [Si gel, EtOAc−petroleum ether (3:2) as eluent], obtaining **10** (66 mg, 0.16 mmol, 62%): colorless needles (EtOAc−*n*-hexane) mp 250−252 °C; $[\alpha]^{18}_D$ +7.3° (*c* 0.287, $CHCl_3$); IR (KBr) ν_{max} 2990, 2940, 1760, 1730, 1450, 1370, 1230, 1110, 1020, 980, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.11 (1H, s, H-6*β*), 4.81 (1H, m, $W_{1/2}$ = 8 Hz, H-2*β*), 4.36 (1H, td, J = 9.1, 2.4 Hz, H_B-15), 4.12 (1H, ddd, J = 10.2, 9.1, 6.7 Hz, H_A-15), 3.20, 2.72 (each 1H, d, J = 3.6 Hz, 2H-18), 2.16 (3H, s, OAc), 2.15 (1H, dt, J = 15.1, 2.8 Hz, equatorial H-3α), 0.99 (3H, d, J = 6.6 Hz, Me-17), 0.74 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 201.8 (s, C-7), 178.8 (s, C-16), 170.5 (s, C-19), 169.5 (s, O*C*OCH$_3$), 72.5 (d, C-6), 71.1 (d, C-2), 66.4 (t, C-15), 61.1 (s, C-4), 51.0 (s, C-5), 49.8 (t, C-18), 48.2 (d, C-8), 44.0 (s, C-9), 41.3 (d, C-10), 38.9 (d, C-13), 35.8 (t, C-3), 33.7 (t, C-11), 27.4 (t, C-1), 26.7 (t, C-14), 22.4 (t, C-12), 20.6 (q, OCO*C*H$_3$), 15.9 (q, C-20), 7.6 (q, C-17); EIMS *m*/*z* [M]$^+$ absent, 203 (0.2), 175 (0.2), 129 (1), 115 (1), 105 (2), 91 (4), 55 (11), 43 (100), 41 (13); *anal.* C 62.71%, H 6.65%, calcd for $C_{22}H_{28}O_8$, C 62.84%, H 6.71%.

Chromium Trioxide−Pyridine Treatment of Scutegalin B (4): Compounds 11 [(13*S*,19*R*)-6α-Acetoxy-4α,18-epoxy-7*β*-hydroxyneoclerodan-16,15-olide 19,2α-(19-*O*-tigloyl)hemiacetal] and 12 [(13*S*,19*R*)-6α-Acetoxy-4α,18-epoxy-7-oxoneoclerodan-16,15-olide 19,2α-(19-*O*-tigloyl)hemiacetal]. To a solution of **4**[8] (320 mg, 0.63 mmol) in pyridine (17 mL) was added a mixture of CrO_3 (1.7 g) and pyridine (17 mL), and the reaction mixture was left at room temperature for 24 h (Sarett oxidation procedure[13]). Then, the reaction mixture was poured into H_2O (100 mL) and extracted with Et_2O (5 × 25 mL). The extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue (170 mg) was chromatographed [Si gel column, EtOAc−petroleum ether (1:1) as eluent], giving **11** (56 mg, 0.11 mmol, 17.5%, most polar constituent) and **12** (102 mg, 0.20 mmol, 32%).

Compound 11: mp 223−226 °C (colorless needles from EtOAc); $[\alpha]^{22}_D$ +43.2° (*c* 0.243, $CHCl_3$); IR (KBr) ν_{max} 3540, 2960, 1770, 1730, 1690, 1375, 1280, 1245, 1150, 1070, 1030, 970, 930, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (1H, qq, J = 7.2, 1.6 Hz, H-3′), 6.70 (1H, s, H-19), 4.52 (1H, d, J = 9.9 Hz, H-6*β*), 4.35 (1H, td, J = 9.0, 2.4 Hz, H_B-15), 4.23 (1H, m,$W_{1/2}$ = 8 Hz, H-2*β*), 4.19 (1H, ddd, J = 9.2, 9.0, 6.5 Hz, H_A-15), 3.60 (1H, t, J = 9.9 Hz, H-7α), 3.04, 2.45 (each 1H, d, J = 4.3 Hz, 2H-18), 1.88 (3H, br d, J = 1.6 Hz, Me-5′), 1.86 (3H, s, OAc), 1.81 (3H, dq, J = 7.2, 1.2 Hz, Me-4′), 1.01 (3H, d, J = 6.6 Hz, Me-17), 0.98 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.9 (s, C-16), 170.5 (s, O*C*OCH$_3$), 166.2 (s, C-1′), 138.6 (d, C-3′), 128.7 (s, C-2′), 91.8 (d, C-19), 72.9 (d, C-6), 71.1 (d, C-7), 67.0 (d, C-2), 66.3 (t, C-15), 60.4 (s, C-4), 49.9 (t, C-18), 41.8 (s, C-5), 41.7 (d, C-10), 40.4 (d, C-8), 39.5 (s, C-9), 39.1 (d, C-13), 36.9 (t, C-3), 34.7 (t, C-11), 28.0 (t, C-1), 26.6 (t, C-14), 23.1 (t, C-12), 20.8 (q, OCO*C*H$_3$), 18.1 (q, C-20), 14.4 (q, C-4′), 11.8 (q, C-5′), 10.7 (q, C-17); EIMS *m*/*z* 506 (0.2) [M]$^+$ 489 (1), 446 (1), 407 (41), 347 (6), 299 (6), 233 (5), 187 (74), 159 (20), 113 (22), 83 (100), 69 (15), 55 (58), 43 (36); *anal.* C 63.79%, H 7.62%, calcd for $C_{27}H_{38}O_9$, C 64.01%, H 7.56%.

Compound 12: an amorphous white solid, mp 115−120 °C; $[\alpha]^{22}_D$ +50.9° (*c* 0.438, $CHCl_3$); IR (KBr) ν_{max} 2940, 1770, 1730, 1450, 1375, 1240, 1110, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (1H, qq, J = 7.1, 1.3 Hz, H-3′), 6.33 (1H, s, H-19), 4.93 (1H, s, H-6*β*), 4.37 (1H, td, J = 8.9, 2.2 Hz, H_B-15), 4.26 (1H, m, $W_{1/2}$ = 8 Hz, H-2*β*), 4.21 (1H, ddd, J = 9.9, 8.9, 6.4 Hz, H_A-15), 3.04, 2.44 (each 1H, d, J = 4.3 Hz, 2H-18), 1.93 (3H, s, OAc), 1.88 (3H, br d, J = 1.3 Hz, Me-5′), 1.81 (3H, dq, J = 7.1, 1.2 Hz, Me-4′), 0.99 (3H, d, J = 6.6 Hz, Me-17), 0.89 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 203.8 (s, C-7), 178.7 (s, C-16), 169.5 (s, O*C*OCH$_3$), 165.7 (s, C-1′), 138.5 (d, C-3′), 128.7 (s, C-2′), 91.3 (d, C-19), 72.8 (d, C-6), 66.9 (d, C-2), 66.4 (t, C-15), 60.6 (s, C-4), 49.8 (t, C-18), 48.7 (d, C-8), 45.8 (s, C-9), 44.0 (s, C-5), 40.8 (d, C-10), 39.0 (d, C-13), 36.4 (t, C-3), 34.4 (t, C-11), 28.0 (t, C-1), 26.8 (t, C-14), 23.4 (t, C-12), 20.3 (q, OCO*C*H$_3$), 17.7 (q, C-20), 14.5 (q, C-4′), 11.8 (q, C-5′), 7.6 (q, C-17); EIMS *m*/*z* 504 (0.2) [M]$^+$, 489 (1), 421 (4), 405 (43), 345 (10), 327 (5), 299 (7), 231 (7), 203 (12), 185 (16), 113 (26), 83 (100), 55 (51), 43 (38); *anal.* C 64.41%, H 7.08%, calcd for $C_{27}H_{36}O_9$, C 64.27%, H 7.19%.

Reaction of Compound 13 with Acetic Anhydride−Pyridine to Give (13*S*)-2α,6α,7*β*-Triacetoxy-4α,18-epoxyneoclerodan-19-al 16,15-lactone (14). Treatment of **13**[8] (33 mg, 0.07 mmol) with Ac_2O−pyridine (1:1, 3 mL) at room temperature for 24 h yielded **14** (31 mg, 0.06 mmol, 86%, after crystallization of the crude of the reaction from EtOAc−*n*-hexane): colorless needles; mp 207−210 °C; $[\alpha]^{25}_D$ +47.0° (*c* 0.285, $CHCl_3$); IR (KBr) ν_{max} 2980, 2950, 1785, 1740, 1725, 1440, 1370, 1250, 1170, 1090, 1040, 980, 940 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.20 (1H, d, $J_{19,10\beta}$ = 1.5 Hz, H-19), 5.17

(1H, dd, J = 11.1, 9.9 Hz, H-7α), 4.86 (1H, d, J = 9.9 Hz, H-6β), 4.70 (1H, m, $W_{1/2}$ = 24 Hz, H-2β), 4.39 (1H, td, J = 8.8, 2.4 Hz, H_B-15), 4.18 (1H, ddd, J = 9.3, 8.8, 6.2 Hz, H_A-15), 3.15 (1H, dd, J_{gem} = 3.6 Hz, $J_{18B,3\alpha}$ = 2.4 Hz, H_B-18), 2.75 (1H, td, J = 12.1, 2.4 Hz, axial H-3α), 2.38 (1H, d, J = 3.6 Hz, H_A-18), 2.03, 2.02, 1.99 (each 3H, s, OAc), 0.86 (3H, d, J = 6.7 Hz, Me-17), 0.78 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 202.4 (d, C-19), 178.9 (s, C-16), 170.5, 170.3, 169.5 (each s, O*C*OCH$_3$), 73.4 (d, C-7), 72.9 (d, C-6), 70.4 (d, C-2), 66.5 (t, C-15), 61.7 (s, C-4), 54.7 (s, C-5), 50.0 (t, C-18), 44.7 (d, C-10), 39.6 (d, C-8), 39.5 (s, C-9), 39.4 (d, C-13), 37.6 (t, C-3), 35.3 (t, C-11), 28.7 (t, C-1), 26.7 (t, C-14), 23.6 (t, C-12), 21.2, 20.7, 20.6 (each q, OCO*C*H$_3$), 19.9 (q, C-20), 10.6 (q, C-17); EIMS m/z [M]$^+$ absent, 465 (0.5) [M − Ac]$^+$, 423 (1), 405 (1), 229 (5), 205 (5), 187 (68), 169 (16), 159 (22), 119 (12), 91 (11), 69 (11), 55 (20), 43 (100), 41 (14); *anal.* C 61.34%, H 7.18%, calcd for $C_{26}H_{36}O_{10}$, C 61.40%, H 7.14%.

Reaction of Compound 13 with Isobutyric Anhydride−Pyridine and Isobutyryl Chloride−Triethylamine: Derivative 15 [(13*S*)-6α,7*β*-Diacetoxy-2α-isobutyryloxy-4α,-18-epoxyneoclerodan-19-al 16,15-lactone]. Treatment of **13**[8] (75 mg, 0.16 mmol) with (^{i}PrCO)$_2$O−pyridine (1:1, 6 mL) at room temperature gave **15** (66 mg, 0.12 mmol, 76.5%, after crystallization of the crude of the reaction from EtOAc−*n*-hexane): colorless needles; mp 243−245 °C; $[\alpha]^{25}_D$ +44.1° (*c* 0.869, $CHCl_3$); IR (KBr) ν_{max} 2980, 2900, 2780, 1770, 1730, 1460, 1390, 1370, 1260, 1230, 1190, 1150, 1100, 1050, 1020, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.21 (1H, d, $J_{19,10\beta}$ = 1.2 Hz, H-19), 5.17 (1H, t, J = 10.3 Hz, H-7α), 4.86 (1H, d, J = 10.3 Hz, H-6β), 4.68 (1H, ddt, J = 12.2, 10.7, 5.2 Hz, H-2β), 4.40 (1H, td, J = 8.8, 2.2 Hz, H_B-15), 4.18 (1H, ddd, J = 9.3, 8.8, 6.2 Hz, H_A-15), 3.16 (1H, dd, J_{gem} = 3.5 Hz, $J_{18B,3\alpha}$ = 2.5 Hz, H_B-18), 2.74 (1H, td, J = 12.2, 2.5 Hz, axial H-3α), 2.49 (1H, sept, J = 7.0 Hz, H-2′), 2.39 (1H, d, J = 3.5 Hz, H_A-18), 2.01, 1.98 (each 3H, s, OAc), 1.14 (6H, d, J = 7.0 Hz, Me-3′, Me-4′), 0.86 (3H, d, J = 6.7 Hz, Me-17), 0.78 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 202.4 (d, C-19), 178.9 (s, C-16), 176.6 (s, C-1′), 170.3, 169.5 (each s, O*C*OCH$_3$), 73.4 (d, C-7), 72.9 (d, C-6), 70.0 (d, C-2), 66.5 (t, C-15), 61.6 (s, C-4), 54.7 (s, C-5), 50.0 (t, C-18), 44.7 (d, C-10), 39.6 (d, C-8), 39.5 (s, C-9), 39.3 (d, C-13), 37.6 (t, C-3), 35.3 (t, C-11), 34.0 (d, C-2′), 28.7 (t, C-1), 26.7 (t, C-14), 23.5 (t, C-12), 20.6, 20.5 (each q, OCO*C*H$_3$), 19.9 (q, C-20), 18.8 (2C, q, C-3′, C-4′), 10.6 (q, C-17); EIMS m/z 536 (0.1) [M]$^+$, 477 (0.1), 447 (0.4), 377 (2), 299 (7), 229 (9), 187 (100), 169 (34), 159 (35), 133 (15), 113 (14), 91 (11), 71 (15), 55 (14), 43 (94), 41 (13); *anal.* C 62.41%, H 7.66%, calcd for $C_{28}H_{40}O_{10}$, C 62.67%, H 7.51%.

To a solution of **13**[8] (71 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (7 mL) was added Et_3N (0.2 mL, 1.4 mmol) at 0 °C under Ar and the reaction mixture stirred for 5 min. Then, ^{i}PrCOCl (0.3 mL, 2.8 mmol) was added and the reaction stirred for a further 2 h, poured into ice-water, and extracted with CH_2Cl_2 (4 × 10 mL). The extract was washed with a saturated aqueous solution of Na_2CO_3, then with H_2O, and dried (Na_2SO_4). Evaporation of the solvents and column chromatography [Si gel, petroleum ether−EtOAc (3:2) as eluent] yielded **15** (40 mg, 0.075 mmol, 49% yield) and starting material (**13**, 25 mg, 0.053 mmol, 35% recovered).

Reaction of Compound 16 with Isobutyric Anhydride−Pyridine: Derivative 17 [(13*S*,19*R*)-7*β*-Acetoxy-4α,18-epoxy-6α-hydroxyneoclerodan-16,15-olide 19,2α-(19-*O*-isobutyryl)hemiacetal]. Treatment of **16**[11] (115 mg, 0.27 mmol) with (^{i}PrCO)$_2$O−pyridine (1:1, 10 mL) at room temperature for 24 h, followed by workup in the usual manner, gave **17** {107 mg, 0.217 mmol, 80%, after chromatographic purification [Si gel column eluted with petroleum ether−EtOAc (1:1)] and crystallization from EtOAc−*n*-hexane}: colorless needles, mp 142−145 °C; $[\alpha]^{18}_D$ +30.9° (*c* 0.268, $CHCl_3$); IR (KBr) ν_{max} 3500, 2970, 2920, 1780, 1740, 1730, 1370, 1260, 1240, 1070, 1030, 960, 930, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.50 (1H, s, H-19), 5.04 (1H, dd, J = 11.0, 9.7 Hz, H-7α), 4.34 (1H, td, J = 8.8, 2.0 Hz, H_B-15), 4.24 (1H, ddd, J = 9.4, 8.8, 5.3 Hz, H_A-15), 4.23 (1H, m, $W_{1/2}$ = 8 Hz, H-2β), 3.33 (1H, d, J = 9.7 Hz, H-6β), 3.20, 2.63 (each 1H, d, J = 3.7 Hz, 2H-18), 2.55 (1H, sept, J = 7.0 Hz, H-2′), 2.07 (3H, s, OAc), 1.21 (6H, d, J = 7.0 Hz, Me-3′, Me-4′), 1.00 (3H, s, Me-20), 0.85 (3H, d, J = 6.7 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 179.1 (s, C-16), 175.1 (s, C-1′), 170.4 (s, O*C*OCH$_3$), 92.5 (d, C-19), 74.1 (d, C-7), 71.5 (d, C-6), 66.9 (d, C-2), 66.5 (t, C-15), 61.9 (s, C-4), 50.7 (t, C-18), 41.7 (s, C-5), 39.8 (s, C-9), 39.7 (d, C-10), 39.3 (d, C-8), 39.2 (d, C-13), 36.4 (t, C-3), 34.8 (t, C-11), 34.2 (d, C-2′), 28.1 (t, C-1), 26.4 (t, C-14), 23.2 (t, C-12), 20.9 (q, OCO*C*H$_3$), 18.5, 18.4 (each q, C-3′, C-4′), 18.1 (q, C-20), 10.6 (q, C-17); *anal.* C 62.96%, H 7.81%, calcd for $C_{26}H_{38}O_9$, C 63.14%, H 7.75%.

Preparation of (13*S*,19*S*)-6α,7*β*-Diacetoxy-4α,18-epoxyneoclerodan-16,15-olide 19,2α-(methyl)acetal (18) Starting from 7-*O*-Acetylscutegalin B (5). Compound **5**[8] was transformed into its corresponding 16,15-lactone derivative by CrO_3·2Py oxidation[13] as previously described.[8] A solution of the 16,15-lactone derivative of **5** (41 mg, 0.075 mmol) and (+)-camphor-10-sulfonic acid (5 mg, 0.02 mmol) in MeOH (6 mL) was stirred at room temperature for 5 min. Then, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the reaction mixture was extracted with EtOAc (4 × 15 mL). The extracts were dried (Na_2SO_4), filtered, and evaporated to dryness, giving a residue from which 31 mg of the methylacetal[16] **18** (0.065 mmol, 86%) were obtained: colorless needles (EtOAc−*n*-hexane), mp 212−214 °C; $[\alpha]^{19}_D$ +35.1° (*c* 0.345, $CHCl_3$); IR (KBr) ν_{max} 2960, 2920, 2820, 1760, 1740, 1380, 1250, 1170, 1100, 1020, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.06 (1H, s, H-19), 5.06 (1H, t, J = 10.4 Hz, H-7α), 4.59 (1H, d, J = 10.4 Hz, H-6β), 4.32 (1H, td, J = 8.8, 2.4 Hz, H_B-15), 4.16 (1H, ddd, J = 9.9, 8.8, 6.6 Hz, H_A-15), 4.13 (1H, m, $W_{1/2}$ = 8 Hz, H-2β), 3.47 (3H, s, OMe), 2.96, 2.35 (each 1H, d, J = 4.4 Hz, 2H-18), 2.54 (1H, dt, J = 14.1, 2.9, equatorial H-3α), 1.99, 1.96 (each 3H, s, OAc), 0.95 (3H, s, Me-20), 0.83 (3H, d, J = 6.6 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.8 (s, C-16), 170.4, 169.6 (each s, O*C*OCH$_3$), 100.6 (d, C-19), 72.9 (d, C-7), 70.0 (d, C-6), 66.4 (d, C-2), 66.3 (t, C-15), 60.6 (s, C-4), 55.4 (q, O*C*H$_3$), 49.5 (t, C-18), 43.1 (s, C-5), 40.5 (d, C-10), 39.9 (d, C-8), 39.7 (s, C-9), 39.1 (d, C-13), 36.8 (t, C-3), 34.6 (t, C-11), 28.1 (t, C-1), 26.9 (t, C-14), 23.1 (t, C-12), 20.7, 20.6 (each q, OCO*C*H$_3$), 18.0 (q, C-20), 10.6 (q, C-17); EIMS m/z 480 (0.1) [M]$^+$, 449 (35) [M − OMe]$^+$, 319 (14), 247 (24), 229 (26), 205 (30), 187 (79), 175 (66), 159 (52), 133 (25), 113 (44), 91 (31), 79 (24), 69 (34), 55 (36), 43 (100), 41 (27); *anal.* C 62.39%, H 7.41%, calcd for $C_{25}H_{36}O_9$, C 62.48%, H 7.55%.

Preparation of (13*S*)-6α,7*β*,15,16-Tetraacetoxy-4α,18-epoxyneoclerodane 2α,19-diol (20) from Compound 8. Treatment of a solution of **8** (56 mg, 0.10 mmol) in CH_2Cl_2−EtOH (1:1, 6 mL) with $NaBH_4$ (8 mg, 0.21 mmol) at room temperature for 5 min yielded, after workup in the usual manner, the derivative **20** (51 mg, 0.09 mmol, 90%) as a thick oil: $[\alpha]^{25}_D$ +24.1° (*c* 0.382, $CHCl_3$); IR (NaCl) ν_{max} 3500, 2960, 2920, 1740 br, 1380, 1265, 1090, 1030, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.11 (1H, dd, J = 11.2, 9.4 Hz, H-7α), 4.70 (1H, d, J = 9.4 Hz, H-6β), 4.29, 4.02 (each 1H, d, J = 12.7 Hz, 2H-19), 4.22, 4.08 (each 1H, dd, J = 6.5, 4.8 Hz, 2H-16), 3.97 (1H, br d, J = 9.1 Hz, H_A-15), 3.73 (1H, m, $W_{1/2}$ = 24 Hz, H-2β), 3.00 (1H, dd, J_{gem} = 3.7 Hz, $J_{18B,3\alpha}$ = 2.5 Hz, H_B-18), 2.25 (1H, d, J = 3.7 Hz, H_A-18), 2.05, 2.04, 2.02, 1.98 (each 3H, s, OAc), 0.79 (3H, d, J = 6.5 Hz, Me-17), 0.76 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.3, 171.0, 170.9, 169.3 (each s, O*C*OCH$_3$), 75.9 (d, C-7), 73.5 (d, C-6), 68.8 (d, C-2), 66.3 (t, C-16), 63.1 (t, C-15), 62.6 (t, C-19), 61.7 (s, C-4), 47.8 (t, C-18), 46.0 (s, C-5), 43.2 (d, C-10), 41.3 (t, C-3), 41.3 (d, C-8), 40.0 (s, C-9), 35.0 (t, C-11), 34.7 (d, C-13), 34.0 (t, C-1), 30.8 (t, C-14), 23.1 (t, C-12), 21.0, 20.8 (2C), 20.6 (each q, OCO*C*H$_3$), 18.6 (q, C-20), 10.4 (q, C-17); EIMS m/z 556 (1) [M]$^+$, 521 (2), 483 (10), 405 (29), 387 (9), 205 (24), 187 (34), 159 (21), 150 (11), 121 (11), 107 (11), 81 (14), 69 (10), 55 (10), 43 (100); *anal.* C 60.11%, H 7.81%, calcd for $C_{28}H_{44}O_{11}$, C 60.41%, H 7.97%.

Preparation of (13*S*)-7*β*-Acetoxy-6α-tigloyloxy-4α,18-epoxyneoclerodane 2α,15,16,19-tetraol (21) from Scutegalin B (4). To a solution of **4** (144 mg, 0.28 mmol) in CH_2Cl_2−EtOH (1:1, 20 mL) at room temperature was added $NaBH_4$ (41 mg, 1.08 mmol) and the reaction stirred for 18 h. After usual workup, the residue was subjected to column chromatography [Si gel, $CHCl_3$−MeOH (9:1) as eluent] yielding **21** (86 mg, 0.17 mmol, 60%): amorphous white solid; mp 87−92

°C; $[\alpha]^{23}_D$ +24.2° (*c* 0.231, $CHCl_3$); IR (KBr) ν_{max} 3420, 2940, 2890, 1740, 1720, 1380, 1260, 1150, 1060, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.73 (1H, qq, J = 6.9, 1.3 Hz, H-3′), 5.15 (1H, t, J = 9.9 Hz, H-7α), 4.78 (1H, d, J = 9.9 Hz, H-6β), 4.33, 4.06 (each 1H, d, J = 11.8 Hz, 2H-19), 3.70−3.50 (5H, m, H-2β, 2H-15, 2H-16), 3.09 (1H, dd, J_{gem} = 3.7 Hz, $J_{18B,3\alpha}$ = 2.4 Hz, H_B-18), 2.27 (1H, d, J = 3.7 Hz, H_A-18), 1.90 (3H, s, OAc), 1.78 (3H, br d, J = 1.3 Hz, Me-5′), 1.69 (3H, dq, J = 6.9, 1.1 Hz, Me-4′), 0.80 (3H, d, J = 6.5 Hz, Me-17), 0.77 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.5 (s, O*C*OCH$_3$), 166.2 (s, C-1′), 138.1 (d, C-3′), 128.2 (s, C-2′), 75.8 (d, C-7), 73.7 (d, C-6), 68.6 (d, C-2), 65.6 (t, C-16), 63.0 (s, C-4), 62.6 (t, C-19), 60.5 (t, C-15), 47.8 (t, C-18), 46.0 (s, C-5), 43.1 (d, C-10), 41.4 (t, C-3), 39.8 (d, C-8), 39.7 (s, C-9), 38.8 (d, C-13), 34.9 (t, C-11), 34.6 (t, C-1), 30.7 (t, C-14), 23.7 (t, C-12), 20.6 (q, OCO*C*H$_3$), 18.7 (q, C-20), 14.1 (q, C-4′), 12.1 (q, C-5′), 10.5 (q, C-17); EIMS *m*/*z* $[M]^+$ absent, 494 (0.1) $[M-H_2O]^+$, 413 (0.1) $[M - OTig]^+$, 229 (1), 205 (4), 187 (8), 159 (8), 147 (5), 121 (12), 107 (10), 95 (10), 83 (100), 69 (19), 55 (83), 43 (43), 41 (15); *anal.* C 63.01%, H 8.39%, calcd for $C_{27}H_{44}O_9$, C 63.26%, H 8.65%.

Treatment of Compounds 9 and 10 with Diisobutylaluminum Hydride. To a solution of **9** (365 mg, 0.66 mmol) in dry toluene (60 mL) at −78 °C DIBAH (6.6 mL of a 1M solution in toluene) was added over a 5 min period under Ar. The reaction mixture was stirred for 40 min, then quenched with 10% aqueous solution of H_2SO_4 (4 mL). Extraction with $CHCl_3$ (4 × 15 mL) and usual workup yielded unreacted **9** (340 mg, 93% recovered). Other attempts at reduce the 19,2α-lactone of **9** with DIBAH (0 °C for 2 h or 50 °C for 1h) were unsuccessful.

Treatment of the 7-ketodilactone **10** with DIBAH in the same conditions yielded a complex mixture of products, which were not investigated.

Treatment of Compound 10 with Sodium Borohydride: Derivative 22 [(13*S*)-6α-Acetoxy-4α,18-epoxy-7α-hydroxyneoclerodane-16,15;19,2α-diolide]. To a solution of **10** (107 mg, 0.25 mmol) in CH_2Cl_2−MeOH (1:1, 20 mL) at 0 °C was added an excess of $NaBH_4$ and the reaction mixture stirred for 1.5 h. Workup in the usual manner yielded a residue from which pure **22** (88 mg, 0.208 mmol, 83%) was obtained: colorless needles (EtOAc−*n*-hexane); mp 231−233 °C; $[\alpha]^{18}_D$ +25.2° (*c* 0.222, $CHCl_3$); IR (KBr) ν_{max} 3510, 3490, 2960, 2940, 1770, 1740, 1720, 1370, 1250, 1140, 1080, 1020, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.82 (1H, m, $W_{1/2}$ = 8 Hz, H-2β), 4.76 (1H, d, J = 4.2 Hz, H-6β), 4.33 (1H, td, J = 8.9, 2.3, H_B-15), 4.16 (1H, ddd, J = 9.5, 8.9, 6.4 Hz, H_A-15), 3.85 (1H, dd, J = 6.7, 4.2, H-7β), 3.20, 2.60 (each 1H, d, J = 3.8 Hz, 2H-18), 2.08 (3H, s, OAc), 1.04 (3H, d, J = 7.0 Hz, Me-17), 0.93 (3H, s, Me-20); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.9 (s, C-16), 174.0 (s, C-19), 170.3 (s, O*C*OCH$_3$), 73.2 (d, C-6), 72.4 (d, C-7), 69.3 (d, C-2), 66.3 (t, C-15), 62.0 (s, C-4), 50.1 (t, C-18), 47.1 (s, C-5), 41.8 (d, C-10), 39.0 (d, C-8), 38.6 (s, C-9), 38.6 (d, C-13), 36.3 (t, C-3), 34.6 (t, C-11), 27.3 (t, C-1), 26.2 (t, C-14), 22.1 (t, C-12), 21.0 (q, OCO*C*H$_3$), 17.1 (q, C-20), 12.0 (q, C-17); EIMS *m*/*z* 423 (0.2) $[M+H]^+$, 405 (0.1), 363 (0.4), 249 (11), 205 (2), 187 (11), 135 (32), 91 (13), 79 (10), 67 (10), 55 (26), 43 (100), 41 (27); *anal.* C 62.37%, H 6.98%, calcd for $C_{22}H_{30}O_8$, C 62.54%, H 7.16%.

Treatment of Compound 22 with Diisobutylaluminum Hydride: Derivatives 23 [(13*S*,16*R* and *S*)-6α-Acetoxy-4α,18-epoxy-7α-hydroxyneoclerodan-19,2α-olide 16,15-hemiacetal]. To a solution of **22** (81 mg, 0.19 mmol) in anhydrous toluene (5 mL) at −20 °C DIBAH (3.2 mL of a 1 M solution in toluene) was added under Ar and over a 2 min period. The reaction mixture was allowed to reach room temperature, then stirred for 8 h. Workup in the usual manner yielded a residue that was chromatographed [Si gel column, EtOAc−petroleum ether (1:1) as eluent], giving 23 mg (0.054 mmol, 28%) of a substance (**23**) whose ^1H NMR spectrum (200 MHz, $CDCl_3$) revealed that it was a 1:1 mixture of C-16 epimers: δ 5.31 (0.5 H, m, H-16), 5.17 (0.5 H, m, H-16), 4.85 (1H, m, H-2β), 4.78 (1H, d, J = 4.2 Hz, H-6β), 4.17 (1H, m, H_B-15), 3.87 (1H, m, H_A-15), 3.84 (1H, dd, J = 4.2, 6.5 Hz, H-7β), 3.21 (1H, d, J = 3.7 Hz, H_B-18), 2.63 (1H, d, J = 3.7 Hz, H_A-18), 2.11 (3H, s, OAc), 1.06 (3H, d, J = 6.9 Hz, Me-17), 0.94 (3H, s, Me-20). Attempts at improving the yield of **23** and/or characterizing other reaction products were unsuccessful.

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(16) It is known that, in compounds such as **5** (Scheme 1) or its 16,15-lactone derivative (see Experimental Section), the *O*-acyl substituent of an esterified hemiacetal is easily and stereoselectively substituted by alkoxide or acyloxy groups under acid catalysis, probably via an oxonium ion (see de la Torre, M. C.; Domínguez, G.; Rodríguez, B.; Perales, A.; Simmonds, M. S. J.; Blaney, W. M. *Tetrahedron* **1994**, *50*, 13553−13566).
(17) Recently, Tomimori and co-workers (Ohno, A,; Kizu, H.; Tomimori, T. *Chem. Pharm. Bull.* **1997**, *45*, 1097−1100) have reported the 19-*O*-esterification of a 6α-acetoxyneoclerodane 19,2α-hemiacetal by reaction of the diterpenoid with an acid, under reflux in toluene and in the presence of molecular sieve (5 Å).

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