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Hemisynthesis of Oxetane-Containing Neoclerodane Diterpenoids

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Dedicated to the memory of our colleague and friend Dr Peter Y. Malakov

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Abstract—The hemisynthesis of the 4α,19-oxetane-containing neoclerodane diterpenoids **25** and **27**, has been achieved from 19-acetylgnaphalin (**4**). Oxetane ring formation has been accomplished by intramolecular oxirane ring opening on the 4β,18-epoxy-neoclerodane **23**, which yields derivative **25**, and by electrophilic cyclization of the $\Delta^{4(18)}$ homoallylic alcohol **26**, which proceeds exclusively via the *4-exo* mode, for obtaining the 18-iodo-4α,19-oxetane **27**. The twisted boat conformation of ring A in derivative **27** favours an intramolecular nucleophilic substitution reaction yielding compound **28**, which possesses a very interesting tetracyclic moiety in its structure. From the $\Delta^{4(18)}$ unsaturated intermediate **21**, access to Δ^{3}-neoclerodane diterpenoids like **30** has been gained. The electrophilic cyclization of the Δ^{3} isomer **31** goes through a *5-endo* mode exclusively, to form the 3α,19-epoxy-neoclerodane **33**.

Introduction

Oxetanes are present in biologically important metabolites like thromboxane A_2,[1] taxoids[2] or the naturally occurring antiviral nucleosides oxetanocins.[3] Nevertheless, they are scarcely found as part of the structure of natural products. They have been identified in the group of diterpenoids.[4,5] The oxetane ring may feature at positions 4α,19,[6–10] 4β,6β,[11,12] and 4β,10β.[10] Teucroxide (**1**),[7] chamaedroxide (**2**)[11] and teusandrin E (**3**)[10] respectively, are representative examples (Chart 1).

The complex structures of neoclerodane diterpenoids have made them attractive targets for total synthesis.[13–16] Moreover, the dense array of functional groups present in these compounds makes them interesting substrates to study the chemistry of polyfunctionalized molecules. An additional feature of neoclerodanes is that they behave as insect antifeedants[17,18] and therefore may be employed as an alternative to the use of broad-spectrum chemical pesticides for crop-protection.

We are currently involved in the study of the chemistry of neoclerodane diterpenoids, focussing on the development of semisynthetic routes for the efficient preparation of neoclerodanes that are difficult to obtain from natural sources.[19–22] The oxetane-containing neoclerodanes attracted our attention as they are minor terpenic constituents of *Teucrium* plants isolated in minute amounts. This has precluded the study of their biological activities and their chemical reactivity. Owing to the lack of efficient routes for the preparation of this class of neoclerodanes, we undertook the semisynthesis of 4α,19-oxetane containing neoclerodanes, like teucroxide (**1**). 19-Acetylgnaphalin (**4**)[23] is a diterpenoid that can be isolated from *T. gnaphalodes* in enough amount to be used in a multistep synthesis and, seemed to be an appropriate starting material

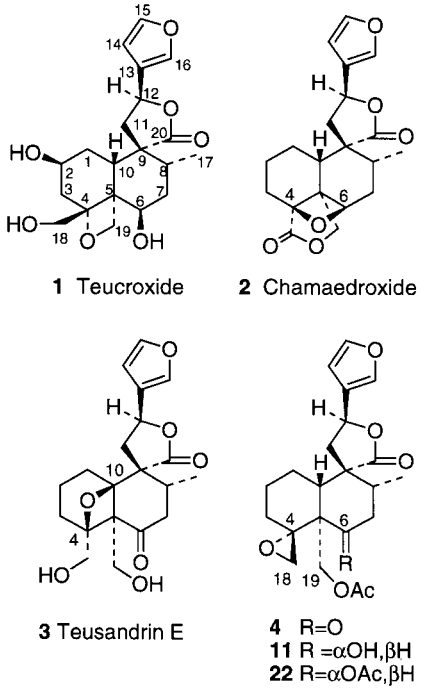

Chart 1.

Keywords: hemisynthesis; diterpenoids; neoclerodanes; oxirane opening; cyclofunctionalization; natural products.

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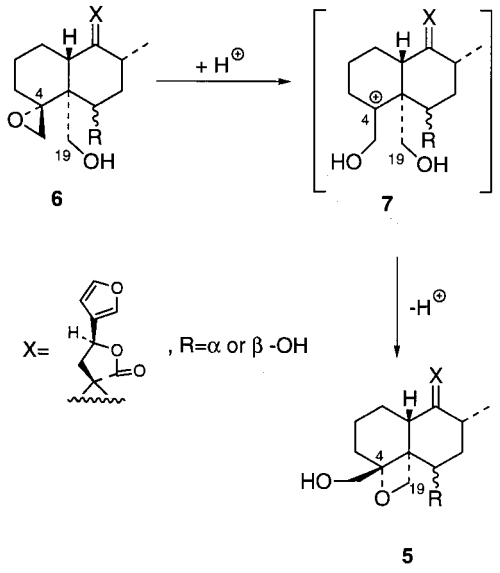
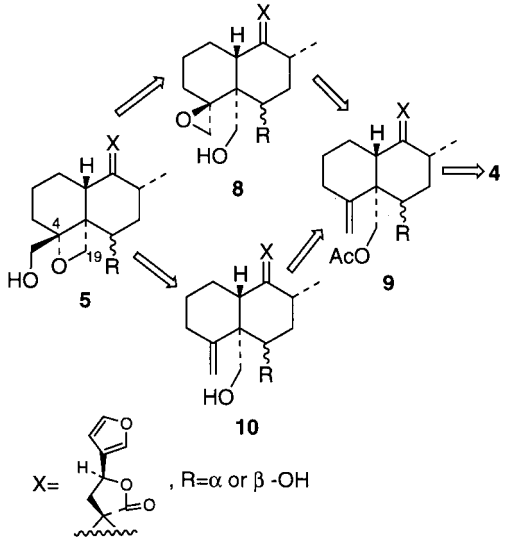


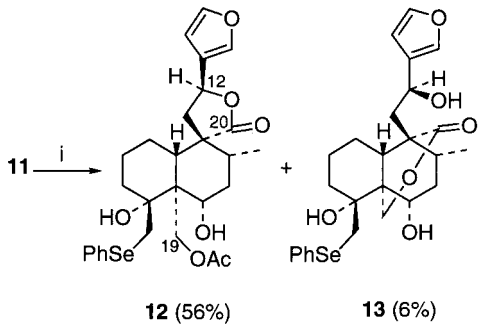
Scheme 1. Proposed biogenetic pathway for oxetane-containing neoclerodanes.

for our study. Neoclerodanes like **4**, having a 4α,18-spiroepoxide, are the most widespread and abundant in *Teucrium* plants, and they have been proposed by us as the biogenetic precursors[24] of the less common diterpenoids, including the 4α,19-oxetane-containing neoclerodanes.

According to our biogenetic hypothesis[9] (Scheme 1), the 4α,19-oxetane grouping (**5**) should arise from the 4α,18-epoxide (**6**) by oxirane ring opening, leading to a carbocation at C-4 (**7**) that may be trapped by the hydroxyl group at C-19. A related process, namely the intramolecular opening of epoxides, is involved in the biosynthesis of polyether antibiotics that contain tetrahydrofuran, tetrahydropyran or spiroketal rings.[25] Furthermore, outside of the biological system, intramolecular cyclization of epoxy alcohols is one of the most important approaches to the synthesis of cyclic ethers.[26–28] Oxetanes may be obtained from 3,4-epoxy alcohols,[29] in a process that generally occurs with complete *anti* stereoselectivity.[30]



Scheme 2. Retrosynthesis of 4α,19-epoxy-neoclerodanes from **4**.



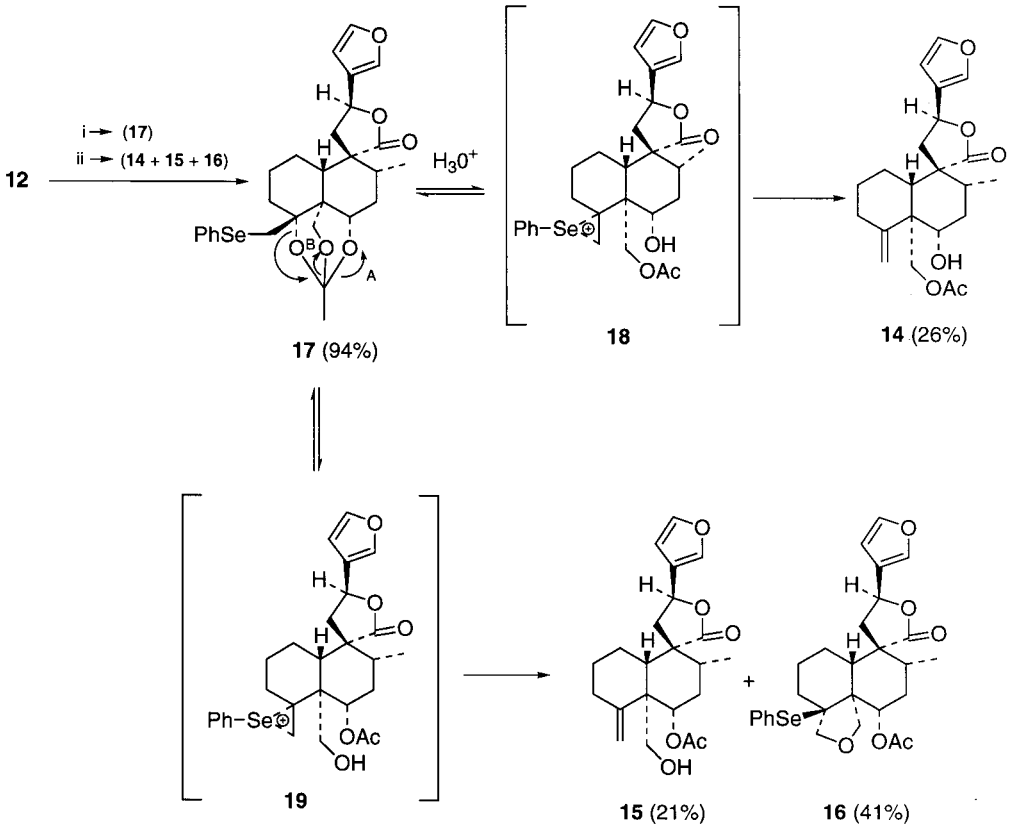
Scheme 3. Key: (i) PhSeSePh, $NaBH_4$; EtOH; room temperature 1.5 h.

Based on these premises, we designed the preparation of 4α,19-oxetane-containing neoclerodanes (**5**) (Scheme 2) by intramolecular cyclization of the appropriate 4β,18-epoxy-19-hydroxyneoclerodane **8**, whose stereochemistry at C-4 necessarily must be the opposite to that of the starting material 19-acetylgnaphalin (**4**). Inversion of the configuration at C-4 could be achieved by epoxidation of a $\Delta^{4(18)}$ exocyclic double bond[14] on a substrate like **9** (Scheme 2), which may, in turn, be obtained by deoxigenation of the natural 4α,18-epoxide. Alternatively, we considered the feasibility of getting the 4α,19-oxetane ring by cyclofunctionalization of intermediate **10** (Scheme 2). As it is known, the cyclofunctionalization of homoallylic alcohols allows the preparation of the oxetane ring.[31–38] It is interesting to note, from a biogenetic point of view, that one $\Delta^{4(18)}$-neoclerodane diterpenoid, related to intermediate **10**, has recently been isolated from *T. polium*.[39] In this paper, we report the successful implementation of the routes in Scheme 2 to access 4α,19-oxetane-containing neoclerodanes.

Results and Discussion

Our synthesis began with the preparation of a derivative having a $\Delta^{4(18)}$ exocyclic double bond similar to **9** (Scheme 2), susceptible to epoxidation and electrophilic cyclization. The 19-acetoxy-4α,18-epoxy-6-oxo-grouping in the neoclerodane framework is very reactive toward basic conditions, yielding the corresponding 19-norderivatives.[22,23] Thus, 19-acetylgnaphalin (**4**) was treated with $NaBH_4$, reducing the C-6 ketone grouping to an α-equatorial alcohol and providing teujaponin B[40] (**11**) in 91% yield.

With the purpose of getting the $\Delta^{4(18)}$ double bond, teujaponin B (**11**) was converted into the β-hydroxyselenide **12** (Scheme 3), by reaction with NaSePh.[41] Epoxide ring opening yielded **12** as the major reaction product (56%), together with a small amount of the regioisomeric γ-lactone **13** (6%). The reaction conditions for the in situ generation of NaSePh, from diphenyl diselenide and $NaBH_4$, had to be carefully tuned to avoid the translactonization from the C-12 to the C-19 position. This isomerization was observed when a slight excess of $NaBH_4$ was employed. Accordingly, $NaBH_4$ had to be used in deficit with respect to diphenyl diselenide.



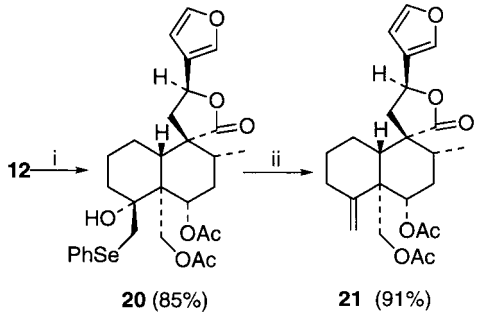
Scheme 4. Key: (i) *p*-TsOH; toluene; 40 min. (ii) *p*-TsOH; toluene; room temperature; 24 h.

β-Hydroxyselenide **12** was treated with *p*-TsOH in order to produce the $\Delta^{4(18)}$ alkene **14** (Scheme 4) through *trans* elimination of seleninic acid.[42,43] A mixture of olefins **14** and **15** was obtained, after 24 h of reaction (26 and 21% yields, respectively). Surprisingly, tetrahydrofuran derivative **16**, which still retains the selenium moiety, was the major reaction product (41% yield).[44]

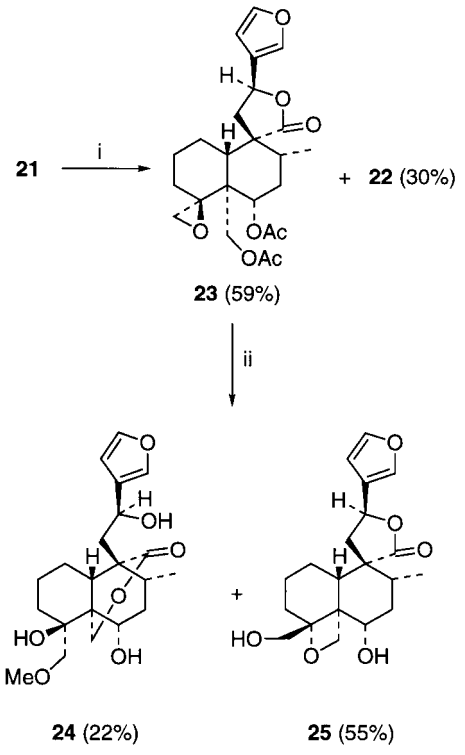
Treatment of **12** with TsOH for shorter reaction times (40 min) allowed the isolation of orthoester **17** in near quantitative yield (Scheme 4). Orthoacetates related to **17** are known as natural[45] and semisynthetic neoclerodanes.[24,46,47] Orthoester **17** was evidenced as a reaction intermediate, since its further acid treatment under the conditions above used to transform the β-hydroxyselenide **12** into **14**, **15** and **16**, leads to an identical reaction mixture. Thus, formation of olefins **14** and **15**, and tetrahydrofuran **16** may be rationalized as shown in Scheme 4. From orthoacetate **17**, the first product formed, two seleniranium cations may be generated. Seleniranium cation **18**, having the acetate group at C-19, can evolve exclusively to olefin **14**. On the contrary, seleniranium cation **19**, in which the acetate group is located at the C-6α position, may lead to olefin **15** by seleninic acid elimination, or may be intramolecularly trapped by the hydroxyl group at C-19 yielding the tetrahydrofuran derivative **16**.

The above results show that the equatorial hydroxyl group at the C-6 carbon is the responsible for the unexpected (and unwelcome) result of the intended elimination reaction on **12**. To increase olefin production, the C-6α hydroxyl group was blocked. In fact acetate **20**, obtained by treatment of **12** with acetic anhydride in pyridine, gave diacetylated olefin **21** in almost quantitative yield by treatment with TsOH in toluene (Scheme 5). Interestingly, acetylteujaponin B (**22**)[48] failed to undergo successive epoxide opening when treated with NaSePh.

As it is known that the β-alkylsubstituted furan ring in neoclerodane diterpenoids is oxidized with *m*-CPBA,[49] magnesium monoperoxyphthalate hexahydrate (MMPP) was used to effect epoxidation of **21**.[50] Thus, treatment of **21** with 3 equiv. of MMPP in methanol for two days at room temperature yielded 4β,18-epoxy neoclerodane **23** as the major product (59% yield) together with acetylteujaponin B **22** (30%, Scheme 6). Thus, inversion of the configuration



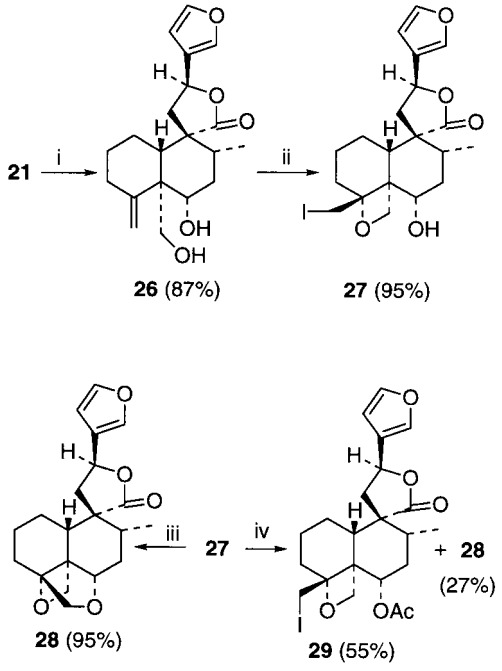
Scheme 5. Key: (i) Ac_2O-pyridine; room temperature; 48 h. (ii) *p*-TsOH; toluene; 50°C; 1 h.



Scheme 6. Key: (i) MMPP; MeOH, room temperature, 48 h. (ii) $_{aq}$NaOH (2%), MeOH; 60°C; 30 min.

at C-4 had been successfully achieved in four steps from a 4α,18-epoxyneoclerodane in an overall yield of 25%.

Conditions for intramolecular epoxide ring opening were next investigated. Treatment of **23** with aqueous NaOH in



Scheme 7. Key: (i) $_{aq}$NaOH (2%), MeOH, 60°C. (ii) NIS, CH_3CN; room temperature; 15 min. (iii) DMSO, 60°C, 24 h. (iv) Ac_2O-pyridine; room temperature; 18 h.

Table 1. Chemical shift of carbon C-2 compounds **22**, **24**, **25** and **27**–**29**

Compound	**22**[a]	**24**	**25**	**27**	**28**	**29**
δ C-2	24.9	19.5	16.0	18.0	16.9	16.6

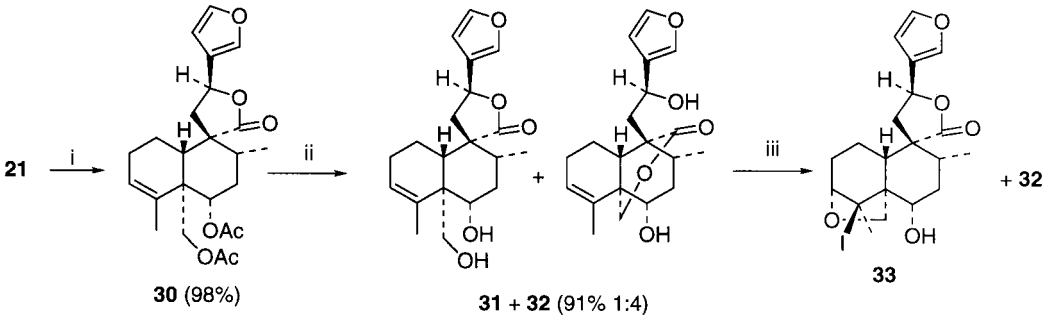
[a] Taken from reference 24.

MeOH yielded lactone **24** (22% yield) and oxetane **25** (55% yield) as the major reaction products.

Having successfully demonstrated the viability of the epoxide ring opening approach for the preparation of the 4α,19-oxetane-containing neoclerodanes, we turned our attention to the preparation of the oxetane moiety by electrophilic cyclofunctionalization of a homoallylic alcohol like **10** (Scheme 2), which in principle can be obtained from intermediate **21**. Thus, treatment of **21** with aqueous NaOH in MeOH at 60°C for 30 min yielded the desired deacetyl derivative **26** as the sole reaction product (87% yield). Translactonization from the C-12 to the more stable C-19 position could be avoided by careful control of the reaction time. The electrophilic cyclization of the homoallylic alcohol **26** with *N*-iodosuccinimide (NIS), in dry MeCN at room temperature, consumed starting material in a few minutes leading to the desired oxetane **27** in almost quantitative yield (Scheme 7).

From a structural point of view, it is interesting to note that carbon C-2 undergoes a strong upfield shift on changing from a 4α,18- to a 4α,19-epoxy-neoclerodane (see Table 1). This shielding is compatible with a twisted boat conformation for ring A in the decalin moiety, forced by the 4α,19-oxetane ring. In this conformation the 4α-oxygen adopts a pseudoaxial configuration, and therefore it must be in a γ-gauche arrangement[51] with respect to C-2, causing a strong shielding on this carbon. The same effect is observed in derivative **24**, in which ring A should be a chair, placing as well the 4β-hydroxyl group and carbon C-2 in a γ-gauche arrangement.

As a consequence of the twisted boat conformation of ring A, in 4α,19-epoxy-neoclerodane **27**, the C-18β-iodomethylene grouping is pseudoequatorial and very easily undergoes intramolecular nucleophilic substitution by attack of the equatorial 6α hydroxyl group. Heating oxetane **27**, at 60°C in DMSO[52,53] for 24 h leads to compound **28** in almost quantitative yield (Scheme 7). Treatment of oxetane **27** with acetic anhydride in pyridine at room temperature for 18 h yielded the expected acetylated derivative **29** in 55% yield, together with the substitution reaction product **28** in 27% yield (Scheme 7). The isolation of derivatives **28** and **29** provides additional proof of the structure assigned to oxetane **27**, and that the oxetane ring formation via a 4-*exo-trig* cyclization of the homoallylic alcohol **26**.[54] In fact, this is the expected result when the regiochemistry of the cyclization is determined by electronic factors.[55–60] In order to check this point in the neoclerodane framework, we prepared the homoallylic alcohol **31** (Scheme 8). Isomerization of the $\Delta^{4(18)}$ exocyclic double bond to the *endo* position was easily achieved by treatment of **21** with *p*-TsOH, yielding derivative **30**. It is interesting to note that Δ^3-neoclerodane diterpenoids are also natural products isolated from *Teucrium* plants.[5] Basic hydrolysis of the



Scheme 8. Key: (i) *p*-TsOH, Toluene, reflux, 4 h. (ii) $_{aq}$NaOH (2%), MeOH; 60°C; 30 min. (iii) NIS, CH_3CN; room temperature; 5 min.

acetate groups of **30** yielded a mixture of inseparable regioisomeric lactones **31** and **32** in a 1:4 ratio. Submission of this mixture to the reaction conditions used for the homoallylic alcohol **26** yielded derivative **33** together with unreacted **32**.

In conclusion, we have developed two efficient semisynthetic routes for the preparation of 4α,19-oxetane-containing neoclerodane diterpenoids from 19-acetylgnaphalin (**4**): the intramolecular epoxide ring opening of the 4β,18-epoxyneoclerodane **23**, and the electrophilic cyclization of the homoallylic alcohol **26**. Additionally, access to Δ^3- and $\Delta^{4(18)}$-neoclerodane diterpenoids has been gained.

Experimental Procedures

General

All reagents were used as obtained from commercial sources. Methylene chloride (CH_2Cl_2) and toluene (C_6H_5–CH_3) were distilled under positive pressure of argon from CaH_2. Other solvents were HPLC grade and were used without purification. Na_2SO_4 was used to remove water from the organic layer in reaction workups. Silica gel 60 F_{254} plates were used for TLC. Flash column chromatography was performed using silica gel (Merck, no. 9385, 230–400 mesh), and mixtures of AcOEt:*n*-hexane or Cl_3CH:MeOH as eluents.

19-Acetylgnaphalin (**4**) was isolated from *T. gnaphalodes* L. collected at 'El Cerro de las Cabezas' in Villamiel (Toledo, Spain).

Melting points were determined on a Kofler block. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. IR spectra were obtained on a Perkin–Elmer 681 spectrophotometer. MS were recorded in the positive EI mode on a Hewlett–Packard HP 5989A instrument (70 eV). Elemental analyses were made with a Carlo Erba EA 1108 apparatus. ^{1}H NMR spectra were recorded on a Varian Unity-500, a Varian INOVA-400, a Varian INOVA-300 or a Bruker 200, at 500, 400, 300 or 200 MHz, respectively. ^{13}C NMR were recorded at 125.7, 100, 75 or 50 MHz. Chemical shifts for ^{1}H NMR are reported with respect to residual $CHCl_3$ (δ 7.25), and with respect to $CDCl_3$ (δ 77.00) for ^{13}C NMR spectra. ^{13}C NMR assignments were determined by gHSQC and gHMBC spectra.

Teucjaponin B (11) from 19-acetylgnaphalin (4). To a solution **4** (1.0 g, 2.49 mmol), in CH_2Cl_2:EtOH (100 mL, 10:1 v/v), at 0°C, $NaBH_4$ (400 mg, 10.6 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Water (100 mL) was added to the reaction mixture and stirred for 1 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL×2). The combined organic layers were washed with brine (100 mL×1) and dried. After removal of the solvents under vacuum, 900 mg (89% yield) of teucjaponin B (**11**)[18] were obtained.

(12*S*)-19-Acetoxy-15,16-epoxy-4α,6α-dihydroxy-18-phenylselenyl-neocleroda-13(16),14-dien-20,12-olide (12) and (12*S*)-15,16-epoxy-4α,6α,12-trihydroxy-18-phenylselenyl-neocleroda-13(16),14-dien-20,19-olide (13). $NaBH_4$ (61 mg, 1.61 mmol) were added in portions to a diphenyldiselenide solution (265 mg, 0.85 mmol) in ethanol (150 mL) at room temperature under argon. When the hydrogen evolution ceased, teucjaponin B (**11**, 490 mg, 1.21 mmol) was added to the reaction mixture and stirred for 1.5 h. The reaction was quenched with water (100 mL) and extracted with CH_2Cl_2 (100 mL×3). The residue obtained after removal of the solvents, was chromatographed using *n*-hexane:AcOEt (1:1) as eluent yielding compounds 12 (380 mg, 56%) and 13 (40 mg, 6%).

Compound 12: [Found: C, 59.62; H, 6.40. $C_{28}H_{34}OSe$ requires C, 59.89; H, 6.10%]; mp 90–95°C (white amorphous solid); $[\alpha]_D^{25}$=+15.4 (*c*=0.467, $CHCl_3$); IR (KBr) ν_{max} 3430 br, 3140, 3130, 3070, 3060, 1760, 1735, 1600, 1580, 1505, 1250, 870, 735, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.58 (2H, m, Ph), 7.40 (2H, m, H-16 and H-15), 7.25 (3H, m, Ph), 6.34 (1H, dd, *J*=1.8, 0.9 Hz, H-14), 5.31 (1H, dd, *J*=9.3, 8.0 Hz, H-12), 5.17 and 5.00 (each 1H, d, *J*= 12.8 Hz, 2H-19), 4.08 (1H, dd, *J*=11.7, 3.7 Hz, H-6β), 3.58 and 3.50 (each 1H, d, *J*=11.8 Hz, 2H-18), 2.34 (1H, dd, *J*=14.0 and 8.0 Hz H_B-11), 2.33 (1H, dd, *J*=14.0, 9.3 Hz, H_A-11), 2.02 (3H, s, OAc), 1.04 (3H, d, *J*=6.6 Hz, Me-17); δ_C (125.7 MHz, $CDCl_3$) 176.2 (s, C-20), 170.1 (s, O*CO*CH_3), 144.1 (d, C-15), 139.5 (d, C-16), 133.5 (d, C-2′ and C-6′); 130.3 (s, C-1′), 129.1 (d, C-3′ and C-5′), 127.3 (d, C-4′), 125.0 (s, C-13), 107.9 (d, C-14), 78.0 (s, C-4), 74.5 (d, C-6), 71.4 (d, C-12), 63.4 (t, C-19), 51.7 (s, C-9), 50.7 (d, C-10), 48.1 (s, C-5), 44.3 (t, C-11), 38.6 (d, C-8), 37.2 (t, C-18), 35.2 (t, C-7), 32.5 (t, C-3), 23.0 (t, C-1), 22.4 (t, C-2), 21.4 (q, OCO*CH*$_3$), 16.2 (q, C-17); *m*/*z* (EI) 562 [M]$^+$ (17), 560 [M]$^+$ (9), 391 (23), 373 (100), 313 (75), 172 (63), 157 (59), 105 (44), 95 (93), 91 (67), 78 (93%).

Compound 13: mp 80–95°C (white amorphous solid); $[\alpha]_D^{25}=-48.1$ (c=0.783, $CHCl_3$); IR (KBr) ν_{max} 3400 br, 3160, 3080, 3060, 1710, 1580, 1505, 870, 740, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (2H, m, Ph), 7.38 (2H, m, H-16 and H-15), 7.26 (3H, m, Ph), 6.40 (1H, t, J=1.3 Hz, H-14), 4.80 (1H, dd, J=11.0, 1.8 Hz, H-12), 4.76 and 4.69 (each 1H, d, J=13.4 Hz, H-19), 4.15 (1H, dd, J=11.3, 4.8 Hz, H-6β), 3.88 (1H, br s, OH-6α), 3.62 (1H, d, J=12.2 Hz, H_B-18), 3.57 (1H, s, OH-4α), 3.49 (1H, dd, J=12.2, 1.6 Hz, H_A-18), 2.37 (1H, dd, J=16.2, 1.8 Hz, H_B-11), 2.04 (1H, dd, J=16.1, 11.0 Hz, H_A-11), 1.54 (1H, ddd, J=12.7, 11.3, 11.3, H-7α), 0.90 (3H, d, J=6.7 Hz, Me-17); δ_C (75.4 MHz, $CDCl_3$) 172.6 (s, C-20), 143.6 (d, C-15), 138.4 (d, C-16), 133.4 (d, C-2′ and C-6′), 130.1 (s, C-13), 130.0 (s, C-1′), 129.3 (d, C-3′ and C-5′), 127.5 (d, C-4′), 108.3 (d, C-14), 77.5 (s, C-4), 73.0 (d, C-6), 68.7 (t, C-19), 63.5 (d, C-12), 49.8 (s, C-9), 43.7 (s, C-5), 41.8 (d, C-10), 37.9 (t, C-7), 37.2 (t, C-18), 36.3 (t, C-11), 34.5 (d, C-8), 33.4 (t, C-3), 25.1 (t, C-1), 21.7 (t, C-2), 16.5 (q, C-17); m/z (EI) 520 $[M]^+$ (3), 518 $[M]^+$ (2), 362 (18), 331 (23), 313 (28), 301 (34), 172 (100), 158 (29), 95 (44), 78 (55%).

(12*S*)-19-Acetoxy-15,16-epoxy-6α-hydroxy-neocleroda-4(18),13(16),14-trien-20,12-olide (14), (12*S*)-6α-acetoxy-15,16-epoxy-19-hydroxy-neocleroda-4(18),13(16),14-trien-20,12-olide (15) and (12*S*)-6α-acetoxy-15,16;18,19-diepoxy-4β-phenylseleny-neocleroda-13(16),14-dien-20,12-olide (16). To a solution of **12** (120 mg, 0.21 mmol) in toluene (90 mL), *p*-TsOH (11 mg, 0.06 mmol) was added and the solution stirred for 24 h at room temperature. Aqueous $NaHCO_3$ saturated solution (150 mL) was then added and the reaction mixture extracted with AcOEt (100 mL×3). Chromatography of the residue with *n*-hexane:AcOEt (3:2) yielded in increasing order of chromatographic polarity **16** (47 mg, 41%,), **15** (17 mg, 21%) and **14** (21 mg, 26%).

Compound 14: [Found: C, 67.89; H, 7.05. $C_{22}H_{28}O_6$ requires C, 68.02; H, 7.27%]; mp 184–186°C (white crystals from EtOAc:*n*-hexane); $[\alpha]_D^{24}=+101.8$ (c=0.325, $CHCl_3$); IR (KBr) ν_{max} 3600, 3130, 3100, 1760, 1730, 1640, 1595, 1500, 1250, 925, 870 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41 (2H, m, H-16 and H-15), 6.36 (1H, dd, J=1.7, 0.8 Hz, H-14), 5.31 (1H, t, J=8.6 Hz, H-12), 5.16 (1H, br s, H_B-18, pro *Z* hydrogen), 4.94 (1H, br s, H_A-18, pro *E* hydrogen), 4.92 (1H, d, J=12.4 Hz, H_B-19), 4.73, (1H, dd, J=12.4, 0.9 Hz, H_A-19), 4.02 (1H, dt, J=11.8, 3.8 Hz, collapsed into dd with D_2O, H-6β), 2.75 (1H, d, J=3.8 Hz, OH-6α), 2.31 (2H, d, J=8.6 Hz, 2H-11), 2.22 (1H, dt, J=13.8, 11.8 H-7α), 2.00 (1H, m, H-2α), 1.99 (3H, s, OAc), 1.82 (1H, dt, J=13.8, 3.9 Hz, H-7β), 1.75 (1H, dtd, J=13.0, 12.7, 4.2 Hz, H-1α), 1.66 (1H, dqd, J=11.8, 6.7, 3.9 Hz, H-8β), 1.58 (1H, dd, J=12.7, 3.2 Hz, H-10β), 1.43 (1H, qt, J=12.7, 5.6 (2) Hz, H-2β), 1.02 (3H, d, J=6.7 Hz, Me-17); δ_C (100 MHz, $CDCl_3$) 176.6 (s, C-20), 170.2 (s, O*CO*CH_3), 150.4 (s, C-4), 144.1 (d, C-15), 139.5 (d, C-16), 125.2 (s, C-13), 109.2 (t, C-18), 108.0 (d, C-14), 73.9 (d, C-6), 71.5 (d, C-12), 61.7 (t, C-19), 54.6 (d, C-10), 51.6 (s, C-9), 50.0 (s, C-5), 43.5 (t, C-11), 38.3 (d, C-8), 35.2 (t, C-7), 32.8 (t, C-3), 28.3 (t, C-2), 23.2 (t, C-1), 21.1 (q, OCO*CH*$_3$), 16.6 (q, C-17); m/z (EI) 388 $[M]^+$ (8), 331 (13), 328 (61), 310 (73), 265 (88), 216 (57), 171 (75), 159 (57), 95 (100), 91 (53%).

Compound 15: [Found: C, 68.34; H, 7.35. $C_{22}H_{28}O_6$ requires C, 68.02; H, 7.27%]; mp 83–88°C (white amorphous solid); $[\alpha]_D^{24}=+57.7$ (c=0.156, $CHCl_3$); IR (KBr) ν_{max} 3580, 3480, 3140, 3080, 1760, 1735, 1640, 1500, 1240, 920, 870 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41 (2H, m, H-16 and H-15), 6.35 (1H, dd, J=1.7, 0.9 Hz, H-14), 5.32 (1H, t, J=8.7 Hz, H-12), 5.22 (1H, dd, J=11.8, 3.3 Hz, H-6β), 4.86 (1H, br s, H_B-18), 4.63 (1H, d, J=12.9 Hz, H_B-19), 4.53 (1H, br s, H_A-18), 3.84 (1H, dd, J=12.9, 6.5 Hz, H_A-19, collapsed into a d, J=12.9 Hz, after D_2O addition), 2.06 (3H, s, OAc), 0.99 (3H, d, J=6.7 Hz, Me-17); m/z (EI) 388 $[M]^+$ (36), 298 (100), 253 (38), 204 (35), 171 (49), 159 (49), 131 (23), 96 (87%).

Compound 16: [Found: C, 62.03; H, 5.70. $C_{28}H_{36}O_6Se$ requires C, 61.88; H, 5.93%]; mp 85–90°C (white amorphous solid); $[\alpha]_D^{25}=+80.1$ (c=0.261, $CHCl_3$); IR (KBr) ν_{max} 3140, 3070, 1765, 1740, 1600, 1580, 1505, 1240, 875, 740, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, dd, J=6.9, 1.9 Hz, H-2′ and H-6′), 7.43 (2H, m, H-16 and H-15), 7.35 (1H, td, J=7.2, 1.9 Hz, H-4′), 7.26 (2H, br t, J=7.2, 6.9 Hz, H-3′ and H-5′), 6.37 (1H, dd, J=1.8, 0.9 Hz, H-14), 5.34 (1H, dd, J=8.9, 8.5 Hz, H-12), 4.90 (1H, dd, J=11.3, 3.5 Hz, H-6β), 4.39 (1H, d, J=10.5 Hz, H_B-19), 4.30 (1H, d, J=7.1 Hz, H_B-18), 4.04 (1H, d, J=10.5 Hz, H_A-19), 3.42 (1H, d, J=7.1 Hz, H_A-18), 2.49 (1H, dd, J=14.2, 8.5 Hz, H_B-11), 2.33 (1H, dd, J=14.2, 8.9 Hz, H_A-11), 2.02 (1H, dd, J=12.5, 2.7 Hz, H-10β), 1.92 (1H, m, H-2α), 1.83 (1H, dt, J=13.0, 3.5 Hz, H-7β), 1.71 (1H, ddd, J=12.9, 12.6, 2.8 Hz, H-3α), 0.97 (3H, d, J=6.6 Hz, Me-17); δ_C (100 MHz, $CDCl_3$) 176.3 (s, C-20), 170.0 (s, O*CO*CH_3), 144.2 (d, C-15), 139.5 (d, C-16), 137.8 (d, C-2′ and C-6′), 129.0 (d, C-3′ and C-5′), 128.9 (d, C-4′), 125.3 (s, C-13), 125.1 (s, C-1′), 108.0 (d, C-14), 80.3 (t, C-18), 77.3 (d, C-6), 71,7 (d, C-12), 67.2 (t, C-19), 57.2 (s, C-4), 53.4 (s, C-5), 51.3 (s, C-9), 47.4 (d, C-10), 42.7 (t, C-11), 37.8 (d, C-8), 34.7 (t, C-3), 33.0 (t, C-7), 23.6 (t, C-2), 23.0 (t, C-1), 21.9 (q, OCO*CH*$_3$), 16.4 (q, C-17); m/z (EI) 544 $[M]^+$ (12), 542 $[M]^+$ (7), 387 (100), 327 (46), 281 (52), 159 (12), 95 (27%).

(12*S*)-15,16-Epoxy-18-phenylselenyl-neocleroda-13(16),14-dien-20,12-olide 4α,6α,19-orthoacetate (17). To a solution of **12** (50 mg, 0.09 mmol) in toluene (30 mL), at room temperature, *p*-TsOH (6 mg, 0.03 mmol) was added. After 15 min, the mixture was diluted with EtOAc (25 mL) and washed with aqueous $NaHCO_3$ saturated solution 50 mL×3). The residue obtained after removal of the solvents was chromatographed with *n*-hexane: AcOEt (7:3) yielding 46 mg of pure **17** (94%): [Found: C, 61.73; H, 5.40. $C_{28}H_{32}O_6Se$ requires C, 61.88; H 5.93%]; mp 90–95°C (white amorphous solid); $[\alpha]_D^{24}=-2.1$ (c=0.706, $CHCl_3$); IR (KBr) ν_{max} 3140, 3130, 3070, 3050, 1755, 1600, 1580, 1505, 870, 745, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (2H, m, Ph), 7.42 (2H, m, H-16 and H-15), 7.26 (3H, m, Ph), 6.35 (1H, dd, J=1.7, 0.9 Hz, H-14), 5.30 (1H, dd, J=9.3, 8.3 Hz, H-12), 5.29 (1H, d, J=10.5 Hz, H_B-19), 4.30 (1H, ddd, J=11.6, 4.0, 2.2 Hz, H-6β), 4.20 (1H, dd, J=10.5, 2.2 Hz, H_A-19), 3.81 (1H, dd, J=11.8, 2.2 Hz, H_B-18), 3.25 (1H, d, J=11.8 Hz, H_A-18), 2.40 (1H, dd, J=14.0, 9.3 Hz, H_B-11), 2.32 (1H, dd, J=14.0, 8.3 Hz, H_A-11), 2.14 (1H, tdd, J=13.3, 4.3, 2.2 Hz, H-3α), 1.82 (1H, dt, J=13.3, 4.0 Hz, H-3β), 1.08

(3H, d, J=6.8 Hz, Me-17); δ_C (75.4 MHz, $CDCl_3$) 176.3 (s, C-20), 144.2 (d, C-15), 139.5 (d, C-16), 133.2 (d, C-2′ and C-6′), 131.1 (s, C-1′), 129.0 (d, C-3′ and C-5′), 127.0 (d, C-4′) 124.9 (s, C-13), 108.7 (s, $CH_3C(OR)_3$), 107.8 (d, C-14), 77.6 (s, C-4), 72.7 (d, C-6), 71.5 (d, C-12), 60.3 (t, C-19), 51.1 (s, C-9), 47.2 (d, C-10), 44.6 (t, C-11), 38.7 (s, C-5), 37.9 (d, C-8), 34.1 (t, C-18), 32.9 (t, C-7), 30.0 (t, C-3), 23.8 (q, $CH_3C(OR)_3$), 22.4 (t, C-1*), 22.2 (t, C-2*), 16.3 (q, C-17), assignments marked with an asterisk may be interchanged; *m/z* (EI) 544 $[M]^+$ (2), 542 $[M]^+$ (1), 373 (100), 331 (25), 313 (23), 171 (4), 95 (9%).

(12*S*)-6α,19-Diacetoxy-15,16-epoxy-4α-hydroxy-18-phenylselenyl-neocleroda-13(16),14-dien-20,12-olide (20). **12** (91 mg, 0.16 mmol) was treated with acetic anhydride: pyridine (15 mL, 1:2 v/v) for 48 h. Solvents were removed and the residue was filtered through silica with EtOAc. After removal of the solvents 82 mg of **20** (85%) were obtained: [Found: C, 59.95; H, 6.28. $C_{30}H_{36}O_8Se$ requires C, 59.70; H, 6.01%]; mp 85–90°C (white amorphous solid); $[\alpha]_D^{25}$= +40.8 (c=0.593, $CHCl_3$); IR (KBr) ν_{max} 3550, 3140, 3060, 1760, 1745, 1600, 1580, 1505, 1240, 875, 740, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.59 (2H, m, Ph), 7.43 (2H, m, H-16 and H-15), 7.26 (3H, m, Ph), 6.36 (1H, dd, J=1.5, 1.0 Hz, H-14), 5.34 (1H, t, J=8.5 Hz, H-12), 5.33 (1H, d, J=12.9 Hz, H_B-19), 5.21 (1H, dd, J=11.5, 4.0 Hz, H-6β), 4.92 (1H, d, J=12.9 Hz, H_A-19), 3.47 (1H, d, J=12.1 Hz, H_B-18), 3.41 (1H, d, J=12.1 Hz, H_A-18), 2.91 (1H, s, OH-4α), 2.36 (2H, d, J=8.5 Hz, 2H-11), 2.06 (3H, s, OAc), 1.96 (3H, s, OAc), 1.30 (1H, m, H-2β), 1.02 (3H, d, J=6.5 Hz, Me-17); *m/z* (EI) 604 $[M]^+$ (5), 602 $[M]^+$ (2), 373 (100), 331 (39), 313 (37), 172 (16), 95 (24%).

(12*S*)-6α,19-Diacetoxy-15,16-epoxy-neocleroda-4(18),13(16),14-trien-20,12-olide (21). A mixture of **20** (2 g, 3.31 mmol) and *p*-TsOH (304 mg, 1.60 mmol) in toluene (50 mL) was heated at 50°C for 1 h. The reaction mixture was cooled down to room temperature. Then, aqueous $NaHCO_3$ saturated solution (125 mL) was added and the mixture extracted with AcOEt (50 mL×3). Working in the usual way a residue was obtained and, after column chromatography with *n*-hexane:AcOEt (1:1), 1.3 g (91%) of pure **21** were obtained: [Found: C, 67.05; H, 7.30. $C_{24}H_{30}O_7$ requires C, 66.96; H, 7.02%]; mp 184–187°C (white crystals from EtOAc:*n*-hexane); $[\alpha]_D^{24}$=+84.6 (c=0.280, $CHCl_3$); IR (KBr) ν_{max} 3150, 3140, 3120, 3080, 1765, 1740, 1730, 1645, 1610, 1505, 1250, 900, 875 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41 (1H, m, H-16), 7.40 (1H, t, J= 1.9 Hz, H-15), 6.35 (1H, dd, J=1.9, 1.0 Hz, H-14), 5.32 (1H, br t, J=8.7 Hz, H-12), 5.23 (1H, d, J=12.9 Hz, H_B-19), 5.11 (1H, ddd, J=11.7, 4.1, 1.2 Hz, H-6β), 4.76 (1H, br s, H_B-18, pro *Z* hydrogen), 4.49 (1H, br s, H_A-18 pro *E* hydrogen), 4.29 (1H, dd, J=12.9, 1.2 Hz, H_A-19), 2.33 (1H, dd, J=14.2, 8.5 Hz, H_B-11), 2.28 (1H, dt, J=13.3, 11.7 Hz, H-7α), 2.27 (1H, dd, J=14.2, 8.9 Hz, H_A-11), 2.26 (1H, ddd, J=13.6, 12.7, 4.4 Hz, H-3β), 2.19 (1H, ddd, J=13.6, 5.5, 2.3 Hz, H-3β), 2.00 (1H, dtt, J=12.7, 4.4, 2.3, H-2α), 1.97 (6H, s, 2×OAc), 1.87 (1H, dddd, J=12.7, 5.5, 3.7, 2.3 Hz, H-1β), 1.80 (1H, qd, J=12.7, 4.4 Hz, H-1α), 1.78 (1H, ddd, J=13.3, 4.1, 4.0 Hz, H-7β), 1.71 (1H, ddq, J=11.7, 6.6, 4.0 Hz, H-8β), 1.63 (1H, dd, J=12.4, 3.7 Hz, H-10β), 1.44 (1H, qt, J=12.7, 5,5 Hz, H-2β), 0.99 (3H, d, J=6.6 Hz, Me-17); δ_C (100 MHz, $CDCl_3$) 176.3 (s, C-20), 170.5 (s, O*CO*CH_3), 170.4 (s, O*CO*CH_3), 150.7 (s, C-4), 144.1 (d, C-15), 139.5 (d, C-16), 125.3 (s, C-13), 108.0 (d, C-14), 107.1 (t, C-18), 75.1 (d, C-6), 71.5 (d, C-12), 60.9 (t, C-19), 54.7 (d, C-10), 51.4 (s, C-9), 48.7 (s, C-5), 43.3 (t, C-11), 38.0 (d, C-8), 33.3 (t, C-3), 31.9 (t, C-7), 28.3 (t, C-2), 23.3 (t, C-1), 21.1 (q, 2×OCO*CH₃*), 16.4 (q, C-17); *m/z* (EI) 430 $[M]^+$ (1), 370 (12), 328 (53), 310 (99), 265 (80), 216 (72), 171 (73), 159 (47), 95 (100%).

(12*S*)-6α,19-Diacetoxy-4β,18;15,16-diepoxy-neocleroda-13(16),14-dien-20,12-olide (23). To a solution of **21** (500 mg, 1.16 mmol) in methanol (100 mL), MMPP (2.16 g, 3.49 mmol) was added at 0°C. The mixture was allowed to reach room temperature and stirred for 48 h. The solvent was removed and aqueous $NaHCO_3$ saturated solution (100 mL) was added and extracted with EtOAc (100 mL×3). Column chromatography of the residue with *n*-hexane:EtOAc (7:3) yielded, in order of increasing polarity, unreacted **21** (200 mg), **23** (157 mg, 59% based on recovered **21**) and **22** (80 mg, 30%).

Compound 23: [Found: C, 64.80; H, 6.50. $C_{24}H_{30}O_8$ requires C, 64.56; H, 6.77%]; mp 194–196°C (white crystals from EtOAc:*n*-hexane); $[\alpha]_D^{24}$=+89.2 (c=0.325, $CHCl_3$); IR (KBr) ν_{max} 3150, 3130, 3120, 3080, 1755, 1730, 1500, 1260, 1240, 875 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.42 (1H, m, H-16), 7.41 (1H, t, J=1.7 Hz, H-15), 6.36 (1H, dd, J=1.7, 1.0 Hz, H-14), 5.34 (1H, br t, J=8.6 Hz, H-12), 5.25 (1H, d, J=12.9 Hz, H_B-19), 4,66 (1H, br dd, J=11.7, 4.4 Hz, H-6β), 4.33 (1H, br d, J=12.9 Hz, H_A-19), 2.78 (1H, d, J=4.3 Hz, H_B-18), 2.59 (1H, d, J=4.3 Hz, H_A-18), 2.41 (1H, dd, J=14.2, 8.5 Hz, H_B-11), 2.31 (1H, dd, J=14.2, 8.8 Hz, H_A-11), 2.14 (1H, td, J=13.2, 4.2 Hz, H-3α), 2.13 (1H, dt, J=13.2, 11.7 Hz, H-7α), 2.01 (3H, s OAc), 1.94 (3H, s, OAc), 1.94 (1H, dd, J=12.7, 2.9 Hz, H-10β), 1.79 (1H, ddd, J=13.2, 4.4, 3.9 Hz, H-7β), 1.66 (1H, ddq, J=11.7, 6.8, 3.9, H-8β), 1.12 (1H, ddd, J=13.2, 3.9, 2.6 Hz, H-3β), 0.95 (3H, d, J=6.8 Hz, Me-17); δ_C (125.7 MHz, $CDCl_3$) 176.5 (s, C-20), 170.0 (s, O*CO*CH_3), 169.8 (s, O*CO*CH_3), 144.1 (d, C-15), 139.5 (d, C-16), 125.2 (s, C-13), 108.0 (d, C-14), 71.8 (d, C-6), 71.7 (d, C-12), 61.6 (t, C-19), 60.8 (s, C-4), 55.3 (t, C-18), 50.9 (s, C-9), 50.0 (d, C-10), 45.8 (s, C-5), 42.8 (t, C-11), 37.4 (d, C-8), 31.6 (t, C-7), 30.9 (t, C-3), 23.1 (t, C-2), 22.5 (t, C-1), 21.4 (q, OCO*CH₃*), 21.0 (q, OCO*CH₃*), 16.5 (q, C-17); *m/z* (EI) 446 $[M]^+$ (2), 331 (100), 326 (19), 314 (18), 281 (14), 187 (10), 105 (10), 95 (25%).

(12*S*)-15,16-Epoxy-4β,6α,12-trihydroxy-18-methoxy-neocleroda-13(16),14-dien-20,19-olide (24) and (12*S*)-4α,19;15,16-diepoxy-6α,18-dihydroxy-neocleroda-13(16),15-dien-20,12-olide (25). 160 mg (0.35 mmol) of **23** in MeOH (100 mL), were treated with aqueous NaOH (30 mL, 2% w/v) for 1 h at 60°C. MeOH was removed and the residue was extracted with CH_2Cl_2 (50 mL×3). After column chromatography with *n*-hexane:EtOAc (1:4) compounds **24** (30 mg, 22%) and **25** (70 mg, 55%) were obtained.

Compound 24: [Found: C, 64.20; H, 7.50. $C_{21}H_{30}O_7$ requires C, 63.94; H, 7.67%]; mp 227–230°C (white crystals from EtOAc:*n*-hexane); $[\alpha]_D^{24}$=−17.1 (c=0.145, $CHCl_3$); IR (KBr) ν_{max} 3500, 3400, 3160, 3130, 1715,

1600, 1505, 875 cm^{-1}; δ_H (400 MHz, $CDCl_3$:MeOH-d_4, 9:1) 7.26 (1H, m, H-16), 7.23 (1H, t, J=1.8 Hz, H-15), 6.30 (1H, dd, J=1.8, 0.9 Hz, H-14), 4.61 (1H, dd, J=8.9, 3.4 Hz, H-12), 4.54 (1H, d, J=12.0 Hz, H_B-19), 4.17 (1H, dd, J=12.0, 1.5 Hz, H_A-19), 3.94 (1H, ddd, J=11.7, 5.5, 1.5 Hz, H-6β), 3.95 (1H, s, OH-4β), 3.94 (1H, s, OH-6α), 3.39 (1H, d, J=10.1 Hz, H_B-18), 3.25 (3H, s, OMe), 2.99 (1H, d, J=10.1 Hz, H_A-18), 2.25 (1H, dd, J=15.8, 3.4 Hz, H_B-11), 2.11 (1H, dd, J=12.6, 3.7 Hz, H-10β), 1.96 (1H, dd, J=15.8, 8.9 Hz, H_A-11), 1.87 (1H, ddq, J=11.7, 6.6, 4.1 Hz, H-8β), 1.78 (1H, ddd, J=13.2, 5.5, 4.1, Hz, H-7β), 1.59 (1H, tddd, J=13.6, 12.9, 3.6, 3.2 Hz, H-2β), 1.19 (1H, dt, J=13.2, 11.7 Hz, H-7α), 0.91 (1H, tdd, J=12.9, 12.6, 4.0 Hz, H-1α), 0.69 (3H, d, J=6.6 Hz, Me-17); δ_C (100 MHz $CDCl_3$:MeOH-d_4, 9:1) 173.8 (s, C-20), 143.1 (d, C-15), 138.3 (d, C-16), 130.1 (s, C-13), 108.3 (d, C-14), 76.9 (t, C-18), 72.8 (s, C-4), 68.3 (d, C-6), 68.1 (t, C-19), 62.2 (d, C-12), 58.9 (q, OMe), 49.7 (s, C-9), 44.6 (s, C-5), 39.3 (d, C-10), 38.1 (t, C-7), 36.1 (t, C-11), 34.1 (d, C-8), 33.5 (t, C-3), 24.3 (t, C-1), 19.5 (t, C-2), 16.3 (q, C-17); m/z (EI) 394 $[M]^+$ (100), 331 (28), 313 (37), 301 (67), 203 (38), 161 (29), 105 (33), 95 (60%).

Compond 25: [Found: C, 65.90; H, 7.39. $C_{20}H_{26}O_6$ requires C, 66.28; H, 7.23%]; mp 188–190°C (white crystals from EtOAc:n-hexane); $[\alpha]_D^{24}$=+14.9 (c=0.321, $CHCl_3$); IR (KBr) ν_{max} 3440 br, 3340 br, 1750, 1600, 1510, 880 cm^{-1}; δ_H (300 MHz, $CDCl_3$:MeOH-d_4 9:1) 7.30 (1H, m, H-16), 7.28 (1H, t, J=1.7 Hz, H-15), 6.23 (1H, dd, J=1.7, 1.0 Hz, H-14), 5.24 (1H, br t, J=8.6 Hz, H-12), 4.53 (1H, d, J=7.2 Hz, H_B-19), 4.49 (1H, d, J=7.2 Hz, H_A-19), 3.69 (1H, dd, J=11.6, 4.3 Hz, H-6β), 3.60 (1H, d, J=13.0 Hz, H_B-18), 3.42 (1H, d, J=13.0 Hz, H_A-18), 2.29 (1H, dd, J=14.0, 8.5 Hz, H_B-11), 2.13 (1H, dd, J=14.0, 8.8 Hz, H_A-11), 1.85 (1H, ddd, J=13.4, 11.7, 11.6 Hz, H-7α), 1.36 (1H, ddd, J=14.5, 4.5, 4.1 Hz, H-3β), 0.80 (3H, q, J=6.5 Hz, Me-17); δ_C (75 MHz, $CDCl_3$:MeOH-d_4 9:1) 177.7 (s, C-20), 143.9 (d, C-15), 139.3 (d, C-16), 124.7 (s, C-13), 107.7 (d, C-14), 90.3 (s, C-4), 72.1 (d, C-12), 69.2 (d, C-6), 68.9 (t, C-19), 64.7 (t, C-18), 51.8 (s, C-9), 49.8 (s, C-5), 42.6 (d, C-10), 40.7 (t, C-11), 37.2 (d, C-8), 34.8 (t, C-7), 30.2 (t, C-3), 21.6 (t, C-1), 16.6 (q, C-17), 16.0 (t, C-2); m/z (EI) 362 $[M]^+$ (10), 331 (32), 313 (23), 250 (31), 179 (41), 161 (38), 105 (40), 95 (93), 94 (100%).

(12*S*)-15,16-Epoxy-6α,19-dihydroxy-neocleroda-4(18), 13(16),14-trien-20,12-olide (26). A mixture of **21** (300 mg, 0.70 mmol) in MeOH (30 mL) and aqueous NaOH (100 mL, 2% w/v) were heated at 60°C for 30 min. The reaction mixture was cooled down to room temperature and extracted with CH_2Cl_2 (100 mL×3). Column chromatography of the residue obtained after removal of the solvent, with n-hexane:EtOAc (7:3) yielded pure **26** (210 mg, 87%): [Found: C, 69.53; H, 7.80. $C_{20}H_{26}O_5$ requires C, 69.34; H, 7.56%]; mp 206–209°C (white crystals from EtOAc); $[\alpha]_D^{24}$=+84.0 (c=0.338, $CHCl_3$); IR (KBr) ν_{max} 3450, 3370, 3130, 3080, 1750, 1640, 1610, 1505, 910, 870 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42 (2H, m, H-16 and H-15), 6.36 (1H, dd, J=1.8, 0.9 Hz, H-14), 5.32 (1H, t, J=8.7 Hz, H-12), 5.26 (1H, br s, H_B-18), 5.05 (1H, br s, H_A-18), 4.75 (1H, dd, J=12.2, 5.3 Hz, collapsed to d after D_2O addition, H_B-19), 4.08 (1H, ddd, J=9.8, 3.7, 3.6 Hz, collapsed to dd after D_2O addition, H-6β), 3.91 (1H, dd, J=12.2, 4.6 Hz, collapsed to d after D_2O addition, H_A-19), 3.22 (1H, br d, J=5.3, 4.6 Hz, OH-19), 2.31 (2H, d, J=8.7 Hz, 2H-11), 2.30 (1H, d, J=3.7 Hz, OH-α), 1.02 (3H, d, J=6.9 Hz, Me-17); m/z (EI) 346 $[M]^+$ (13), 298 (51), 253 (32), 204 (35), 171 (55), 159 (55), 131 (26), 105 (31), 96 (100), 95 (77%).

(12*S*)-4α,19;15,16-Diepoxy-6α-hydroxy-18-iodo-neocleroda-13(16),14-dien-20,12-olide (27). *N*-Iodosuccinimide (195 mg, 0.87 mmol) was added to a solution of **26** (200 mg, 0.58 mmol) in dry acetonitrile (100 mL) under argon, at room temperature. The reaction mixture was stirred for 15 min, and then diluted with AcOEt (100 mL) and washed with $Na_2S_2O_5$ aqueous solution (100 mL×3). The residue obtained after elimination of the solvents was chromatographed with AcOEt as eluent yielding 260 mg of pure **27** (95% yield): [Found: C, 50.65; H, 5.52. $C_{20}H_{25}IO_5$ requires C, 50.86; H, 5.34%]; mp 135–140°C, decom. (pale yellow crystals from EtOAc:n-hexane); $[\alpha]_D^{21}$=+30.6 (c=0.111, $CHCl_3$); IR (KBr) ν_{max} 3590, 3140, 3110, 1760, 1600, 1500, 870 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42 (2H, m, H-16 and H-15), 6.36 (1H, dd, J=1.7, 0.8 Hz, H-14), 5.35 (1H, br t, J=8.7 Hz, H-12), 4.65 (1H, d, J=7.8 Hz, H_B-19), 4.47 (1H, d, J=7.8 Hz, H_A-19), 4.12 (1H, dd, J=11.4, 4.1 Hz, H-6β), 4.02 (1H, d, J=9.5, Hz, H_B-18), 3.62 (1H, d, J=9.5 Hz, H_A-18), 2.41 (1H, dd, J=14.0, 8.5 Hz, H_B-11), 2.27 (1H, dd, J=14.0, 8.9 Hz, H_A-11), 2.14 (1H, dt, J=12.9, 11.4 Hz, H-7α), 0.96 (3H, d, J=6.6 Hz, Me-17); δ_C (75 MHz, $CDCl_3$) 177.6 (s, C-20), 144.1 (d, C-15), 139.5 (d, C-16), 124.7 (s, C-13), 107.9 (d, C-14), 86.9 (s, C-4), 72.1 (d, C-12), 69.9 (d, C-6), 67.8 (t, C-19), 51.9 (s, C-9), 48.8 (s, C-5), 43.9 (d, C-10), 40.7 (t, C-11), 37.4 (d, C-8), 35.9 (t, C-7), 33.9 (t, C-3), 22.3 (t, C-1), 18.0 (t, C-2), 16.7 (q, C-17), 11,1 (t, C-18); m/z (EI) 472 $[M]^+$ (12), 378 (25), 360 (37), 314 (48), 299 (47), 281 (36), 220 (49), 161 (36), 105 (46), 96 (44), 95 (90), 94 (100%).

(12*S*)-4α,19;6α,18;15,16-Triepoxy-neocleroda-13(16),14-dien-20,12-olide (28). The iodo derivative **27** (50 mg, 0.11 mmol) in DMSO (20 mL) was heated at 60°C for 24 h. After elimination of the solvent compound **28** (35 mg, 95%) was obtained: [Found: C, 69.88; H, 7.30. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.02%]; mp 175–177°C (white crystals from EtOAc:n-hexane); $[\alpha]_D^{19}$=+10.5 (c=0.133, $CHCl_3$); IR (KBr) ν_{max} 3150, 3140, 3130, 1760, 1600, 1505, 875 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45 (1H, m, H-16), 7.43 (1H, t, J=1.9 Hz, H-15), 6.38 (1H, dd, J=1.9, 1.0 Hz, H-14), 5.36 (1H, t, J=8.8 Hz, H-12), 4.55 (1H, d, J=7.9 Hz, H_B-19), 4.52 (1H, d, J=7.9 Hz, H_A-19), 4.25 (1H, d, J=10.2 Hz, H_B-18), 3.40 (1H, d, J=10.2 Hz, H_A-18), 3.14 (1H, dd, J=12.3, 3.4 Hz, H-6β), 2.36 (2H, d, J=8.8 Hz, 2H-11), 2.32 (1H, m, $W_{1/2}$ 36 Hz, H-2β), 2.19 (1H, td, J=12.3, 11.4 Hz, H-7α), 2.10 (1H, m, $W_{1/2}$ 34 Hz, H-1α), 2.02 (1H, dt, J=12.3, 3.4 Hz, H-7β), 1.95 (1H, dt, J=14.5, 3.7 Hz, H-3β), 1.73 (1H, dd, J=13.2, 6.4 Hz, H-10β), 1.65 (1H, ddq, J=11.4, 6.7, 3.4 Hz, H-8β), 1.48 (1H, ddd, J=14.5, 13.0, 5.6 Hz, H-3α), 1.06 (3H, d, J=6.7 Hz, Me-17); δ_C (100 MHz, $CDCl_3$) 176.4 (s, C-20), 144.2 (d, C-15), 139.8 (d, C-16), 124.8 (s, C-13), 108.0 (d, C-14), 90.9 (s, C-4), 85.0 (d, C-6), 80.5 (t, C-18), 71.8 (d, C-12), 71.1 (t, C-19), 51.9 (s, C-9), 48.2 (s, C-5), 43.7 (d, C-10), 41.3 (t, C-11), 39.8 (d, C-8), 31.5 (t, C-7), 24.4 (t, C-3), 19.1 (t, C-1), 16.9 (t, C-2), 16.1 (q, C-17); m/z (EI) 344 $[M]^+$ (1),

314 (80), 286 (20), 269 (29), 220 (100), 187 (33), 161 (28), 147 (33), 105 (37), 96 (74), 95 (76), 94 (46%).

(12*S*)-6α-Acetoxy-4α,19;15,16-diepoxy-18-iodo-neocleroda-13(16),14-dien-20,12-olide (29) and 28. Treatment of **27** (100 mg, 0.21 mmol) with Ac_2O:pyridine (1:1, 2 mL) at room temperature for 48 h yielded a mixture of **29** and **28** (78 mg), which were separated by column chromatography. Elution with *n*-hexane:EtOAc (4:1) and (1:4) yielded successively **29** (58 mg, 55%) and **28** (20 mg, 27%).

Compound 29: [Found: C, 51.02; H, 5.40. $C_{22}H_{27}IO_6$ requires C, 51.37; H, 5.29%]; mp 75–80°C (white amorphous solid); $[\alpha]_D^{19}=+59.8$ (c=0.589, $CHCl_3$); IR (NaCl) ν_{max} 3150, 3120, 1760, 1740, 1600, 1505, 1240, 875 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.43 (1H, m, H-16), 7.42 (1H, t, J=1.8 Hz, H-15), 6.36 (1H, dd, J=1.8, 0.9 Hz, H-14), 5.38 (1H, br t, J=8.7, Hz, H-12), 5.19 (1H, dd, J=11.6, 4.4 Hz, H-6β), 4.67 (2H, s, 2H-19), 3.58 and 3.24 (each 1H, d, J=9.9 Hz, 2H-18), 2.44 (1H, dd, J=14.0, 8.6 Hz, H_B-11), 2.28 (1H, dd, J=14.0, 8.9 Hz, H_A-11), 2.19 (3H, s, OAc), 2.04 (1H, dt, J=12.8, 11.6 Hz, H-7α), 1.85 (1H, dt, J=12.8, 4.4 Hz, H-7β), 0.93 (3H, d, J=6.7 Hz, Me-17); δ_C (100 MHz, $CDCl_3$) 177.1 (s, C-20), 170.4 (s, O*CO*CH_3), 144.2 (d, C-15), 139.5 (d, C-16), 124.9 (s, C-13), 108.0 (d, C-14), 86.5 (s, C-4), 73.1 (d, C-6), 72.1 (d, C-12), 68.7 (t, C-19), 51.9 (s, C-9), 47.2 (s, C-5), 43.7 (d, C-10), 41.1 (t, C-11), 37.2 (d, C-8), 32.7 (t, C-3), 31.7 (t, C-7), 21.9 (q, OCO*CH₃*), 21.6 (t, C-1), 16.7 (q, C-17), 10.0 (t, C-18); *m/z* (EI) 514 $[M]^+$ (1), 454 (5), 409 (4), 342 (12), 309 (27), 281 (58), 215 (83), 173 (40), 119 (42), 105 (48), 95 (100), 94 (79%).

(12*S*)-6α,19-Diacetoxy-15,16-epoxy-neocleroda-3,13(16),14-trien-20,12-olide (30). A mixture of **21** (200 mg, 0.47 mmol) and *p*-TsOH (20 mg, 0.11 mmol) in toluene (20 mL) was refluxed for 4 h. The reaction mixture was diluted with EtOAc (25 mL) and washed with aqueous $NaHCO_3$ saturated solution (50 mL×3). The residue obtained after solvent removal was chromatographed using *n*-hexane:EtOAc (4:1) yielding 196 mg (98%) of pure **30**: [Found: C, 66.73; H, 7.35. $C_{24}H_{30}O_7$ requires C, 66.96; H, 7.02%]; mp 146–148°C (white crystals from EtOAc:*n*-hexane); $[\alpha]_D^{20}=+18.7$ (c=0.127, $CHCl_3$); IR (KBr) ν_{max} 3090, 1745, 1730, 1720, 1695, 1340, 1210, 945, 850 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41 (1H, m, H-16), 7.39 (1H, t, J=1.9 Hz, H-15), 6.35 (1H, dd, J=1.9, 0.9 Hz, H-14), 5.39 (1H, m, H-3), 5.38 (1H, br t, J= 8.6 Hz, H-12), 4.94 (1H, d, J=12.1 Hz, H_B-19), 4.81 (1H, d, J=12.1 Hz, H_A-19), 4.80 (1H, dd, J=11.7, 4.1 Hz, H-6β), 2.37 (1H, dd, J=14.1, 8.5 Hz, H_B-11), 2.32 (1H, dd, J=14.1, 8.8 Hz, H_A-11), 2.03 (3H, s, OAc), 1.95 (3H, s, OAc), 1.63 (3H, d, J=1.3 Hz, Me-18), 0.98 (3H, d, J=6.6 Hz, Me-17); δ_C (50 MHz, $CDCl_3$) 176.7 (s, C-20), 170.4 (s, O*CO*CH_3), 170.3 (s, O*CO*CH_3), 144.1 (d, C-15), 139.5 (d, C-16), 136.8 (s, C-4), 125.3 (2C, s C-13 and d C-3), 108.0 (d, C-14), 76.0 (d, C-6), 71.9 (d, C-12), 62.4 (t, C-19), 51.5 (s, C-9), 51.0 (d, C-10), 45.5 (s, C-5), 45.4 (t, C-11), 38.2 (d, C-8), 32.8 (t, C-7), 25.2 (t, C-2), 22.0 (q, C-18), 21.7 (q, OCO*CH₃*), 21.2 (q, OCO*CH₃*), 19.9 (t, C-1), 16.3 (q, C-17);); *m/z* (EI) 430 $[M]^+$ (absent), 370 (8), 310 (52), 265 (66), 216(63), 171 (49), 157 (41), 105 (41), 95 (73), 81 (38), 43 (100%).

(12*S*)-15,16-Epoxy-6α,19-dihydroxy-neocleroda-3,13(16),14-trien-20,12-olide (31) and (12*S*)-15,16-epoxy-6α,12-dihydroxy-neocleroda-3,13(16),14-trien-20,19-olide (32). A mixture of **30** (200 mg, 0.47 mmol) in MeOH (20 mL) and aqueous NaOH solution (70 mL, 2% w/v) was heated at 60°C for 45 min. The reaction mixture was cooled down to room temperature and extracted with CH_2Cl_2 (100 mL×3). After removal of the solvents an inseparable mixture of **31** and **32** (150 mg, 91%) in a 1:4 ratio (^1H NMR spectrum) was obtained.

(12*S*)-3α,19;15,16-Diepoxy-6α-hydroxy-4β-iodo-neocleroda-13(16),14-dien-20,12-olide (33). To the mixture of regioisomers **31**+**32** (150 mg, 0.43 mmol) in dry acetonitrile (80 mL), *N*-iodosuccinimide (148 mg, 0.66 mmol) was added at room temperature, and the reaction mixture was stirred for 5 min. The reaction mixture was diluted with EtOAc (80 mL) and washed with $Na_2S_2O_5$ saturated solution (80 mL×3). The residue obtained after removal of the solvents was chromatographed with *n*-hexane:EtOAc (7:3) as eluent, yielding **33** (10 mg) and unreacted **32** (110 mg).

Compound 32: [Found: C, 69.10; H, 7.74. $C_{20}H_{26}O_5$ requires C, 69.34; H, 7.56%]; mp 160–162°C (white crystals from EtOAc:*n*-hexane); $[\alpha]_D^{20}=-39.4$ (c=0.226, $CHCl_3$); IR (KBr) ν_{max} 3420, 2920, 1700, 1650, 1175, 1140, 1020, 870 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40 (1H, m, H-16), 7.39 (1H, t, J=1.9 Hz, H-15), 6.42 (1H, dd, J=1.9, 1.0 Hz, H-14), 5.50 (1H, 1H, m, H-3), 4.85 (1H, d, J=12.0 Hz, H_B-19), 4.81 (1H, dd, J=9.5, 2.9 Hz, H-12), 4.25 (1H, d, J=12.0 Hz, H_A-19), 3.83 (1H, dd, J=12.1, 6.6 Hz, H-6β), 2.42 (1H, dd, J=15.9, 2.9 Hz, H_B-11), 2.24 (1H, dd, J=15.9, 9.5 Hz, H_A-11), 1.81 (3H, d, J=1.6 Hz, Me-18), 0.89 (3H, d, J=6.6 Hz, Me-17); *m/z* (EI) 346 $[M]^+$ (27), 298 (7), 218 (31), 173 (70), 159 (51), 145 (39), 131 (52), 119 (41), 111 (75), 105 (88), 95 (100), 81 (57), 69 (53), 55 (39), 41 (63%).

Compound 33: [Found: C, 51.03; H, 5.50. $C_{20}H_{25}IO_5$ requires C, 50.86; H, 5.34%]; mp 170°C, decomp. (spontaneous crystallyzation); $[\alpha]_D^{27}=+24.1$ (c=0.270, $CHCl_3$); IR (KBr) ν_{max} 3560 (sharp), 1740, 1500, 1460, 950, 870 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.43 (2H, m, H-16 and H-15), 6.37 (1H, dd, J=1.4, 0.7 Hz, H-14), 5.41 (1H, t, J=8.8 Hz, H-12), 4.36 (1H, d, J=8.8 Hz, H_B-19), 4.17 (1H, dd, J= 8.8, 1.2 Hz, H_A-19), 3.99 (1H, d, J=4.4 Hz, H-3β), 3.93 (1H, dd, J=12.1, 4.4 Hz, H-6β), 2.46 (1H, dd, J=14.2, 8.3 Hz, H_B-11), 2.43 (3H, s, Me-18), 2.38 (1H, dd, J=14.2, 8.9 Hz, H_A-11), 2.20 (1H, q, J=12.5 Hz, H-7α), 2.09 (1H, dddd, J=14.2, 6.7, 4.4, 1.1 Hz, H-2α), 1.64 (1H, ddd, J=12.5, 4.4, 3.4 Hz, H-7β), 1.00 (3H, d, J=6.8 Hz, Me-17); δ_C (125 MHz, $CDCl_3$) 177.2 (s, C-20), 144.1 (d, C-15), 139.4 (d, C-16), 125.2 (s, C-13), 108.0 (d, C-14), 83.3 (d, C-3), 72.0 (d, C-12), 69.0 (d, C-6), 65.9 (s, C-4), 60.3 (t, C-19), 53.4 (s, C-5), 52.8 (s, C-9), 52.5 (d, C-10), 43.4 (t, C-11), 38.1 (t, C-7), 37.5 (d, C-8), 36.2 (q, C-18), 31.1 (t, C-2), 20.7 (t, C-1), 16.7 (q, C-17);); *m/z* (EI) 472 $[M]^+$ (2), 345 $[M\text{-}I]^+$ (59), 299 (8), 253 (12), 159 (39), 145 (27), 121 (30), 105 (58), 95 (100), 81 (59%).

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