PREPARATION OF E-SECOLUPANE ACIDS AND LACTONES+

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Anhydrides of 3β,28-diacetoxy-21,22-secolup-18-ene-21,22-dioic acid (**1**) and (19*R*)-3β,28-diacetoxy-18β,19-epoxy-21,22-secolupane-21,22-dioic acid (**11**) undergo alkaline hydrolysis yielding the corresponding dicarboxylic acids. Depending on reaction conditions, these acids are further transformed yielding various lactones, liberating C-28 hydroxymethyl group, or undergoing decarboxylation leading to nor derivatives. This method has been used to prepare a diverse series of E-secolupane derivatives including lactonoacids (*e.g.* **2** and **15**), lactones (**4**, **16** and **17**), 28-nor derivatives (**3** and **6**) and 21,28-dinor derivatives (**12** and **13**). Derivatives of (19*R*)-3β,28-dihydroxy-18β,19-epoxy-21,22-secolupane-21,22-dioic acid 21,28-lactone (**15c**), bearing a free carboxylic group, are labile and can only be isolated as the corresponding dilactones **17**. The C-22 carboxylic group forms a β-lactone by a nucleophilic α-directed attack on the C-18 epoxide ring carbon atom resulting in (19*R*)-3β,19-dihydroxy-21,22-secolupane-21,28:22,18α-dilactone (**17b**) and related derivatives. The structure and stereochemistry of the compounds discussed in this contribution were derived from IR, MS, ^{1}H and ^{13}C NMR spectra (1D and 2D COSY, TOCSY, NOESY, HSQC, HMBC). Using these NMR techniques and measuring the solvent influence on the IR carbonyl stretching frequencies of the dilactones **17**, an equilibrium between the two E-ring conformations was shown to exist.

Keywords: Triterpenes; Triterpenoids; Lupane; Secolupane; NMR spectroscopy, ^{1}H and ^{13}C.

Interesting biological activity has been reported for a number of lupane-derived triterpenoids (*cf.* refs[2–10] and references cited therein). For this reason a number of simple betulinic acid and betuline derivatives were screened for biological activity revealing several compounds that show high anti-HIV-1 virus activity and simultaneously low toxicity (*cf.*, *e.g.*, refs[2–4]

+ Part CXI in the series Triterpenes; Part CX, see ref.[1]

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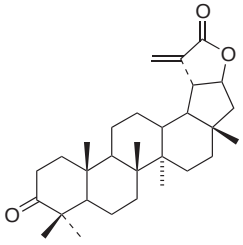
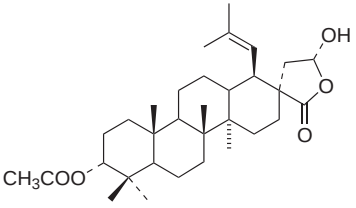
and references cited therein). In the case of betulinic acid and some related compounds, cytotoxic activity (especially against human melanome[5]) was observed[5–7]. Similar activity was found in several lactones derived from lupane[8,9] (*e.g.* ochraceolide A) or E-secolupane[10] (*e.g.* radermasinin) skeletons. From structure–activity relationship studies[3,5–7] the presence of a free carboxylic group in the triterpenoid compounds was shown to be essential for this type of activity. In this contribution, a preparation of analogous E-secolupane mono- and dicarboxylic acids, bearing in addition lactone or other oxygen containing groups, is presented.



ochraceolide A



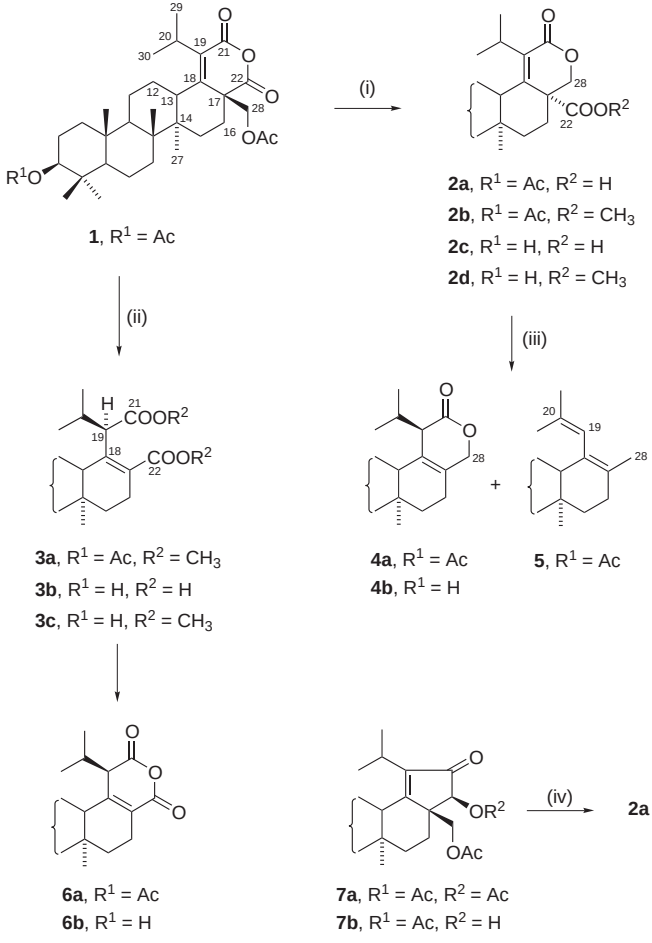
radermasinin

3β,28-Diacetoxy-21,22-secolup-18-ene-21,22-dioic acid anhydride (**1**) and 18β,19β-epoxy-21-oxolupane-3β,28-diyl diacetate (**8**) were used as starting materials for this investigation. Anhydride **1** can be prepared[11] by direct functionalisation of lupane-3β,28-diyl diacetate using chromium trioxide, or by oxidation of lup-18-ene-3β,28-diyl diacetate or 21-oxolup-18-ene-3β,28-diyl diacetate using the same oxidant. The epoxy ketone **8** can be prepared[12] by a reaction of 21-oxolup-18-ene-3β,28-diyl diacetate with peracids.

The unsaturated anhydride **1** was treated with a solution of potassium hydroxide in a mixture of benzene and ethanol at room temperature to selectively hydrolyse the primary acetoxy group in position 28, giving lactonoacid **2a** after acidification of the reaction mixture. The lactonoacid **2a** was treated by an ether solution of diazomethane to yield methyl ester **2b** (Scheme 1).

The 3-hydroxy acid **2c** was obtained by hydrolysis of the 3β-acetate moiety of lactonoacid **2a**, using potassium hydroxide in a refluxing mixture of benzene/ethanol. This acid was further characterised as methyl ester **2d**. According to TLC, the lactone ring of the lactonoacid **2a** is also hydrolysed under alkaline conditions, but undergoes re-lactonisation after acidification. The lactonoacid **2a** was prepared by an alternative route from 21-oxolup-18-ene-3β,22β,28-triyl triacetate (**7a**), obtained from epoxy

ketone **8** by a sulfuric acid catalysed reaction with acetic acid[13]. The lactonoacid **2a** was formed as a major product in a reaction of triacetate **7a** with peracetic acid. As a minor product, a hydroxy ketone was isolated and found to be identical to the 22β-hydroxy ketone **7b** prepared earlier[13]. The reaction of triacetate **7a** with peracetic acid probably starts with acid hydrolysis of the 22β-acetate moiety followed by oxidation of hydroxy ketone **7b** to anhydride **1**. Oxidation may proceed *via* the 21,22-diketone which, however, was not isolated. To sum up, alkaline hydrolysis of the cyclic anhydride and of the 28-acetate moiety in the unsaturated anhydride **1** followed



1, R^1 = Ac

2a, R^1 = Ac, R^2 = H
2b, R^1 = Ac, R^2 = CH_3
2c, R^1 = H, R^2 = H
2d, R^1 = H, R^2 = CH_3

3a, R^1 = Ac, R^2 = CH_3
3b, R^1 = H, R^2 = H
3c, R^1 = H, R^2 = CH_3

4a, R^1 = Ac
4b, R^1 = H

5, R^1 = Ac

6a, R^1 = Ac
6b, R^1 = H

7a, R^1 = Ac, R^2 = Ac
7b, R^1 = Ac, R^2 = H

(i) KOH/ethanol, benzene, r.t.; (ii) KOH/ethylene glycol, reflux; (iii) triethylene glycol, reflux; (iv) peracetic acid, Ac_2O, H_2SO_4/$CHCl_3$,reflux

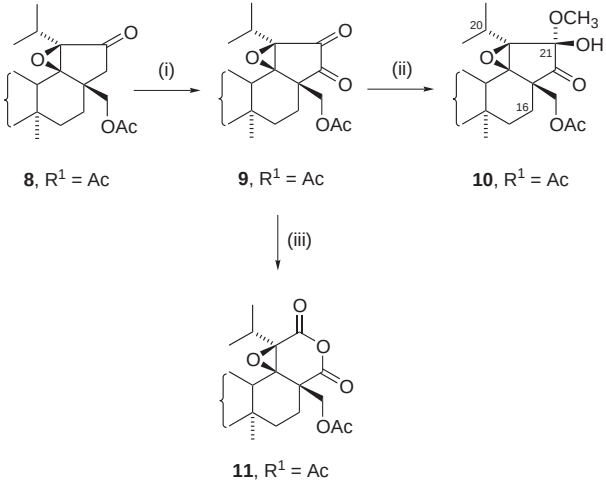
SCHEME 1

by lactonisation gives the lactonoacid **2a**. With the exception of hydroxy ketone **7b**, no other intermediates were isolated.

On treatment of the unsaturated anhydride **1** with a 10% potassium hydroxide solution in boiling ethylene glycol, a loss of the 28-hydroxymethyl group was observed yielding 28-nor-21,22-seco diacid **3b**. The diacid **3b** readily undergoes cyclisation to give 28-nor anhydride **6b** and consequently any attempts to isolate and purify the diacid **3b** failed. However, treatment of the crude diacid **3b** by diazomethane resulted in a separable mixture of 28-nor anhydride **6b** and the desired stable dimethyl ester **3c**. On acetylation of the free hydroxyl moiety in position 3 in diester **3c** and anhydride **6b** using acetic anhydride in pyridine, the corresponding 3-*O*-acetyl derivatives **3a** and **6a**, respectively, were prepared.

When heated to 270 °C (boiling triethylene glycol) the lactonoacid **2a** undergoes decarboxylation to give 22-nor lactone **4a** as a major product. As a minor product in this reaction, diene **5** was obtained upon loss of two molecules of carbon dioxide from the lactonoacid **2a**. According to TLC, alkaline hydrolysis of lactone **4a** at room temperature leads to opening of the lactone ring which, however, re-lactonises readily after acidification. When the same hydrolysis was performed at elevated temperature, 3-hydroxy lactone **4b** was obtained after acidification.

The 18,19-epoxy anhydride **11** was prepared from diketone **9**, obtained by oxidation of the epoxy ketone **8**, using selenium dioxide (Scheme 2). An



8, R^1 = Ac **9**, R^1 = Ac **10**, R^1 = Ac

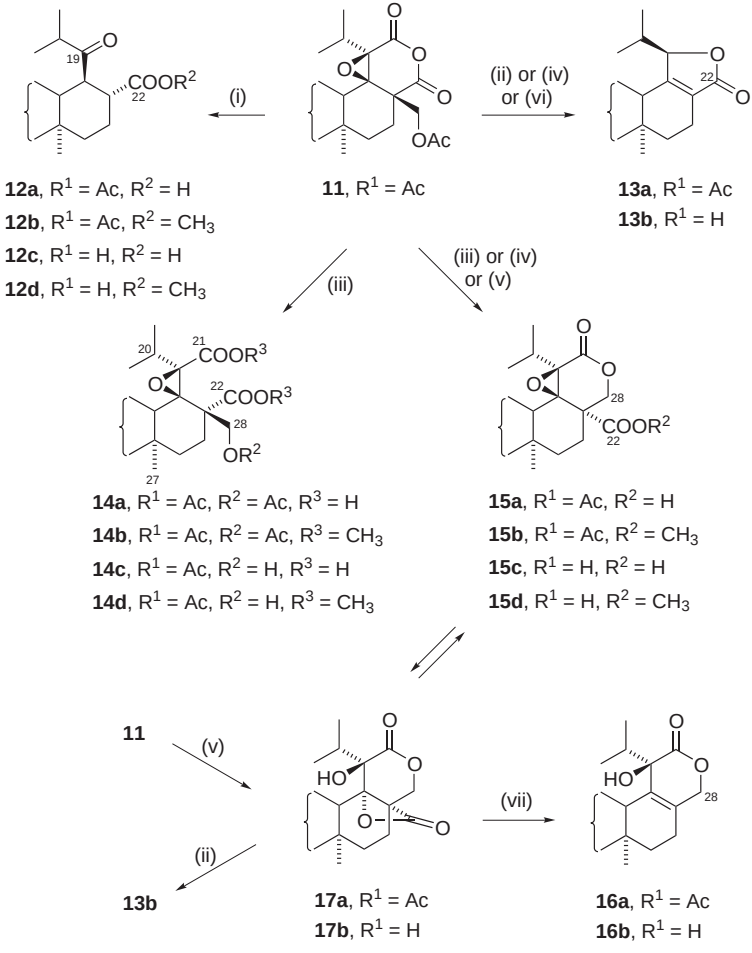
11, R^1 = Ac

(i) selenium dioxide/dioxane, AcOH, reflux; (ii) methanol, reflux; (iii) peracetic acid/$CHCl_3$,r.t.

SCHEME 2

attempt to crystallise diketone **9** from methanol resulted in the isolation of a hemiacetal characterised as 21β-hydroxy-21α-methoxy-22-oxo derivative **10** on the basis of NMR data (*cf.* below). Oxidation of diketone **9** using peracetic acid yielded epoxy anhydride **11**.

Chemical behaviour of epoxy anhydride **11** in alkaline medium strongly depends on reaction conditions (Scheme 3).



12a, R^1 = Ac, R^2 = H
12b, R^1 = Ac, R^2 = CH_3
12c, R^1 = H, R^2 = H
12d, R^1 = H, R^2 = CH_3

11, R^1 = Ac

13a, R^1 = Ac
13b, R^1 = H

14a, R^1 = Ac, R^2 = Ac, R^3 = H
14b, R^1 = Ac, R^2 = Ac, R^3 = CH_3
14c, R^1 = Ac, R^2 = H, R^3 = H
14d, R^1 = Ac, R^2 = H, R^3 = CH_3

15a, R^1 = Ac, R^2 = H
15b, R^1 = Ac, R^2 = CH_3
15c, R^1 = H, R^2 = H
15d, R^1 = H, R^2 = CH_3

17a, R^1 = Ac
17b, R^1 = H

16a, R^1 = Ac
16b, R^1 = H

(i) KOH/ethylene glycol, reflux; (ii) KOH/dioxane, H_2O, reflux; (iii) KOH/ethanol, benzene, r.t.; (iv) KOH/ethanol,benzene, reflux; (v) HCl/$CHCl_3$, methanol, reflux; (vi) KOH/ethanol, benzene, H_2O, reflux; (vii) triethylene glycol, 210-220 °C

SCHEME 3

Treatment of epoxy anhydride **11** with potassium hydroxide in a mixture of benzene/ethanol at room temperature (method *A* in Experimental) results in an instantaneous opening of the cyclic anhydride. After 1 min, acidification of the reaction mixture was carried out using dilute hydrochloric acid. Diacid **14a** was isolated keeping both 3β and 28 acetate groups intact. Its reaction with diazomethane yielded the corresponding dimethyl ester **14b**.

Prolonged treatment (5 h) of epoxy anhydride **11** with potassium hydroxide at room temperature under otherwise analogous conditions (method *B*) results (in addition to the opening of the cyclic anhydride) in hydrolysis of the acetate group in position 28. However, it was not possible to isolate the expected diacid **14c**, not even in the corresponding lactonoacid form **15a** (as one would have expected from analogous behaviour of the unsaturated acid **2a**). During the work-up in diethyl ether, the formation of a crystalline product was observed. Its structure was assigned (*cf.* below) as dilactone **17a**. After its separation, the remaining mother liquor was treated with diazomethane to yield a mixture of products from which dimethyl ester **14d** and methyl ester **15b** containing a lactone ring between the 28-hydroxy group and carboxyl group on C-19 were isolated. On acetylation of the 28-hydroxy group in dimethyl ester **14d** dimethyl ester diacetate **14b** was obtained.

When alkaline hydrolysis of epoxy anhydride **11** was performed in a boiling mixture of benzene/ethanol (method *C*), the acetate group at position 3 was hydrolysed although only partially, as potassium salts precipitated out of the reaction mixture forming a dense slurry which could not be dissolved even by addition of ethanol. Subsequent acidification and work-up provided a complex mixture of products from which dilactone **17b** crystallised out as the major product. TLC analysis of the remaining mother liquor revealed dilactone **17a** still bearing the 3-acetate group and also lactones **13a** and **13b**. Dilactone **17b** was acetylated to give the corresponding acetate **17a**.

When alkaline hydrolysis of epoxy anhydride **11** was performed in a boiling mixture of dioxane/water (method *D*) or in a boiling mixture of benzene/ethanol/water, a homogeneous reaction mixture was obtained which, in addition to complete hydrolysis of both acetate groups, substantial changes occurred in the E-ring. These changes included loss of the carboxyl group from C-19, of the hydroxymethyl group from C-17 and an opening of the epoxide ring. γ-Lactone **13b** was isolated as the major product of this transformation. The identical product was also obtained from dilactone **17a**

after exposure to analogous reaction conditions. Lactone **13b** was further acetylated to give the corresponding acetate **13a**.

When alkaline hydrolysis of epoxy anhydride **11** was performed in a boiling solution of 10% potassium hydroxide in ethylene glycol (method *E*), a loss of the 28-hydroxymethyl group occurred, analogous to that of the unsaturated anhydride **1**. Besides this loss, decarboxylation in position C-19 and rearrangement of the epoxide to the 19-oxo derivative occurred. After acidification and subsequent work-up the dinor acid **12c** was obtained. This was further characterised as methyl ester **12d**, acetate **12a** and methyl ester acetate **12b**.

Acid hydrolysis (hydrochloric acid in a refluxing mixture of chloroform/methanol, method *F*) of epoxy anhydride **11** provided dilactone **17b** in a high yield. This dilactone could also be prepared by acid-catalysed deacetylation of dilactone **17a** under analogous conditions. On heating to 210–220 °C in triethylene glycol, dilactone **17a** liberates 1 equivalent of carbon dioxide to give unsaturated lactone **16a** bearing a hydroxy group in position 19β. Alkaline hydrolysis of lactone **16a** yielded the corresponding 3-hydroxy derivative **16b**.

Interestingly, lactonoacids **15a** and **15c** were never isolated as free carboxylic acids but only in the dilactone form **17a** and **17b**. In these dilactones, the C-28 carboxyl group undergoes lactonisation into the 18α position with simultaneous 18β,19β-epoxide ring opening and subsequent formation of the 19β-hydroxy group. This form of the dilactones appears to be very stable and its formation was already observed during the work-up. On the other hand, the treatment of dilactones **17a** and **17b** with an ethereal solution of diazomethane opens the β-lactone ring, the initial epoxide ring is then regenerated and finally methyl esters **15b** and **15d** are formed, respectively.

The structure elucidation of the new compounds was achieved by spectroscopic analyses (MS, IR, ^{1}H and ^{13}C NMR). The detailed NMR analysis utilising two-dimensional techniques (COSY, NOESY, TOCSY, HSQC and HMBC) was particularly useful. These techniques enabled an accurate determination of the functional group positions in the D and E rings as well as their stereochemical configurations. In the case of compounds **2d**, **3a**, **4a**, **6a**, **9**–**11**, **12b**, **13b**, **14b**, **15b**, **16a** and **17a**, a complete assignment of the ^{1}H and ^{13}C signals was achieved (*cf.* Tables I–VII). In the case of the remaining compounds, the assignment of carbon signals is based on DEPT spectra and analogies.

In the case of methyl esters **2d** and **15b**, α-configuration of the methoxycarbonyl group on C-17 was assigned on the basis of spatial contact be-

TABLE I
^{1}H chemical shifts and coupling constants (in parentheses) of compounds **2d**, **3a**, **4a** and **6a**

Proton	**2d**	**3a**[a]	**4a**	**6a**
1α	0.97	1.04	1.062 td (12.0, 4.0)	1.072 td (12.7, 4.3)
1β	1.69	1.70	1.70	1.72
2a	1.60	1.66	1.61	1.64
2b	1.64	1.66	1.68	1.68
3α	3.199 dd (11.3, 4.7)	4.484 m (ΣJ = 16.2)	4.489 m (ΣJ = 16.5)	4.486 dd (11.3, 5.2)
5α	0.729 dd (11.8, 2.6)	0.83	0.83	0.84
6a	1.45	1.39	1.42	1.41
6b	1.62	1.56	1.57	1.58
7α	1.292 td (12.7, 4.1)	1.38	1.42	1.40
7β	1.42	1.49	1.52	1.53
9α	1.45	1.43	1.44	1.45
11α	1.65	1.58	1.63	1.70
11β	1.48	1.25	1.28	1.37
12α	1.45	1.26	1.08	1.28
12β	1.88 dm (11.4)	2.12	1.74	1.75
13β	2.837 dd (10.9, 2.9)	2.32	2.344 bd (13.0)	2.433 dm (12.5)
15α	1.44	1.40	1.45	1.57
15β	1.199 td (12.8, 6.3)	1.50	1.50	1.52
16α	2.328 m (ΣJ = 35.2)	2.34	1.94 m	2.20
16β	1.43	2.34	1.88 bdd (17.5, 6.4)	2.681 ddm (18.6, 5.9)
19α	–	3.70	2.991 m	3.365 t (2.7)
20	2.831 septet (6.7)	2.30	1.986 septet d (7.0, 4.3)	2.077 septet d (7.0, 3.0)
23	0.975 s	0.854 s	0.858 s	0.866 s
24	0.779 s	0.847 s	0.853 s	0.858 s
25	0.878 s	0.878 s	0.895 s	0.906 s
26	0.989 s	0.941 s	0.990 s	1.003 s
27	0.848 s	0.961 s	0.877 s	0.882 s
28a	3.797 d (10.4)	–	4.431 dm (15.7)[b]	–
28b	4.172 d (10.4)	–	4.740 dm (15.7)[c]	–
29	1.472 d (6.9)[d]	1.000 d (6.4)	0.915 d (7.0)[d]	1.221 d (6.9)
30	1.113 (6.7)[e]	0.830 d (6.8)	1.143 d (7.0)[e]	0.840 d (6.9)
3β-OAc	–	2.033 s	2.048 s	2.052 s
21-OCH_3	–	3.668 s	–	–
22-OCH_3	3.700 s	3.704 s	–	–

[a] Measured at 50 °C. [b] 28α. [c] 28β. [d] *pro-R*. [e] *pro-S*.

TABLE II
^{13}C chemical shifts of compounds **2a**–**2d**, **3a**, **3c**, **4a**, **4b**, **6a** and **6b**

Carbon	**2a**	**2b**	**2c**	**2d**	**3a**[a]	**3c**[a]	**4a**	**4b**	**6a**	**6b**
1	38.44	38.47	38.75	38.79	38.63	38.95	38.51	38.86	38.51	38.88
2	23.63	23.63	27.09	27.33	23.74	27.50	23.61	27.33	23.57	27.28
3	80.74	80.64	78.97	78.75	80.88	78.98	80.70	78.79	80.59	78.73
4	37.85	37.84	38.84	38.91	37.90	38.95	37.79	38.84	37.79	38.84
5	55.70	55.74	55.63	55.65	55.78	55.73	55.60	55.53	55.57	55.49
6	18.28	18.26	18.36	18.38	18.25	18.36	18.11	18.23	18.07	18.20
7	33.13	33.11	33.15	33.17	33.89	33.97	33.78	33.86	33.66	33.75
8	40.01	39.99	40.01	39.99	40.47	40.46	39.72	39.73	40.40	40.40
9	51.15	51.18	51.24	51.26	50.91	51.01	50.62	50.71	50.40	50.49
10	37.22	37.20	37.26	37.28	37.20	37.29	37.11	37.20	37.10	37.20
11	21.92	21.92	21.90	21.90	21.71	21.70	21.16	21.15	21.16	21.17
12	28.03	28.07	28.05	28.10	24.87	24.90	23.81	23.85	24.36	24.41
13	42.59	42.46	42.57	42.48	42.78b	42.81b	38.40	38.45	40.14	40.18
14	41.51	41.53	41.48	41.52	40.09	40.10	40.32	40.31	39.66	39.68
15	27.44	27.43	27.43	27.45	27.60	27.61	27.62	27.64	27.19	27.21
16	26.65	26.87	26.65	26.88	25.62	25.64	23.22	23.25	21.56	21.59
17	45.18	45.45	45.24	45.47	129.64b	129.66b	124.11	124.13	122.09	122.13
18	153.72	154.18	154.10	154.23	143.59	143.64	130.20	130.28	155.39	155.45
19	136.03	135.65	135.80	135.66	54.67b	54.66b	46.51	46.56	49.54	49.57
20	28.76	28.69	28.69	28.69	29.27	29.27	31.50	31.52	31.95	31.99
21	163.59	163.59	163.70	163.61	174.08	174.11	171.53	171.65	167.10	167.18
22	178.93	175.37	178.89	175.40	170.41	170.44	–	–	161.67	161.69
23	27.87	27.85	27.86	27.89	27.93	27.97	27.86	27.91	27.85	27.92
24	16.43	16.40	15.26	15.25	16.45	15.32	16.43	15.33	16.44	15.33
25	16.43	16.40	16.33	16.34	16.56	16.51	16.56	16.50	16.59	16.54
26	15.96	15.96	15.94	15.96	15.51	15.52	15.56	15.57	15.39	15.41
27	17.83	17.33	17.78	17.35	14.62	14.66	13.64	13.67	14.27	14.30
28	73.94	74.03	73.92	74.02	–	–	70.77	70.79	–	–
29	21.65	21.62	21.64	21.63	23.53	23.54	21.61	21.61	20.93	20.95
30	20.86	20.87	20.85	20.88	20.40	20.39	18.07	18.11	16.36	16.38
CH_3COO	21.30	21.28	–	–	21.18	–	21.27	–	21.27	–
CH_3COO	171.07	170.95	–	–	170.80	–	170.89	–	170.93	–
21-OCH_3	–	–	–	–	51.51	51.52	–	–	–	–
22-OCH_3	–	53.16	–	53.12	51.30	51.32	–	–	–	–

[a] Measured at 50 °C.

TABLE III
^{1}H chemical shifts and coupling constants (in parentheses) of compounds **9**, **10**, **11** and **12b**

Proton	**9**	**10**	**11**	**12b**
1α	1.05	1.05	1.05	1.04
1β	1.75	1.74	1.74	1.70
2a	1.67	1.62	1.67	1.66
2b	1.76	1.66	1.67	1.66
3α	4.479 m (ΣJ = 16.3)	4.489 m (ΣJ = 16.5)	4.475 m (ΣJ = 16.0)	4.472 m (ΣJ = 16.2)
5α	0.82	0.82	0.82	0.83
6a	1.42	1.42	1.42	1.42
6b	1.58	1.57	1.56	1.55
7a	1.45	1.42	1.43	1.42
7b	1.45	1.44	1.43	1.42
9α	1.31	1.33	1.28	1.37
11α	1.60	1.55	1.60	1.46
11β	1.28	1.20	1.26	1.24
12α	1.28	1.31	1.34	1.25
12β	1.78	1.74	1.72	1.25
13β	2.92 dd (12.8, 3.4)	2.669 dd (12.5, 3.2)	3.028 dd (12.1, 3.1)	1.80
15α	1.54	1.22	1.26	1.36
15β	1.68	1.82	1.92	1.52
16α	1.868 td (13.8, 4.4)	1.970 td (13.6, 4.3)	1.90	1.70
16β	1.28	1.68	1.87	1.82
17β	–	–	–	2.547 ddd (12.7, 11.3, 4.3)
18α	–	–	–	2.906 t (11.1)
20	2.301 septet (7.0)	2.254 septet (7.2)	2.293 septet (6.9)	2.540 septet (6.9)
23	0.857 s	0.860 s	0.855 s	0.848 s
24	0.851 s	0.848 s	0.847 s	0.834 s
25	0.919 s	0.907 s	0.914 s	0.853 s
26	1.162 s	1.130 s	1.200 s	0.990 s
27	1.129 s	1.220 s	1.139 s	1.002 s
28*pro-R*	4.300 d (11.8)	4.301 d (11.8)	4.441 d (11.8)	–
28*pro-S*	4.865 d (11.8)	4.555 d (11.8)	5.245 d (11.8)	–
29	1.254 d (6.9)[a]	1.255 d (7.2)[a]	1.244 d (6.9)[a]	1.022 d (6.9)
30	1.337 d (7.0)[b]	1.344 d (7.2)[b]	1.409 d (7.0)[b]	1.035 d (6.9)
3β-OAc	2.050 s	2.049 s	2.048 s	2.043 s
28-OAc	2.075 s	2.085 s	2.095 s	–
OH	–	3.689 s	–	–
OCH_3	–	3.165 s	–	3.587 s

[a] *pro-R*. [b] *pro-S*.

TABLE IV
^{13}C chemical shifts of compounds **9**, **10**, **11**, **12a**, **12b**, **12d**, **13a** and **13b**

Carbon	**9**	**10**	**11**	**12a**	**12b**	**12d**	**13a**	**13b**
1	38.55	38.55	38.52	38.47	38.48	38.80	38.56	38.87
2	23.57	23.61	23.52	23.60	23.61	27.33	23.60	27.30
3	80.62	80.73	80.56	80.82	80.80	78.87	80.64	78.75
4	37.77	37.78	37.73	37.76	37.77	38.84	37.82	38.91
5	55.46	55.46	55.36	55.42	55.44	55.35	55.65	55.55
6	18.03	18.09	17.97	18.05	18.04	18.16	18.10	18.24
7	34.30	34.34	34.22	33.97	33.95	34.01	33.89	33.95
8	41.35	41.22	41.74	40.57	40.53	40.52	40.33	40.31
9	51.36	51.35	51.35	50.46	50.51	50.59	50.93	51.00
10	37.19	37.20	37.12	37.04	37.05	37.14	37.25	37.33
11	21.28	21.40	21.71	20.86	20.89	20.87	21.04	21.04
12	23.68	24.25	25.11	27.40	27.44	27.48	24.59	24.61
13	38.47	37.78	38.95	41.32	41.18	41.16	38.97	38.99
14	43.35	43.68	43.89	40.91	40.91	40.89	40.66	40.67
15	26.38	26.42	26.59	30.17	30.13	30.14	27.87	27.85
16	26.46	24.80	28.70	24.86	24.95	24.96	18.10	18.11
17	50.30	52.15	52.97	46.57	46.87	46.85	125.18	125.17
18	75.32	71.97	71.19	51.07	51.50	51.54	166.07	166.14
19	69.16	70.48	64.97	219.02	218.96	218.89	85.82	85.83
20	25.92	29.18	29.19	43.01	42.95	42.90	30.23	30.23
21	193.05	98.63	163.87	–	–	–	–	–
22	200.35	209.25	167.03	180.51	175.66	175.69	173.94	173.97
23	27.92	27.93	27.89	27.88	27.89	27.93	27.87	27.92
24	16.48	16.49	16.46	16.40	16.41	15.34	16.43	15.32
25	16.78	16.81	16.78	16.46	16.47	16.34	16.55	16.49
26	16.41	16.60	16.53	15.69	15.70	15.70	15.49	15.49
27	16.48	16.60	17.90	14.57	14.43	14.66	14.18	14.21
28	61.64	61.80	64.12	–	–	–	–	–
29	18.18	20.02	19.07	18.05	17.88	17.89	13.78	13.80
30	17.36	19.18	17.79	17.52	17.52	17.53	20.38	20.38
3β-CH_3COO	21.28	21.29	21.25	21.29	21.29	–	21.29	–
3β-CH_3COO	170.96	170.98	170.93	171.08	171.01	–	170.95	–
28-CH_3COO	20.94	21.08	20.91	–	–	–	–	–
28-CH_3COO	170.88	170.98	170.87	–	–	–	–	–
OCH_3	–	49.08	–	–	51.61	51.61	–	–

TABLE V
^{1}H chemical shifts and coupling constants (in parentheses) of compounds **13b**, **14b**, **15b** and **16a**

Proton	**13b**	**14b**	**15b**	**16a**
1α	0.99	1.04	1.02	1.04
1β	1.72	1.73	1.63	1.730 dt (13.1, 3.7)
2a	1.60	1.66	1.64	1.63
2b	1.67	1.66	1.64	1.66
3α	3.21 m	4.476 m (ΣJ = 16.3)	4.465 m (ΣJ = 16.0)	4.493 m (ΣJ = 16.6)
5α	0.76 dd (11.0, 3.0)	0.82	0.82	0.83
6a	1.45	1.42	1.29	1.42
6b	1.62	1.58	1.29	1.55
7a	1.42	1.42	1.31	1.37
7b	1.55	1.51	1.38	1.52
9α	1.50	1.22	1.47	1.46
11α	1.66	1.56	1.60	1.58
11β	1.38	1.20	1.18	1.34
12α	1.37	1.37	1.47	1.25
12β	1.73	1.82	1.91 dm (13.6)	2.520 dq (11.6, 3.0)
13β	2.467 dm (13.0)	2.588 dd (12.8, 2.9)	2.156 dd (12.7, 2.0)	2.579 bd (12.1)
15α	1.58	1.37	1.38	1.45
15β	1.49	1.86	1.58	1.56
16α	2.13 m	1.82	2.331 m (ΣJ = 34.3)	2.08 m
16β	2.313 dm (18.0)	2.00	1.37	1.827 ddm (17.4, 5.8)
19α	4.718 m	–	–	–
20	2.066 septet d (6.9, 2.1)	2.428 septet (7.0)	1.770 septet (6.9)	2.244 septet (7.0)
23	0.987 s	0.857 s	0.848 s	0.857 s
24	0.784 s	0.846 s	0.848 s	0.851 s
25	0.883 s	0.886 s	0.864 s	0.889 s
26	1.021 s	1.097 s	0.981 s	0.996 s
27	0.883 s	1.220 s	0.874 s	0.969 s
28a	–	4.359 d (10.5)[a]	3.865 d (10.4)	4.813 ddd (15.7, 3.6, 1.2)[b]
28b	–	4.739 d (10.5)[c]	4.257 d (10.4)	4.454 dd (15.7, 2.4)[d]
29	0.667 d (6.9)	0.983 d (6.8)	1.405 d (6.9)	0.968 d (7.0)[a]
30	1.172 d (6.9)	1.172 d (6.8)	1.292 d (6.9)	0.902 d (7.0)[b]
3β-OAc	–	2.047 s	2.048 s	2.052 s
28-OAc	–	2.048 s	–	–
OH	–	–	–	3.576 s
21-OCH_3	–	3.628 s	–	–
22-OCH_3	–	3.583 s	3.761 s	–

[a] *pro-R*. [b] 28α. [c] *pro-S*. [d] 28β.

TABLE VI
^{13}C chemical shifts of compounds **14a**, **14b**, **14d**, **15b**, **15d**, **16a**, **16b** and **17b**

Carbon	**14a**	**14b**	**14d**	**15b**	**15d**	**16a**	**16b**	**17b**
1	38.46	38.51	38.45	38.38	38.71	38.52	38.80	38.78
2	23.61	23.60	23.61	23.60	27.31	23.67	27.32	27.34
3	80.74	80.71	80.75	80.64	78.75	80.84	78.85	78.75
4	37.77	37.76	37.76	37.83	38.91	37.82	38.83	38.87
5	55.58	55.52	55.59	55.83	55.75	55.66	55.53	55.32
6	17.97	17.99	17.98	18.42	18.55	18.18	18.26	18.31
7	33.32	33.87	33.60	33.09	33.15	33.88	33.90	33.19
8	42.13	41.96	42.14	41.64	41.65	40.30	40.26	41.83
9	52.00	51.85	51.80	50.97	51.06	51.24	51.27	51.09
10	37.05	37.07	37.05	37.23	37.32	37.09	37.12	37.22
11	22.37	22.24	22.10	22.70	22.70	21.61	21.56	20.87
12	25.65	26.09	25.78	24.40	24.43	26.08	26.05	23.16
13	43.68	43.00	43.49	44.12	44.13	40.21	40.18	39.21
14	40.37	41.96	41.06	42.18	42.18	40.57	40.51	39.61
15	26.39	26.69	27.06	25.89	25.91	27.40	27.37	27.28
16	26.69	27.11	29.43	25.95	25.98	24.19	24.15	24.46
17	52.20	52.85	53.29	46.51	46.54	125.69	125.65	55.18
18	72.56	71.24	71.95	69.68	69.70	133.65	133.63	86.01
19	72.86	73.20	73.81	67.52	67.54	76.75	76.71	81.06
20	31.83	29.51	29.62	30.45	30.44	38.07	38.00	31.71
21	177.39	168.12	168.63	165.98	166.01	173.86	173.82	171.24
22	179.41	172.25	173.89	174.70	174.75	–	–	171.24
23	27.87	27.90	27.89	27.85	27.90	27.86	27.85	27.89
24	16.46	16.48	16.46	16.34	15.22	16.43	15.28	15.30
25	16.75	16.84	16.72	16.19	16.14	16.66	16.51	16.44
26	15.55	16.20	15.84	16.58	16.58	15.61	15.56	15.58
27	21.03	19.31	20.54	17.59	17.63	15.19	15.18	15.58
28	66.42	65.19	65.78	71.31	71.31	72.73	72.68	69.33
29	18.39	18.63	18.39	18.93	18.95	16.61	16.64	18.05
30	19.02	18.70	18.72	18.07	18.08	17.17	17.12	17.76
3β-CH_3COO	21.24	21.27	21.24	21.27	–	21.30	–	–
3β-CH_3COO	171.00	170.96	170.91	170.96	–	171.01	–	–
28-CH_3COO	21.82	20.88	–	–	–	–	–	–
28-CH_3COO	170.54	170.58	–	–	–	–	–	–
21-OCH_3	–	51.78	51.47	–	–	–	–	–
22-OCH_3	–	51.09	51.24	52.80	52.76	–	–	–

TABLE VII
^{1}H and ^{13}C chemical shifts and coupling constants (in parentheses) of dilactone **17a** in $CDCl_3$ and DMSO-d_6. Assignment based on 2D correlations

Proton	$CDCl_3$	DMSO-d_6[a]	Carbon	$CDCl_3$	DMSO-d_6[b]
1α	1.06	1.03	1	38.48	37.71
1β	1.70	1.63	2	23.62	23.33
2a	1.60	1.56	3	80.65	79.79
2b	1.66	1.62	4	37.80	37.34
3α	4.48 m (ΣJ = 16.3)	4.39 m (ΣJ = 16.0)	5	55.41	54.54
5α	0.83	0.88	6	18.19	17.76
6a	1.55	1.49	7	33.13	32.78
6b	1.38	1.40	8	41.84	41.40
7a	1.36	1.32	9	51.02	50.19
7b	1.40	1.39	10	37.14	36.75
9α	1.44	1.50	11	20.88	20.81
11α	1.63	1.58	12	23.14	23.33
11β	1.40	1.30	13	39.17	36.65
12α	1.46	1.42	14	39.62	40.17
12β	1.92 dq (13.3, 2.9)	1.75 dm (13.7)	15	27.25	25.83
13β	2.14 dd (11.5, 2.4)	2.27 dd (11.9, 1.8)	16	24.41	20.46
15α	1.48	1.41	17	55.19	56.68
15β	1.22	1.20	18	85.97	85.96
16α	2.28 td (14.5, 6.4)	1.87 td (14.3, 5.4)	19	81.04	79.04
16β	1.61	1.33	20	31.71	32.08
20	2.31 septet (6.6)	2.11 septet (6.6)	21	171.19	166.70
23	0.85 s	0.80 s	22	170.95	173.07
24	0.84 s	0.81 s	23	27.84	27.53
25	0.89 s	0.85 s	24	16.42	16.30
26	0.96 s	0.98 s	25	16.49	16.23
27	0.97 s	0.91 s	26	15.57	15.36
28α	4.62 d (11.8)	4.15 d (11.6)	27	15.57	16.08
28β	4.38 d (11.8)	4.59 d (11.6)	28	69.30	66.61
29	1.02 d (6.9)	1.07 d (6.8)	29	18.05	18.08
30	1.16 d (6.4)	1.17 d (6.4)	30	17.75	17.76
OH	3.55 bs	6.69 s	CH_3COO	21.28	20.95
OAc	2.05 s	2.00 s	CH_3COO	170.95	170.08

[a] Tetramethylsilane as the internal standard. [b] δ(DMSO-d_6) 39.50 ppm.

tween the protons of the methoxy group and the 14α-methyl group (H-27) found in NOESY spectrum. Methyl groups on C-20 (H-29 and H-30) were identified using NOESY cross-peaks of H-29 (*pro-R*) with H-12β. In carbon spectrum of compounds **3a** and **3c**, the signals belonging to atoms in positions 13, 17 and 19 are broad, implying a dynamic equilibrium of several conformers probably arising from a hindered rotation about the C(18)–C(19) bond. In order to completely assign proton and carbon signals and to confirm the supposed structure, NMR spectra of both compounds were also taken at 50 °C. A distinct sharpening of the corresponding signals was observed.

The position of the tetrasubstituted double C(17)–C(18) bond in lactone **4a** was confirmed using HMBC correlation between both carbon atoms in positions 17 and 18 with protons of the methylene group in position 28 and with H-19. The β-configuration of the isopropyl group in position 19 arises from a combination of spatial contacts involving H-19α with both protons H-12, and from a contact of H-20 with H-13β. The configuration of the C-19 isopropyl group in anhydride **6a** and lactone **13b** was assigned in an analogous way.

In the case of epoxy derivatives **9**, **10**, **11** and **15b** and also in the case of lactone **16a**; the configuration of the isopropyl group was found to be opposite (α). This assignment was confirmed by NOESY cross-peak between H-30 and H-27 signals. In the case of hemiacetal **10**, the position of the methoxy group was assigned using HMBC data, in which cross-peaks arising from coupling of the carbon atom in position 21 with protons of the methoxy group and also with H-20 were observed. α-Configuration of the methoxy group was assigned using NOESY contact between protons OCH_3 and H-16α. There is an important cross-peak in NOESY spectrum of compound **14b** arising from spatial contact between H-20 and protons of 14α-methyl group (H-27). This cross-peak confirms the orientation of the isopropyl group under the plane of the skeleton. The contact between protons H-13β and H-16β also found in this spectrum implies that, to at least some degree, the D ring exists in a boat conformation.

In proton spectrum of diene **5** taken at 25 °C, two broad signals (δ 5.37 and 5.49) having approximately the same intensity were found. These signals were assigned to the olefinic proton at position 19. A distinct sharpening of these signals was observed at lower temperatures. Higher temperatures, on the other hand, led to their coalescence. Analogous changes were observed in majority of the remaining signals but especially in the signals of methyl protons. In NOESY spectrum of diene **5** exchange cross-peaks between both signals of the olefinic proton in position 19 were observed,

implying that in solution there is an equilibrium between two slowly interconverting conformers. This was further confirmed by ^{13}C NMR data in which two series of signals were observed. Analogously to the ^{1}H spectrum, changes in temperature led to changes in the shape of most of the ^{13}C signals.

UV spectrum of diene **5** only shows a weak absorption, which does not correspond to either purely *s-trans* or purely *s-cis* arrangements of the diene system. In both existing conformers, both double bonds are unlikely to be coplanar due to the steric interactions of one of the C-20 methyl groups with the methylene group in position 12 in the *s-trans* form, and with the 28-methyl group in the *s-cis* form.

The existence of a four-membered lactone ring and an intramolecularly bonded hydroxy group in dilactones **17a** and **17b** is inferred from IR data (≈1830 and 3476 cm^{-1}; Table X). Based on a complete assignment of proton and carbon NMR signals of dilactone **17a** taken in $CDCl_3$ (Table VII), and especially on HMBC data (Table VIII), the position of all functional groups in rings D and E was assigned with the exception of the hydroxy group; in the HMBC spectrum no cross-peak of the hydroxyl proton was found. When the spectrum was taken in DMSO-d_6, cross-peaks arising from the coupling between the hydroxyl proton and carbon atoms 18, 19 and 21 (Table VIII) were detected. This implies that the hydroxy group is attached to C-19. Moreover, when compared with a spectrum taken in $CDCl_3$, the chemical shifts of protons H-16α and H-20 recorded in DMSO-d_6 were significantly altered and no longer overlapping. As shown by NOESY cross-peaks (most importantly H-16α/H-27) and by coupling constants of H-16α, which is spin-spin coupled with protons on C-15 (≈14.5 and ≈6 Hz) in both solvents, the D ring occurs in a half-chair conformation.

According to molecular models, the six-membered lactone ring (ring E) of dilactones **17** can assume two conformations. In the first one, the carbonyl groups of the lactones are oriented towards the α-side of the skeleton and are nearly parallel (conformer A, Fig. 1). In the second one, the carbonyl groups assume a different orientation and are nearly antiparallel (conformer B). In the IR spectra of both dilactones **17** taken in solution, two carbonyl bands were detected corresponding to a six-membered lactone. The band at higher frequency (≈1760 cm^{-1}) was assigned to the conformer A having the parallel dipoles C=O, whereas the band at lower frequency (≈1745 cm^{-1}) was assigned to the antiparallel conformer B. The relative intensities of both bands (expressed in Table X as the ratio between the integrated absorption intensity of the higher-frequency band and the intensity

TABLE VIII
Selected HMBC-correlations of dilactone **17a** in $CDCl_3$ and DMSO-d_6 (w, weak; m, medium; s, strong response)

Proton	$CDCl_3$	DMSO-d_6
13β	11 (m), 12 (m), 14 (s), 15 (w), 18 (m), 19 (s), 27 (m)	14 (m), 19 (w), 27 (m)
16α	15 (s), 17 (s), 18 (s), 22 (s), 28 (s)	15 (m), 17 (m), 18 (m), 22 (s), 28 (m)
20	19 (s), 21 (s), 29 (s), 30 (s)	19 (m), 21 (m), 29 (m), 30 (m)
23	3 (s), 4 (s), 5 (s), 24 (s)	3 (s), 4 (s), 5 (s), 24 (s)
24	3 (s), 4 (s), 5 (s), 23 (s)	3 (s), 4 (s), 5 (s), 23 (s)
25	5 (s), 9 (s), 10 (s)	5 (s), 9 (s), 10 (s)
26	7 (s), 8 (s), 9 (s), 14 (s)	7 (s), 8 (s), 9 (m), 14 (s)
27	8 (s), 13 (s), 14 (s), 15 (s)	8 (s), 13 (s), 14 (s), 15 (s)
28α	16 (s), 17 (m), 18 (s), 21 (s), 22 (s)	17 (s), 18 (s), 21 (s), 22 (s)
28β	16 (s), 17 (s), 18 (s), 21 (s), 22 (s)	17 (s), 18 (s), 22 (s)
29	19 (s), 20 (s), 30 (s)	19 (s), 20 (s), 30 (s)
30	19 (s), 20 (s), 29 (s)	19 (s), 20 (s), 29 (s)
OH	–	18 (s), 19 (w), 21 (s)

TABLE IX
Selected NOESY-correlations of dilactone **17a** in $CDCl_3$ and DMSO-d_6 (w, weak; m, medium; s, strong response)

Proton	$CDCl_3$	DMSO-d_6
3α	1α (m), 5α (m), 23 (s)	1α (m), 5α (s), 23 (s)
12β	11β (s), 12α (s), 29 (s), 30 (s)	11β (s), 12α (s), 29 (s)
13β	11β (w), 12β (s), 15β (s), 26 (s)	11β (s), 12β (m), 15β (s), 26 (s)
16α	15α (m), 16β (s), 27 (s)	15α (s), 16β (s), 27 (s)
20	12β (s), 13β (s), 28α (s)	12β (s), 13β (s)
28α	16β (m), 29 (w)	16β (s)
28β	16β (s)	16β (s)
OH	–	13β (m), 20 (s), 28β (s), 30 (s)

TABLE X

Carbonyl stretching frequencies of lactones **17a** and **17b**. The parameters of overlapping bands were obtained by mathematical separation

Lactone	Solvent	ν(C=O), cm^{-1}				k_A [a]	k_ε [a]
		β-Lactone	δ-Lactone		Acetate		
			conformer A	conformer B			
17a	CCl_4 [b]	1831	1765	1745	1735	0.09	0.14
	Dioxane	1834	1758	≈1733 [c]	≈1733 [c]	[d]	[d]
	Nujol	1833	–	≈1737 [c]	≈1737 [c]	–	–
17b	Cyclohexane	1840	1767 [e]	1746	–	0.03	0.07
	CCl_4 [f]	1834	1766	1745	–	0.13	0.18
	Dioxane	1834	1759	1742 [e]	–	0.62	1.23
	Nitromethane	1829	1757	1742 [e]	–	1.16	1.80
	Nujol	1810	1759	–	–	–	–

[a] $k_A = A(1760\ cm^{-1})/A(1745\ cm^{-1})$, $A = \pi/2\Delta\nu_{1/2}\varepsilon$; $k_\varepsilon = \varepsilon(1760\ cm^{-1})/\varepsilon(1745\ cm^{-1})$. [b] ν(OH): 3476 cm^{-1}. [c] Overlapping bands. [d] The parameter could not be obtained. [e] Shoulder. [f] ν(OH): 3476 cm^{-1} (19β-OH), 3631 and 3609 sh cm^{-1} (3β-OH).

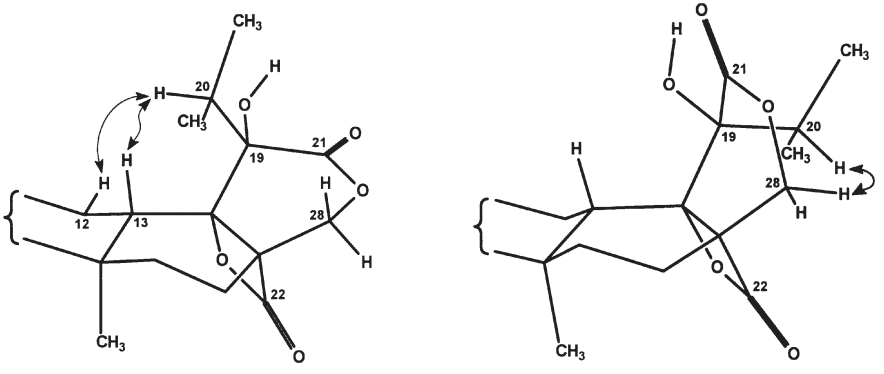


FIG. 1

Conformers A and B of dilactones **17** with important NOESY contacts

of the lower-frequency band (k_A), and as a ratio between the corresponding molar absorption coefficients (k_ε)) vary depending on the solvent used. This becomes most apparent in dilactone **17b** where the spectrum is not complicated by the overlapping acetate group carbonyl band as in **17a**. Increasing the polarity of the solvents used (cyclohexane, tetrachloromethane, dioxane and nitromethane) caused an increase in both k_A and k_ε, which in other words means that, with an increase of solvent polarity, the population of conformer A increases. The equilibrium of two possible conformers is further supported by NOESY data of dilactone **17a** in $CDCl_3$. In this spectrum spatial contacts H-20/H-13β and H-20/H-12β (possible only in conformer A) and at the same time spatial contact H-20/H-28α (possible only in conformer B) were detected (Table IX and Fig. 1). In NOESY spectrum taken in DMSO-d_6, the cross-peak H-20/H-28α was not found.

Surprisingly, in IR spectrum of dilactone **17a** taken in a Nujol suspension, the ≈1760 cm^{-1} band was absent. Analogously, the IR spectrum of a Nujol suspension of dilactone **17b** revealed a complete absence of the ≈1745 cm^{-1} band. It is likely that in a crystalline state dilactone **17a** exists only as conformer B, whereas **17b** only exists as conformer A.

To conclude, the readily available anhydrides **1** and **11** are a valuable entry into synthesis of novel E-secolupane acids and lactones. In both the series of analogues studied, in the 18(19)-unsaturated series and in the 18β,19β-epoxy series, the anhydride ring easily opened to diacids under alkaline conditions. Depending on reaction conditions, these diacids can be further transformed into lactonoacids (*e.g.* **2**, **15**), dilactones **17**, or they liberate the hydroxymethyl group or undergo decarboxylation respectively to yield various nor derivatives (**3**–**6**, **12**, **13**, **16**). Results of biological assays of compounds prepared here will be published elsewhere[14].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotation measurements at 23 °C were carried out in chloroform (*c* 0.3–0.5) on an automatic polarimeter AUTOPOL III (Rudolph Research), accuracy ±2; they are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded in chloroform (unless stated otherwise) on a Perkin–Elmer PE 684 spectrometer; wavenumbers are given in cm^{-1}. UV spectra were measured on a Unicam SP-700 instrument in cyclohexane. ^1H and ^{13}C NMR spectra were recorded on a Varian ^{UNITY}INOVA 400 FT spectrometer (^1H at 400 MHz, ^{13}C at 100.58 MHz) in deuteriochloroform with tetramethylsilane as the internal standard (in ^{13}C NMR, δ($CDCl_3$) 77.00 ppm). Chemical shift values (δ-scale, ppm) and coupling constants (*J*, Hz) in the ^1H NMR spectra were obtained by first-order analysis. Electron-impact mass spectra were measured on an INCOS 50 (Finnigan MAT) instrument (ionising electron energy 75 eV, ion source tempera-

ture 150 °C). The samples were introduced by direct inlet at heating rate 10 mA/s. Relative abundance is related to the most abundant ion in the region of $m/z > 50$.

Column chromatography was carried out on silica gel Kieselgel 60 (Merck). The course of reactions and purity of the samples were checked by thin-layer chromatography (TLC) on DC-Alufolien Kieselgel 60 foils (Merck). Spots were detected by spraying with 10% sulfuric acid and subsequent heating. Preparative TLC was performed on silica gel 60 G (Merck); compounds were detected by UV light (254 nm) after spraying with 0.3% solution of morin in methanol. The identity of samples prepared by different procedures was verified by TLC, IR and ^{1}H NMR spectra. Analytical samples were dried over phosphorus pentoxide at 100 °C under reduced pressure.

The usual work up entails dilution of the reaction mixture with water, extraction of products with ether, successive washing of the ethereal layer with dilute (1:4) hydrochloric acid (if necessary) and water, drying over anhydrous magnesium sulfate and evaporation of the solvent. The hydroxy derivatives were acetylated with a mixture of acetic anhydride and pyridine (1:1) at room temperature for 15–20 h and the reaction mixture was worked up in the usual manner. After crystallisation, the acetyl derivatives were obtained in 70–90% yield. Methyl esters were prepared by treatment of the corresponding acids with an ethereal solution of diazomethane.

Alkaline Hydrolysis of Anhydride **1**

Method A (at room temperature): A solution of potassium hydroxide (159 mg, 2.84 mmol) in ethanol (3 ml) was added to a solution of anhydride **1** (500 mg, 0.88 mmol, ref.[11]) in benzene (40 ml). The mixture was left standing for 4 h at room temperature, acidified with dilute hydrochloric acid and worked up in the usual manner. Crystallisation from a chloroform–ether mixture afforded compound **2a** (410 mg, 89%).

3β-Acetoxy-28-hydroxy-21,22-secolup-18-ene-21,22-dioic acid 21,28-lactone (**2a**): M.p. 244–246 °C, $[\alpha]_D$ –40. IR: 3300–2700, 1718 b, 1583, 1244. ^{1}H NMR: 0.86 s, 6 H (CH_3-23, CH_3-24), 0.90 s, 3 H (CH_3-25), 0.94 s, 3 H (CH_3-27), 0.99 s, 3 H (CH_3-26), 1.11 d, 3 H (CH_3-30, J = 6.8), 1.47 d, 3 H (CH_3-29, J = 6.8) (7 × CH_3); 1.88 dm, 1 H (H-12β, $J \approx 13.5$); 2.05 s, 3 H (OAc); 2.37 m, 1 H (H-16α, ΣJ = 35.1); 2.83 septet, 1 H (H-20, J = 6.8); 2.83 bd, 1 H (H-13β, $J \approx 11.0$); 3.84 d, 1 H (H-28a, J = 10.5); 4.22 d, 1 H (H-28b, J = 10.5); 4.48 dd, 1 H (H-3α, ΣJ = 16.2). For ^{13}C NMR, see Table II. MS, *m/z* (%): 484 (M^+ – 44, 12), 468 (3), 454 (7), 442 (82), 424 (12), 203 (59), 189 (100).

3β-Acetoxy-28-hydroxy-21,22-secolup-18-ene-21,22-dioic acid 21,28-lactone 22-methyl ester (**2b**, obtained from acid **2a**): M.p. 293–295 °C (chloroform–methanol), $[\alpha]_D$ –46. IR: 1721 b, 1689 sh, 1255. ^{1}H NMR: 0.85 s, 3 H (CH_3-27), 0.86 s, 6 H (CH_3-23, CH_3-24), 0.90 s, 3 H (CH_3-25), 0.99 s, 3 H (CH_3-26), 1.11 d, 3 H (CH_3-30, J = 6.8), 1.47 d, 3 H (CH_3-29, J = 6.8) (7 × CH_3); 1.89 m, 1 H (H-12β); 2.05 s, 3 H (OAc); 2.33 m, 1 H (H-16α, ΣJ = 35.9); 2.83 septet, 1 H (H-20, J = 6.8); 2.83 dd, 1 H (H-13β, J_1 = 10.9, J_2 = 2.9); 3.71 s, 3 H (OCH_3); 3.79 d, 1 H (H-28a, J = 10.4); 4.17 d, 1 H (H-28b, J = 10.4); 4.48 dd, 1 H (H-3α, ΣJ = 16.3). For ^{13}C NMR, see Table II. MS, *m/z* (%): 542 (M^+, 20), 512 (5), 499 (4), 482 (56), 467 (16), 454 (3), 439 (31), 347 (9), 303 (5), 265 (73), 203 (50), 189 (73), 55 (100). For $C_{33}H_{50}O_6$ (542.8) calculated: 73.03% C, 9.29% H; found: 73.19% C, 9.40% H.

Method B (at 200 °C): A mixture of anhydride **1** (450 mg, 0.79 mmol) and potassium hydroxide (2.5 g, 45 mmol) in ethylene glycol (25 ml) was refluxed for 40 min. The reaction mixture was acidified with dilute hydrochloric acid and worked up in the usual manner.

Ether was distilled off and the residue (410 mg) was treated with diazomethane. Separation by column chromatography in a light petroleum–ether mixture (1:1) afforded dimethyl ester **3c** (110 mg, 28%) and noranhydride **6b** (235 mg, 67%).

Dimethyl (19R)-3β-hydroxy-28-nor-21,22-secolup-17-ene-21,22-dioate (**3c**): Non-crystalline, $[\alpha]_D$ –62. IR: 3617, 1730, 1709, 1605, 1435. ^{1}H NMR (at 50 °C): 0.77 s, 3 H (CH_3-24), 0.83 d, 3 H (CH_3-30, J = 6.8), 0.86 s, 3 H (CH_3-25), 0.94 s, 3 H (CH_3-26), 0.97 s, 3 H (CH_3-27), 0.98 s, 3 H (CH_3-23), 1.00 d, 3 H (CH_3-29, J = 6.3) (7 × CH_3); 2.12 m, 1 H (H-12β); 2.25–2.40 m, 4 H (H-13β, H-16α, H-16β, H-20); 3.20 dd, 1 H (H-3α, J_1 = 11.3, J_2 = 4.9); 3.67 s, 3 H, 3.70 s, 3 H (2 × OCH_3). For ^{13}C NMR, see Table II. MS, *m/z* (%): 502 (M^+, 3), 484 (1), 470 (100), 459 (13), 442 (14), 427 (6), 249 (59), 189 (23).

Dimethyl (19R)-3β-acetoxy-28-nor-21,22-secolup-17-ene-21,22-dioate (**3a**, obtained from dimethyl ester **3c**): M.p. 134–136 °C (methanol), $[\alpha]_D$ –48. IR: 1725, 1713, 1435, 1604, 1255. For ^{1}H and ^{13}C NMR, see Tables I and II. MS, *m/z* (%): 544 (M^+, 2), 512 (70), 501 (7), 484 (6), 452 (1), 249 (100), 189 (35), 69 (96). For $C_{33}H_{52}O_6$ (544.8) calculated: 72.76% C, 9.62% H; found: 72.57% C, 9.51% H.

(19R)-3β-Hydroxy-28-nor-21,22-secolup-17-ene-21,22-dioic acid anhydride (**6b**): M.p. 194–195 °C (methanol), $[\alpha]_D$ +10. IR: 3616, 1786, 1736, 1720, 1648, 1604. ^{1}H NMR: 0.78 s, 3 H (CH_3-24), 0.84 d, 3 H (CH_3-30, J = 6.9), 0.88 s, 6 H (CH_3-25, CH_3-27), 0.99 s, 3 H (CH_3-23), 1.00 s, 3 H (CH_3-26), 1.22 d, 3 H (CH_3-29, J = 6.9) (7 × CH_3); 2.08 d of septets, 1 H (H-20, J_1 = 3.0, J_2 = 6.9); 2.19 m, 1 H (H-16α, ΣJ = 43.6); 2.43 dm, 1 H (H-13β, J = 12.7); 2.68 bdd, 1 H (H-16β, J_1 = 18.6, J_2 = 6.1); 3.22 dd, 1 H (H-3α, J_1 = 11.4, J_2 = 4.8); 3.36 bt, 1 H (H-19α, J = 2.6). For ^{13}C NMR, see Table II. MS, *m/z* (%): 456 (M^+, 11), 438 (28), 423 (9), 414 (13), 400 (27), 397 (23), 395 (21), 386 (5), 381 (6), 369 (3), 317 (2), 303 (3), 289 (2), 235 (9), 221 (19), 207 (23), 189 (47), 55 (100). For $C_{29}H_{44}O_4$ (456.7) calculated: 76.27% C, 9.71% H; found: 76.50% C, 9.85% H.

(19R)-3β-Acetoxy-28-nor-21,22-secolup-17-ene-21,22-dioic acid anhydride (**6a**, obtained from noranhydride **6b**): M.p. 264–266 °C (methanol), $[\alpha]_D$ –13. IR: 1785, 1734, 1721, 1648, 1252. For ^{1}H and ^{13}C NMR, see Tables I and II. MS, *m/z* (%): 498 (M^+, 1), 456 (14), 438 (63), 428 (6), 423 (18), 395 (27), 383 (17), 217 (13), 203 (16), 189 (50), 69 (100).

Oxidation of Triacetate **7a**

Acetic anhydride (2 ml), sulfuric acid (0.01 ml) and peracetic acid (32%, 1 ml, 4.2 mmol) were added to a solution of triacetate **7a** (110 mg, 0.17 mmol, ref.[13]) in chloroform (2 ml). The reaction mixture was refluxed for 14 h. During this period, additional peracetic acid was added in two 1 ml portions. After cooling to room temperature the reaction mixture was diluted with ether and poured into a solution of sodium hydrogencarbonate. The products were taken up in ether; the ethereal layer was successively washed with a 5% solution of potassium iodide, solution of sodium hydrogensulfite and water. After drying over anhydrous sodium sulfate, the ether was distilled off. Separation of products by preparative TLC gave 22β-hydroxy-21-oxolup-18-ene-3β,28-diyl diacetate (**7b**) (28 mg, 30%), m.p. 193–196 °C (methanol) (ref.[13] gives 213–214 °C) and lactonoacid **2a** (56 mg, 62%), both being identical with the authentic samples.

Hydrolysis of Lactonoacid **2a**

A solution of lactonoacid **2a** (200 mg, 0.38 mmol) and potassium hydroxide (200 mg, 3.57 mmol) in a mixture of benzene (5 ml) and ethanol (3 ml) was refluxed for 3 h. After

cooling to room temperature the reaction mixture was acidified with dilute hydrochloric acid (1:4) and worked up as usual. Crystallisation from ether afforded diacid **2c** (150 mg, 81%).

3β,28-Dihydroxy-21,22-secolup-18-ene-21,22-dioic acid 21,28-lactone (**2c**): M.p. 197–203 °C (decomp.), $[\alpha]_D$ –59. IR: 3693, 3614, 2400–3500, 1723, 1710, 1604. ^{1}H NMR: 0.77 s, 3 H (CH_3-24), 0.87 s, 3 H (CH_3-25), 0.94 s, 3 H (CH_3-27), 0.97 s, 3 H (CH_3-23), 0.99 s, 3 H (CH_3-26), 1.11 d, 3 H (CH_3-30, J = 6.8), 1.47 d, 3 H (CH_3-29, J = 6.8) (7 × CH_3); 1.87 dm, 1 H (H-12β, J = 13.1); 2.36 m, 1 H (H-16α, ΣJ = 35.5); 2.83 septet, 1 H (H-20, J = 6.8); 2.83 dd, 1 H (H-13β, J_1 = 13.6, J_2 = 2.9); 3.22 dd, 1 H (H-3α, J_1 = 11.3, J_2 = 4.7); 3.83 d, 1 H (H-28a, J = 10.5); 4.21 d, 1 H (H-28b, J = 10.5); 4.80 bs, 2 H (2 × OH). For ^{13}C NMR, see Table II. MS, *m/z* (%): 486 (M^+, 1), 468 (3), 442 (11), 424 (6), 412 (2), 400 (41), 381 (4), 251 (26), 207 (18), 189 (30), 55 (100).

3β,28-Dihydroxy-21,22-secolup-18-ene-21,22-dioic acid 21,28-lactone 22-methyl ester (**2d**, obtained by methylation from acid **2c**): M.p. 265–271 °C (chloroform–heptane), $[\alpha]_D$ –61. IR: 1730, 1720, 1586. For ^{1}H and ^{13}C NMR, see Tables I and II. MS, *m/z* (%): 500 (M^+, 10), 482 (8), 457 (0.6), 439 (4), 346 (3), 292 (2), 265 (56), 189 (29), 55 (100). For $C_{31}H_{48}O_5$ (500.7) calculated: 74.36% C, 9.66% H; found: 74.51% C, 9.82% H.

Decarboxylation of Lactonoacid **2a**

Method A (without solvent): Lactonoacid **2a** (150 mg, 0.28 mmol) was heated at 270 °C for 3 min and the mixture of products (140 mg) was separated by preparative TLC in a light petroleum–ether mixture (10:3) to give lactone **4a** (53 mg, 39%). This compound was identical with the sample obtained using method *B*.

Method B (in triethylene glycol): Lactonoacid **2a** (130 mg, 0.25 mmol) in triethylene glycol (2.5 ml) was refluxed for 10 min and the reaction mixture was worked up as usual. Preparative TLC in a light petroleum–ether mixture (1:1) afforded lactone **4a** (86 mg, 72%) and diene **5** (8 mg, 7%).

(19R)-3β-Acetoxy-22-nor-21,22-secolup-17-ene-21,28-lactone (**4a**): M.p. 234–236 °C (methanol), $[\alpha]_D$ +54. IR: 1722, 1602, 1255. For ^{1}H and ^{13}C NMR, see Tables I and II. MS, *m/z* (%): 484 (M^+, 6), 442 (29), 424 (3), 409 (3), 381 (9), 217 (27), 203 (56), 189 (100), 135 (60). For $C_{31}H_{48}O_4$ (484.7) calculated: 76.82% C, 9.98% H; found: 76.63% C, 10.11% H.

21,22-Dinor-19,21-secolupa-17,19-dien-3β-yl acetate (**5**): M.p. 162–163 °C (methanol), $[\alpha]_D$ +20. IR: 1719, 1605, 1257. ^{1}H NMR (at 0 °C): 0.84 s, 6 H, 0.86 s, 4.5 H, 0.90 s, 1.5 H, 0.94 s, 1.5 H, 0.95 s, 1.5 H, 1.45 s, 3 H, 1.47 s, 3 H, 1.73 d, 3 H (J = 1.2) (8 × CH_3); 2.06 s, 3 H (OAc); 4.48 m, 1 H (H-3α, ΣJ = 16.4), 5.37 bs, 0.5 H, 5.49 bs, 0.5 H (H-19). ^{1}H NMR (at 55 °C): 0.85 s, 3 H, 0.86 s, 3 H, 0.88 s, 3 H, 0.90 bs, 3 H, 0.97 s, 3 H, 1.47 bs, 6 H, 1.73 d, 3 H (J = 1.2) (8 × CH_3); 2.02 s, 3 H (OAc); 4.49 m, 1 H (H-3α, ΣJ = 16.4), 5.44 bs, 1 H (H-19). UV (cyclohexane): λ_{max}, nm (log ε): 228 (3.57). MS, *m/z* (%): 440 (M^+, 23), 425 (0.7), 412 (0.4), 397 (0.4), 380 (0.7), 365 (1), 337 (0.4), 249 (3), 203 (4), 189 (14), 177 (41), 149 (100). For $C_{30}H_{48}O_2$ (440.7) calculated: 81.76% C, 10.98% H; found: 81.62% C, 11.10% H.

Hydrolysis of Lactone **4a**

Method A (at room temperature): A solution of potassium hydroxide (106 mg, 1.89 mmol) in ethanol (2 ml) was added to the solution of lactone **4a** (100 mg, 0.21 mmol) in benzene (20 ml) and the mixture was set aside at room temperature for 2 h. TLC analysis showed that only the salt of an acid was present in the solution. pH of the reaction mixture was ad-

justed to 7 with dilute hydrochloric acid. The usual work up afforded the starting lactone **4a** (96 mg, 91%).

Method B (under reflux): A solution of lactone **4a** (100 mg, 0.21 mmol) and potassium hydroxide (106 mg, 1.89 mmol) in a 1:1 benzene–ethanol mixture (40 ml) was refluxed for 2 h. During this period an insoluble salt was formed. After 2 h the reaction mixture was acidified with dilute hydrochloric acid (1:4) and worked up in the usual manner. Crystallisation from chloroform–methanol afforded compound **4b** (82 mg, 90%).

*(19R)-3*β*-Hydroxy-22-nor-21,22-secolup-17-ene-21,28-lactone* (**4b**): M.p. 245–250 °C, $[\alpha]_D$ +49. IR: 3605, 1727, 1605. ^{1}H NMR: 0.78 s, 3 H (CH_3-24), 0.87 s, 3 H (CH_3-27), 0.88 s, 3 H (CH_3-25), 0.92 d, 3 H (CH_3-29, J = 6.8), 0.98 s, 3 H (CH_3-23), 0.99 s, 3 H (CH_3-26), 1.14 d, 3 H (CH_3-30, J = 6.8) (7 × CH_3); 1.90 m, 2 H (H-16α, H-16β); 1.99 d of septets, 1 H (H-20, J_1 = 4.4, J_2 = 6.9); 2.35 dm, 1 H (H-13β, J = 12.8); 2.99 m, 1 H (H-19α); 3.21 m, 1 H (H-3α, ΣJ = 15.9); 4.43 dm, 1 H (H-28a, J = 15.7); 4.74 dm, 1 H (H-28b, J = 15.7). For ^{13}C NMR, see Table II. MS, *m/z* (%): 442 (M^+, 19), 424 (2), 409 (1), 400 (65), 381 (7), 221 (7), 207 (14), 203 (16), 189 (32), 55 (100). For $C_{29}H_{46}O_3$ (442.7) calculated: 78.68% C, 10.47% H; found: 78.77% C, 10.56% H.

18β,19β-Epoxy-21,22-dioxolupane-3β,28-diyl Diacetate (**9**)

A suspension of epoxy ketone **8** (1.5 g, 2.7 mmol, ref.[12]) and selenium dioxide (3.6 g, 32.4 mmol) in a mixture of dioxane (60 ml) and anhydrous acetic acid (60 ml) was refluxed with stirring for 8 h. The separated selenium was filtered off, the reaction mixture was diluted with water and extracted with chloroform. The organic layer was washed with water, filtered on alumina and washed with a saturated solution of sodium hydrogencarbonate to give a neutral pH. After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. Crystallisation from chloroform–heptane mixture afforded diketone **9** (870 mg, 56%), m.p. 247–249 °C, $[\alpha]_D$ +81. IR: 1762, 1750, 1729, 1250. For ^{1}H and ^{13}C NMR, see Tables III and IV. MS, *m/z* (%): 570 (M^+, 6), 554 (2), 542 (5), 527 (5), 510 (5), 498 (71), 483 (8), 470 (82), 455 (10), 437 (19), 429 (77), 307 (8), 277 (44), 263 (11), 249 (11), 203 (29), 189 (66), 55 (100). For $C_{34}H_{50}O_7$ (570.8) calculated: 71.55% C, 8.83% H; found: 71.76% C, 8.95% H. Upon attempted crystallisation from methanol, diketone **9** gave compound **10**.

*18*β*,19*β*-Epoxy-21*β*-hydroxy-21*α*-methoxy-22-oxolupane-3*β*,28-diyl diacetate* (**10**): M.p. 245–247 °C, $[\alpha]_D$ –81. IR: 3530, 1800, 1725, 1250. For ^{1}H and ^{13}C NMR, see Tables III and IV. MS, *m/z* (%): 602 (M^+, 2), 584 (1), 571 (3), 557 (3), 541 (2), 529 (14), 514 (12), 499 (27), 470 (20), 455 (9), 429 (18), 395 (3), 277 (8), 249 (5), 203 (18), 189 (31), 55 (100).

(19*R*)-3β,28-Diacetoxy-18β,19-epoxy-21,22-secolupane-21,22-dioic Acid Anhydride (**11**)

To a solution of diketone **9** (560 mg, 0.98 mmol) in chloroform (5 ml), peracetic acid (32%, 20 ml, 84.2 mmol) was added and the reaction mixture was left standing at room temperature for 14 days. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was successively washed with water, 5% solution of potassium iodide, solution of sodium hydrogensulfite and water. The solution was dried with anhydrous magnesium sulfate and evaporated. The residue was crystallised from a chloroform–heptane mixture to afford epoxy anhydride **11** (420 mg, 73%), m.p. 261–263 °C, $[\alpha]_D$ +25. IR: 1803, 1756, 1727, 1255. For ^{1}H and ^{13}C NMR, see Tables III and IV. MS, *m/z* (%): 586 (M^+, 1), 570 (0.7), 544

(2), 542 (0.8), 526 (39), 511 (13), 483 (29), 468 (13), 323 (3), 217 (10), 203 (19), 189 (100). For $C_{34}H_{50}O_8$ (586.8) calculated: 69.60% C, 8.59% H; found: 69.39% C, 8.47% H.

Hydrolysis of Epoxy Anhydride **11**

Method A (at room temperature, 1 min): A solution of potassium hydroxide in ethanol (19 mg/ml, 3 ml, 1.02 mmol) was added to a solution of epoxy anhydride **11** (200 mg, 0.34 mmol) in benzene (20 ml). After 1 min at room temperature, the mixture was acidified with dilute hydrochloric acid (1:4) and worked up as usual. Crystallisation from a chloroform–heptane mixture afforded diacid **14a** (140 mg, 67%).

(19R)-3β,28-Diacetoxy-18β,19-epoxy-21,22-secolupane-21,22-dioic acid (**14a**): M.p. 153–155 °C, $[\alpha]_D$ +2. IR: 2500–3300, 1742, 1721, 1693, 1256. ^{1}H NMR: 0.85 s, 3 H (CH_3-24), 0.86 s, 3 H (CH_3-23), 0.88 s, 3 H (CH_3-25), 1.04 s, 3 H (CH_3-26), 1.07 d, 3 H (CH_3-29, J = 6.9), 1.22 s, 3 H (CH_3-27), 1.38 d, 3 H (CH_3-30, J = 6.9) (7 × CH_3); 2.05 s, 3 H, 2.13 s, 3 H (2 × OAc); 2.29 septet, 1 H (H-20, J = 6.9); 2.75 bd, 1 H (H-13β, $J \approx 12.0$); 4.31 d, 1 H (H-28a, J = 10.8); 4.48 m, 1 H (H-3α, ΣJ = 16.0); 4.75 d, 1 H (H-28b, J = 10.8). For ^{13}C NMR, see Table VI. MS, *m/z* (%): 544 (M^+ – 60, 5), 526 (20), 511 (9), 500 (2), 483 (15), 470 (8), 457 (47), 429 (5), 397 (6), 341 (9), 249 (11), 217 (9), 203 (26), 189 (100).

Dimethyl (19R)-3β,28-diacetoxy-18β,19-epoxy-21,22-secolupane-21,22-dioate (**14b**, obtained by methylation from diacid **14a**): M.p. 213–215 °C (chloroform–ether), $[\alpha]_D$ +23. IR: 1738, 1729, 1255. For ^{1}H and ^{13}C NMR, see Tables V and VI. MS, *m/z* (%): 632 (M^+, 73), 616 (0.2), 590 (3), 572 (3), 559 (5), 529 (0.2), 517 (13), 497 (3), 469 (3), 457 (23), 415 (7), 369 (7), 355 (3), 249 (18), 203 (45), 189 (100). For $C_{36}H_{56}O_9$ (632.8) calculated: 68.33% C, 8.92% H; found: 68.54% C, 8.77% H.

Method B (under the conditions of partial hydrolysis of the 28-acetoxy group): A solution of potassium hydroxide in ethanol (19 mg/ml, 3 ml, 0.51 mmol) was added to a solution of epoxy anhydride **11** (100 mg, 0.17 mmol) in a 1:1 benzene–ethanol mixture (20 ml). The reaction mixture was left standing at room temperature for 5 h, then it was acidified with dilute hydrochloric acid (1:4) and worked up in the usual manner. Crystallisation from chloroform–ether mixture afforded dilactone **17a** (70 mg, 75%).

(19R)-3β-Acetoxy-19-hydroxy-21,22-secolupane-21,28:22,18α-dilactone (**17a**): M.p. 202–205 °C (decomp.), $[\alpha]_D$ +39. For ^{1}H and ^{13}C NMR, see Table VII. MS, *m/z* (%): 544 (M^+, 3), 500 (1), 484 (13), 469 (5), 457 (36), 441 (7), 413 (3), 397 (5), 341 (2), 249 (7), 217 (9), 203 (11), 189 (100). For $C_{32}H_{48}O_7$ (544.7) calculated: 70.56% C, 8.88% H; found: 70.68% C, 8.93% H. Mother liquors from the crystallisation of **17a** were treated with diazomethane and separated by preparative TLC in a benzene–ether mixture (1:1) to afford methyl ester **15b** (10 mg, 11%) and dimethyl ester **14d** (10 mg, 10%).

(19R)-3β-Acetoxy-18β,19-epoxy-28-hydroxy-21,22-secolupane-21,22-dioic acid 21,28-lactone 22-methyl ester (**15b**): M.p. 286–288 °C (chloroform–ether), $[\alpha]_D$ +53. IR: 1737, 1256. For ^{1}H and ^{13}C NMR, see Tables V and VI. MS, *m/z* (%): 558 (M^+, 1), 516 (0.4), 498 (24), 483 (15), 455 (7), 427 (2), 411 (1), 399 (5), 369 (6), 355 (1), 295 (2), 281 (1), 263 (7), 249 (19), 217 (7), 203 (17), 189 (100). For $C_{33}H_{50}O_7$ (558.8) calculated: 70.94% C, 9.02% H; found: 70.70% C, 9.17% H. Methyl ester **15b** was also obtained by the treatment of dilactone **17a** with ethereal solution of diazomethane.

Dimethyl (19R)-3β-acetoxy-18β,19-epoxy-28-hydroxy-21,22-secolupane-21,22-dioate (**14d**): M.p. 290–292 °C (chloroform–ether), $[\alpha]_D$ +30. IR: 3588, 1728, 1437, 1258. ^{1}H NMR: 0.84 s, 3 H (CH_3-24), 0.86 s, 3 H (CH_3-23), 0.88 s, 3 H (CH_3-25), 0.95 d, 3 H (CH_3-29, J = 7.0),

1.06 s, 3 H (CH_3-26), 1.23 s, 3 H (CH_3-27), 1.25 d, 3 H (CH_3-30, J = 7.0) (7 × CH_3); 2.05 s, 3 H (OAc); 2.41 septet, 1 H (H-20, J = 7.0); 2.64 dd, 1 H (H-13β, J_1 = 12.6, J_2 = 2.7); 3.61 s, 3 H, 3.64 s, 3 H (2 × OCH_3); 3.79 dd, 1 H (H-28a, J_1 = 11.4, J_2 = 8.1); 3.93 dd, 1 H (H-28b, J_1 = 11.4, J_2 = 5.4); 4.47 dd, 1 H (H-3α, J_1 = 10.5, J_2 = 5.7). For ^{13}C NMR, see Table VI. MS, *m/z* (%): 590 (M^+, 23), 559 (2), 531 (3), 513 (2), 498 (5), 486 (5), 475 (17), 469 (13), 457 (3), 445 (21), 415 (14), 399 (7), 369 (4), 339 (10), 249 (11), 203 (41), 189 (75), 55 (100). Dimethyl ester **14d** was acetylated to dimethyl ester diacetate **14b**, identical with the sample obtained using method *A*.

Method C (in a boiling benzene–ethanol mixture): Epoxy anhydride **11** (110 mg, 0.19 mmol) was added to a 2.5% solution (10 ml) of potassium hydroxide in a benzene–ethanol mixture (1:1, 20 ml) and the solution was refluxed for 2 h. During this period a significant portion of insoluble compounds separated which could not be dissolved by addition of ethanol. After usual work up dilactone **17b** (73 mg, 78%) was obtained by crystallisation from chloroform–heptane mixture. As byproducts, dilactone **17a**, unsaturated lactone **13b** and its 3-acetate **13a** were identified by TLC.

(19R)-3β,19-Dihydroxy-21,22-secolupane-21,28:22,18a-dilactone (**17b**): M.p. 167–171 °C (decomp.) (chloroform–heptane), $[\alpha]_D$ +30. ^{1}H NMR: 0.77 s, 3 H (CH_3-24), 0.86 s, 3 H (CH_3-25), 0.96 s, 3 H (CH_3-26), 0.97 s, 6 H (CH_3-23, CH_3-27), 1.02 d, 3 H (CH_3-29, J = 6.8), 1.17 d, 3 H (CH_3-30, J = 6.8) (7 × CH_3); 1.92 dq, 1 H (H-12β, J_1 = 13.0, 3 × J_2 = 2.4); 2.13 dd, 1 H (H-13β, J_1 = 11.2, J_2 = 2.4); 2.28 td, 1 H (H-16α, 2 × J_1 = 14.4, J_2 = 6.4); 2.31 septet, 1 H (H-20, 6 × J = 6.8); 3.21 m, 1 H (H-3α, ΣJ = 16.0); 3.50 s, 1 H (OH); 4.38 d, 1 H (H-28β, J = 11.6); 4.62 d, 1 H (H-28α, J = 11.6). For ^{13}C NMR, see Table VI. MS, *m/z* (%): 502 (M^+, 0.9), 484 (2), 469 (0.6), 458 (2), 441 (2), 415 (100), 397 (6), 381 (1), 335 (1), 313 (1), 217 (7), 207 (35), 189 (35), 135 (68). By treatment with ethereal solution of diazomethane dilactone **17b** was obtained methyl ester **15d**.

(19R)-18β,19-epoxy-3β,28-dihydroxy-21,22-secolupane-21,22-dioic acid 21,28-lactone 22-methyl ester (**15d**): M.p. 259–261 °C (methanol), $[\alpha]_D$ +37. IR (CCl_4): 3631, 1756, 1745, 1737 sh. ^{1}H NMR: 0.77 s, 3 H (CH_3-24), 0.84 s, 3 H (CH_3-25), 0.87 s, 3 H (CH_3-27), 0.97 s, 3 H (CH_3-23), 0.98 s, 3 H (CH_3-26), 1.29 d, 3 H (CH_3-30, J = 6.9), 1.40 d, 3 H (CH_3-29, J = 6.9) (7 × CH_3); 1.77 septet, 1 H (H-20, J = 6.9); 1.90 dm, 1 H (H-12β, J = 11.1); 2.16 dd, 1 H (H-13β, J_1 = 12.8, J_2 = 2.1); 2.32 m, 1 H (H-16α, ΣJ = 34.3); 3.18 m, 1 H (H-3α,ΣJ = 16.2); 3.75 s, 3 H (OCH_3); 3.86 d, 1 H (H-28a, J = 10.4); 4.26 d, 1 H (H-28b, J = 10.4). For ^{13}C NMR, see Table VI. MS, *m/z* (%): 516 (M^+, 3), 498 (12), 483 (8), 455 (3), 442 (1), 427 (5), 415 (6), 399 (2), 369 (5), 295 (2), 217 (7), 207 (86), 189 (77), 55 (100).

Method D (in aqueous dioxane): A solution of epoxy anhydride **11** (50 mg, 0.08 mmol) and potassium hydroxide (0.1 g, 2 mmol) in a 1:1 mixture of dioxane and water (4 ml) was refluxed for 3 h. After the usual work up and purification by preparative TLC in a chloroform–ethyl acetate mixture (5:1), compound **13b** was obtained (28 mg, 77%).

(19R)-3β-Hydroxy-21,28-dinor-19,21-secolup-17-ene-22,19-lactone (**13b**): M.p. 260–266 °C (ether), $[\alpha]_D$ +44. IR: 3617, 1742, 1670. For ^{1}H and ^{13}C NMR, see Tables V and IV. MS, *m/z* (%): 428 (M^+, 26), 410 (22), 395 (19), 386 (2), 367 (7), 289 (7), 275 (29), 261 (5), 247 (11), 220 (23), 207 (100), 193 (74), 189 (52). For $C_{28}H_{44}O_3$ (428.7) calculated: 78.46% C, 10.35% H; found: 78.23% C, 10.20% H. The more polar fraction (≈10 mg) from chromatography was treated with diazomethane to give a mixture of four compounds. TLC analysis showed that the main product was ester **15b**. The same products were obtained when the hydrolysis of epoxy anhydride **11** with potassium hydroxide was performed in a mixture benzene–ethanol–water (2:5:1) under reflux for 3 h.

(19R)-3β-Acetoxy-21,28-dinor-19,21-secolup-17-ene-22,19-lactone (**13a**, obtained from lactone **13b**): M.p. 263–266 °C (chloroform–heptane), $[\alpha]_D$ +44. IR: 1741, 1722, 1669, 1254. ^{1}H NMR: 0.67 d, 3 H (CH_3-29, *J* = 7.0), 0.86 s, 3 H (CH_3-24), 0.87 s, 3 H (CH_3-23), 0.88 s, 3 H (CH_3-27), 0.91 s, 3 H (CH_3-25), 1.02 s, 3 H (CH_3-26), 1.17 d, 3 H (CH_3-30, *J* = 7.0) (7 × CH_3); 2.05 s, 3 H (OAc); 2.07 septet d, 1 H (H-20, J_1 = 7.0, J_2 = 2.1); 2.13 m, 1 H (H-16α); 2.31 dm, 1 H (H-16β, *J* = 18.1); 2.46 dm, 1 H (H-13β, *J* = 12.5); 4.48 m, 1 H (H-3α, Σ*J* = 16.2); 4.72 m, 1 H (H-19α). For ^{13}C NMR, see Table IV. MS, *m/z* (%): 470 (M^+, 3), 455 (0.8), 428 (7), 426 (2), 410 (63), 395 (35), 367 (17), 289 (8), 275 (14), 249 (8), 207 (55), 189 (100), 55 (100).

Method E (in ethylene glycol): A mixture of epoxy anhydride **11** (500 mg, 0.85 mmol), potassium hydroxide (2 g, 36 mmol) and ethylene glycol (20 ml) was refluxed for 3 h. The reaction mixture was worked up in the usual manner and the residue was extracted with boiling ether (3 × 7 ml). The insoluble residue was identified as acid **12c** (160 mg, 42%).

3β-Hydroxy-19-oxo-21,28-dinor-19,21-secolupan-22-oic acid (**12c**): M.p. 248–250 °C (chloroform–heptane). MS, *m/z* (%): 446 (M^+, 6), 428 (1), 403 (8), 384 (0.2), 375 (0.1), 357 (6), 229 (0.8), 217 (1), 207 (20), 189 (17), 71 (100). For $C_{28}H_{46}O_4$ (446.7) calculated: 75.29% C, 10.38% H; found: 75.38% C, 10.49% H.

3β-Acetoxy-19-oxo-21,28-dinor-19,21-secolupan-22-oic acid (**12a**, obtained from acid **12c**): M.p. 214–217 °C (heptane), $[\alpha]_D$ +37. IR: 3507, 2600–3300, 1741, 1724, 1712, 1256. ^{1}H NMR: 0.83 s, 3 H (CH_3-24), 0.84 s, 3 H (CH_3-23), 0.85 s, 3 H (CH_3-25), 0.98 s, 3 H (CH_3-26), 0.99 s, 3 H (CH_3-27), 1.03 d, 6 H (CH_3-29, CH_3-30, *J* = 7.0) (7 × CH_3); 1.75 m, 1 H (H-13β); 1.87 dq, 1 H (H-16β, J_1 = 13.0, 3 × J_2 = 3.5); 2.04 s, 3 H (OAc); 2.57 septet, 1 H (H-20, *J* = 7.0); 2.58 ddd, 1 H (H-17β, J_1 = 13.4, J_2 = 10.5, J_3 = 4.0); 2.89 t, 1 H (H-18α, 2 × *J* = 11.0); 4.47 m, 1 H (H-3α, Σ*J* = 16.2). For ^{13}C NMR, see Table IV. MS, *m/z* (%): 488 (M^+, 6), 445 (4), 444 (3), 428 (2), 357 (12), 249 (1), 217 (1), 203 (5), 189 (23), 71 (100). Ethereal extract (180 mg) after isolation of acid **12c** was treated with diazomethane and the product was purified by preparative TLC in a light petroleum–ether mixture (1:5) to afford methyl ester **12d** (110 mg, 28%).

Methyl 3β-hydroxy-19-oxo-21,28-dinor-19,21-secolupan-22-oate (**12d**): M.p. 199–203 °C (chloroform–heptane), $[\alpha]_D$ +27. IR: 3615, 1727, 1703, 1603, 1438. ^{1}H NMR: 0.76 s, 3 H (CH_3-24), 0.83 s, 3 H (CH_3-25), 0.97 s, 3 H (CH_3-23), 0.99 s, 3 H (CH_3-26), 1.01 s, 3 H (CH_3-27), 1.02 d, 3 H (CH_3-29, *J* = 7.0), 1.03 d, 3 H (CH_3-30, *J* = 7.0) (7 × CH_3); 2.54 septet, 1 H (H-20, *J* = 7.0); 2.55 ddd, 1 H (H-17β, J_1 = 12.8, J_2 = 11.2, J_3 = 4.3); 2.90 t, 1 H (H-18α, 2 × *J* = 11.1); 3.19 m, 1 H (H-3α, Σ*J* = 16.0); 3.59 s, 3 H (OCH_3). For ^{13}C NMR, see Table IV. MS, *m/z* (%): 460 (M^+, 12), 442 (1), 428 (1), 417 (20), 389 (1), 371 (14), 339 (0.8), 311 (1), 289 (0.6), 217 (3), 207 (14), 189 (3), 71 (100). For $C_{29}H_{48}O_4$ (460.7) calculated: 75.61% C, 10.50% H; found: 75.83% C, 10.41% H.

Methyl 3β-acetoxy-19-oxo-21,28-dinor-19,21-secolupan-22-oate (**12b**): M.p. 195–197 °C (chloroform–heptane) and after resolidification m.p. 205–206 °C, $[\alpha]_D$ +35. IR: 1726, 1438, 1257. For ^{1}H and ^{13}C NMR, see Tables III and IV. MS, *m/z* (%): 502 (M^+, 20), 471 (2), 459 (48), 442 (5), 427 (2), 411 (2), 399 (5).

Method F (acid catalyzed hydrolysis): Anhydride **11** (100 mg, 0.17 mmol) was refluxed with hydrochloric acid (35%, 0.5 ml, 5.66 mmol) in a 1:1 mixture of chloroform and methanol (4 ml) for 4 h. After the usual work up, the residue was extracted with boiling ether (2 × 5 ml). The insoluble fraction was dilactone **17b** (68 mg, 80%), m.p. 170–171 °C (decomp.), identical with the sample obtained from hydrolysis of epoxy anhydride **11** using method *C*.

Hydrolysis of Dilactone **17a**

Method A (alkaline hydrolysis): A solution of dilactone **17a** (30 mg, 0.5 mmol) and potassium hydroxide (0.2 g, 4 mmol) in a mixture of benzene (2 ml) and ethanol (5 ml) was refluxed for 3 h. An insoluble gel that formed in the reaction mixture, was dissolved by addition of water (1 ml). The reaction mixture was worked up in the usual manner and products were separated by preparative TLC (benzene–ether 5:1). Lactone **13b** (16 mg, 67%), m.p. 264–268 °C (ether) was obtained, and found to be identical with the sample obtained from anhydride **11** using method *D*.

Method B (acid catalyzed deacetylation): A solution of dilactone **17a** (30 mg, 0.5 mmol) in a mixture of chloroform (1 ml), methanol (1 ml) and hydrochloric acid (35%, 0.3 ml, 3.40 mmol) was refluxed for 4 h. After usual work up the residue was extracted with boiling ether (3 × 3 ml) and the insoluble fraction was crystallised from a chloroform–heptane mixture. Dilactone **17b** (18 mg, 64%) obtained has m.p. 167–169 °C (decomp.), $[\alpha]_D$ +30 and was identical with the sample obtained from anhydride **11** using method *C*.

Decarboxylation of Dilactone **17a**

Dilactone **17a** (70 mg, 0.13 mmol) in triethylene glycol (2 ml) was heated at 210–220 °C for 5 min. After the usual work up and crystallisation from a chloroform–ether mixture, compound **16a** was obtained (42 mg, 65%).

(19R)-3β-Acetoxy-19-hydroxy-22-nor-21,22-secolup-17-ene-21,28-lactone (**16a**): M.p. 250–251 °C (decomp.), $[\alpha]_D$ +35. IR: 3534, 1723, 1254. For ^{1}H and ^{13}C NMR, see Tables V and VI. MS, *m/z* (%): 500 (M^+, 5), 472 (0.2), 457 (100), 456 (15), 442 (4), 413 (11), 397 (18), 353 (3), 283 (1), 249 (1), 217 (4), 203 (18), 189 (11). For $C_{31}H_{48}O_5$ (500.7) calculated: 74.36% C, 9.66% H; found: 74.47% C, 9.82 % H. Lactone **16a** was hydrolyzed under the same conditions as lactone **4a** in method *B* to give compound **16b**.

(19R)-3β,19-Dihydroxy-22-nor-21,22-secolup-17-ene-21,28-lactone (**16b**): M.p. 247–250 °C (chloroform–heptane), $[\alpha]_D$ +28. IR: 3614, 3521, 1723, 1603. ^{1}H NMR: 0.78 s, 3 H (CH_3-24), 0.87 s, 3 H (CH_3-25), 0.90 d, 3 H (CH_3-30, J = 7.0), 0.97 d, 3 H (CH_3-29, J = 7.0), 0.98 s, 6 H (CH_3-23, CH_3-27), 1.00 s, 3 H (CH_3-26) (7 × CH_3); 2.08 m, 1 H (H-16α); 2.24 septet, 1 H (H-20, J = 7.0); 2.55 m, 2 H (H-12β, H-13β); 3.21 dd, 1 H (H-3α, J_1 = 11.3, J_2 = 5.0); 3.60 s, 1 H (OH); 4.45 dd, 1 H (H-28a, J_1 = 15.7, J_2 = 2.1); 4.81 dd, 1 H (H-28b, J_1 = 15.7, J_2 = 2.6). For ^{13}C NMR, see Table VI. MS, *m/z* (%): 458 (M^+, 2), 442 (0.1), 425 (0.6), 414 (100), 397 (6), 371 (6), 341 (1), 323 (1), 269 (1), 217 (3), 203 (8), 189 (14), 135 (56).

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