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# SYNTHESIS OF DITERPENE ANALOGUES OF CARDENOLIDES

Arturo San Feliciano*, Manuel Medarde, Esther Caballero, Belén Hebrero and Fernando Tomé.
Department of Organic Chemistry. Facultad de Farmacia. 37007. Salamanca. Spain.

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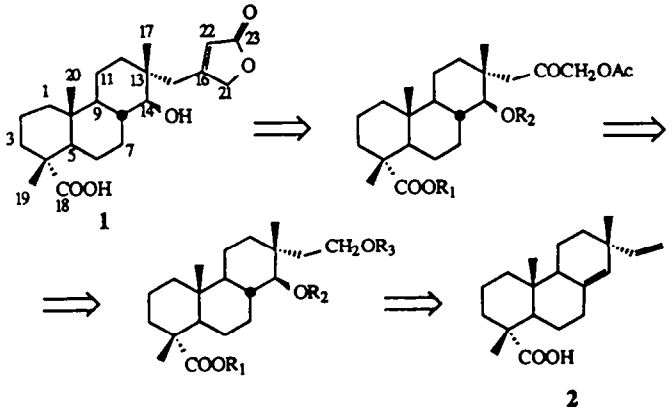
Abstract: The synthesis of diterpene analogues of cardenolides from sandaracopimaric acid has been achieved. Funtionalization in $C_{14}$ and $C_{16}$ was carried out by hydroboration-oxidation and the formation of the butenolide ring was conducted through a Reformatsky-type reaction.

The search for new inotropic analogues of cardenolides receives justification in the need for obtaining substances with a better therapeutic index and in establishing the structural requirements for a positive interaction with the inotropic receptor of cardiac glycosides[1,2,3].

With these aims in mind, we have developed a line of research directed towards obtaining compounds that maintain, on different structural residues, a butenolide and a hydroxyl group in an arrangement similar to that of the cardiac genins[4]. This situation can be achieved on a diterpene skeleton such as isopimarane, which shows a close structural relationship with the steroid system.

In the present work we describe the synthesis of the lactone **1** from sandaracopimaric acid **2**, a compound that can be obtained from several specia of the families Cupresaceae and Pinaceae[5].

In the retrosynthetic study (scheme I), we planned the construction of the butenolide ring from an acetoxymethylketone grouping, which can be obtained from a carboxyl group on $C_{16}$. The introduction of this group and that of the hydroxyl group at position $C_{14\beta}$ can be carried out by successive funtionalization of positions 16 and 14, through selective hydroboration-oxidation of sandaracopimaric acid, in the sequence already described by us[6].

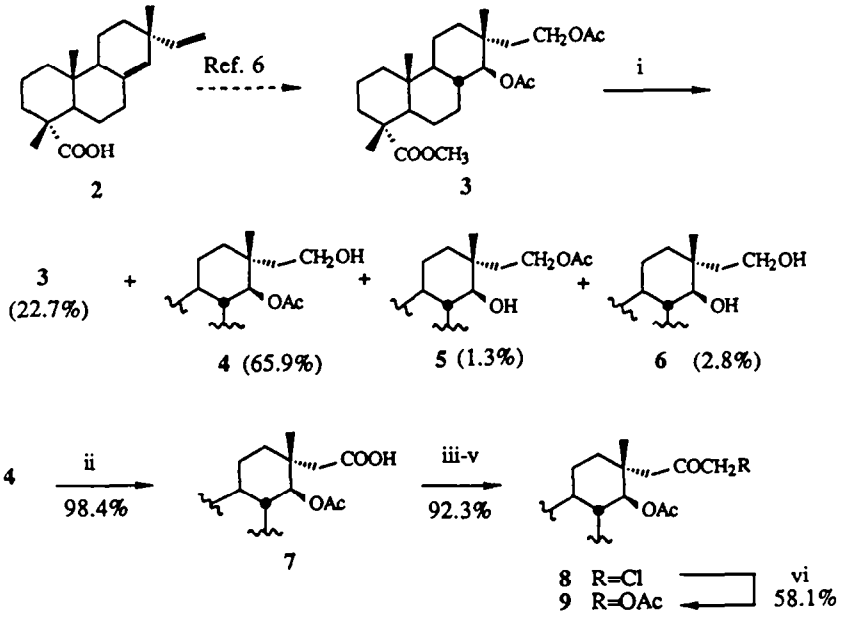



Scheme I

## RESULTS AND DISCUSSION

The synthesis of compound **1** was carried out as depicted in schemes II, III and IV, starting with the conversion of sandaracopimaric acid (**2**) into the ester diacetate **3**[6].

Deacetylation of **3** at $C_{16}$ was carried out by selective saponification, taking into account the easier accessibility of the acetate on $C_{16}$ with respect to the acetate on $C_{14}$. Thus, by treatment with $NaHCO_3$-$H_2O$/ MeOH (1:3) over 40 h at room temperature, a mixture of products was obtained with methyl 14ß-acetoxy-16-hydroxy-13-*epi*-pimaran-18-oate (**4**) as the expected major component. Using other proportions of $NaHCO_3$-$H_2O$/ MeOH (1:5 or 1:2) and using longer reaction times a smaller yield of **4** was obtained. The minor products **5** and **6**, once acetylated and mixed with **3**, were subjected several times to treatment with base leading to a 93% total yield in compound **4** (scheme II).

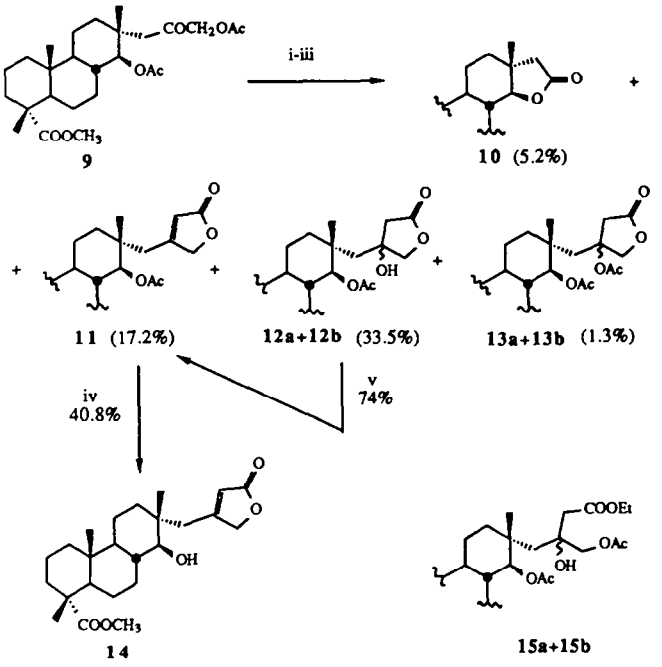



i. $NaHCO_3$-$H_2O$/MeOH (1:3); ii. Jones; iii. $SOCl_2$; iv. $CH_2N_2$; v. HCl(g); vi. $NaOAc/Ac_2O$

Scheme II

The oxidation of **4** with Jones reagent ($CrO_3/H_2SO_4$) led to the acetoxyacid **7**, from which the side chain was lengthened by one carbon atom. The transformation of **7** into its acid chloride followed by treatment with diazomethane afforded the derived diazoketone, which was transformed into the chloromethylketone **8** by reaction with HCl (g)[7]. Substitution of the chloride by acetate led to the acetoxyketone **9**[8] (scheme II).

To construct the butenolide, the Horner-Emmons reaction[9] was attempted but discarded since this reaction carried out with triethyl phosphonoacetate and substrates analogous to the α-acetoxyketone **9** led to mixtures of *E* and *Z* isomers (7:3), with a predominance of the *E* isomer, which did not lactonize under either acid or basic conditions. In order to avoid this problem, we performed a Reformatsky-type reaction on **9** (scheme III). Thus, treatment with ethyl bromoacetate and Zinc[8,10] afforded a complex product which after basic treatment and later acetylation led to the following products: **10** (5.2%), **11** (17.2%), **12a+12b** (33.5%) and **13a+13b** (1.3%).




i. Reformatsky; ii. $NaHCO_3$-$H_2O$/MeOH; iii. $Ac_2O$/Pyr; iv. concentrated HCl/$Et_2O$/EtOH; v. $SOCl_2$/Pyr

Scheme III

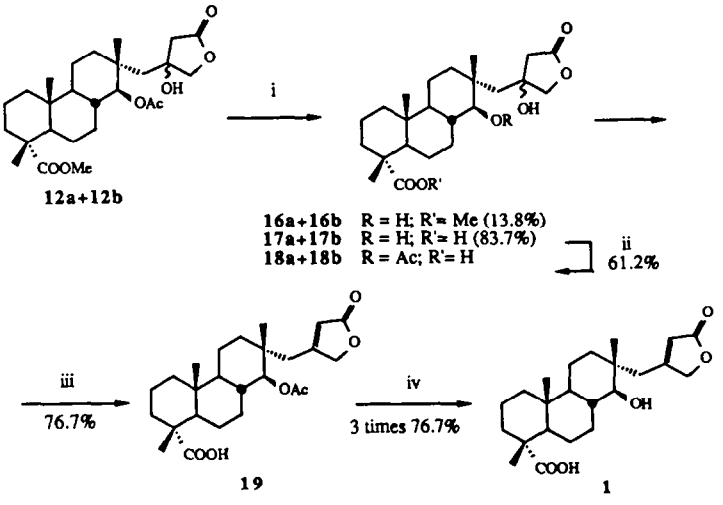
The γ-lactone **10** is a compound resulting from the degradation of the acetoxymethylketone grouping[11] to the carboxylic acid and lactonization at position 14. **11** is one of the expected products in which it was possible to observe the spectroscopic characteristics of the butenolide system (IR: 1790, 1755 and 1640 $cm^{-1}$; $^1H$ NMR: 5.90 (1H, *brs*) and 4.72 (2H, *m*) ppm and $^{13}C$ NMR: 74.8, 118.9, 166.4 and 173.6 ppm).

Selective hydrolysis of the $C_{14}$-acetate of **11** in acid medium[12] was produced without affecting the carbomethoxy group at $C_{18}$ nor the butenolide, to give a mixture of **14** and **11**. After chromatographic separation, the recovered portion of **11** was subjected to several hydrolisis-separation processes, producing an almost quantitative transformation into **14**. The best yields were obtained with ether/ethanol/concentrated hydrochloric acid at a proportion of 1:1:0.6. Substances **12a+12b** and **13a+13b** are mixtures of epimers at $C_{16}$ that differ in some signals of their NMR spectra (Tables III and IV).

When the product of the Reformatsky reaction was not subjected to any basic treatment, component separation proved to be more difficult, because apart from producing the above mentioned **10**, **11** and **12a+12b**, compounds **15a+15b** were also present in the reaction product. Saponification of this mixture yielded **12a+12b** and under the same conditions **13a+13b** was converted into the butenolide **11**, which accounts for the low percentage isolated of **13a+13b** and the absence of **15a+15b** in the Reformatsky reaction described above. Another reaction carried out to increase the butenolide yield was the dehydration of **12a+12b** with $SOCl_2$.

The attempts to carry out the hydrolysis of the methyl ester on $C_{18}$ in the presence of the butenolide on $C_{15}$ were first made with HOAc/quinoline, because the hydrolysis of axial and equatorial esters has been described under these conditions[13] and in our hands it had been effective on methyl sandaracopimarate, and secondly with KOH/t-BuOH. In both cases, the butenolide was degraded in a similar fashion as the cardiac glycosides[14].

As a consequence, the synthesis of **1** was performed from **12a+12b**. Treatment of **12a+12b** with saturated KOH(*t*-BuOH) led to mixtures of epimers **16a+16b** and **17a+17b**. The mixture of acetylated epimers **18a+18b** was dehydrated to **19**, whose hydrolysis in acid medium occurred in a similar way to that described for **11**, yielding a mixture of the final product **1** and of **19** (scheme IV).




i.KOH/ *t*-BuOH; ii. $Ac_2O$/Pyr; iii. $SOCl_2$/Pyr; iv. concentrated HCl/$Et_2O$/EtOH

Scheme IV

The structure of compounds **1-19** was established by means of their spectroscopic properties[15]. Compounds **1** and **14** are currently being studied regarding their inotropic activity and the results will be published elsewhere.

TABLE I. $^1$H NMR data (200MHz) for compounds 1, 3-11, 14 and 19.

| H | 1* | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 14 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 2.97 *d* | 4.50 *d* | 4.50 *d* | 2.94 *d* | 2.95 *d* | 4.56 *d* | 4.56 *d* | 4.53 *d* | 3.51 *d* | 4.52 *d* | 2.88 *d* | 4.53 *d* |
| | (9.5) | (10.1) | (10.1) | (9.7) | (9.8) | (10.2) | (10.2) | (9.7) | (11.1) | (10.0) | (9.7) | (10.0) |
| 15 | 2.69 *d* | | | | | 2.21 *d* | 2.40 *s* | 2.23 *s* | 2.27 *s* | 2.30 *d* | 2.53 *d* | 2.31 *d* |
| | (13.2) | | | | | (13.7) | | | | (13.8) | (13.5) | (13.8) |
| 15 | 2.49 *d* | | | | | 2.13 *d* | | | | 2.23 *d* | 2.41 *d* | 2.22 *d* |
| | (13.2) | | | | | (13.7) | | | | (13.8) | (13.5) | (13 8) |
| 16 | | 4.09 *t* | 3.67 *m* | 4.19 *t* | 3.69 *m* | | | | | | | |
| | | (7.6) | | (7.4) | | | | | | | | |
| 17 | 1.06 *s* | 0.98 *s* | 0.93 *s* | 0.91 *s* | 0.88 *s* | 1.07 *s* | 1.07 *s* | 1.07 *s* | 0.98 *s* | 1 00 *s* | 0.94 *s* | 1.00 *s* |
| 19 | 1.39 *s* | 1.16 *s* | 1.15 *s* | 1.19 *s* | 1.17 *s* | 1.16 *s* | 1.17 *s* | 1.16 *s* | 1.18 *s* | 1.16 *s* | 1.17 *s* | 1.16 *s* |
| 20 | 0.90 *s* | 0.95 *s* | 0.88 *s* | 0.90 *s* | 0.88 *s* | 0.98 *s* | 0.89 *s* | 0.88 *s* | 0.95 *s* | 0.89 *s* | 0.88 *s* | 0.90 *s* |
| 21 | 4.89 *s* | | | | | | | | | 4.72 *m* | 4.77 *d* | 4.73 *m* |
| | | | | | | | | | | | (1.9) | |
| 22 | 6.06 *s* | | | | | | | | | 5.90*brs* | 5.86*brs* | 5.91*brs* |
| OMe | | 3 62 *s* | 3.62 *s* | 3.66 *s* | 3.64 *s* | 3.63 *s* | 3.62 *s* | 3.62 *s* | 3.65 *s* | 3.63 *s* | 3.65 *s* | |
| OAc | | 2.06 *s* | 2.06 *s* | 2.05 *s* | | 2.07 *s* | 2.06 *s* | 2.06 *s* | | 2.08 *s* | | 2.08 *s* |
| | | 2.01 *s* | | | | | 4.03 *s* | 2.14 *s* | | | | |
| | | | | | | | | 4.55 *s* | | | | |

* Pyr
$CDCl_3$. δ (ppm), from internal TMS. J Hz.

TABLE II. $^{13}$C NMR data (50.3 MHz) for compounds 1, 3-11, 14 and 19.

| C | 1* | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 14 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 37.8 | 38.2 | 38.2 | 38.2 | 38.2 | 38.1 | 38.2 | 38.1 | 38.0 | 38.2 | 38.2 | 38 2 |
| 2 | 18.8 | 18.1 | 18.1 | 18.1 | 18.1 | 18.1 | 18.0 | 18.0 | 18.1 | 18.1 | 18.1 | 18 0 |
| 3 | 35.9 | 36.8 | 36.7 | 36.9 | 36.2 | 36.7 | 36.4 | 36.7 | 37.0 | 36.8 | 36.9 | 36.9 |
| 4 | 47.6 | 47.5 | 47.5 | 47.5 | 47.4 | 47.5 | 47.4 | 47.4 | 47.6 | 47.5 | 47.6 | 47.2 |
| 5 | 49.9 | 49.3 | 49 2 | 49.6 | 49.6 | 49.2 | 49.1 | 49.1 | 51.0 | 49.2 | 49.5 | 49 0 |
| 6 | 24.5 | 23.6 | 23.8 | 23.9 | 24.0 | 23.6 | 23.5 | 23.5 | 23.4 | 23.6 | 23.8 | 23 8 |
| 7 | 31.8 | 30.3 | 30.4 | 31.0 | 31.1 | 30.2 | 30.2 | 30.2 | 30.6 | 30.3 | 30.8 | 30 4 |
| 8 | 39.3 | 36.5 | 36.6 | 38.2 | 38.0 | 36.7 | 36.1 | 36.4 | 34.2 | 37.0 | 38.8 | 37.1 |
| 9 | 54.7 | 54.2 | 54.2 | 54.4 | 54.5 | 54.0 | 53.9 | 54.0 | 54.5 | 54.0 | 54.2 | 54.1 |
| 10 | 36.5 | 36.2 | 36.2 | 35.6 | 36.9 | 36.2 | 36.6 | 36.1 | 36.6 | 36.2 | 36.3 | 36.2 |
| 11 | 19.9 | 19.2 | 19.2 | 19.3 | 19.4 | 19.2 | 19.0 | 19.0 | 19.6 | 19.2 | 19.5 | 19.2 |
| 12 | 38.7 | 35.0 | 35.0 | 36.2 | 38.2 | 35.0 | 34.7 | 34.6 | 33.6 | 35.5 | 35.8 | 35.5 |
| 13 | 40.0 | 36.8 | 36.9 | 37.3 | 37.7 | 37 6 | 38.0 | 38.1 | 40.9 | 38.6 | 39.4 | 38.6 |
| 14 | 80.4 | 82.6 | 82.8 | 81.5 | 81.5 | 82.6 | 82.4 | 82.7 | 91.5 | 82.4 | 81.1 | 82.6 |
| 15 | 40.6 | 39.3 | 43.5 | 40.2 | 46.5 | 45.5 | 49.1 | 48.7 | 46.2 | 40.1 | 40.4 | 40.1 |
| 16 | 169.3 | 60.8 | 58.6 | 61.4 | 58.3 | 176.8 | 200.6 | 202.2 | 200.8 | 166.4 | 167.8 | 166.5 |
| 17 | 17.9 | 17.5 | 18.1 | 16.9 | 15.8 | 17.0 | 17.2 | 17.0 | 17.5 | 18.1 | 17.5 | 18.0 |
| 18 | 181.4 | 178.9 | 179.0 | 179.2 | 179.4 | 179.0 | 178.8 | 178.8 | 179.1 | 178.9 | 179.2 | 184.5 |
| 19 | 17.5 | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 | 16.6 | 16.6 | 16.6 | 16.7 | 16.7 | 16.5 |
| 20 | 14.8 | 14.4 | 14.4 | 14.5 | 14.5 | 14.1 | 14.3 | 14.3 | 14.7 | 14.5 | 14.6 | 14.5 |
| 21 | 75.4 | | | | | | | | | 74.8 | 75.1 | 74.8 |
| 22 | 116.3 | | | | | | | | | 118.9 | 118.4 | 118.9 |
| 23 | 174.3 | | | | | | | | | 173.6 | 174.0 | 173.8 |
| OMe | | 51,7 | 51.7 | 51.7 | 51.7 | 51.6 | 51.7 | 51.7 | 51.9 | 51.8 | 51.8 | |
| OAc | | 20.8(2) | 20.8 | 21.0 | | 20.8 | 20.7 | 20.7 | | 20.3 | | 20 5 |
| | | 170.8(2) | 171.7 | 170.9 | | 171.0 | 170.9 | 170.9 | | 170.4 | | 171.0 |
| Others | | | | | | | 49.6 | | 20.3 | | | |
| | | | | | | | | 69.1 | | | | |
| | | | | | | | | 169.9 | | | | |

* Pyr
$CDCl_3$. δ (ppm), from internal TMS.

TABLE III. $^1$H NMR data (200MHz) for the pairs of epimeric compounds 12-13, 15-18.

| H | 12a | 12b | 13a | 13b | 15a | 15b | 16a | 16b | 17a | 17b* | 18a | 18b |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 4.89 *d* (9.9) | 4.92 *d* (9.9) | 4.78 *d* (10.9) | 4.69 *d* (10.9) | 4.58 *d* (10.0) | 4.61 *d* (10.0) | 3.12 *d* (9.8) | | 3 19 *d* (9.6) | 4 89 *d* (10.0) | 4.91 *d* (9 8) | |
| 17 | 0.95 *s* | | 1.00 *s* | 1.01 *s* | 1.04 *s* | | 1.00 *s* | 0 95 *s* | 1.20 *s* | 1.16 *s* | 0 96 *s* | |
| 19 | 1.16 *s* | | 1.16 *s* | 1.17 *s* | 1.16 *s* | | 1.18 *s* | | 1.38 *s* | | 1.16 *s* | |
| 20 | 0 89 *s* | | 0 88 *s* | 0.95 *s* | 0.89 *s* | | 0.88 *s* | | 0.89 *s* | 0.85 *s* | 0.90 *s* | |
| 21 | 4.10 *d* (9.8) | 3.90 *d* (9.7) | 4.10 *d* (10.4) | 4.18 *d* (10.6) | 4.00 *d* (11.3) | 3.99 *d* (11.3) | 4.03 *d* (9.7) | 4.23 *d* (11.5) | 4.22 *d* (9.1) | 4.42 *d* (9.1) | 4.12 *d* (9.6) | 3 95 *d* (10.2) |
| 21 | 4.44 *d* (9.8) | 4.06 *d* (9.7) | 4.45 *d* (10.4) | 4.40 *d* (10.6) | 4.16 *d* (11.3) | 4.08 *d* (11.3) | 4.25 *d* (9.7) | 4.38 *d* (11.5) | 4.50 *d* (9.1) | 4.62 *d* (9.1) | 4.46 *d* (9.6) | 4.06 *d* (10 2) |
| 22 | 2.48 *s* | 2.44 *d* (17.2) | 2.68 *d* (17,9) | 2.10 *d* (18.0) | 2.55 *s* | 2.60 *s* | 2.65 *s* | 2.45 *d* (17.9) | 2.97 *s* | 2.85 *s* | 2.47 *d* (17.9) | 2.48 *d* (17.9) |
| 22 | 2.48 *s* | 2.75 *d* (17.2) | 3.00 *d* (17.9) | 3.10 *d* (18.0) | | | 2.65 *s* | 2.60 *d* (17.9) | | | 2.50 *d* (17.9) | 2.68 *d* (17.9) |
| OMe | 3.62 *s* | | 3.62 *s* | | 3.62 *s* | | 3.65 *s* | | | | | |
| OAc | 2.12 *s* | | 2.03 *s*, 2.07 *s* | | 2.07 *s* | | | | | | 2.08 *s* | |
| Others | | | | | 1.28*t* (7.1) | | | | | | | |
| | | | | | 4.16 *c* (7.1) | 4.15 *c* (7.1) | | | | | | |

* Pyr

$CDCl_3$. $\delta$ (ppm), from internal TMS. J Hz.

TABLE IV. $^{13}$C NMR data (50.3 MHz) for the pairs of epimeric compounds 12-13, 15-18.

| C | 12a | 12b | 13a | 13b | 15a | 15b | 16a | 16b | 17a | 17b* | 18a | 18b |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 38.1 | | 38.2 | | 38.2 | | 38.2 | | 38.6 | | 38.0 | |
| 2 | 18.0 | | 18.1 | | 18.1 | | 18.2 | | 18.8 | | 18.0 | |
| 3 | 36.7 | | 36.8 | | 36.6 | | 37.0 | | 37 6 | | 36.9 | |
| 4 | 47.5 | | 47.5 | | 47.6 | | 47.6 | | 47.7 | | 47.2 | |
| 5 | 49.2 | | 49.3 | | 49.3 | | 49.4 | | 49.9 | | 49.0 | |
| 6 | 23.5 | | 23.6 | | 23.7 | | 23.8 | | 24.6 | | 23.6 | |
| 7 | 30.5 | | 30.4 | | 30.6 | | 30.7 | | 31.9 | | 30.6 | |
| 8 | 36.5 | | 36.8 | | 36.6 | | 38.5 | | 39.0 | | 36.6 | |
| 9 | 54.0 | | 53.9 | | 54.2 | | 54.2 | | 54.8 | | 53.9 | |
| 10 | 36.2 | | 36.4 | | 35.8 | | 36.3 | | 36.5 | | 36.2 | |
| 11 | 19.1 | | 19.2 | | 19.3 | | 19.1 | | 19.7 | | 19.2 | |
| 12 | 34.4 | | 36.2 | | 36.2 | | 38.2 | | 39.3 | | 38.0 | |
| 13 | 38.9 | | 38.8 | | 38.9 | | 39.2 | | 40.1 | | 38.9 | |
| 14 | 83.2 | | 83.5 | | 84.0 | | 82.4 | | 82.2 | 82.1 | 83.2 | |
| 15 | 46.3 | 45.1 | 41.3 | | 43.5 | 42.9 | 52.8 | 53.8 | 52.1 | 52.9 | 46.3 | 45.3 |
| 16 | 77.1 | 76.8 | 85.3 | | 73.3 | | 75.7 | 76.4 | 76.5 | 77.1 | 76.4 | 77.0 |
| 17 | 20.2 | | 17.6 | | 18.8 | | 16.7 | | 17.6 | | 21.0 | |
| 18 | 179.0 | | 179.0 | | 179.0 | | 179.3 | | 181.4 | | 184.3 | |
| 19 | 16.6 | | 16.8 | | 16.8 | | 16.7 | | 17.6 | | 16.4 | |
| 20 | 14.4 | | 14.5 | | 14.4 | | 14.6 | | 14.8 | | 14.4 | |
| 21 | 80.2 | 81.0 | 77.1 | 75.0 | 69.5 | 70.1 | 81.1 | 79.9 | 81.5 | 80.7 | 80.2 | 80.6 |
| 22 | 45.7 | 43.9 | 44.3 | 45.0 | 45.7 | 45.1 | 43.8 | 45.0 | 44.7 | 45.5 | 45.8 | 44.3 |
| 23 | 175.1 | | 174.3 | | 179.0 | | 175.2 | | 177.1 | | 175.2 | |
| OMe | 51.8 | | 51.9 | | 51.8 | | 51.9 | | | | | |
| OAc | 21.0 | | 20.7, 22.1 | | 20.8, 20.9 | | | | | | 20.4 | |
| | 172.9 | | 170.4, 171.1 | | 170.4, 171.4 | | | | | | 173.2 | |
| Others | | | | | 14.1, 60.6 | | | | | | | |

* Pyr

$CDCl_3$. $\delta$ (ppm), from internal TMS.

## EXPERIMENTAL

General: The solvents and reagents were purified and dried by standard techniques. Mps are uncorrected. The IR spectra were taken in 4% $CHCl_3$ solution and NMR spectra were obtained in $CDCl_3$ solution (200 MHz for $^1H$, 50.3 MHz for $^{13}C$), unless otherwise stated. Chemical shifts are reported in ppm (δ) downfield from internal TMS. Optical rotations were measured at 20°C on a digital polarimeter. Mass spectra were obtained under electron impact (70 eV) and ultraviolet spectra were obtained in methanol.

Methyl 14ß-acetoxy-16-hydroxy-13-*epi*-pimaran-18-oate (4):

70 ml of saturated $NaHCO_3$ (aq) were added to a stirred solution of **3** (7.4 g, 17 mmol) in 210 ml of methanol and maintained with vigorous stirring for 30 h at 25°C. The mixture was then diluted with water, extracted with EtOAc and washed with brine. After the usual work up the crude product (7.1 g) was chromatographed over silica gel to yield: unreacted **3** (1.7 g, 22.7%; Hexane/EtOAc 6:4); **5** (75 mg, 1.3%; Hexane/EtOAc 6:4); **4** (3.7 g, 65.9%; Hexane/EtOAc 6:4) and **6** (170 mg, 2.8%; EtOAc).

Acetylation of **5** and **6** gave a further amount of diacetate **3**, that was again saponified. After seven times, the partial saponification of **3** yielded 6.2 g of **4** (93%).

**4.** $[\alpha]^{20}(\lambda)$: +8.7° (589), +9.3° (578), +10.5° (546), +19.3° (436), +32.8° (365), c = 1.14% ($CHCl_3$).

IR: 3520, 1740, 1270, 1160, 1040 $cm^{-1}$.

$^1H$-NMR: Table I. $^{13}C$-NMR: Table II.

**Methyl 16-acetoxy-14ß-hydroxy-13-*epi*-pimaran-18-oate (5):**

$[\alpha]^{20}(\lambda)$: -4.0° (589), -4.3° (578), -4.6° (546), -7.0° (436), -9.3° (365), c = 0.93% ($CHCl_3$).

IR: 3500, 1745, 1730, 1250, 1140, 1060 $cm^{-1}$.

$^1H$-NMR: Table I. $^{13}C$-NMR: Table II.

**Methyl 14ß,16-dihydroxy-13-*epi*-pimaran-18-oate (6):**

Mp = 136-137°C. $[\alpha]20(\lambda)$: -16.2° (589), -17.4° (578), -20.2° (546), -31.0° (436), -47.4° (365), c = 0.98% ($CHCl_3$).

IR: 3220, 1720, 1230, 1140, 1100, 1060 $cm^{-1}$.

$^1H$-NMR: Table I. $^{13}C$-NMR: Table II.

14ß-acetoxy-18-methoxy-18-oxo-13-*epi*-pimaran-16-oic acid (7):

A stirred solution of alcohol **4** (6 g, 16.2 mmol) in acetone (160 ml) at 0°C was titrated with Jones reagent ($CrO_3/H_2SO_4$). The mixture was extracted with EtOAc when the orange colour persisted. After the usual work up 6.1 g of **7** (98.4%) were obtained.

**7.** Mp = 176-178°C. $[\alpha]^{20}(\lambda)$: +19.4° (589), +20.6° (578), +23.2° (546), +41.2° (436), +67.3° (365), c = 1.03% ($CHCl_3$).

IR: 3300-2500, 1740, 1720, 1250, 1040 $cm^{-1}$.

$^1H$-NMR: Table I. $^{13}C$-NMR: Table II.

Methyl 16-acetoxymethyl-14ß-hydroxy-16-oxo-13-*epi*-pimaran-18-oate (9):

Acetoxyacid **7** (6 g, 14.7 mmol) was converted into the acylchloride with thionylchloride (25 ml) in dry benzene. An ethereal solution of the acylchloride was added dropwise to an excess of ethereal diazomethane and maintained for 3 h between -5°C and 0°C. Afterwards, a HCl(g) current was bubbled through the reaction mixture for 1 h. By usual work up **8** (6 g, 92.3%) was obtained.

5.9 g (13.4 mmol) of **8**, acetic anhydride (119 ml) and anhydrous sodium acetate (20 g, 217 mmol) were refluxed under $N_2$ for 4 h. After extraction, the organic layer was evaporated and the residue was chromatographed over $SiO_2$ to give **9** (3.6 g, 58.1%).

Methyl **14ß-acetoxy-16-chloromethyl-16-oxo-13-*epi*-pimaran-18-oate (8):**
Mp = 142-144°C. $[\alpha]^{20}(\lambda)$: +22.0° (589), +23.5° (578), +27.3° (546), +53.6° (436), +112.4° (365), c = 1.13% ($CHCl_3$).
IR: 1740, 1730, 1250, 1040, 980, 910, 870 $cm^{-1}$.
$^1$H-NMR: Table I. $^{13}$C-NMR: Table II.
9. Mp = 82-86°C. $[\alpha]^{20}(\lambda)$: +10.2° (589), +10.9° (578), +12.5° (546), +23.1° (436), +43.1° (365), c = 0.98% ($CHCl_3$).
IR: 1745, 1720, 1250, 1170, 1130, 1030 $cm^{-1}$.
$^1$H-NMR: Table I. $^{13}$C-NMR: Table II.

Reformatsky reaction

A- A solution of ethyl bromoacetate (96 ml, 0.86 mol) and α-acetoxyketone **9** (450 mg, 0.96 mmol) in dry benzene was added dropwise, to a stirred mixture of active granulated zinc (450 mg, 6.8 mmol) in dry benzene The mixture was refluxed for 6 h, and the zinc compound was decomposed as usual with dilute HCl (aq). Extraction with EtOAc yielded 450 mg of reaction product. After several saponifications, acetylations and chromatographies, **10** (9.8%), **11** (17.8%), **12a+12b** (22.8%), and **15a+15b** (5.6%) were obtained.
**18-methoxy-18-oxo-13-*epi*-pimaran-14ß,16-olide (10):**
Mp = 191-193°C. $[\alpha]^{20}(\lambda)$: -61.3° (589), -64.5° (578), -73.5° (546), -126.3° (436), c = 1.04% ($CHCl_3$).
IR: 1780, 1720, 1250, 1170, 1070, 1045, 990 $cm^{-1}$.
$^1$H-NMR: Table I. $^{13}$C-NMR: Table II.
**Methyl 14ß-acetoxy-16-carboxymethyliden-16-hydroxymethyl-13-*epi*-pimaran-18-oate γ-lactone (11):**
$[\alpha]^{20}(\lambda)$: +24.9° (589), +26.3° (578), +29.9° (546), +52.4° (436), c = 1.22% ($CHCl_3$).
IR: 1790, 1755, 1725, 1640, 1250, 1180, 1040 $cm^{-1}$.
UV $\lambda_{max}$ nm (ε): 212 (20300).
$^1$H-NMR: Table I. $^{13}$C-NMR: Table II.
**Methyl 14ß-acetoxy-16-carboxymethyl-16-hydroxy-16-hydroxymethyl-13-*epi*-pimaran-18-oate γ-lactone (12a+12b):**
IR: 3380, 1780, 1720, 1250, 1140, 1100, 1050, 1020, 820 $cm^{-1}$.
$^1$H-NMR: Table III. $^{13}$C-NMR: Table IV.
**Methyl 14ß-acetoxy-16-acetoxymethyl-16-ethoxycarbonylmethyl-16-hydroxy-13-*epi*-pimaran-18-oate (15a+15b):**
IR: 3480, 1740, 1720, 1250, 1100, 1030, 970 $cm^{-1}$.
$^1$H-NMR: Table III. $^{13}$C-NMR: Table IV.

B- The reaction was carried out in the conditions described in A with zinc (2.6 g, 39.7 mmol), **9** (2.6 g, 5.6 mmol) and ethyl bromoacetate (35 ml, 314 mmol). The mixture was refluxed under $N_2$ for 6 h and the zinc compound was decomposed as usual with dilute HCl (aq). Extraction with EtOAc yielded 3 g of reaction product. After column chromatography **10** (100 mg, 5.2%) and another complex mixture (2.2 g) were obtained. This latter mixture was stirred in $NaHCO_3$-$H_2O$/MeOH (100/120 ml) for 72 h at 25°C and was extracted with EtOAc to give 1.25 g of reaction product. The aqueous layer was acidified and after extraction yielded 960 mg.

By acetylation and chromatography of both fractions: **11** (430 mg, Hexane/EtOAc 65:35) and **12** (280 mg, Hexane/EtOAc 1:1) were isolated from the neutral fraction and **13** (38 mg, Hexane/EtOAc 6:4) and **12** (590 mg, Hexane/EtOAc 1:1) were obtained from the acid fraction.

Methyl 14ß,16-diacetoxy-16-carboxymethyl-16-hydroxymethyl-13-epi-pimaran-18-oate γ-lactone (13a+13b)
IR: 1785, 1745, 1725, 1250, 1040, 980 $cm^{-1}$.
$^1$H-NMR: Table III. $^{13}$C-NMR: Table IV.

Dehydration of 12a+12b:

A solution of **12a+12b** (45 mg, 0.097 mmol), pyr (1.2 ml) and $SOCl_2$ (0.5 ml) was stirred under $N_2$ for 45 min at 25°C. The solution was diluted with water, extracted with EtOAc and after the usual work up, the crude product was chromatographed (hexane/EtOAc 65:35) to give **11** (32 mg, 74%).

Methyl 16-carboxymethyliden-14ß-hydroxy-16-hydroxymethyl-13-*epi*-pimaran-18-oate γ-lactone (14):

**11** (85 mg, 0.19 mmol) in $Et_2O$/EtOH/concentrated HCl (1:1:0.6) was maintained for 4 days at room temperature and then extracted with EtOAc. By chromatography (hexane/EtOAc 6:4) of the reaction product, unreacted **11** (37.2 mg, 43.4%) and **14** (31.8 mg, 40.8%) were obtained.
**14**. $[\alpha]^{20}(\lambda)$: +8.6° (589), +10.9° (578), +19.1° (546), c = 0.70% ($CHCl_3$).
IR: 3600, 1790, 1720, 1640, 1260, 1110, 1040, 990, 900, 870 $cm^{-1}$.
MS: 404 ($M^+$, 21), 345 (61), 307 (61), 247 (99), 229 (90), 173 (17).
UV $\lambda_{max}$ nm (ε): 217 (5050).
$^1$H-NMR: Table I. $^{13}$C-NMR: Table II.

16-carboxymethyliden-14ß-hydroxy-16-hydroxymethyl-13-*epi*-pimaran-18-oic γ-lactone acid (1):

Saponification of methylester group in $C_{18}$: **12** (250 mg, 0.56 mmol) in saturated KOH(*t*-BuOH) (20 ml) was stirred under $N_2$ at 100°C for 1 h and at 40°C for 12 h. The reaction mixture was extracted with EtOAc to give **16a+16b** (31.4 mg, 13.8%) and the aqueous layer was acidified with 2N HCl (aq) and extracted with EtOAc yielding **17a+17b** (184 mg, 83.7%).

Methyl 16-carboxymethyl-16-hydroxymethyl-14ß,16-dihydroxy-13-*epi*-pimaran-18-oate γ-lactone (16a+16b):
IR: 3600, 3350, 1785, 1720, 1260, 1110, 1050, 1040, 1030, 990 $cm^{-1}$.
$^1$H-NMR: Table III. $^{13}$C-NMR: Table IV.

16-carboxymethyl-16-hydroxymethyl-14ß,16-dihydroxy-13-*epi*-pimaran-18-oic acid γ-lactone (17a+17b):
IR (1% KBr): 3600-2400, 3250, 1785, 1735, 1700, 1100, 1050, 990 $cm^{-1}$.
$^1$H-NMR ($C_5D_5N$). Table III. $^{13}$C-NMR: Table IV.

By acetylation of **17a+17b** (145 mg) and chromatography over deactivated $SiO_2$ (5% $H_2O$), **18a+18b** (98 mg, 61.2%) were isolated.

**18a+18b** (95 mg, 0.19 mmol), pyr (2.4 ml) and $SOCl_2$ (1 ml) were stirred under $N_2$, in the same conditions of dehydration of **12a+12b**, to give **19** (70 mg, 76.7%).

Hydrolysis of **19**: The reaction of **19** (65 mg, 0.15 mmol) under the same conditions employed in the acidic hydrolysis of **11**, yielded unreacted **19** (32 mg, 50%) and **1** (22 mg, 38,1%).

16-carboxymethyliden-14ß-hydroxy-16-hydroxymethyl-13-*epi*-pimaran-18-oic acid γ-lactone (1):
$[\alpha]^{20}(\lambda)$: -3.4° (589), -3.7° (578), -4.1° (546), c = 1.00% (Pyr).
IR (1%KBr): 3600-2700, 3500, 1725, 1695, 1630, 1200, 1100, 1030, 990 $cm^{-1}$.
MS: 390 ($M^+$, 2), 345 (5), 275 (10), 293 (10), 247 (31), 229 (21), 173 (8).
$^1$H-NMR ($C_5D_5N$). Table: III. $^{13}$C-NMR: Table IV.

**14ß-acetoxy-16-carboxymethyl-16-hydroxy-16-hydroxymethyl-13-*epi*-pimaran-18-oic acid γ-lactone (18a+18b):**

IR : 3600-2400, 3420, 1780, 1735, 1700, 1260, 1140, 1125, 1060, 1030, 970 $cm^{-1}$.

$^1$H-NMR: Table III. $^{13}$C-NMR: Table VI.

**14ß-acetoxy-16-carboxymethyliden-16-hydroxymethyl-13-*epi*-pimaran-18-oic acid γ-lactone (19):**

IR: 3500-2400, 3500, 1795, 1750, 1730, 1700, 1650, 1200, 1100 $cm^{-1}$.

$[\alpha]^{20}(\lambda)$: +25.3° (589), +26.2° (578), +30.4° (546), +53.5° (436), c = 0.97% ($CHCl_3$).

UV $\lambda_{max}$ nm (ε): 213 (10617).

$^1$H-NMR: Table I. $^{13}$C-NMR: Table II.

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