Tetrahedron Vol 45, No 14, pp 4497 to 4506, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

PREPARATION OF 4α,8β-DIMETHYL-4β-METHOXYCARBONYL-17A-OXA-D-HOMO-ANDROSTAN-17-ONE, INTERMEDIATE OF INTEREST IN THE SYNTHESIS OF 8β-METHYL-TESTOLACTONE

F. Bermejo González, M. Bordell Martín, A. Fernández Mateos* and R. Rubio González

Dpto. Química Orgánica. Fac. Ciencias Químicas. Plaza de los Caídos 1-5. 37008 Salamanca. Spain.

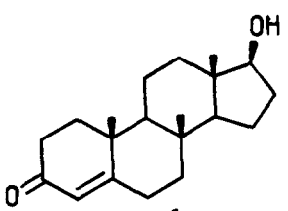
(*Received in UK* 17 *April* 1989)

SUMMARY

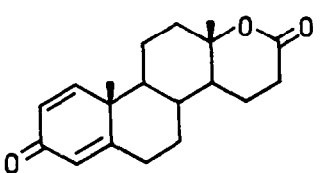
The biomimetic cyclization of the terpenic derivatives 13 and 14 towards the synthesis of 4α,8β-dimethyl-4β-methoxycarbonyl-17a-oxa-D-homo-androstan-17-one 18 is described.

INTRODUCTION

The discovery of the anabolic properties developed by 8β-methyl-17β-hydroxy-4-androsten-3-one 1[1], together with the clinical use found for 17a-oxa-D-homoandrosta-1,4-diene-3,17-dione 2 in causing objective regression in breast cancer of some patients[2] prompted us to develop the synthesis of 8β-methyl-androstanes, intermediates of interest in the preparation of potentially useful therapeutic agents for the treatment of cancer.

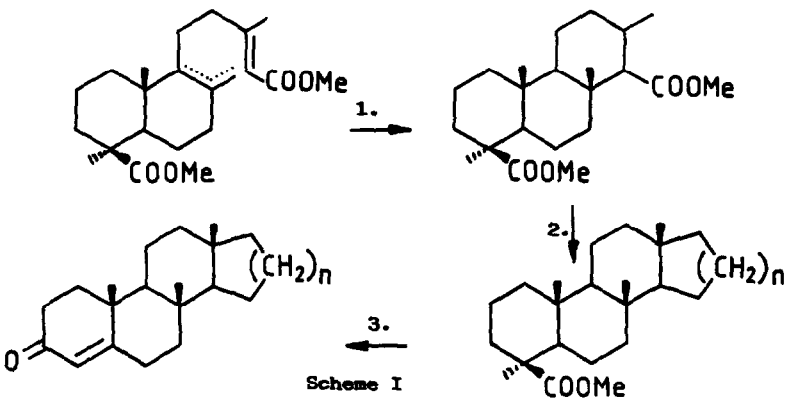


1



2

The transformation of the terpenic derivatives with a labdane backbone 3 and 4 into 8β-methyl steroids requires a three-step synthetic sequence: 1. Ring C formation with concomitant insertion of the angular methyl group at C_8. 2. Ring D construction and 3. Ring A transformations. (Scheme I)



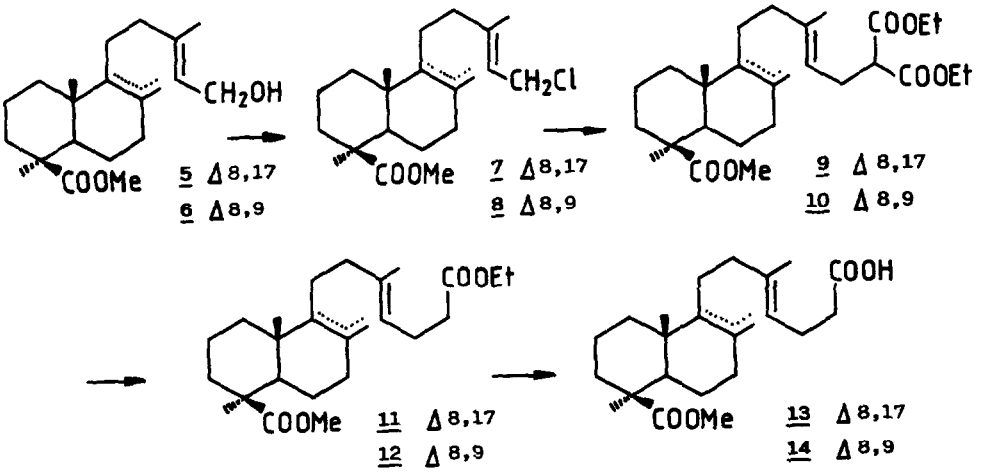
Scheme I

METHODS AND RESULTS

The synthetic strategy that we envisaged for the synthesis of the δ-lactonic intermediate 18 (Fig. 1) found inspiration in the biomimetic cyclizations of a large number of bicyclic analogs[3] and attempts to achieve the two first steps of the above mentioned sequence simultaneously. The olefinic cyclization of the terpenic derivatives 13 and 14 represents a new contribution to the Stork-Eschenmoser postulate[4].

a) Preparation of substrates

Preparation of the olefinic acids 13 and 14, substrates for the cyclization studies was satisfactorily achieved by trivial chemical transformations starting from the methyl isocupresate 5 and its $\Delta^{8,9}$ isomer 6[5] with 50% and 25% overall yields respectively, according to the reaction sequence shown in scheme II.



Scheme II

Transformation of 5 into the halide 7 was achieved by treatment of 5 with tetrachloromethane and triphenyl phosphine at 75ºC (90%)[6].

Condensation of 7 with sodium diethyl-malonate in refluxing ethanol led to the triester 9 with a 70% isolated yield[7].

Decarboxylation of the triester 9 was successfully achieved by treatment of 9 with sodium chloride, dimethyl sulfoxide and water at 80ºC for 20 h. The olefinic diester 11 was isolated by flash chromatography of the crude (80%)[8].

Saponification of 11 with refluxing ethanolic potassium hydroxide was completed after 3 hours. Isolation of the olefinic carboxylic acid was quantitative after acidulation and ether extraction of the saponified extract.

The isomeric diterpenic acid 14 was obtained from 6 by performing the identical transformation sequence affording 13 from 5.

Confirmation of the structures corresponding to the different intermediates was made by conventional spectroscopic methods (see experimental).

b) Cyclization attempts

* Cyclization of carboxylic acid 13

-Treatment of olefinic acid 13 with formic acid (90%) at 90ºC for 45 min. (Table I, entry 1) afforded a neutral fraction (76%) composed of a mixture of lactones 15 (57%), $[\alpha]_D^{20}$= +56.6º (c=1.09, $CHCl_3$) and 18 (20%), $[\alpha]_D^{20}$= +12.2º (c=1.12, $CHCl_3$) which was easily separated by flash chromatography on silicagel (fig. I).

Table I

Entry	Substrate	reaction conditions	Yields (%) 15	16	17	18
1	13	HCOOH (90%) 90ºC, 45 min.	57	--	--	19
2	13	H_2SO_4/AcOH 5ºC, 8 h.	--	58	--	18
3	13	H_3PO_4 (85%) 25ºC, 48 h.	--	34	6	14
4	14	HCOOH (98%) 90ºC, 90 min.	--	43	11	6

The formation of 15 can be accounted for in terms of the protonation of the Δ^{13} double bond followed by nucleophilic attack of the oxygen lone pair at the C-13 cation and isomerization of the $\Delta^{8,17}$ double bond.

Lactone 18 may be formed by a cyclization process initiated by the formation of the C-8 cation and concluded by nucleophilic attack of the carbonylic oxygen at the C-13 cation.

-Treatment of 13 with the acidic mixture H_2SO_4/AcOH 25/1 at 4ºC for 8 h. (table I, entry 2) led to a neutral fraction (76%) of lactones 16 (58%) $[\alpha]_D^{20}$= -67.6º (c=1.0, $CHCl_3$) and 18 (18%) which was fractionated by flash chromatography on silicagel. Lactone 16 was presumably formed by cationic rearrangement of 15 with methyl migration from C_{10} to C_9 and $\Delta^{5,10}$ olefin formation.

-Reaction of 13 with H_3PO_4 (85%) at 25ºC for 48 h. (table I, entry 3) led to a neutral fraction (54%) which was fractionated by flash chromatography. Two of the isolated products had identical spectroscopic properties to the lactones 16 (34%) and 18 (14%). In addition, a new lactone 17, $[\alpha]_D^{20}$= +16.4º (c=2.8, $CHCl_3$) was also isolated (6%). The new lactone may be formed by nucleophilic attack of the Δ^{13} double bond at the C-8 cation followed by hydride migration from C-14 to C-13 and further lactonization.

* Cyclization of carboxylic acid 14

Treatment of carboxylic acid 14 with HCOOH (98%) at 90ºC for 90 min. (table I, entry 4) led to the isolation of a neutral fraction representing

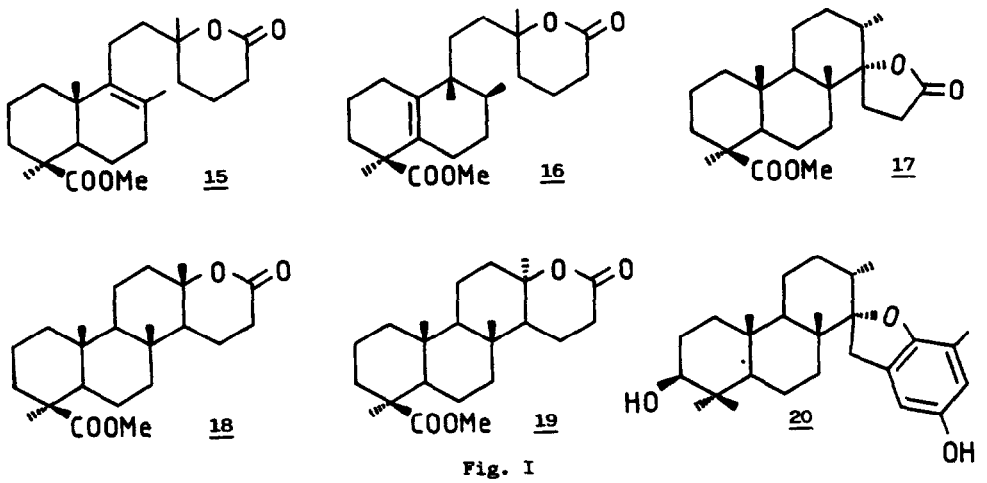


Fig. I

60% of the crude material.

Flash chromatography of this mixture led to the isolation of three lactones: 16 (43%), 17 (11%) and 18 (6%). The lower yield obtained for lactone 18 may be satisfactorily explained by its isomerization to 17, probably due to the greater thermodynamic stability of the γ-lactonic ring.

c) Structural assignments

-The presence of the lactone moiety in 15 was substantiated by the existence of an ir absorption at ν : 1730 cm^{-1} together with the presence of a signal at δ : 84.36 ppm in the ^{13}C-nmr spectrum corresponding to the quaternary carbon C-13 (Table II)[9].

-The rearranged lactone 16 also exhibited an ir absorption at ν : 1720 cm^{-1}, confirming the formation of a δ-lactone. It also showed four methyl signals in the ^{1}H-nmr spectrum at δ: 0.85 (d); 0.89 (s); 1.25 (s) and 1.35 (s) ppm. and a tetrasubstituted double bond in the ^{13}C-nmr spectrum, as shown by the signals centered at δ : 135.40 (C-5) and δ : 132.00 (C-10) ppm (Table III). The base peak of 16 in the mass spectrum appeared at m/z ; 235 and corresponded to the loss of of the side chain[10].

The spectroscopic properties obtained for the δ-lactone 18 (table III) are very similar to those exhibited by testololactone[11] and related compounds. The C-13 configuration has been confirmed by the synthesis of epimer lactone 19[12] in which the ^{13}C-nmr spectrum displays a signal at δ : 28.9 ppm. corresponding to an equatorial methyl group at C-16 (Table III).

Table II

	^{1}H-NMR	^{13}C-NMR	
	δ (C_{16})	δ C_{16}	δ C_{13}
15	1.38	25.95	84.36
16	1.35	24.40	84.47
17	1.37	22.84	83.54
18	1.34	28.91	81.74

The stereochemistry suggested for lactone 17 is based on the spectroscopic properties obtained for stypodiol 20, whose structure has been confirmed by X-ray analysis and which has been obtained by an analogous cyclization process[3c].

Table III

	15	16	17	18
C-1	37.47	36.05	39.92	40.24
C-2	19.49	20.13	20.22	19.20
C-3	37.83	36.45	37.79	37.82
C-4	44.04	40.70	43.91	43.90
C-5	53.71	135.40	56.71	57.11
C-6	19.27	20.13	19.54	18.78
C-7	34.46	36.23	38.16	41.52
C-8	127.40	36.74	33.76	37.82
C-9	138.10	47.79	50.61	54.01
C-10	39.83	132.00	34.72	37.50
C-11	21.92	16.77	19.02	17.08
C-12	41.92	31.26	32.97	41.40
C-13	84.36	84.47	36.64	83.54
C-14	32.06	31.83	94.01	60.01
C-15	19.64	16.70	20.41	19.64
C-16	25.95	24.40	17.36	22.84
C-17	19.69	16.01	16.44	15.82
C-18	28.35	26.22	28.62	28.62
C-19	178.00	178.00	177.8	177.60
C-20	16.05	21.05	14.05	14.03
C-21	29.05	29.78	30.81	29.05
C-22	171.10	171.00	169.00	171.50
C-23	51.08	51.67	51.09	51.11

Experimental section

Organic extracts were dried with commercially dried Na_2SO_4 and evaporated under reduced pressure below 40°C. Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were determined on a digital Perkin Elmer 241 polarimeter in a 1-dm cell. The ^1H nmr spectra were recorded on a Hitachi Perkin Elmer R-24 60-MHz spectrometer and on a Bruker WP-200-SY spectrometer operating at 200 MHz. The ir spectra were determined on a Beckman 33-IR spectrophotometer as indicated in each case. Mass spectra were measured on a V.G.TS-250 apparatus. Microanalyses were performed using a Carlo Erba 1106 elemental analyser. All compounds discussed in this paper were obtained in a chromatographically homogeneous state.

15-chloro-19-methoxycarbonyl-8(17)-E-13-labdadiene 7

A mixture of 5 (4 g, 12 mmol), Ph_3P (13.3 g, 12.5 mmol), and CCl_4 (37 ml) was heated for 24 h, to 75-80ºC with stirring under nitrogen. The reaction mixture was cooled and filtered. After removal of the solvent, the residue was treated with hexane and the mixture was filtered on celite. Evaporation of the solvent gave 7 (3.8 g, 90.5%). ν_{max}^{film}:1735, 1660, 730 cm^{-1}; ^1H nmr (60 MHz, $CDCl_3$):δ:0.50 (s,3H), 1.26 (s,3H), 1.70 (s,3H), 3.57 (s,3H), 4.03 (d,J:7 Hz,2H), 4.45 (s,1H), 4.60 (s,1H), 5.35 (t,J:7 Hz,1H) ppm; MS: m/e:353 (M^+,10). Anal. calcd. for $C_{21}H_{33}O_2Cl$: C:71.49, H:9.36, Cl:10.07. Found: C:71.68, H:9.41, Cl:10.14.

15-(diethoxycarbonyl-methyl)-19-methoxycarbonyl-8(17),E-13-labdadiene 9

Diethyl malonate (2 g, 12.15 mmol) was added dropwise at room temperature under nitrogen to a stirred solution of sodium (270 mg, 11.7 mmol) in dry ethanol (5.4 ml) and the mixture was refluxed. Then, a solution of 7 (3.8 g, 10.8 mmol) in ethanol (3.6 ml) was added. After 2 h the reaction mixture was cooled, the solvent was removed and the residue was dissolved in water. The aqueous solution was acidified and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the crude product on silica gel gave 9 (3.6 g, 70%) using hexane:ether (90:10) as the eluent. $[\alpha]_D^{20}$=+29.9º (c:1.29, $CHCl_3$); ν_{max}^{film}:1750, 1660 cm^{-1}; ^1H nmr (60 MHz, $CDCl_3$):δ:0.50 (s,3H), 1.17 (s,3H), 1.23 (t,J:7.5 Hz.3H), 1.60 (s,3H), 3.58 (s,3H), 4.13 (c,J:7.5 Hz,2H), 4.43 (s,1H), 4.75 (s,1H), 4.97 (t,J:7 Hz,1H) ppm; MS: m/e:476 (M^+,7), 122 (100), 107 (39), 94 (34), 81 (58). Anal. calcd. for $C_{28}H_{44}O_6$: C:70.59, H:9.24. Found: C:70.63, H:9.28.

15-(ethoxycarbonylmethyl)-19-methoxycarbonyl-8(17),E-13-labdadiene 11

A mixture of 9 (3.6 g, 7.56 mmol), NaCl (884 mg, 15.1 mmol), H_2O (272 mg, 15.1 mmol) and Me_2SO (7.3 ml) was heated to 180ºC with stirring for 14 h under nitrogen. The reaction mixture was cooled and diluted with ethyl acetate (500 ml); this solution was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the crude product on silica gel gave 11 (2.4 g, 80%) eluted with hexane:ether (90:10). $[\alpha]_D^{20}$=+27.5º (c:0.24, $CHCl_3$); ν_{max}^{film}:1730, 1650 cm^{-1}; ^1H nmr (60 MHz, $CDCl_3$):δ:0.53 (s,3H), 1.16 (s,3H), 1.23 (t,J:7 Hz,3H), 1.59 (s,3H), 3.60 (s,3H), 4.05 (c,J:7 Hz,2H), 4.43 (s,1H), 4.76 (s,1H), 5.00 (t,J:7 Hz,1H) ppm. MS: m/e:404 (M^+,12). Anal. calcd. for $C_{25}H_{40}O_4$: C:74.26, H:9.90. Found: C:74.35, H:9.93.

15-carboxymethyl-19-methoxycarbonyl-8(17),E-13-labdadiene 13

A solution of KOH (94 mg, 1.7 mmol) in EtOH (1.8 ml), H_2O (0.29 ml) and 11 (308 mg, 0.76 mmol) was refluxed with stirring for $2\frac{1}{2}$ h under nitrogen. After cooling and removal of the solvent, the residual solid was dissolved in water and the solution was extracted with ether. The extract was washed with brine,

dried (Na_2SO_4), filtered and evaporated to afford 11 (287 mg, 100%). $[\alpha]_D^{20}$=+37.6º (c:0.93, $CHCl_3$); ν_{max}^{film}:3600-2800, 1720, 1645 cm^{-1}; ^1H nmr (60 MHz, $CDCl_3$):δ:0.50 (s,3H), 1.20 (s,3H), 1.60 (s,3H), 3.58 (s,3H), 4.50 (s,1H), 4.80 (s,1H), 5.03 (t,J:7.5 Hz,1H) ppm. MS: m/e:376 (M^+,4), 189 (40), 121 (100), 107 (37), 81 (42). Anal. calcd. for $C_{23}H_{36}O_4$: C:73.41, H:9.57. Found: C:73.50, H:9.62.

BIOMIMETIC CYCLIZATION OF 13

A.- With HCOOH

A solution of 13 (287 mg, 0.76 mmol) in HCOOH (3 ml) was heated to 90ºC with stirring for 45 min under nitrogen. After removal of the solvent, the resulting residue was partitioned between ether and 2N aqueous NaOH solution. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the crude product on silica gel using hexane:ether (75:25) as eluent gave 15 (162 mg, 56.4%) and 18 (54 mg, 19%). Compound 15:$[\alpha]_D^{20}$=+56.6º (c:1.09, $CHCl_3$); ν_{max}^{film}:1730 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$):δ:0.76 (s,3H), 1.19 (s,3H), 1.38 (s,3H), 1.58 (s,3H), 3.63 (s,3H) ppm. MS: m/e:376 (M^+,7), 185 (65), 138 (100), 176 (60), 174 (85). Anal. calcd. for $C_{23}H_{36}O_4$: C:73.40, H:9.57. Found: C:73.52, H:9.61.

Compound 18: $[\alpha]_D^{20}$=+12.2º (c:1.12, $CHCl_3$); P.f.=214-215ºC; ν_{max}^{film}:1715 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$):δ:0.65 (s,3H), 0.86 (s,3H), 1.17 (s,3H), 1.37 (s,3H), 3.64 (s,3H) ppm. MS: m/e:376 (M^+,17), 81 (65), 55 (100), 43 (69), 41 (74). Anal. calcd. for $C_{23}H_{36}O_4$: C:73.40, H:9.57. Found: C:73.53, H:9.60.

B.- With AcOH+H_2SO_4

A solution of AcOH (25 ml), H_2SO_4(c) (1 ml), and 13 (100 mg,0.26 ml) was left to stand for 8 h with occasional stirring. Following this, cold water was added and the mixture was extracted with ether. The extract was washed with water, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the crude product on silica gel using hexane:ether (75:25) as eluent gave 16 (58 mg, 58%). $[\alpha]_D^{20}$=-67.6º (c:1.0, $CHCl_3$); ν_{max}^{film}:1720 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$):δ:0.85 (d,J:6 Hz,3H), 0.89 (s,3H), 1.25 (s,3H), 1.35 (s,3H), 3.63 (s,3H) ppm. MS: m/e:376 (M^+,3), 235 (100), 175 (48), 173 (41), 119 (26). Anal. calcd. for $C_{23}H_{36}O_4$: C:73.40, H:9.57. Found: C:37.52, H:9.61.

Using the same eluent 18 (18 mg, 18%) was obtained.

C.- With H_3PO_4

A mixture of 13 (650 mg, 1.7 mmol) and H_3PO_4 (5g) was vigorously stirred for 48 h at room temperature. Cold water was added and the mixture was partitioned between ether and 2N aqueous NaOH solution. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated. Chromatography of the crude product on silica gel using hexane:ether (80:20) as the eluent gave 17 (40 mg, 6%). $[\alpha]_D^{20}$=+16.4º (c:2.8, $CHCl_3$); ν_{max}^{film}:1765, 1725 cm^{-1}; ^1H nmr

(200 MHz, $CDCl_3$):δ:0.66 (s,3H), 0.85 (d,J:6 Hz,3H), 0.93 (s,3H), 1.16 (s,3H), 3.63 (s,3H) ppm. MS: m/e:376 (M^+,12). Anal. calcd. for $C_{23}H_{36}O_4$: C:73.40, H:9.57. Found: C:73.52, H:9.61.

Lactones 16 (220 mg,34%) and 18 (95 mg, 14%) were also isolated by elution with hexane:ether (75:25).

15-chloro-19-methoxycarbonyl-8,E-13-labdadiene 8

Thionyl chloride (1.8 g, 15.4 mmol) was added to a stirred ice-water solution of 6 (4.3 g, 12.9 mmol) in pyridine (1.2 g, 15.4 mmol). The mixture was heated for 1 h to 90-5ºC. After cooling at room temperature it was diluted with cold water and extracted with ether. The extract was washed with 2N aqueous NaOH solution and brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the crude product on silica gel using hexane:ether (95-5) as the eluent gave 8 (2.1 g, 45.6%). ν_{max}^{film}:1720, 1665, 770 cm^{-1}; ^1H nmr (60 MHz, CCl_4):δ:0.70 (s,3H), 1.15 (s,3H), 1.57 (s,3H), 3.52 (s,3H), 3.96 (d,J:7 Hz,2H), 5.1 (t,J:7 Hz,1H) ppm. MS: m/e:353 (M^+,10). Anal. calcd. for $C_{21}H_{33}OCl$: C:71.49, H:9.36, Cl:10.07. Found: C:71.68, H:9.41, Cl:10.14.

15-(diethoxycarbonyl-methyl)-19-methoxycarbonyl-8,E-13-labdadiene 10

The halide 8 (2.1 g, 5.95 mmol) was converted into 10 (1.9 g, 70%) by a method similar to that used for the preparation of 9; 10: $[\alpha]_D^{20}$:+74.7º (c:1.12, $CHCl_3$); ν_{max}^{film}:1725 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$):δ:0.70 (s,3H), 1.12 (s,3H), 1.20 (t,J:6 Hz,6H), 1.55 (s,3H), 1.60 (s,3H), 3.50 (s,3H), 4.03 (c,J:6 Hz,4H), 4.92 (t,J:6 Hz,1H) ppm. MS: m/e:476 (M^+,14). Anal.calcd. for $C_{28}H_{44}O_6$: C:70.59, H:9.24. Found: C:70.63, H:9.28.

15-(ethoxycarbonyl-methyl)-19-methoxycarbonyl-8,E-13-labdadiene 12

The triester 10 (1.1 g, 2.23 mmol) was converted into 12 (696 mg, 80%) by a method similar to that used for the preparation of 11; 12: $[\alpha]_D^{20}$=+75.9º (c:0.81, $CHCl_3$); ν_{max}^{film}:1730 cm^{-1}; ^1H nmr (60 MHz, CCl_4):δ:0.72 (s,3H), 1.15 (s,3H), 1.20 (t,J:7 Hz,3H), 1.58 (s,3H), 1.65 (s,3H), 3.52 (s,3H), 4.03 (c,J:7 Hz,2H), 5.00 (t,J:7 Hz,1H) ppm. MS: m/e:404 (M^+,15). Anal. calcd for $C_{25}H_{40}O_4$: C:74.26, H:9.90. Found: C:74.35, H:9.93.

15-carboxymethyl-19-methoxycarbonyl-8,E-13-labdadiene 14

The olefinic diester 12 (522 mg, 1.29 mmol) was converted into 14 (480 mg, 99%) by a method similar to that used for the preparation of 13. 14: $[\alpha]_D^{20}$=+42.08º (c:1.15,$CHCl_3$); ν_{max}^{film}:3600-2800, 1725 cm^{-1}; ^1H nmr (60 MHz, CCl_4):δ:0.75 (s,3H), 1.18 (s,3H), 1.57 (s,3H), 1.62 (s,3H), 3.55 (s,3H), 5.00 (t,J:7 Hz,1H) ppm. MS: m/e:376 (M^+,12). Anal. calcd. for $C_{23}H_{36}O_4$: C:73.41, H:9.57. Found: C:73.50, H:9.62.

BIOMIMETIC CYCLIZATION OF 14

The product 14 (480 mg, 1.27 mmol) was treated with HCOOH (5 ml) according to the procedure previously described, affording 16 (206 mg, 43%), 17 (52 mg, 11%), and 18 (26 mg, 5.5%).

REFERENCES

1.- Nagata, W.; Tomita, T.; Itazaki, H. Japan. 3166 ('67). Chem. Abstr. 67, 32889w (1967).

2.- Baran J.S., J. Org. Chem. 30, 3564 (1965).

3.- a) Herz W.; Siva Prasad J., J. Org. Chem. 47, 4173 (1982).
b) Ohloff G.; Giersch W.; Schulte-Elte K.H. and Vial C., Helv. Chim. Acta 59, 1140 (1976).
c) González A.G.; Alvarez N.A.; Martín J.D.; Norte M.; Pérez C. and Rovirosa J.; Tetrahedron 38, 719 (1982).

4.- a) Stork G. and Burgstahler A.W., J. Am. Chem. Soc., 77, 5968 (1955).
b) Eschenmoser A.; Ruzicka L.; Jäger O. and Arigoni D., Helv. Chim. Acta 38, 1890 (1955).

5.- Preparation of the terpenic derivatives 5 and 6 was carried out by trivial transformation of the dimethyl ester of agatic acid obtained from natural sources.

6.- Hunt C.B.; Mac Sweeny D.F. and Ramage R., Tetrahedron 1491 (1971).

7.- Dietrich P. and Lederer E., Helv. Chim. Acta 35, 140 (1952).

8.- Krapcho A.P., Synthesis 805 (1982).

9.- The absolute stereochemistry at C-13 in 15 and 16 remains undetermined since we lack experimental evidence (X-ray analysis) for the correct assignement of the absolute configuration. Both compounds occur as colorless oils.

10.- The absolute stereochemistry at C-8 and C-9 in 16 has been proposed in view of our experence ganied in the acid-promoted rearrangements in the labdane series: Pascual Teresa J.; Urones J.G.; Sanchez Marcos I.; Bermejo F.; Basabe P. and Queimadelos P., An. Quím. 79, C, 451 (1973); Pascual Teresa J.; Urones G.J.; Marcos S.I.; Bermejo F. and Basabe P., Phytochemistry 22, 2783 (1983); Urones G.J.; Pascual Teresa J.; Sanchez Marcos I.; Diaz Martín D.; Martín Garrido N. and Alfayate Guerra R., Phytochemistry 26, 1077 (1987).

11.- Brannon D.R., Martín J., Oehlschlager A.C., Durham N.N. and Zalkow L.H.; J. Org. Chem., 30, 760 (1965).
Gasic M.J., Djarmati Z. and Pelletier S.W.; J. Org. Chem. 41, 1219 (1976).

12.- M. Rosa Rubio. Ph. Thesis. University of Salamanca. 1986.