Synthesis of β-Methylfurolabdanes from (+)-Sclareolide

Sergio Rosselli,[a] Maurizio Bruno,*[a] Ivana Pibiri,[a] and Franco Piozzi[a]

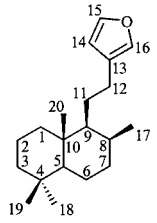
Keywords: Heterocycles / Labdanes / Methylfuranoids / Synthesis / Terpenes

An efficient synthesis of the methylfurolabdane **3** from (+)-sclareolide (**6**) via the hydroxyalkenes **12** is reported. Alternative modes of cyclization of **12** allowed the synthesis of methyldihydrofuran derivatives **4** and **5** and methyltetrahydrofuran derivatives **15**.

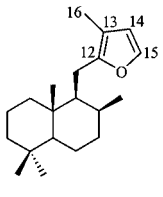
Introduction

Labdane diterpenoids are very widespread natural products.[1] Several have a furan ring connected to the rest of the isoprene structure at position 3 (e.g., **1**). Very occasionally, natural labdanes with a furan ring connected to the rest of the structure through position 2 and carrying an external carbon atom on position 3 (e.g., **2**) have been found. In our labdane diterpenoid synthesis program, we decided to perform the partial synthesis of the furan **3** and of its epimeric dihydro derivatives **4** and **5**, all containing the structural features exemplified by **2**.

Compound **3** had been isolated from the cuticular wax of the leaves of *Nicotiana tabacum*.[2] Product **4** had been obtained[3] by sensitized photooxygenation of (12*Z*)-abienol, a labdane also occurring in large quantities in the same *N. tabacum* cuticular wax. It is believed that the large number of labdane diterpenoids occurring in tobacco, highly susceptible to light and oxidation, are responsible for its flavour, and that they are formed during aerobic treatment for tobacco manufacture. As chiral starting material, we chose the commercially available (+)-sclareolide (**6**).



1



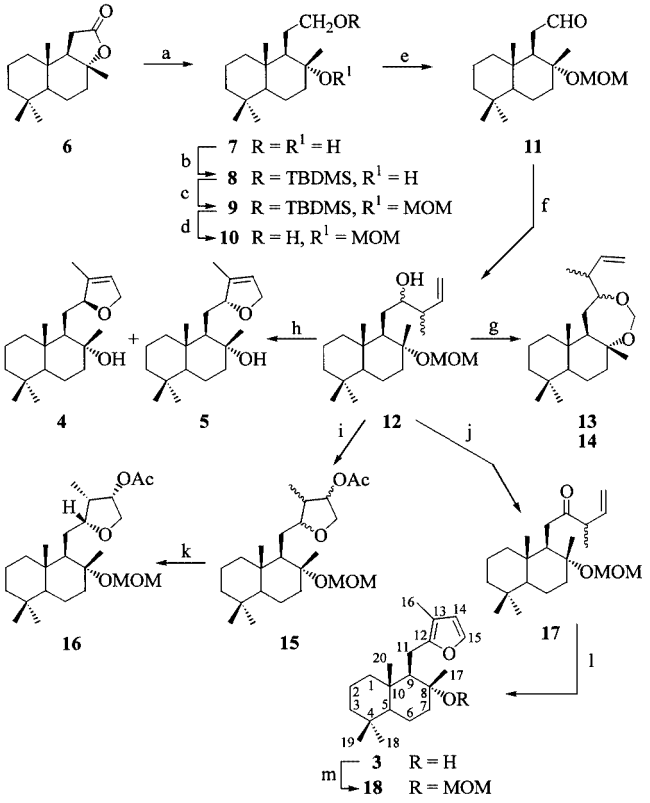
2

[a] Dipartimento di Chimica Organica, Università di Palermo, Viale delle Scienze, 90128 Palermo, Italy
Fax: (internat.) + 39-091/596825
E-mail: bruno@dicpm.unipa.it

Results and Discussion

Treatment of sclareolide (**6**) with *trans*-crotylmagnesium bromide was not a suitable route, since only a complex mixture of tertiary alcohols originating from the addition of two molecules of the organometallic reagent was obtained. Reduction of sclareolide (**6**) with $LiAlH_4$ gave the diol **7**.[4] Any attempt at selective oxidation of the primary alcohol to an aldehyde gave sclareolide (**6**) once more, due to the nucleophilic addition of the free hydroxy group at C-8 to the carbonyl group and further oxidation of the hemiacetal to lactone. Consequently, we performed a selective protection of the primary alcohol of compound **7** with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give **8**, the tertiary hydroxy group of which was in turn protected with methoxymethyl chloride (MOMCl) to afford **9** (Scheme 1). Other protective groups such as acetyl or benzoyl did not react with the tertiary alcohol, probably due to steric hindrance. Oxidation of **10**, derived from **9** by selective deprotection, gave the aldehyde **11**. Treatment of **11** with *trans*-crotylmagnesium chloride yielded a mixture of hydroxyalkenes **12**. An attempt to reduce the number of diastereoisomers by use of the stereoselective Nozaki procedure was made.[5] Under those conditions, however, the methoxymethyl group unfortunately reacted to give a mixture of diastereoisomeric seven-membered ring formyl acetals **13**; this side reaction has also recently been reported by other authors.[6] The major diastereoisomer **14** was isolated and characterized, although the configurations of the two chiral centres was not ascertained.

Three different strategies were performed in order to obtain the heterocyclic ring. The first, used in natural products chemistry,[7] involves the use of $Tl(OAc)_3$ as an electrophilic agent. Treatment of compound **12** with $Tl(OAc)_3$ in AcOH as solvent accordingly gave a mixture of diastereoisomeric acetoxytetrahydrofurans **15** and the aldehyde **11**. When the same reaction was carried out in CH_2Cl_2 as solvent, the aldehyde **11** was the main compound. Purification of the



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, Et_2O, 0 °C, 2 h, 89%; (b) *tert*-butyldimethylsilyl chloride, DMAP, TEA, CH_2Cl_2, room temp., 24 h, 97%; (c) MOMCl, DIPEA, CH_2Cl_2, 0 °C to room temp., 24 h, 90%; (d) TBAF, THF, 0 °C to room temp., 16 h, 93%; (e) PDC, CH_2Cl_2, room temp., 24 h, 80%; (f) *trans*-crotylmagnesium chloride, THF, 4 h, 82%; (g) $CrCl_3$, Mn, *trans*-crotyl bromide, TMSCl, THF, r.t, 9 h, 27%; (h) *N*-(phenylseleno)phthalimide, CSA, room temp., 30 min, H_2O_2/THF (24:1), room temp., 4 h, 22% (**4**) and 30% (**5**); (i) $Tl(OAc)_3$, AcOH/$CHCl_3$ (2:1), 0 °C to room temp., 2 h, 17%; (k) column chromatography (silica gel); (j) CrO_3, pyridine, room temp., 24 h, 65%; (l) OsO_4, NMO, THF/*t*BuOH/H_2O (8:1:1), *p*TsOH, room temp., 24 h, 51%; (m) *p*TsOH, MeOH/H_2O (4:1), room temp., 24 h, 43%

mixture of acetoxytetrahydrofurans **15** allowed us to isolate the main compound **16**, the relative configuration of which was determined by NOE experiments. Irradiation of the signal of 14-H at δ = 5.24 ppm caused 1.0%, 5.6% and 7.1% enhancements in the intensities of 12-H, 15-H_A and 13-H, respectively, while irradiation of 12-H (δ = 4.22 ppm) enhanced the signal of 13-H (2.1%) and irradiation of 13-H (δ = 2.42 ppm) gave clear enhancements in the signals of 14-H (8.9%), 12-H (8.8%) and the 16-CH_3 protons (1.3%). These observations clearly showed that 12-H, 13-H and 14-H were on the same side of the tetrahydrofuran ring and allowed us to assign the (12*R**,13*S**,14*S**) relative stereochemistry to the C-12/C-16 fragment.

Alternatively, treatment of **12** with camphorsulfonic acid and *N*-(phenylseleno)phthalimide, followed by H_2O_2 oxidation, gave the dihydrofuran **4**, previously obtained by photooxygenation,[3] and its C-12 epimer **5**. The two epimers were isolated by column chromatography and characterized. It was not possible to prepare the furan derivative by oxidation of compounds **4** or **5** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in CH_2Cl_2.

Finally, the mixture of hydroxyalkenes **12** was also oxidized (CrO_3) to afford the ketone **17**; the latter, according to Trost's strategy,[8] was oxidized with OsO_4 and cyclized with *p*-toluenesulfonic acid to provide the derivative **18**. Deprotection of the tertiary hydroxy group yielded the desired product **3**, identical with the substance occurring in *N. tabacum*.

Experimental Section

General: IR spectra were obtained with a Perkin−Elmer 1310 spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ solution with a Bruker AC 250E instrument at 250 MHz, and chemical shifts are reported with respect to residual $CHCl_3$ (δ = 7.27 ppm). The ^1H NMR spectroscopic data refer to protons with assigned signals, while excluding overlapped and therefore unattributable signals. ^{13}C NMR spectra were recorded in $CDCl_3$ solution with the same apparatus at 62.7 MHz, and chemical shifts are reported with respect to solvent signals ($CDCl_3$: δ_C = 77.00). ^{13}C NMR assignments were determined by DEPT spectra. MS were recorded with a Finnigan TSQ70 instrument (70 eV, direct inlet). Elemental analyses were carried out with a Perkin−Elmer 240 apparatus. Merck silica gel (70−230 mesh), deactivated with 15% H_2O, was used for column chromatography (CC). For ease of comparison we have adopted the labdane skeleton numeration for the methyl groups in compounds **6**−**11**.

Reduction of Sclareolide (6): $LiAlH_4$ (225 mg, 5.9 mmol) was added, under Ar at 0°, to a solution of sclareolide (**6**, 2 g, 8 mmol) in 60 mL of anhydrous diethyl ether (Et_2O). The mixture was stirred for 2 h and then quenched by the dropwise addition of 60 mL of saturated aqueous NH_4Cl. After filtration through Celite, the solution was extracted three times with Et_2O. The combined organic layers were dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 1:1) to give **7** (1.8 g, 89%).

13,14,15,16-Tetranor-8α,12-labdanediol (7): White crystals (recrystallized from petroleum ether/ethyl acetate, 9:1). M.p. 133−134 °C. $[\alpha]_D^{25}$ = −15.7 (*c* = 1.06, $CHCl_3$) (ref.[4] −15). $C_{16}H_{30}O_2$ (254.40): calcd. C 75.53, H 11.89; found C 75.58, H 11.93.

12-(*tert*-Butyldimethylsilyloxy)-8α-hydroxy-13,14,15,16-tetranorlabdane (8): Dimethylaminopyridine (285 mg, 2.3 mmol), triethylamine (1.1 mL, 7.9 mmol) and *tert*-butyldimethylsilyl chloride (1.17 g, 7.8 mmol) were added at room temp. under Ar to a solution of diol **7** (1.8 g, 7.1 mmol) in 20 mL of dry CH_2Cl_2. The mixture was stirred for 24 h, concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 1:1) to provide compound **8** (2.54 g, 97%) as an oil. $[\alpha]_D^{25}$ = −13.5 (*c* = 1.38 $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3448, 2930, 2858, 1464, 1389, 1256, 1086, 935, 835, 777 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.07 [s, 6 H, $(CH_3)_2Si$], 0.77 (s, 6 H, 20-H_3 and 19-H_3), 0.86 (s, 3 H, 18-H_3), 0.90 [s, 9 H, $(CH_3)_3CSi$], 1.12 (s, 3 H, 17-H_3), 1.91 (dt, *J* = 12.1, 3.1 Hz, 1 H, 7-H_β), 3.45 (dt, *J* = 10.0, 3.9 Hz, 1 H, H_B-12), 3.79 (dt, *J* = 4.3, 10.0 Hz, 1 H, H_A-12) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 1. EIMS: *m*/*z* (%) = $[M]^+$ absent, 311 (1), 293 (2), 235 (1), 219 (100), 191 (7), 163 (16), 137 (6), 123 (13), 109 (13), 95 (8). $C_{22}H_{44}O_2Si$ (368.66): calcd. C 71.67, H 12.03; found C 71.58, H 11.95.

Table 1. ^{13}C NMR spectroscopic data for compounds **3**−**5**, **8** and **9**

C[a]	3	4	5	8	9
1	39.4 t	39.4 t	39.8 t	39.5 t	39.7 t
2	18.6 t	18.4 t	18.6 t	18.4 t	18.3 t
3	41.8 t	42.0 t	41.8 t	41.3 t	41.9 t
4	33.3 s	33.3 s	33.4 s	33.2 s	33.1 s
5	56.0 d	56.1 d	55.6 d	56.2 d	56.0 d
6	20.4 t	20.5 t	20.5 t	20.4 t	19.9 t
7	44.1 t	44.0 t	44.9 t	43.9 t	40.2 t
8	73.4 s	71.9 s	72.9 s	71.7 s	79.7 s
9	59.9 d	58.6 d	56.1 d	59.0 d	55.7 d
10	38.8 s	39.3 s	38.7 s	39.9 s	38.5 s
11	21.2 t	29.8 t	29.1 t	27.7 t	29.4 t
12	151.9 s	89.8 d	87.7 d	64.9 t	65.5 t
13	113.1 s	138.2 s	138.5 s		
14	113.1 d	120.0 d	120.5 d		
15	139.6 d	73.6 t	74.1 t		
16	10.1 q	12.5 q	12.7 q		
17	23.9 q	24.5 q	24.2 q	24.5 q	20.4 q
18	33.5 q	33.4 q	33.5 q	33.4 q	33.3 q
19	21.6 q	21.5 q	21.5 q	21.5 q	21.4 q
20	15.2 q	15.3 q	15.7 q	15.3 q	15.8 q
$(CH_3)_3C$				25.9 q	26.0 q
$(CH_3)_3C$				18.2 s	18.3 s
$Si(CH_3)_2$				−5.5 q	−5.2 q
OCH_2O					89.7 t
OCH_3					53.0 q

[a] 62.7 MHz, $CDCl_3$ solution.

Table 2. ^{13} C NMR spectroscopic data for compounds **10**, **11**, **14**, **16**, and **18**

C[a]	10	11	14	16	18
1	39.3 t	40.0 t	40.2 t	39.4 t	39.2 t
2	18.2 t	18.4 t	18.6 t	18.5 t	18.5 t
3	41.8 t	41.7 t	41.7 t	41.9 t	41.7 t
4	33.1 s	33.1 s	33.3 s	33.4 s	33.2 s
5	55.8 d	55.9 d	55.7 d	55.8 d	55.7 d
6	19.9 t	19.8 t	19.7 t	20.1 t	20.0 t
7	40.1 t	40.0 t	42.1 t	40.0 t	40.0 t
8	79.7 s	78.8 s	78.5 s	80.7 s	79.4 s
9	57.7 d	54.4 d	54.0 d	54.5 d	54.9 d
10	39.0 s	38.1 s	38.5 s	38.6 s	38.9 s
11	28.2 t	40.0 t	27.2 t	26.3 t	21.4 t
12	64.0 t	202.9 d	78.7 d	82.1 d	152.4 s
13			42.4 d	39.4 d	112.4 s
14			141.4 d	76.8 d	112.8 d
15			114.9 t	71.3 t	138.9 d
16			17.4 q	8.2 q	10.0 q
17	20.1 q	21.4 q	20.8 q	21.0 q	21.5 q
18	33.3 q	33.3 q	33.4 q	33.3 q	33.4 q
19	21.4 q	20.6 q	21.5 q	21.4 q	21.5 q
20	15.6 q	15.9 q	15.4 q	16.1 q	15.6 q
OCH_2O	89.7 t	89.7 t	87.6 t	89.7 t	89.8 t
OCH_3	55.4 q	55.3 q		54.9 q	56.2 q
OAc				170.7 s	
				21.0 q	

[a] 62.7 MHz, $CDCl_3$ solution.

12-(*tert*-Butyldimethylsilyloxy)-18α-(methoxymethoxy)-3,14,15,16-tetranorlabdane (9): Diisopropylethylamine (DIPEA, 2.95 mL, 21.0 mmol) and methoxymethyl chloride (MOMCl, 1.4 mL, 18.4 mmol) were added at 0° under Ar to a solution of compound **8** (2.5 g, 6.8 mmol) in 20 mL of dry CH_2Cl_2. The mixture was stirred for 24 h, 20 mL of CH_2Cl_2 was added, and the mixture was washed in turn with an aqueous solution of HCl (0.1 M), saturated aqueous $NaHCO_3$ and H_2O. The organic layer was dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 19:1) to provide compound **9** (2.52 g, 90%) as an oil. $[\alpha]_D^{25} = -1.1$ ($c = 2.89$, $CHCl_3$). IR (film): $\tilde{\nu}_{max.} = 2927$, 2858, 1440, 1389, 1260, 1086, 1031, 935, 835 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.04 [s, 6 H, $(CH_3)_2Si$], 0.77 (s, 3 H, 20-H_3), 0.81 (s, 3 H, 19-H_3), 0.85 (s, 3 H, 18-H_3), 0.89 [s, 9 H, $(CH_3)_3CSi$], 1.19 (s, 3 H, 17-H_3), 1.91 (dt, $J = 12.1$, 3.1 Hz, 1 H, 7-H_β), 3.32 (s, 3 H, OCH_3), 3.50 (dt, $J = 10.0$, 3.9 Hz, 1 H, 12-H_B), 3.65 (dt, $J = 4.3$, 10.0 Hz, 1 H, 12-H_A), 4.64 (d, $J = 7.5$ Hz, 1 H, OCH_2O), 4.70 (d, $J = 7.5$ Hz, 1 H, OCH_2O) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 1. EIMS: *m*/*z* (%) = $[M]^+$ absent, 380 (2), 323 (3), 293 (15), 219 (58), 191 (75), 149 (42), 95 (72), 75 (50), 45 (100). $C_{24}H_{48}O_3Si$ (412.71): calcd. C 69.84, H 11.72; found C 69.89, H 11.66.

12-Hydroxy-8α-(methoxymethoxy)-13,14,15,16-tetranorlabdane (10): Tetrabutylammonium fluoride (TBAF, 3.8 g, 14.6 mmol) was added at 0° under Ar to a solution of compound **9** (2.5 g, 6.1 mmol) in 20 mL of dry THF. After 20 min, the cooling bath was removed and the mixture was stirred for 16 h and then partitioned between Et_2O and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 3:2) to give compound **10** (1.7 g, 93%) as an oil. $[\alpha]_D^{25} = -15.7$ ($c = 2.99$ $CHCl_3$). IR (film): $\tilde{\nu}_{max.} =$ 3250, 2930, 2854, 1439, 1387, 1267, 1240, 1134, 1074, 1036, 968, 935 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.75 (s, 3 H, 20-H_3), 0.79 (s, 3 H, 19-H_3), 0.83 (s, 3 H, 18-H_3), 1.17 (s, 3 H, 17-H_3), 1.99 (dt, $J = 12.1$, 3.1 Hz, 1 H, 7-H_β), 3.32 (s, 3 H, OCH_3), 3.42 (dt, $J = 10.0$, 3.9 Hz, 1 H, 12-H_B), 3.65 (dt, $J = 10.0$, 4.3 Hz, 1 H, 12-H_A), 4.70 (s, 2 H, OCH_2O) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 2. EIMS: *m*/*z* (%) = $[M]^+$ absent, 266 (10), 249 (22), 237 (37), 221 (36), 219 (25), 191 (32), 177 (100), 137 (28), 109 (63), 95 (52). $C_{18}H_{34}O_3$ (298.45): calcd. C 72.43, H 11.48; found C 72.36, H 11.53.

8α-(Methoxymethoxy)-13,14,15,16-tetranorlabdan-12-al (11): Pyridinium dichromate (PDC, 2.8 g, 8.8 mmol) was added with stirring to a solution of compound **10** (1.5 g, 5 mmol) in 10 mL of dry CH_2Cl_2. The mixture was stirred for 24 h and, after filtration through Florisil, concentrated to give an oil that was distilled at reduced pressure in a bulb-to-bulb apparatus. Compound **11** (1.19 g, 80%) was obtained as an oil. $[\alpha]_D^{25} = -22.4$ ($c = 3.25$ $CHCl_3$). IR (film): $\tilde{\nu}_{max.} = 2926$, 2870, 2822, 2719, 1722, 1466, 1445, 1389, 1273, 1149, 1130, 1092, 1032, 918 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.78 (s, 3 H, 20-H_3), 0.82 (s, 3 H, 19-H_3), 0.86 (s, 3 H, 18-H_3), 1.19 (s, 3 H, 17-H_3), 2.30 (ddd, 1 H, $J = 12.7$, 4.5, 1.4 Hz, 11-H_B), 2.40 (ddd, 1 H, $J = 12.7$, 7.8, 3.7 Hz, 11-H_A), 3.27 (s, 3 H, OCH_3), 4.60 (s, 2 H, OCH_2O), 9.58 (dd, $J = 3.7$, 1.4 Hz, 1 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 2. EIMS: *m*/*z* (%) = $[M]^+$ absent, 295 (2) $[M - 1]^+$, 265 (6), 251 (10), 235 (72), 217 (54), 191 (100), 177 (34), 160 (15), 146 (14), 133 (25), 121 (26), 106 (46), 80 (11), 67 (12), 43 (40). $C_{18}H_{32}O_3$ (296.44): calcd. C 72.92, H 10.88; found C 72.81, H 10.84.

Treatment of Compound 11 with *trans*-Crotylmagnesium Chloride: A solution of *trans*-crotylmagnesium chloride in dry THF (0.5 M, 10 mL, 5.0 mmol) was added dropwise under Ar to a solution of compound **11** (1 g, 3.4 mmol) in 10 mL of dry THF. After 4 h, the mixture was concentrated under vacuum and partitioned between

Et_2O (25 mL) and saturated aqueous NH_4Cl (3 times). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 19:1) to give a mixture (1:1:2:2) of four diastereoisomeric hydroxyalkenes **12** (1 g, 82%) as an oil. IR (film): $\tilde{\nu}_{max.}$ = 3470, 3074, 2926, 2872, 1637, 1466, 1419, 1389, 1153, 1128, 1078, 1036, 914 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.77 (s, 3 H, 20-H_3), 0.80 (s, 3 H, 19-H_3), 0.86 (s, 3 H, 18-H_3), 1.04 (d, 1.5 H, *J* = 7.0 Hz, 16-CH_3), 1.05 (d, 1.5 H, *J* = 7.0 Hz, 16-CH_3), 1.20, 1.23, 1.24 (s, 3 H, 17-H_3), 2.23 (m, 1 H, 13-H), 3.33, 3.36 (s, 3 H, OCH_3), 3.35 (m, 0.5 H, 12-H), 3.67 (m, 0.5 H, 12-H), 4.64−4.75 (m, 2 H, OCH_2O), 4.98−5.07 (m, 2 H, 15-H_A and 15-H_B), 5.84 (m, 1 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz, δ [ppm]): C-1 (40.0 t, 40.0 t, 39.9 t, 39.3 t), C-2 (18.5 t, 18.5 t, 18.2 t, 18.2 t), C-3 (41.9 t, 41.9 t, 41.7 t, 41.7 t), C-4 (33.1 s, 33.1 s, 33.1 s, 33.1 s), C-5 (55.9 d, 55.9 d, 55.9 d, 55.9 d), C-6 (19.8 t, 19.8 t, 19.7 t, 19.7 t), C-7 (40.7 t, 40.7 t, 39.2 t, 39.2 t), C-8 (80.6 s, 80.6 s, 80.1 s, 80.1 s), C-9 (58.0 d, 58.0 d, 57.9 d, 57.9 d), C-10 (39.3 s, 39.3 s, 38.6 s, 38.6 s), C-11 (30.4 t, 30.2 t, 30.2 t, 29.8 t), C-12 (76.7 d, 76.5 d, 73.8 d, 73.6 d), C-13 (44.8 d, 44.2 d, 44.1 d, 44.0 d), C-14 (141.9 d, 141.8 d, 141.5 d, 141.0 d), C-15 (114.9 t, 114.3 t, 114.2 t, 114.0 t), C-16 (16.5 q, 16.5 q, 15.8 q, 15.8 q), C-17 (20.9 q, 20.3 q, 20.2 q, 20.0 q), C-18 (33.4 q, 33.4 q, 33.2 q, 33.2 q), C-19 (21.6 q, 21.6 q, 21.3 q, 21.3 q), C-20 (15.6 q, 15.6 q, 15.5 q, 15.5 q), O−CH_2−O (89.8 t, 89.8 t, 89.6 t, 89.6 t), OCH_3 (54.4 q, 54.4 q, 54.2 q, 54.2 q). EIMS: *m*/*z* (%) = 352 (5) $[M]^+$, 303 (10), 291 (100), 273 (20), 235 (50), 191 (58), 177 (16), 137 (10), 69 (7), 43 (5).

Treatment of Compound 11 with *trans*-Crotyl Bromide and Mn/$CrCl_3$ (Nozaki's Procedure): Compound **11** (100 mg, 0.34 mmol), *trans*-crotyl bromide (70 μL, 86 mg, 0.54 mmol) and trimethylsilyl chloride (TMSCl, 0.1 mL, 0.8 mmol) were added at room temp. under Ar and with stirring to a suspension of $CrCl_3$ (4 mg, 0.03 mmol) and Mn (30 mg, 0.55 mmol) in 5 mL of dry THF. The mixture was stirred for 6 h, H_2O (10 mL) was added, and the mixture was stirred for a further 3 h and extracted with ethyl acetate (3 times). The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 33:1) to give a mixture of four diastereoisomeric (1:1:6:12) formyl acetals **13** (30 mg, 27%). Further purification by CC (silica gel; petroleum ether/diethyl ether, 19:1) allowed us to isolate the major diastereoisomer **14** (18 mg) as an oil. $[\alpha]_D^{25}$ = −34.9 (*c* = 0.90 $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3020, 2920, 2860, 1640, 1458, 1418, 1385, 1372, 1360, 1260, 1130, 1128, 1052, 916, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.76 (s, 3 H, 20-H_3), 0.80 (s, 3 H, 19-H_3), 0.89 (s, 3 H, 18-H_3), 1.08 (d, *J* = 6.6 Hz, 3 H, 16-CH_3), 1.27 (s, 3 H, 17-H_3), 2.35 (m, 1 H, 13-H), 3.65 (ddd, *J* = 9.0, 5.6, 5.0 Hz, 1 H, 12-H), 4.80 (d, *J* = 8.0 Hz, 1 H, OCH_2O), 4.91 (d, *J* = 8.0 Hz, 1 H, OCH_2O), 5.01 (dd, *J* = 10.2, 1.3 Hz, 1 H, 15-H_B), 5.04 (dd, *J* = 17.8, 1.3 Hz, 1 H, 15-H_A), 5.68 (ddd, 1 H, *J* = 17.8, 10.2, 8.3 Hz, 14-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 2. EIMS: *m*/*z* (%) = $[M]^+$ absent, 273 (7), 247 (14), 235 (25), 217 (15), 205 (8), 191 (100), 177 (27), 163 (15), 149 (23), 135 (28), 121 (41), 107 (64), 94 (46), 81 (54), 67 (53), 43 (58). $C_{21}H_{36}O_2$ (320.50): calcd. C 78.69, H 11.32; found C 78.74, H 11.36.

Cyclization of Compounds 12 with $Tl(OAc)_3$: $Tl(OAc)_3{\cdot}6(H_2O)$ (280 mg, 0.57 mmol) was added at 0° to a solution of compounds **12** (200 mg, 0.57 mmol) in 2 mL of AcOH and 1 mL of $CHCl_3$. The mixture was stirred for 2 h, and then allowed to warm to ambient temperature and stirred for 22 h. At this point the mixture was neutralized with a solution of Na_2CO_3 (0.5 M) and extracted with $CHCl_3$ (3 times). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 9:1, 4:1, 7:3) to give a complex mixture of isomers **15** (40 mg, 17%), the starting material (37 mg, 17%) and the aldehyde **11** (13 mg, 8%).

Compounds 15: ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.78 (s, 1.5 H, 20-H_3), 0.79 (s, 1.5 H, 20-H_3), 0.80 (s, 1.8 H, 19-H_3), 0.85 (s, 1.2 H, 19-H_3), 0.86 (s, 3 H, 18-H_3), 0.96 (d, 1.2 H, *J* = 6.9 Hz, 16-CH_3), 0.98 (d, 1.5 H, *J* = 6.9 Hz, 16-CH_3), 0.99 (d, 0.3 H, *J* = 6.9 Hz, 16-CH_3), 1.18 (s, 1.2 H, 17-H_3), 1.21 (s, 0.3 H, 17-H_3), 1.24 (s, 1.5 H, 17-H_3), 2.07 (s, 1.2 H, OAc), 2.08 (s, 1.5 H, OAc), 2.09 (s, 0.3 H, OAc), 2.42 (m, 1 H, 13-H), 3.32 (s, 1.5 H, OCH_3), 3.33 (s, 0.3 H, OCH_3), 3.35 (s, 1.2 H, OCH_3), 3.73 (dd, 0.5 H, *J* = 10.4, 2.7 Hz, 15-H_B), 3.75 (m, 0.1 H, 15-H_B), 3.76 (dd, 0.4 H, *J* = 10.3, 3.7 Hz, 15-H_B), 4.01 (dd, 0.5 H, *J* = 10.4, 5.7 Hz, 15-H_A), 4.03 (m, 0.1 H, 15-H_A), 4.04 (dd, 0.4 H, *J* = 10.3, 6.5 Hz, 15-H_A), 4.05 (m, 0.5 H, 12-H), 4.22 (ddd, 0.5 H, *J* = 10.3, 6.9, 3.9 Hz, 12-H), 4.52 (d, 0.1 H, *J* = 7.5 Hz, OCH_2O), 4.57 (d, 0.4 H, *J* = 7.5 Hz, OCH_2O), 4.59 (d, 0.5 H, *J* = 7.5 Hz, OCH_2O), 4.78 (d, 0.5 H, *J* = 7.5 Hz, OCH_2O), 4.83 (d, 0.4 H, *J* = 7.5 Hz, OCH_2O), 4.90 (d, 0.1 H, *J* = 7.5 Hz, OCH_2O), 5.24 (m, 1 H, 14-H).

(12*R,13*S**,14*S**)-14-Acetoxy-8-(methoxymethoxy)-12,15-epoxylabdan (16):** CC of the mixture **15** (silica gel; petroleum ether/ethyl acetate, 19:1, 9:1, 4:1) allowed us to isolate compound **16** (7 mg) as an oil. $[\alpha]_D^{25}$ = +16.7 (*c* = 0.60, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2947, 2881, 1740, 1464, 1387, 1367, 1244, 1148, 1038, 916 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.78 (s, 3 H, 20-H_3), 0.80 (s, 3 H, 19-H_3), 0.86 (s, 3 H, 18-H_3), 0.98 (d, *J* = 6.9 Hz, 3 H, 16-CH_3), 1.24 (s, 3 H, 17-H_3), 2.08 (s, 3 H, OAc), 2.42 (sext, 1 H, *J* = 6.9 Hz, 13-H), 3.32 (s, 3 H, OCH_3), 3.73 (dd, *J* = 10.4, 2.7 Hz, 1 H, 15-H_B), 4.01 (dd, *J* = 10.4, 5.7 Hz, 1 H, 15-H_A), 4.22 (ddd, 1 H, *J* = 10.3, 6.9, 3.9 Hz, 12-H), 4.59 (d, *J* = 7.5 Hz, 1 H, OCH_2O), 4.78 (d, *J* = 7.5 Hz, 1 H, OCH_2O), 5.24 (ddd, *J* = 6.9, 5.7, 2.7 Hz, 1 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 2. EIMS: *m*/*z* (%) = $[M]^+$ absent, 365 (3), 349 (5), 306 (3), 305 (18), 192 (10), 177 (37), 157 (100), 143 (22), 123 (18), 109 (23), 95 (30), 83 (31), 69 (22), 55 (39), 45 (58). $C_{24}H_{42}O_5$ (410.58): calcd. C 70.20, H 10.31; found C 70.14, H 10.26.

Cyclization of Compounds 12 with *N*-(Phenylseleno)phthalimide: Camphorsulfonic acid (92 mg, 0.40 mmol) and then *N*-(phenylseleno)phthalimide (212 mg, 0.7 mmol) were added to a solution of compounds **12** (200 mg, 0.57 mmol) in 5 mL of dry CH_2Cl_2. The mixture was stirred for 30 min and then poured onto a chromatography column of silica gel. Elution with petroleum ether/ethyl acetate (17:3) allowed the isolation of an oil (207 mg) which was dissolved in THF and added to 0.2 mL of a solution of H_2O_2 (3.5%) in THF. After 4 h, the solution was concentrated and subjected to CC (silica gel; petroleum ether/ethyl acetate, 19:1, 17:3) to give, in order of increasing polarity, 38 mg (22%) of compound **4** and 52 mg (30%) of compound **5**.

(12*S*)-12,15-Epoxy-13-labden-8-ol (4): Oil. $[\alpha]_D^{25}$ = −11.2 (*c* = 0.41, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3416, 2926, 2854, 1670, 1448, 1387, 1365, 1157, 1084, 1070, 1055, 937 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.80 (s, 3 H, 20-H_3), 0.81 (s, 3 H, 19-H_3), 0.88 (s, 3 H, 18-H_3), 1.12 (s, 3 H, 17-H_3), 1.74 (br. s, 3 H, 16-CH_3), 4.49−4.65 (m, 3 H, 12-H, 15-H_A and 15-H_B), 5.45 (t, *J* = 1.5 Hz, 1 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 1. EIMS: *m*/*z* (%) = $[M]^+$ absent, 288 (5), 273 (3), 191 (10), 177 (10), 149 (6), 137 (15), 123 (9), 111 (18), 109 (20), 97 (100), 83 (48). $C_{20}H_{34}O_2$ (306.47): calcd. C 78.38, H 11.18; found C 78.29, H 11.14.

(12*R*)-12,15-Epoxy-13-labden-8-ol (5): Oil. $[\alpha]_D^{25}$ = +5.9 (*c* = 0.22, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3416, 2926, 2854, 1670, 1448, 1387,

1365, 1157, 1084, 1070, 1055, 937 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.78 (s, 3 H, 20-H_3), 0.79 (s, 3 H, 19-H_3), 0.87 (s, 3 H, 18-H_3), 1.20 (s, 3 H, 17-H_3), 1.75 (br. s, 3 H, 16-CH_3), 4.51 (br. d, 1 H, *J* = 10.2 Hz, 15-H_B), 4.61 (br. d, 1 H, *J* = 10.2 Hz, 15-H_A), 4.88 (m, 1 H, 12-H), 5.49 (br. s, 1 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 1. EIMS: *m*/*z* (%) = $[M]^+$ absent, 288 (5), 273 (2), 191 (8), 177 (5), 149 (4), 137 (6), 123 (6), 111 (10), 109 (13), 97 (100), 83 (42). $C_{20}H_{34}O_2$ (306.47): calcd. C 78.38, H 11.18; found C 78.45, H 11.21.

Oxidation of Compounds 12: CrO_3 (230 mg, 2.30 mmol) was added with stirring to a solution of compounds **12** (400 mg, 1.14 mmol) in 20 mL of pyridine. The mixture was stirred at room temp. for 24 h, diluted with 40 mL of Et_2O, extracted with 20% aqueous HCl (3 times), washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 19:1) to give a C-13 epimeric mixture (3:2) of ketones **17** (260 mg, 65%) and 60 mg of starting material.

Compounds 17: Oil. IR (film): $\tilde{\nu}_{max.}$ = 2928, 2874, 1716, 1635, 1458, 1387, 1365, 1146, 1090, 1034, 916 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.79 (s, 3 H, 20-H_3), 0.80 (s, 1.2 H, 19-H_3), 0.82 (s, 1.8 H, 19-H_3), 0.87 (s, 1.2 H, 18-H_3), 0.88 (s, 1.8 H, 18-H_3), 1.17 (d, 1.2 H, *J* = 7.0 Hz, 16-CH_3), 1.18 (d, 1.8 H, *J* = 7.0 Hz, 16-CH_3), 1.19 (s, 3 H, 17-H_3), 2.32 (t, 0.4 H, *J* = 5.5 Hz, 11-H_B), 2.39 (t, 0.6 H, *J* = 5.5 Hz, 11-H_B), 2.53 (t, 0.6 H, *J* = 5.5 Hz, 11-H_A), 2.60 (t, 0.4 H, *J* = 5.5 Hz, 11-H_A), 3.27 (s, 1.8 H, OCH_3), 3.28 (s, 1.2 H, OCH_3), 3.33 (m, 1 H, 13-H), 4.45 (d, 0.4 H, *J* = 7.3 Hz, OCH_2O), 4.47 (d, 0.6 H, *J* = 7.3 Hz, OCH_2O), 4.67 (d, 0.6 H, *J* = 7.3 Hz, OCH_2O), 4.71 (d, 0.4 H, *J* = 7.3 Hz, OCH_2O), 5.10 (dt, 0.6 H, 10.2, 1.3 Hz, 15-H_B), 5.12 (dt, 0.4 H, 10.2, 1.3 Hz, 15-H_B), 5.17 (dt, 0.6 H, 17.8, 1.3 Hz, 15-H_A), 5.20 (dt, 0.4 H, 17.8, 1.3 Hz, 15-H_A), 5.83 (ddd, 0.6 H, 17.8, 10.2, 8.2 Hz, 14-H), 5.85 (ddd, 0.4 H, 17.8, 10.2, 8.2 Hz, 14-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz, δ [ppm]): C-1 (39.4 t, 39.4 t), C-2 (18.4 t, 18.3 t), C-3 (41.8 t, 41.8 t), C-4 (33.2 s, 33.2 s), C-5 (55.8 d, 55.7 d), C-6 (20.0 t, 20.0 t), C-7 (39.7 t, 39.6 t), C-8 (79.2 s, 79.1 s), C-9 (53.2 d, 53.0 d), C-10 (38.4 s, 38.4 s), C-11 (37.0 t, 36.9 t), C-12 (211.0 s, 210.9 s), C-13 (51.5 d, 51.0 d), C-14 (138.5 d, 138.3 d), C-15 (116.4 t, 116.2 t), C-16 (16.0 q, 15.9 q), C-17 (21.9 q, 21.5 q), C-18 (33.3 q, 33.3 q), C-19 (21.5 q, 21.5 q), C-20 (16.2 q, 16.2 q), OCH_2O (89.8 t, 89.8 t), OCH_3 (55.0 q, 54.9 q). EIMS: *m*/*z* (%) = $[M]^+$ absent, 318 (5), 305 (10), 295 (23), 289 (53), 265 (20), 233 (18), 191 (100), 177 (12), 149 (18), 137 (30), 95 (30), 69 (30), 45 (38). $C_{22}H_{38}O_3$ (350.42): calcd. C 75.38, H 10.93; found C 75.31, H 10.89.

Cyclization of Compounds 17: Ketones **17** (220 mg, 0.63 mmol) were dissolved at room temp in a mixture of THF (8 mL), *t*BuOH (1 mL) and H_2O (1 mL). *N*-Methylmorpholine *N*-oxide (100 mg, 0.85 mmol) and a crystal of OsO_4 were added to the solution, with stirring. After 6 h, *p*-toluenesulfonic acid (440 mg, 2.31 mmol) was added and the mixture was stirred for 18 h, a saturated aqueous $NaHCO_3$ solution was added, and the mixture was extracted with $CHCl_3$ (3 times). The combined organic layers were washed with H_2O, dried (Na_2SO_4), concentrated and chromatographed by CC (silica gel; petroleum ether/ethyl acetate, 19:1) to give compound **18** (113 mg, 51%).

8α-(Methoxymethoxy)-12,15-epoxy-12,14-labdadiene (18): Oil. $[\alpha]_D^{25}$ = −3.4 (*c* = 2.15 $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2926, 2845, 1510, 1464, 1443, 1387, 1148, 1130, 1094, 1036, 918 cm^{-1}. ^1H NMR ($CDCl_3$ 250 MHz): δ = 0.80 (s, 3 H, 20-H_3), 0.86 (s, 3 H, 19-H_3), 0.93 (s, 3 H, 18-H_3), 1.26 (s, 3 H, 17-H_3), 1.93 (s, 3 H, 16-CH_3), 2.50 (dd, *J* = 15.5, 7.0 Hz, 1 H, 11-H_B), 2.79 (dd, *J* = 15.5, 3.7 Hz, 1 H, 11-H_A), 3.33 (s, 3 H, OCH_3), 4.50 (d, *J* = 7.6 Hz, 1 H, OCH_2O), 4.77 (d, *J* = 7.6 Hz, 1 H, OCH_2O), 6.11 (d, *J* = 1.4 Hz, 1 H, 14-H), 7.20 (d, *J* = 1.4 Hz, 1 H, 15-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 2. EIMS: *m*/*z* (%) = $[M]^+$ absent, 287 (64), 286 (100), 243 (12), 215 (10), 191 (63), 177 (81), 162 (39), 148 (70), 133 (40), 105 (29), 96 (26), 46 (12). $C_{22}H_{36}O_3$ (348.51): calcd. C 75.81, H 10.41; found C 75.86, H 10.45.

Deprotection of Compound 18: Compound **18** (100 mg, 0.29 mmol) was dissolved in a MeOH/H_2O mixture (4:1, 10 mL), and *p*-toluenesulfonic acid (10 mg, 0.05 mmol) was added at room temp., with stirring. After 24 h, the mixture was concentrated and subjected to CC (silica gel; petroleum ether/ethyl acetate, 9:1) to give 44 mg (43%) of compound **3** and 49 mg of unchanged material.

12,15-Epoxy-12,14-labdadien-8-ol (3): Amorphous solid. $[\alpha]_D^{25}$ = −2.2 (*c* = 1.31, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 3435, 2924, 2847, 1510, 1445, 1387, 1149, 1089, 937 cm^{-1}. ^1H NMR ($CDCl_3$ 250 MHz): δ = 0.81 (s, 3 H, 20-H_3), 0.87 (s, 3 H, 19-H_3), 0.89 (s, 3 H, 18-H_3), 1.25 (s, 3 H, 17-H_3), 1.98 (s, 3 H, 16-CH_3), 2.62 (dd, *J* = 15.7, 5.0 Hz, 1 H, 11-H_B), 2.72 (dd, *J* = 15.7, 5.9 Hz, 1 H, 11-H_A), 6.13 (br. s, 1 H, 14-H), 7.23 (br. s, 1 H, 15-H) ppm. ^{13}C NMR ($CDCl_3$, 62.7 MHz): see Table 1. EIMS: *m*/*z* (%) = 304 (20) $[M]^+$, 286 (50), 205 (4), 191 (12), 161 (15), 148 (95), 133 (25), 108 (15), 95 (67), 83 (100), 69 (7), 47 (12). $C_{20}H_{32}O_2$ (304.46): calcd. C 78.89, H 10.59; found C 78.72, H 10.63.

Acknowledgments

This work, the preliminary results of which were presented as a communication at the XXVIIth National Meeting of the Organic Chemistry Division (Italian Chemical Society), Trieste, Italy, September 3−7, 2001, was supported by the Italian Government MIUR Research Funds (40% and 60%).

[1] J. R. Hanson, *Nat. Prod. Rep.* **2002**, *19*, 125−132 and previous reviews.
[2] I. Wahlberg, K. Karlsson, M. Curvall, T. Nishida, C. R. Enzell, *Acta Chem. Scand., Ser. B* **1978**, *32*, 203−215.
[3] I. Wahlberg, I. Wallin, K. Nordfors, T. Nishida, C. R. Enzell, W. W. Reid, *Acta Chem. Scand., Ser. B* **1979**, *33*, 541−543.
[4] A. F. Barrero, E. A. Manzaneda, J. Altarejos, S. Salido, J. M. Ramos, M. S. J. Simmonds, W. M. Blaney, *Tetrahedron* **1995**, *51*, 7435−7450.
[5] A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349−12357.
[6] C. Yu, B. Liu, L. Hu, *Tetrahedron Lett.* **2000**, *41*, 819−822.
[7] H. M. C. Ferraz, T. J. Brocksom, A. C. Pinto, M. A. Abla, D. H. T. Zocher, *Tetrahedron Lett.* **1986**, *27*, 811−814.
[8] B. M. Trost, J. A. Flygare, *J. Org. Chem.* **1994**, *59*, 1078−1082.

Received April 17, 2002
[O02212]