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Synthesis of a 1-acetyl-3α,6-dimethyl-hexahydroazulene. Versatile Intermediate for the Preparation of Terpenoids with Bicycle[5.3.0]decane System

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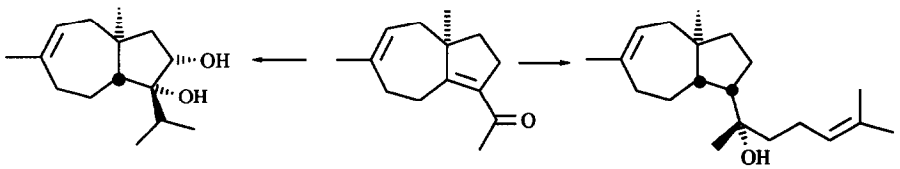
Abstract: A new method for the transformation of cycloheptenone **2** into enone **35** through the dione **5** has been achieved in 7 steps with an overall yield of 53%. The cycloheptenone **2** was synthesised from (±)-nerolidol. The enone **35** is a versatile precursor for the preparation of terpenoids either sesquiterpenes or diterpenes with a bicycle-[5.3.0]decane system.

INTRODUCTION

Seven-membered cyclic systems are often used in the construction of complex natural products. The perhydroazulene or the fused bicycle[5.3.0]decane systems is one of the most commonly encountered of the cycloheptane derivatives in bioactive natural compounds.[1] The carbocyclic system bicycle[5.3.0]decane construction has been approached using different strategies: either by the seven-membered ring construction over an existing five-membered ring, or the five-membered ring formation over a pre-existing seven-membered ring, or from other carbocyclic systems.[2,3] Recently, the synthesis of sesquiterpenoids with bicycle[5.3.0]decane skeleton from tropinone or tropane derivatives has also been described.[4,5]

In this paper, a detailed study on the transformation of cycloheptenone **2** (scheme 1) into the enone **35**, through the key intermediate dione **5**, which has a *seco*-carotane skeleton, is reported. Enone **35** is a versatile synthetic intermediate for the synthesis of carotane sesquiterpenoids **I**[1] and superior homologs as tormesane skeleton diterpenoids **II**[6].



I **35** **II tormesol**

RESULTS AND DISCUSSION

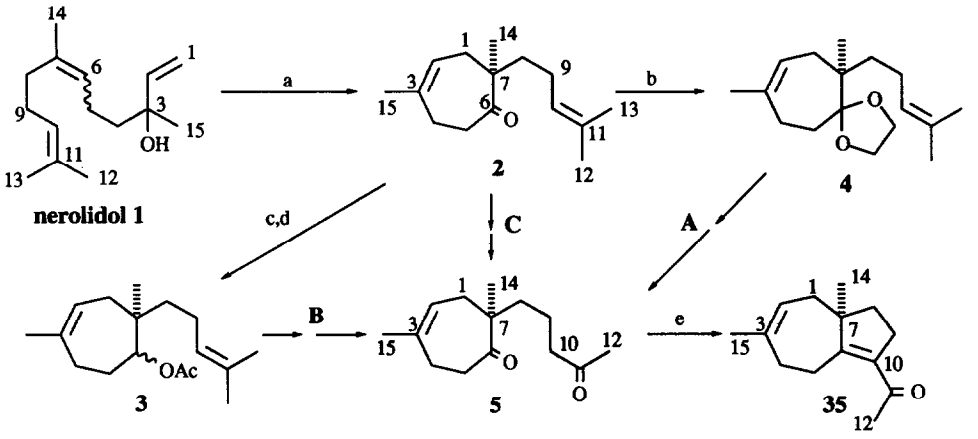
The starting material, cycloheptenone **2**, has been obtained from Z/E (±) nerolidol with a 73% yield following the procedure of Demole and Enggist.[7] The dione **5** was obtained from **4**, **3** and **2** in three different

Table 1. CATALYTIC ALLYLIC OXIDATIONS OF **4**, **2** AND **3**.

N°	Substrate mmol			e SeO_2	e Coox	e Cat	t h	#	4 %	6 7 %		8 %	9 %	2 %	10 %	11 %	3 %	12 %	13 %
1	1.3			0.02	6.2[a]	0.1[c]	24	a	12	16									
2	1.3			0.02	6.2[a]	0.1[c]	24	b	15	25									
3	1.5			0.02	4.6[a]	0.1[c]	48	c	5	6		5							
4	1.3			0.37	3.8[a]	13[d]	3	e	19	5									
5	1.5			0.37	3[b]	13[d]	19	e			6		5						
6	1.9			0.37	3[b]	13[d]	0.7	f	4	17									
7		1.5		0.02	6.7[a]	0.1[c]	8.5	d						82		14			
8		1.2		0.12	12[a]	0.1[c]	16	d						7	7	12			
9		2.0		0.02	6[b]	0.1[c]	1.5	d						60	10				
10			0.8	0.02	6[a]	0.1[c]	23	d									15	7	36
11			4.7	0.02	5.3[a]	0.1[c]	7	d									37	3	51

-All allylic oxidations were performed in CH_2Cl_2 solutions at room temperature. - [a, b] The cooxidant was ^tBuOOH, either 80% in di*terc*-butylperoxide or 3M in toluene respectively. - [c, d] The homogeneous catalysis was carry out with salicylic acid and the heterogeneous one with silicagel, respectively. - #: work-up: see experimental section. [e]: mmol/mmol of substrate.

ways (routes **A**, **B** and **C**, respectively). In these three routes, the two fundamental steps are the same: functionalization of the side chain on C-12 and subsequent degradation of it. The substrates **3** and **4** are easily available from **2** (Scheme 1).



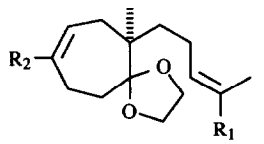
Scheme 1. a. NBS/CCl_4/Δ/collidine/Δ; b. Ethylene glycol/TsOH; c. LAH; d. Ac_2O/Py; e. KOH/EtOH.

Before proceeding with the three routes, the behaviour of the three starting material **2**, **3** and **4** in the allylic oxidation will be seen.

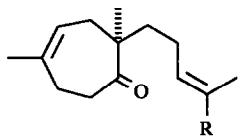
Functionalization on C-12 using either **2**, **3** or **4** as substrates was carried out by treatment with selenium dioxide under different conditions. Table 1 shows the results of oxidations of **2**, **3** and **4** with SeO_2, under catalytic homogeneous[8] and heterogeneous[9] conditions.

The oxidation of **4** provides **6**, **7**, **8** and **9**. The oxidation product **6** possess a hydroxyl group on C-12, **7**, **8** and **9** are polyoxidated products on C-12 and C-15: two aldehyde groups in **7**, two hydroxyl groups in **8**, an hydroxyl group on C-15 and an aldehyde on C-12 in **9**. The best yields were obtained when the oxidation is followed by reduction with metallic hydrides (entries 2 and 6),[10] even though most of the crude reaction product was retained in the chromatographic column.

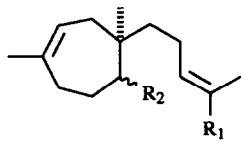
The catalytic oxidation of **2** was very discouraging, not only because transformation to the desired product was very poor, but also because when the reaction time is greater, complex mixtures were obtained. The allylic alcohol **11** or aldehyde **10** are obtained from **2** depending on the ^tBuOOH concentration used (entries 7 and 9).



	R_1	R_2
4	Me	Me
6	CH_2OH	Me
7	CHO	CHO
8	CH_2OH	CH_2OH
9	CHO	CH_2OH
14	CHO	Me
15	Me	CH_2OH



	R
2	Me
10	CHO
11	CH_2OH



	R_1	R_2
3	Me	OAc
12	CHO	OAc
13	CH_2OH	OAc
34	Me	OTBDMS

The best result is obtained from **3** whose catalytic oxidation afforded aldehyde **12** and allylic alcohol **13**, the latter is obtained in 75% yield based on the transformed product.

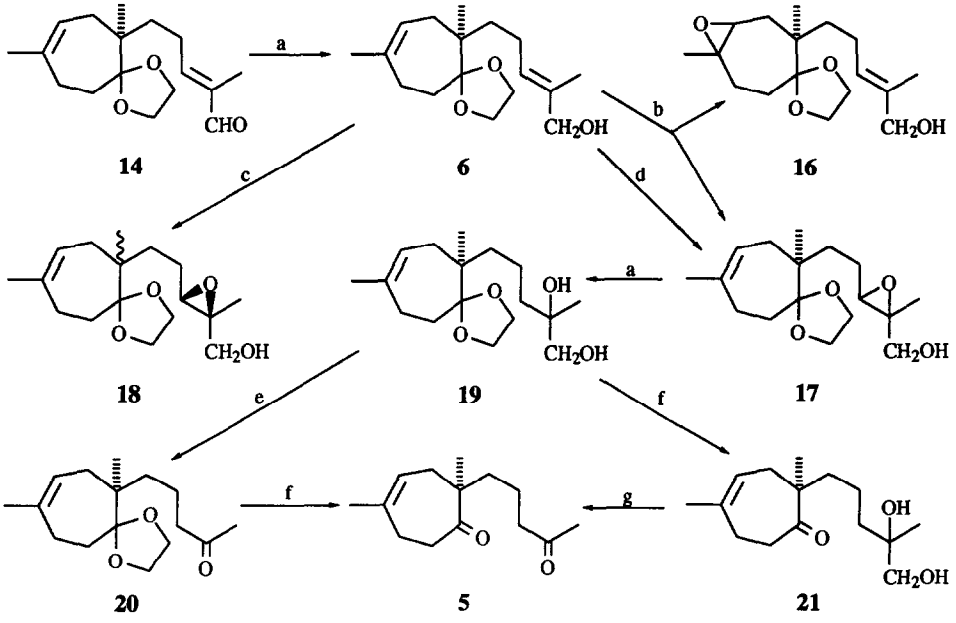
The allylic oxidation has also been carried out using **34** as the substrate but no satisfactory results were achieved.

Table 2 shows the results of stoichiometric oxidations of **2** and **4** with SeO_2 with[11] or without[12] pyridine. Compound **4** afforded in addition to **6** another hydroxy derivative **15**, the product of functionalization on Me-15, and the aldehyde **14**, easily transformable by reduction into **6**. Treatment of **2** with SeO_2/Py gave alcohol **11** (52%), aldehyde **10** (26%) and starting material (15%). In conclusion the best yield in the oxidation of either **2** or **4** was obtained in presence of pyridine and using stoichiometric quantities of SeO_2.

Table 2. STOICHIOMETRIC ALLYLIC OXIDATIONS OF **4** AND **2**

N°	Substrate mmol 4	2	SeO_2 mmol/ mmol	Py mmol/ mmol	t h	2 %	4 %	6 %	10 %	11 %	14 %	15 %
1	19		0.5	0.6	3		21	28			8	5
2	0.34		0.5		22	8	18	20			7	5
3		19	0.5	0.6	7	15			26	52		

Now that the behaviour of **2**, **3** and **4** towards the allylic oxidation has been summarised, three different routes to **5** will be described.



Scheme 2. a. LAH; b. *m*-CPBA; c. L(+)DET/Ti(^{i}PrO)$_4$/^{t}BuOOH; d. VO(acac)$_2$/^{t}BuOOH; e. H_5IO_6; f. TsOH; g. LTA.

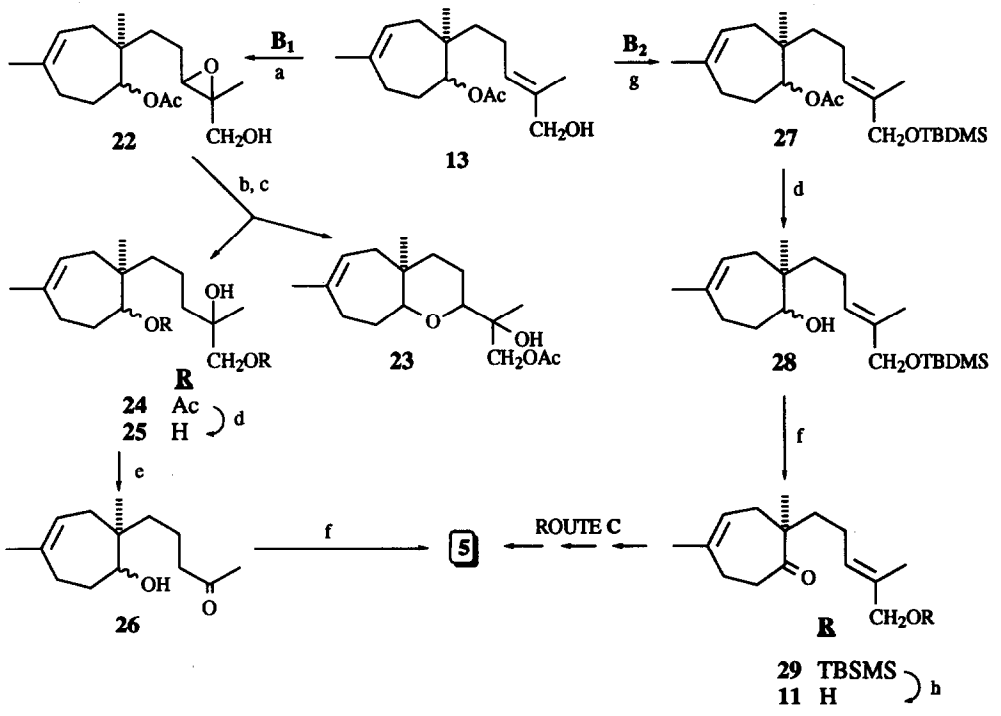
Route A. From **4** to **5**. The transformations of **6** and **14** (allylic oxidation products of **4**) into **5**, are shown in Scheme 2.

Reduction of **14** with $LiAlH_4$ gave **6** in a quantitative yield. Oxidation of **6** with *m*-CPBA was not chemoselective, in fact a mixture of **16** and **17** was obtained, in which both double bonds were epoxidised at the same time, and no double epoxidation product was formed.

In order to resolve the racemic mixture of **6** Sharpless asymmetric epoxidation[13] of **6** with L(+)DET/Ti(^{i}PrO)$_4$/^{t}BuOOH was carried out, but unfortunately a mixture of diastereomers **18** (86%), not separable by CC was obtained, so the epoxidation was carry out with VO(acac)$_2$/^{t}BuOOH[14], affording the epoxy derivative **17** only, which was reduced to diol **19**. The diastereomeric diols obtained from reduction of **18**, could not be separated as well.

The oxidation of **19** with H_5IO_6 gave **20** with an excellent yield, however hydrolysis of **20** with TsOH/MeOH yielded **5** in a poor yield, probably because some side reactions take place under acidic conditions. The opposite strategy from **19**: that is, deprotection, followed by oxidation with LTA, afforded **5** quantitatively.

Route B. From **3** to **5**. Dione **5** can be obtained from acetyl derivative **3**, through the hydroxy derivative **13**, following paths $\mathbf{B_1}$ or $\mathbf{B_2}$ (scheme 3). The most important difference between these routes is : in path $\mathbf{B_1}$, the hydroxyl group on C-12 is free, and in path $\mathbf{B_2}$ is protected as a silyl ether.

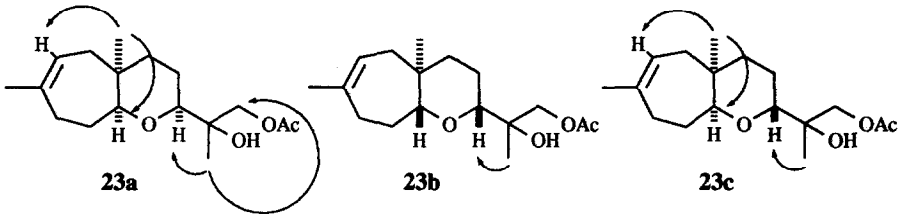


Scheme 3. a. VO(acac)$_2$/^{t}BuOOH; b. LAH; c. Ac_2O/Py; d. NaOH/MeOH; e. LTA; f. CrO_3/Py; g. TBDMSCl/Et_3N; h. Bu_4NF.

Oxidation of **13** with VO(acac)$_2$ gave epoxide **22** (95%), reduction and subsequent acetylation and CC of the acetyl derivatives afforded a mixture of **23** and **24**, in a disappointing 1:2 ratio.

Alkaline hydrolysis of **24** yielded triol **25**, whose oxidation with LTA gave ketone **26**. The oxidation of **26** with CrO_3/Py[15] afforded **5** with a better yield (90%) than when it was carried out by Swern oxidation[16] (80%).

By CC of the mixture **23**, three isomers were isolated, the relative stereochemistry fall of them was assigned by nOe experiments, which can be seen below.

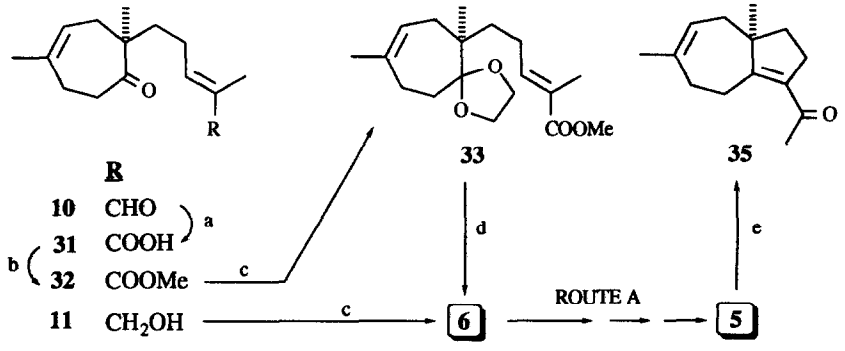


Recently some natural *seco*-carotanes (for instance Rugosal D)[17] have been isolated, being very similar to the pyranyl derivatives **23**.

The formation of the pyranil derivatives **23**, in the reduction of **21** with LAH implies a lower yield in path $\mathbf{B_1}$. So, it was decided to avoid the simultaneous presence of the hydroxyl group, generated during the course of the reaction, and the epoxide group on C-10, already present in the molecule. This idea provided a new route from **13** (path $\mathbf{B_2}$), (scheme 3).

Protection of the primary hydroxyl group of **13** with TBDMSCl[18] gave **27** in excellent yield, alkaline hydrolysis of this afforded the hydroxy derivative **28** in quantitative yield. Oxidation of **28** with CrO_3/Py gave ketone **29** (80%), deprotection with TBAF[19] afforded **11**, the key product in route C (*vide infra*). Although path $\mathbf{B_2}$, where the silyl derivatives are used as protecting groups, is longer, the final yield is better than path $\mathbf{B_1}$.

Finally the **route C** in which **5** has been synthesised directly from **2**, requires the use of aldehyde **10** and alcohol **11**, both being allylic oxidation products of **2** (Scheme 4), already described.



Scheme 4. a. $NaClO_2$; b. CH_2N_2; c. Ethylene glycol/TsOH; d. LAH; e. KOH/EtOH.

Protection of **11** with ethylene glycol / TsOH gave **6**, quantitatively. Transformation of **6** into **5** has been described previously as route **A**, scheme 2.

Oxidation of aldehyde **10** with $NaClO_2$[20] afforded acid **31** that was esterified with CH_2N_2, and protected

Table 3. ^{13}C NMR data ($CDCl_3$, 50.3 MHz)

C	2	4	5*	6	7	8	9	10	11	14	15	17	19	20	21	26	32	33	35*
1	35.1	30.6	34.7	30.6	30.2	31.1	30.9	35.1	35.1	30.6	31.1	30.5	30.6	30.5	35.1	33.6	35.0	30.6	37.8
2	121.6	122.6	121.5	122.4	152.4	123.8	123.1	121.1	121.5	122.5	124.1	122.2	122.5	122.4	121.5	122.1	121.2	122.1	121.1
3	136.9	140.1	136.9	140.3	147.1	143.5	144.0	137.3	137.0	140.1	143.5	140.5	140.3	140.2	136.8	139.6	137.1	140.6	139.3
4	31.9	28.0	31.9	27.9	17.6	23.9	23.9	31.9	31.8	27.9	23.9	27.8	27.9	27.9	31.9	28.8	31.8	27.9	33.1
5	38.9	33.3	38.0	33.3	33.6	33.0	33.0	37.9	38.5	33.3	33.1	33.3	33.4	33.9	39.3	34.6	37.8	33.1	24.1
6	216.6	115.4	216.6	115.3	114.2	115.4	114.7	215.7	216.4	115.3	115.2	115.1	115.4	115.2	217.1	80.4	215.0	115.1	164.7
7	53.7	44.5	53.6	44.4	45.2	44.4	44.3	53.4	53.6	44.4	44.5	44.1	44.5	44.4	53.9	38.8	53.5	44.4	52.6
8	37.9	34.3	38.0	34.0	35.0	34.0	33.1	37.0	37.9	34.7	34.3	30.5	34.9	33.3	37.9	29.5	37.1	33.4	37.3
9	22.9	22.6	18.8	22.3	24.0	22.3	23.7	24.2	22.6	23.0	22.9	23.1	18.0	18.5	18.5	17.8	23.7	23.5	30.8
10	124.2	125.6	44.0	127.3	154.4	127.2	155.4	153.7	125.8	153.0	125.4	60.9	39.9	44.8	39.5	44.6	141.9	143.6	133.3
11	131.7	130.7	208.4	134.3	139.3	134.3	139.0	139.6	135.2	140.1	131.0	61.1	73.0	208.8	72.8	209.2	127.8	127.1	199.3
12	25.6	25.7	29.8	69.1	195.0	69.0	195.1	194.9	68.8	194.0	25.6	65.8	70.0	29.6	69.8	29.7	168.6	169.8	30.2
13	17.5	17.5	-	13.5	9.1	13.6	8.9	9.1	13.5	10.1	17.6	14.1	23.4	-	23.3	-	12.3	12.2	-
14	22.1	19.8	22.3	19.8	20.2	19.9	19.8	22.5	22.2	19.8	19.8	19.8	19.8	19.7	22.2	23.7	22.2	19.8	23.6
15	25.1	25.3	25.2	25.3	193.0	67.9	67.6	25.1	25.1	25.3	68.1	25.2	25.2	25.2	25.1	25.2	25.2	25.3	25.9
$(-O-CH_2-)_2$		64.9		64.9	65.2	65.0	64.9			65.0	65.0	64.9	64.9	64.9			-	65.0	
COOMe																	51.6	51.6	

* The assignment has been done by 2D Heteronuclear Experiments ($^1H/^{13}C$ HCCORR).

giving **33**, whose reduction afforded **6**. The overall transformation of **10** into **6** was obtained with a 79% yield, this being a considerable improvement of route **C** yield.

The overall yields for the transformation of **2** into **5** according to the different alternative routes are shown in the following table:

ROUTE	% (from **2**)
A	30
$\mathbf{B_1}$	18
$\mathbf{B_2}$	23
C	63

Several conclusions could be drawn about the results for each route:

For route **A**, the allylic oxidation of compound **4** is the reason for the low overall yield, since the remaining transformations take place with an excellent yield.

For route **B**, the allylic oxidation of **3** takes place with good yield (75% of the transformed product), but in this case, the yields are lower due to the formation of the tetrahydro-pyranyl derivatives **23** in path $\mathbf{B_1}$ and because of the number steps in path $\mathbf{B_2}$.

For route **C**, the yield is higher than double compared to routes **A** and **B** not only because the best allylic oxidation yield is part of this route but also because both **10** and **11** can be used for the obtention of **6**, increasing the yield on this compound (73%).

Finally the treatment of **5** with KOH/EtOH afforded **35** swiftly in 84% yield, being an excellent starting point for the synthesis of tormesol and other natural compounds.

EXPERIMENTAL

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. ^1H and ^{13}C NMR spectra were performed in deuterochloroform and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively in a Bruker WP–200 SY. Chemical shifts are reported in δ, ppm and coupling constants (J) are given in Hz. MS spectra were performed on a VG–TS 250 spectrometer at 70 eV ionizing voltage. Mass Spectra are presented as m/z (% rel. int.). Diethyl ether, THF and benzene were distilled from sodium, pyridine and dichloromethane were distilled from Calcium hydride under Ar atmosphere.

TREATMENT OF **1** WITH NBS/COLLIDINE : **2**

N-bromosuccinimide (15.84 g, 90 mmol) was added to a solution of 20 g (90 mmol) of (±)-nerolidol (*cis/trans* mixture) in CCl_4 (150 ml), the reaction was stirred for 55 hours at room temperature. Then, hexane (230 ml) was added, the mixture filtered and collidine (40 ml, 303 mmol) was added, the solvent was removed and the residue was stirred at 110ºC for 24 hours, and then was heated at 170ºC under N_2 for 16 hours, the mixture was allowed to cool and poured into 10% aqueous HCl and extracted with ether, the organic phase was washed with $NaHCO_3$ and water and dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude reaction product (18 g) was chromatographed (*n*-hexane:EtOAc, 97:3) affording **2** (14.6 g, 73%). Colourless oil. IR(film) ν_{max} cm^{-1}: 1705, 1455, 1375, 1210, 1060, 830 and 750. ^1H δ: 5.47(1H, t, J= 6.3 Hz, H-2), 5.05(1H, t, J= 6.3 Hz, H-10), 1.66(6H, s), 1.57(3H, s), 1.06(3H,s). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 220[M^+]

(10), 203(11), 163(8), 151(9), 138(100), 123(95), 110(94), 95(74), 81(59), 69(80).

REDUCTION OF **2** WITH $LiAlH_4$ AND SUBSEQUENT ACETYLATION: **3**

$LiAlH_4$ (366 mg, 9.6 mmol) was added to a solution of **2** (6.4 g, 29 mmol) in dry ether (30 ml) and the mixture was stirred for 1 hour at room temperature under N_2. Then ether (60 ml), some drops of water and Na_2SO_4 were added, the mixture was left for 30 minutes. Following this, it was filtered and the solvent evaporated to give 5.3 g, of crude product, which was acetylated with Ac_2O (1 ml) in pyridine (1 ml). The reaction mixture was left for 12 hours, then poured into ice-water and extracted with ether. The ether extracts were combined and washed with 2N HCl, $NaHCO_3$ and H_2O, dried (Na_2SO_4) and removal of the solvent afforded **3** (5.8 g, 76% overall). Oil. IR(film) ν_{max} cm^{-1}: 1725, 1435, 1360, 1230, 1035, 1010 and 970. ^1H δ: 5.38(1H, m, H-2), 5.10(1H,m, H-10), 4.80(1H, m, H-6'), 4.70(1H, m, H-6), 2.04(3H, s, OCOMe), 2.05(3H, s, OCOMe'), 1.73(3H, s), 1.68(3H, s), 1.60(3H, s), 0.89(3H, s, Me-14), 0.83(3H, s, Me-14').

PROTECTION OF **2** WITH $(CH_2OH)_2$/TsOH: **4**

Ethylene glycol (20 ml) and TsOH (0.17 g) was added to compound **2** (5 g, 22.7 mmol) dissolved in dry benzene (50 ml) and refluxed for 24 h into a Dean-Stark trap. Then it was washed with brine, $NaHCO_3$, water and dried over Na_2SO_4. The solvent was evaporated to afford **4** (5.77 g, 97%) as a colourless oil. IR(film)ν_{max} cm^{-1}: 1440, 1370, 1150, 1090, 1050, 940, 850 and 820. ^1H δ: 5.38(1H, t, J= 6.3 Hz, H-2), 5.10(1H, t, J= 6.3 Hz, H-10), 3.94(4H, m, -O-CH_2-CH_2-O-), 1.74(3H, s), 1.67(3H, s), 1.60(3H,s), 0.88(3H, s). ^{13}C δ: see table 3.

CATALYTIC AND HOMOGENEOUS ALLYLIC OXIDATIONS OF **4**, **2** AND **3**.

General Procedure Table 1. Entries (1-3) and (7-11).

To a solution of selenium dioxide (0.02 mmol/mmol of substrate, except in entry 8, in which was added 0.12 mmol/mmol of sustrate) and salicylic acid (0.10 mmol/mmol of substrate) in dry CH_2Cl_2 (2 ml/mmol of sustrate), chilled in an ice-water bath, was added ^{t}BuOOH (80% in di*terc*-butylperoxide, except in entry 9, in which was used ^{t}BuOOH 3M in toluene, 4.6-6.7 mmol/mmol of substrate; see table 1) in one portion. Then was added a solution of the substrate **4**, **2** or **3** (0.8-4.7 mmol) in CH_2Cl_2 (2-3 ml) was added during 10 minutes. The resulting solution was stirred at room temperature.

The work-up in each case is as follows:

a) **Entry 1**. (340 mg, 1.3 mmol of **4**). After 24 hours at room temperature, Me_2S (0.4 ml) was added, and the mixture was stirred for 5 hours at room temperature. After that the solution was chilled in an ice-water bath, neutralized with 20% aqueous K_2CO_3 and extracted with ether, washed with water and brine and dried (Na_2SO_4). Removal of the solvent afforded 290 mg of the crude product that was chromatographed affording **6** (58 mg, 16%) and **4** (42 mg, 12%). **6** is a colourless oil. IR(film) ν_{max} cm^{-1}: 3400, 1430, 1390, 1140, 1090, 1060, 1000, 950 and 820. ^1H δ: 5.38(2H, t, J= 6.8 Hz, H-2 and H-10), 3.97-3.92(6H, m, H-12 and -O-CH_2-CH_2-O-), 1.74(3H, s, Me-15), 1.66(3H, s, Me-13), 0.87(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 280[M^+] (16), 218(6), 263(5), 195(17), 182(30), 163(14), 139(20), 113(60), 99(33), 86(100), 67(57).

b) **Entry 2**. (340 mg, 1.3 mmol of **4**). After 24 hours at room temperature, the reaction was diluted with benzene (10 ml) and concentrated *in vacuo*. Ether (10 ml) was added to the residue, cooled in an ice-water bath

and $LiAlH_4$ (40 mg, 1.05 mmol) was added and the mixture stirred for 2 hours at room temperature. The reaction was worked-up as usual, giving 298 mg of crude product that was chromatographed affording **4** (54 mg, 15%) and **6** (91 mg, 25%).

c) **Entry 3**. (403 mg, 1.5 mmol of **4**). After 48 hours at room temperature, 10% tartaric acid (5 ml) was added and the mixture stirred for 30 minutes. The reaction mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed and ether (10 ml) was added, followed by 5 ml of 1N NaOH solution, and stirred at 0°C for 30 minutes. The organic phase was washed with brine, dried (Na_2SO_4), evaporated *in vacuo* and purified by column chromatography on silica gel affording **4** (18 mg, 5%), **6/7** (23 mg, 6%) and a mixture in which **8** (5%) could be identified. **8** IR(film) ν_{max} cm^{-1}: 3390, 1450, 1375, 1080, 1000, 945 and 900. ^1H δ: 5.68(1H, m, H-2), 5.38(1H, m, H-10), 4.30(2H, s), 4.17(2H, s), 1.65(3H, s, Me-13), 0.89(3H, s, Me-14). ^{13}C δ: see table 3.

d) **Entries 7-11**. After stirring at room temperature (see Table 1), the reaction mixture was diluted with benzene (10-15 ml), and concentrated *in vacuo*. Ether (30-35 ml) was added to the residue, then washed with 10% KOH and water and concentrated *in vacuo* to give a yellow liquid. The mixture, cooled in an ice-water bath, was dissolved in cold acetic acid (1-5 ml) and dimethyl sulfide (0.3-1.3 ml). The cooling bath was removed after the addition was complete, and the mixture stirred for 5 hours at room temperature. Then the solution was chilled in an ice-water bath, neutralized with 20% K_2CO_3, and poured into ether. The organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude mixture was chromatographed on a silicagel column, eluted with *n*-hexane:EtOAc mixtures of increasing polarity, affording **10** and **11** from **2** and **12** and **13** from **3** (see table 1).

10. IR(film) ν_{max} cm^{-1}: 2640, 1690, 1630, 1430, 1370, 1190 and 1050. ^1H δ: 9.36(1H, s, H-12), 6.41(1H, t, J= 6.3 Hz, H-10), 5.47(1H, t, J= 6.3 Hz, H-2), 1.72(3H, s), 1.67(3H, s), 1.10(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 234[M^+] (23), 216(10), 177(6), 166(13), 151(26), 138(100), 123(53), 110(72), 95(56), 81(48), 69(39).

11. IR(film) ν_{max} cm^{-1}: 3410, 1703, 1440, 1380, 1220, 1070 and 1010. ^1H δ: 5.49(1H, t, J= 6.3 Hz, H-2), 5.35(1H, t, J= 6.3 Hz, H-10), 3.98(2H, s, H-12), 1.70(3H, s), 1.65(3H, s), 1.10(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 236[M^+] (3), 218(23), 200(7), 150(41), 138(90), 110(100), 95(43), 81(44), 67(45), 55(46), 41(83).

12. ^1H δ: 9.40(1H, s, H-12), 9.38(1H, s, H-12'), 6.70(1H, m, H-10), 6.48(1H, m, H-10'), 5.38(1H, m, H-2), 5.10(1H, m, H-2'), 4.80(2H, m, H-6 and H-6'), 2.04(3H, s, OCOMe), 2.03(3H, s, OCOMe'), 1.74(6H, s, Me-15 and 15'), 0.94(3H, s, Me-14), 0.88(3H, s, Me-14').

13. IR(film) ν_{max} cm^{-1}: 3380, 1735, 1450, 1375, 1240, 1020, 835 and 735. ^1H δ: 5.38(2H, m, H-2 and H-10), 4.81(1H, m, H-6), 4.70(1H, m, H-6'), 4.00(2H, m, H-12), 2.06(3H, s, OCOMe), 2.05(3H, s, OCOMe'), 1.74(3H, s), 1.67(3H, s), 0.92(3H, s, Me-14), 0.85(3H, s, Me-14').

CATALYTIC AND HETEROGENEOUS ALLYLIC OXIDATIONS.

General Procedure Table 1. Entries (4-6), .

^{t}BuOOH (3-3.8 mmol/mmol of sustrate, see table 1) was added to a solution of selenium dioxide supported

on silica gel[9] (5%, 1.1-1.5 g) in CH_2Cl_2 (4-5 ml) and stirred for 15 minutes at room temperature under argon, then a solution of **4** (1.3-1.9 mmol) in CH_2Cl_2 (2-3 ml) was added dropwise.

The work-up in each case is as follows:

e) **Entries 4 and 5**. After 3 and 19 hours, respectively, at room temperature, the reaction mixture was filtered washing with CH_2Cl_2. The filtrate was washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent gave 265 mg (entry 4) and 400 mg (entry 5) of crude products that were chromatographed affording **4** (50 mg, 19%) and **6** (19 mg, 5%) [entry 4] and **7** (21 mg, 6%) and **9** (17 mg, 5%) [entry 5].

7. IR(film) ν_{max} cm^{-1}: 1695, 1630, 1440, 1365, 940, 740 and 700. ^1H δ: 9.38(1H, s, H-15), 9.37(1H, s, H-12), 6.73(1H, t, J= 6.3 Hz, H-2), 6.46(1H, t, J= 6.3 Hz, H-10), 3.97(4H, m, -O-CH_2-CH_2-O-), 1.74(3H, s, Me-13), 1.00(3H, s, Me-14). ^{13}C δ: see table 3.

9. IR(film) ν_{max} cm^{-1}: 3390, 2695, 1665, 1630, 1440, 1360, 930 and 880. ^1H δ: 9.36(1H, s, H-12), 6.50(1H, t, J= 6.3 Hz, H-10), 5.65(1H, t, J= 6.3 Hz, H-2), 4.05-3.95(6H, m, H-15 and -O-CH_2-CH_2-O-), 1.74(3H,s, Me-13), 0.94 (3H, s, Me-14). ^{13}C δ: see table 3.

f) **Entry 6**. After 45 minutes at room temperature 5% $NaHCO_3$ was added (1ml) and the mixture was stirred for 5 minutes, and then filtered, washing with CH_2Cl_2. The filtrate was washed with water, brine and dried (Na_2SO_4), after removal of the solvent, ether (5 ml) was added and $LiAlH_4$ (49 mg, 1.3 mmol), the mixture was stirred for 5 hours at room temperature. The reaction was worked-up as usual, affording 267 mg of crude product that was chromatographed to give **4** (13 mg, 4%) and **6** (63 mg, 17%).

STOICHIOMETRIC ALLYLIC OXIDATIONS (Table 2).

General procedure without pyridine

Entry 2. Selenium dioxide (19 mg, 0.17 mmol) was added to **4** (89 mg, 0.34 mmol) in 95% ethanol (5 ml) and the solution was heated at reflux for 22 hours. After cooling and filtering through celite, ethanol was evaporated giving an orange-yellow oil which was dissolved in ether. The solution was washed with water, $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated to afford 87 mg of crude product that was cromatographed affording **2** (6 mg, 8%), **4** (16 mg, 18%), **14** (7 mg, 7%), **6** (19 mg, 20%) and **15** (5 mg, 5%).

14. IR(film) ν_{max} cm^{-1}: 2780, 1690, 1650, 1150, 1090, 1060, 960, 910 and 840. ^1H δ: 9.14(1H, s, H-12), 6.47(1H, t, J= 6.3 Hz, H-10), 5.40(1H, t, J= 6.3 Hz, H-2), 3.95(4H, m, -O-CH_2-CH_2-O-), 1.76(3H, s, Me-15), 1.58 (3H, s, Me-13), 0.92 (3H, s, Me-14). ^{13}C δ: see table 3.

15. IR(film) ν_{max} cm^{-1}: 3430, 1440, 1390, 1140, 1090, 1050, 1000, 950, 890 and 830. ^1H δ: 5.67(1H, t, J= 6.3 Hz, H-2), 5.10(1H, t, J= 6.3 Hz, H-10), 4.05-3.93(6H, m, H-15 y -O-CH_2-CH_2-O-), 1.67(3H, s, Me-13), 1.60 (3H, s, Me-12), 0.90 (3H, s, Me-14). ^{13}C δ: see table 3.

General procedure with pyridine

Entries 1 and 3. A mixture of **4** or **2** (19 mmol), freshly sublimed selenium dioxide (1.05 g, 9.5 mmol), and dry pyridine (1 ml, 12 mmol) in 95% ethanol (70 ml) wass heated under reflux for 3 or 7 hours, respectively. After cooling and filtration through celite, the solvent was removed *in vacuo* and the residue extracted with ether. The combined extracts were washed with 2N HCl and water, dried (Na_2SO_4) and evaporated to give a crude oil, that was cromatographed affording:

entry 1. **4** (1.08 g, 21%), **14** (350 mg, 8%), **6** (1.48 g, 28%) and **15** (260 mg, 5%).

entry 3. **2** (915 mg, 22%), **10** (1.16 g, 26%) and **11** (2 g, 45%).

REDUCTION OF **14** WITH $LiAlH_4$: **6**

$LiAlH_4$ (38 mg, 1 mmol) was added to a stirred solution of **14** (300 mg, 1.08 mmol) in dry ether (6 ml) and the mixture was stirred for 3 hours at room temperature under N_2. The usual work-up afforded **6** (278 mg, 92%).

TREATMENT OF **6** WITH MCPBA: **16/17**

*m*CPBA (26 mg, 0.15 mmol) was added to compound **6** (31 mg, 0.10 mmol) dissolved in CH_2Cl_2 (4 ml). The reaction mixture was stirred at room temperature for 45 minutes. The solvent was removed and the residue extracted with ether, washed with $NaHCO_3$ and H_2O and dried over Na_2SO_4, filtered and evaporated to afford a mixture of **16/17** (29 mg, 98 %). IR(film) ν_{max} cm^{-1}: 3400, 1650, 1250, 1170, 940 and 870. ^1H δ: 5.40(1H, m), 3.90(4H, m), 3.60(2H, m), 3.00(1H, m), 2.70(1H, m), 1.70(3H, s), 1.60(3H, s), 1.30(3H, m), 0.90(3H, s).

SHARPLESS EPOXIDATION OF **6**: **18**

L(+)DET (0.36 ml, 2 mmol) was added to a mixture of $Ti(^iPrO)_4$ (0.6 ml, 2 mmol), CaH_2 (0.8 mg, 0.019 mmol) and silicagel (1.2 mg) in 10 ml of dry CH_2Cl_2, under argon at -23°C. After 10 minutes, **6** (577 mg, 2 mmol) in CH_2Cl_2 (10 ml) was added and stirred for 10 minutes. After that *tert*–butyl hydroperoxide (3M, 1.4 ml, 4.2 mmol) was added. The mixture was stirred for 3 hours at -23°C, then 10% tartaric acid (7.5 ml) was added and the mixture stirred for 30 minutes at -23°C, and for 1 hour at room temperature until the aqueous phase cleared. After separation and concentration *in vacuo*, the residue was diluted with ether, and then 12 ml of 1N NaOH solution was added, and stirred at 0°C for 30 minutes. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated to give 851 mg. The crude product was dissolved in 34 ml of 10% NaOH/MeOH and stirred during 24 hours at room temperature. After removal of the solvent, water was added and the mixture was extracted with ether, washed with 2N HCl and water. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give **18** (507 mg, 86%). IR(film) ν_{max} cm^{-1}: 3430, 1450, 1380, 1090, 1060, 960, 895 and 850. ^1H δ: 5.26(1H, m H-2), 3.89(4H, m, -O-CH_2-CH_2-O-), 3.52(2H, m, H-12), 2.90(1H, t, J= 5.8 Hz, H-10), 1.69(3H, s, Me-15), 1.23(3H, s, Me-13), 0.81(3H, s, Me-14). EIMS m/z (rel. int.): 296[M^+] (20), 265(7), 214(6), 181(40), 153(17), 139(27), 113(39), 86(100), 55(48).

EPOXIDATION OF **6** WITH $VO(acac)_2$/^{t}BuOOH: **17**

tert–Butyl hydroperoxide (3M, 6 ml, 18 mmol) was added dropwise to a solution of **6** (4.6 g, 16.43 mmol) and vanadyl acetyl acetonate (62 mg, 0.22 mmol) in 60 ml of benzene was heated at reflux. The initially colourless solution of **6** in benzene turned bright green upon addition of the $VO(acac)_2$. The colour faded as the reflux temperature was approached and then turned deep red as the ^{t}BuOOH was added. The reaction was monitored by tlc and judged complete after 10 minutes. During this time the deep red colour turns to yellow and then to light green. The reaction mixture was cooled to 25°C and then washed sequentially with water, 2N HCl, 20% $NaHSO_3$, 6% $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give **17** (4.76 g, 98%). IR(film) ν_{max} cm^{-1}: 3430, 1450, 1380, 1090, 1060, 960, 895 and 850. ^1H δ: 5.26(1H, m H-2), 3.89(4H, m, -O-CH_2-

CH_2-O-), 3.52(2H, m, H-12), 2.90(1H, t, J= 5.8 Hz, H-10), 1.69(3H, s, Me-15), 1.23(3H, s, Me-13), 0.81(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 296[M^+] (20), 265(7), 214(6), 181(40), 153(17), 139(27), 113(39), 86(100), 55(48).

REDUCTION OF **17** WITH $LiAlH_4$: **19**

$LiAlH_4$ (247 mg, 6.5 mmol) was added to a stirred solution of **17** (1.94 g, 6.5 mmol) in dry THF (30 ml) and the mixture stirred for 30 minutes at room temperature under N_2. The usual work-up afforded **19** (1.88g, 97%). IR(film) ν_{max} cm^{-1}: 3400, 1440, 1380, 1090, 1060, 960, 890 and 850. ^1H δ: 5.33(1H, t, J= 6.3 Hz, H-2), 3.93(4H, m, -O-CH_2-CH_2-O-), 3.45(1H, d, J= 10.7 Hz, H-12), 3.38(1H, d, J= 10.7 Hz, H-12), 1.72(3H, s, Me-15), 1.15(3H, s, Me-13), 0.84(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 298[M^+] (35), 267(8), 181(23), 153(20), 139(15), 113(32), 86(100), 67(15), 55(16).

TREATMENT OF **19** WITH H_5IO_6: **20**

H_5IO_6 (78 mg, 0.3 mmol) was added to compound **19** (101 mg, 0.3 mmol) dissolved in THF (2ml) and water (1.5 ml) and stirred at room temperature for 1 hour. Then the mixture was extracted with ether, washed with 10% $NaHCO_3$, water and dried over Na_2SO_4 and the solvent removed to give **20** (77 mg, 96%). IR(film) ν_{max} cm^{-1}: 1710, 1640, 1080, 980, 935, 885, 850, 820 and 720. ^1H δ: 5.30(1H, t, J= 6.3 Hz, H-2), 3.90(4H, m, -O-CH_2-CH_2-O-), 2.33(2H, t, J= 7.3 Hz, H-10), 2.08(3H, s, Me-12), 1.69 (3H, s, Me-15), 0.81 (3H, s, Me-14). ^{13}C δ: see table 3.

HYDROLYSIS OF **20** WITH TsOH: **5**

TsOH (44 mg) was added to **20** (60 mg, 0.2 mmol) dissolved in MeOH (5 ml). The reaction was maintained under N_2 atmosphere at room temperature for 6 hours. The solvent was removed and diluted with ether, washed with $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated *in vacuo* to give **5** (11 mg, 25%). IR(film) ν_{max} cm^{-1}: 1710, 1440, 1370, 1200, 1170, 1090, 895 and 810. ^1H δ: 5.47(1H, t, J= 6.3 Hz, H-2), 2.10(3H, s, Me-12), 1.64(3H, s, Me-15), 1.03(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 222[M^+] (11), 204(41), 161(31), 146(33), 137(91), 119(65), 107(100), 93(58), 81(95), 67(68), 55(57).

HYDROLYSIS OF **19** WITH TsOH: **21**

TsOH (576 mg) was added to **19** (1 g, 3.35 mmol) dissolved in MeOH (40 ml). The reaction was maintained under N_2 atmosphere at room temperature for 30 minutes. After the usual work-up **21** (808 mg, 95%) was obtained.

OXIDATION OF COMPOUND **21** WITH LTA: **5**

LTA (1.6 g, 3.64 mmol) was added to a solution of **21** (900 mg, 3.54 mmol) in dry benzene (25 ml). The reaction mixture was stirred at room temperature for 30 minutes. Then some drops of ethylene glicol were added, and filtered, washing with benzene, and concentrated *in vacuo* to give **5** (763 mg, 97%).

EPOXIDATION OF **13** WITH $VO(acac)_2$/^{t}BuOOH: **22**

^{t}BuOOH (3M, 4 ml, 12 mmol) was added dropwise to a solution of **13** (2 g, 7.2 mmol) and $VO(acac)_2$ (28 mg, 0.10 mmol) in 15 ml of benzene heated at reflux. The reaction was monitored by tlc and judged complete after 45 minutes. Usual work-up gave **22** (1.92 g, 97%). IR(film) ν_{max} cm^{-1}: 3440, 1720, 1365, 1230, 1010 and 855. ^1H δ: 5.32(1H, m, H-2), 4.75(1H, m, H-6), 4.69(1H, m, H-6'), 3.60(1H, m, H-12), 2.98(1H, m, H-

10), 2.02(3H,s, OCOMe), 2.02(3H, s, OCOMe'), 1.70(3H, s, Me-15), 1.24(3H, s, Me-13), 1.21(3H, s, Me-13'), 0.86(3H, s, Me-14), 0.84(3H, s, Me-14'). EIMS m/z (rel. int.): 296[M+] (8), 279 (20), 272 (30), 251 (20), 235 (7), 205 (10), 187 (17), 159 (30), 134 (45), 121 (80), 105 (77), 93 (100), 81 (85), 67 (65).

REDUCTION OF **22** WITH $LiAlH_4$ AND SUBSEQUENT ACETYLATION.

$LiAlH_4$ (446 mg, 11.7 mmol) was added to a solution of **22** (1.4 g, 4.7 mmol) in dry THF (40 ml). The solution was heated under reflux for 6 hours. Usual work-up gave 1.4 g. The crude product obtained was acetylated with pyridine (1 ml) and Ac_2O (1 ml). The reaction mixture was left for 12 hours. After the usual work-up, the crude reaction product was chromatographed affording the mixture **23** (408 mg, 29%) and **24** (832 mg, 59%).

24. IR(film) ν_{max} cm^{-1}: 3430, 1720, 1440, 1380, 1250 and 1050. ^1H δ: 5.32(1H, t, J= 6.3 Hz, H-2), 4.80(1H, m, H-6), 4.70(1H, m, H-6'), 3.98(2H, m, $\underline{CH_2}OAc$), 2.11(3H, s, $CH_2OCO\underline{Me}$), 2.05(3H, s, OCOMe), 2.04(3H, s, OCOMe'), 1.73(3H, s, Me-15), 1.19(3H, s, Me-13), 0.87(3H, s, Me-14), 0.82(3H, s, Me-14'). ^{13}C δ: 34.8(C-1), 121.8(C-2), 140.3(C-3), 26.5(C-4), 33.9(C-5), 82.7(C-6), 80.4(C-6'), 38.3(C-7), 28.2(C-8), 17.2(C-9), 40.1(C-10), 71.9(C-11), 71.2(C-12), 23.9(C-13), 20.8(C-14), 25.3(C-15), 171.0(Me$\underline{C}$OO) and 21.2($\underline{Me}$COO). EIMS m/z (rel. int.): 340[M+] (2), 280(31), 263(17), 221(8), 202(44), 161(28), 148(43), 132(91), 107(73), 93(91), 81(100), 67(66), 55(74).

The mixture **23** was chromatographed on silicagel to give **23a**, **23b** ($CHCl_3$:Et_2O 95:5) and **23c** ($CHCl_3$:Et_2O 9:1) in a ratio 1:1:1.

23a. IR(film) ν_{max} cm^{-1}: 3450, 1740, 1375, 1240, 1090 and 1045. ^1H δ 5.31(1H, m, H-2), 4.24(1H, d, J= 11.2 Hz, H-12), 4.10(1H, d, J= 11.2 Hz, H-12), 3.29(2H, m, H-6 and H-10), 2.09(3H, s, -OCOMe), 1.71(3H, s, Me-15), 1.20(3H, s, Me-13), 0.82(3H, s, Me-14). ^{13}C δ: 31.8(C-1), 122.5(C-2), 140.8(C-3), 26.6(C-4), 40.7(C-5), 82.5(C-6), 34.0(C-7), 27.4(C-8), 21.8(C-9), 84.5(C-10), 73.0(C-11), 68.5(C-12), 24.2(C-13), 20.3(C-14), 25.2(C-15), 171.1(Me$\underline{C}$OO) and 20.9($\underline{Me}$COO).

23b. IR(film) ν_{max} cm^{-1}: 3440, 1750, 1470, 1380, 1250, 1080 and 1050. ^1H δ: 5.28(1H, m, H-2), 4.15(1H, d, J= 11.2 Hz, H-12), 4.02(1H, d, J= 11.2 Hz, H-12), 3.44(1H, m, H-6), 3.29(1H, m, H-10), 2.10(3H, s, -OCOMe), 1.71(3H, s, Me-15), 1.16(3H, s, Me-13), 1.07(3H, s, Me-14). ^{13}C δ: 30.0(C-1), 120.6(C-2), 140.3(C-3), 26.2(C-4), 38.2(C-5), 82.9(C-6), 35.2(C-7), 29.8(C-8), 21.2(C-9), 73.6(C-10), 73.0(C-11), 68.4(C-12), 26.6(C-13), 20.3(C-14), 24.9(C-15), 171.1(Me$\underline{C}$OO) and 20.9($\underline{Me}$COO).

23c. IR(film) ν_{max} cm^{-1}: 3440, 1740, 1450, 1380, 1240, 1100, 850 and 790. ^1H δ: 5.36(1H, m, H-2), 4.10(1H, d, J= 11.2 Hz, H-12), 3.99(1H, d, J= 11.2 Hz, H-12), 3.67(1H, t, J= 5.9 Hz, H-6), 3.53(1H, dd, J_1= 11.2 Hz and J_2= 3.9 Hz, H-10), 2.11(3H, s, -OCOMe), 1.74(3H, s, Me-15), 1.26(3H, s, Me-13), 0.89(3H, s, Me-14).^{13}C δ: 29.8(C-1), 122.6(C-2), 139.0(C-3), 27.7(C-4), 39.3(C-5), 81.8(C-6), 34.9(C-7), 38.3(C-8), 20.0(C-9), 75.3(C-10), 75.1(C-11), 69.2(C-12), 17.8(C-13), 21.8(C-14), 25.7(C-15), 171.0(Me$\underline{C}$OO) and 20.9($\underline{Me}$COO).

HYDROLYSIS OF **24** WITH NaOH/MeOH: **25**

Compound **24** (593 mg, 2 mmol) was treated with 4 ml NaOH in MeOH (10%) for 2 hours at room temperature. Usual work-up, removal of the solvent and concentration *in vacuo* gave **25** (435 mg, 97%).

IR(film) ν_{max} cm^{-1}: 3400, 1470, 1445, 1380, 1220, 1020, 755 and 655. ^1H δ: 5.31(1H, m, H-2), 3.43(3H, m, H-6 y H-12), 1.72(3H, s, Me-15), 1.15(3H, s, Me-13), 0.93(3H, s, Me-14), 0.77(3H, s, Me-14'). ^{13}C δ: 34.7(C-1), 122.2(C-2), 140.3(C-3), 28.2(C-4), 28.5(C-4'), 34.7(C-5), 80.6(C-6), 39.7(C-7), 29.5(C-8), 17.5(C-9), 39.0(C-10), 73.0(C-11), 69.8(C-12), 70.1(C-12'), 23.4(C-13), 24.0(C-14) and 25.3(C-15). EIMS m/z (rel. int.): 256[M^+] (4), 238(8), 207(13), 189(22), 161(15), 149(21), 121(54), 109(70), 95(70), 81(100), 69(84).

OXIDATION OF COMPOUND **25** WITH LTA: **26**

LTA (774 mg, 1.7 mmol) was added to a solution of **25** (435 mg, 1.7 mmol) in dry benzene (20 ml). The reaction mixture was stirred at room temperature for 30 minutes. Usual work-up gave **26** (360 mg, 94%). IR(film) ν_{max} cm^{-1}: 3425, 1715, 1460, 1375, 1075, 1055, 1025, 900 and 840. ^1H δ: 5.32(1H, m, H-2), 3.55(1H, dd, J= 3.4 Hz and 8.8 Hz, H-6'), 3.49(1H, dd, J= 3.4 Hz and 9.3 Hz, H-6), 2.41(2H, t, J= 6.5 Hz, H-10), 2.13(3H, s, Me-12), 1.72(3H, s, Me-15), 0.94(3H, s, Me-14) 0.79(3H, s, Me-14').

SWERN OXIDATION OF **26**: **5**

To a solution of oxalyl chloride (0.08 ml, 0.93 mmol), CH_2Cl_2 (2 ml), under argon atmosphere was slowly added a solution of DMSO/CH_2Cl_2 (1.87 mmol/1 ml) at -60ºC. After 30 minutes, **26** (191 mg, 0.85 mmol) in CH_2Cl_2 (2 ml) was added and maintained for 1 hour at -60ºC. Then, Et_3N (0.6 ml) was added and the reaction warmed to room temperature. After 10 minutes, H_2O (5 ml) is added and the mixture was extracted with ether, washed with 2N HCl and H_2O. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. The crude reaction product was chromatographed affording **5** (151 mg, 80%).

OXIDATION OF **26** WITH CrO_3/Py: **5**

CrO_3 (300 mg, 3 mmol) was added to a solution of pyridine (0.5 ml, 6 mmol) in CH_2Cl_2 (8 ml). The mixture was stirred vigorously at room temperature. After 30 minutes **26** (112 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) was added and stirred for 2.5 hours. The reaction mixture was filtered and evaporated, extracted with ether, washed with 5% NaOH, 5% HCl, 6% $NaHCO_3$,brine and dried over Na_2SO_4. Removal of the solvent afforded 100 mg of **5** (90%).

PROTECTION OF **13** WITH TBDMSCl: **27**

tert–Butyldimethylsilyl chloride (295 mg, 1.9 mmol) was added to a solution of **13** (536 mg, 1.9 mmol), triethylamine (0.26 ml, 1.9 mmol), DMAP (5 mg) in dry CH_2Cl_2 (5 ml). After 25 hours at room temperature, the reaction mixture was extracted with ether, washed with 2N HCl, 5% $NaHCO_3$, H_2O and dried over Na_2SO_4. After evaporation of the solvent the crude reaction product afforded after CC **27** (674 mg, 90%) and **13** (55 mg, 10%).

27. IR(film) ν_{max} cm^{-1}: 1740, 1460, 1370, 1240, 1060, 1020, 830, 780 and 680. ^1H δ: 5.36(2H, m, H-2 and H-10), 4.80(1H, m, H-6), 4.70(1H, m, H-6'), 4.00(2H, m, H-12), 2.05(3H, s, OCOMe'), 2.04(3H, s, OCOMe), 1.73(3H, s), 1.63(3H, s), 0.91(9H, s, $SiCMe_3$), 0.85(3H, s, Me-14), 0.07(6H, s, $SiMe_2$).

HYDROLYSIS OF **27** WITH NaOH/MeOH: **28**

Compound **27** (350 mg, 0.85 mmol) was treated with 4 ml of NaOH in MeOH (10%) for 4 hours at room temperature. After usual work-up, the crude reaction product was chromatographed affording **28** (306 mg, 98%).

IR(film) ν_{max} cm^{-1}: 3400, 1450, 1370, 1060, 1010, 820 and 740. ^1H δ: 5.36(2H, m, H-2 and H-10), 4.00(2H, s, H-12), 3.51(1H, m, H-6), 3.41(1H, m, H-6'), 1.72(3H, s), 1.59(3H, s), 0.97(3H, s, Me-14), 0.90(9H, s, $SiCMe_3$), 0.82(3H, s, Me-14'), 0.05(6H, s, $SiMe_2$).

OXIDATION OF **28** WITH CrO_3/Py: **29**

CrO_3 (360 mg, 1.02 mmol) was added to a solution of pyridine (0.6 ml, 7.2 mmol) in CH_2Cl_2 (10 ml) and stirred vigorously at room temperature. After 30 minutes **28** (218 mg, 0.6 mmol) in CH_2Cl_2 (5 ml) was added and stirred for 7 hours at room temperature. Usual work-up gave **29** (168 mg, 80%). IR(film) ν_{max} cm^{-1}: 1705, 1460, 1390, 1250, 1110, 1070, 830, 790 and 680. ^1H δ: 5.47(1H, m, H-2), 5.35(1H, m, H-10), 3.97(2H, s, H-12), 1.66(3H, s), 1.56(3H, s), 1.07(3H, s, Me-14), 0.90(9H, s, $SiCMe_3$), 0.05(6H, s, $SiMe_2$). ^{13}C δ: see table 35.1(C-1), 121.6(C-2), 138.9(C-3), 31.9(C-4), 38.6(C-5), 215.0(C-6), 53.7(C-7), 37.9(C-8), 22.5(C-9), 124.2(C-10), 134.8(C-11), 68.6(C-12), 13.3(C-13), 22.2(C-14), 25.1(C-15), -5.2($SiMe_2CMe_3$), 18.4($SiMe_2CMe_3$) and 26.0($SiMe_2CMe_3$).

TREATMENT OF **29** WITH TBAF: **11**

1M tetrabutylammonium fluoride (TBAF) solution in THF (0.1 ml) was added to a solution of **29** (56 mg, 0.15 mmol) in 5 ml of THF. The mixture was heated under reflux for 2.5 hours. After cooling, ether was added, washed with H_2O, dried (Na_2SO_4), filtered and evaporated to give **11** (33 mg, 93%).

DEPROTECTION OF **29** WITH AcOH:THF:H_2O: **11**

A mixture of AcOH:THF:H_2O (4:1:1) was added to compound **29** (46 mg, 0.12 mmol) and stirred for 5 hours at room temperature. Then the reaction mixture was extracted with ether, washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4) and the solvent removed to give **11** (28 mg, 99%).

PROTECTION OF **11** WITH $(CH_2OH)_2$/TsOH: **6**

$(CH_2OH)_2$ (13 ml) and TsOH (97 mg) were added to compound **11** (3.08 g, 13 mmol) dissolved in dry benzene (30 ml) and refluxed for 7 hours into a Dean-Stark trap. Usual work-up gave **6** (3.58 g, 98%).

OXIDATION OF **10** WITH $NaClO_2$ AND SUBSEQUENT ESTERIFICATION: **32**

A solution of sodium chlorite (3.55 g, 39 mmol) and sodium dihydrogenphosphate (5.07 g, 29.06 mmol) in 34 ml of water was added dropwise to a solution of aldehyde **10** (1g, 4.27 mmol) in 50 ml of *tert*–butyl alcohol and 21.2 ml of 2-methyl-2-butene over a 10 minutes period. The pale yellow reaction mixture was stirred at room temperature for 24 hours. Volatile components were then removed under vacuum, the residue was acidified with HCl and extracted with hexane, washed with water, dried (Na_2SO_4) and concentrated to give **31** (960 mg, 90%). IR(film) ν_{max} cm^{-1}: 3340, 1695, 1450, 1390 and 1295. **31** (960 mg) was esterified with a saturated solution of CH_2N_2 in ether and the mixture was left 12 hours. The solvent was removed to give **32** (1g, 100%). IR(film) ν_{max} cm^{-1}: 1710, 1660, 1430, 1370, 1280, 1100, 810 and 740. ^1H δ: 6.65(1H, m, H-10), 5.43(1H, m, H-2), 3.67(3H, s, COOMe), 1.76(3H, s), 1.63(3H, s), 1.04(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int.): 264[M+] (15), 232(11), 219(4), 205(7), 177(8), 151(22), 138(99), 120(71), 110(99), 95(89), 81(79), 67(100), 55(98).

PROTECTION OF **32** WITH $(CH_2OH)_2$/TsOH: **33**

$(CH_2OH)_2$ (8 ml) and TsOH (51 mg) were added to compound **32** (1.79 g, 6.79 mmol) dissolved in dry

benzene (50 ml). Usual work-up gave **33** (2 g, 96%). IR(film) ν_{max} cm^{-1}: 1710, 1630, 1430, 1380, 1290, 1090, 1080, 950 and 740. ^1H δ: 6.78(1H, m, H-10), 5.37(1H, m, H-2), 3.92(4H, m, -O-CH_2-CH_2-O-), 3.71(3H, s, COOMe), 1.82(3H, s), 1.73(3H, s), 0.88(3H, s, Me-14). ^{13}C δ: see table 3.

REDUCTION OF **33** WITH $LiAlH_4$: **6**

$LiAlH_4$ (386 mg, 10.1 mmol) was added to a solution of **33** (3.11 g, 10.2 mmol) in dry ether (30 ml). The solution was stirred at room temperature for 7.5 hours. Usual work-up afforded **6** (2.65 g, 93%).

REDUCTION OF **2** WITH $LiAlH_4$ AND SUBSEQUENT PROTECTION WITH TBDMSOTf: **34**

TBDMSOTf (0.90 ml, 5 mmol) was added to a solution of the alcohol obtained from the reduction of **2**, (566 mg, 2.55 mmol), in CH_2Cl_2 (5 ml) and 2,6-lutidine (1.17 ml, 10.2 mmol), cooled in an ice-water bath, under argon,. After 10 minutes the cooling bath was removed, and the mixture stirred for 1 hour at room temperature. After that, a saturated solution of $NaHCO_3$ (5 ml) was added, extracted with ether, washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **34** (856 mg, 100%).

ALDOLIC CONDENSATION OF **5** WITH KOH/EtOH: **35**

KOH/EtOH 3M (3 ml) was added to a solution of **5** (758 mg, 3.41 mmol) in EtOH (20 ml), and stirred at room temperature. After 28 hours was diluted with H_2O and extracted with ether, washed with diluted HCl and H_2O, dried over Na_2SO_4 and concentrated *in vacuo* . The crude product afforded after CC **35** (586 mg, 84%). UV (EtOH) λ max (nm): 255 (ε 5400). IR(film) ν_{max} cm^{-1}: 1676, 1653, 1613, 1452, 1437, 1370, 1356, 1263, 1206 and 760. ^1H δ: 5.37(1H, t, J= 6.3 Hz, H-2), 2.21(3H, s, Me-12), 1.69(3H, s, Me-15), 0.99(3H, s, Me-14). ^{13}C δ: see table 3. EIMS m/z (rel. int): 204(M^+, 6), 175(7), 161(100), 145(9), 131(15), 119(19), 105(27), 91(39), 77(34), 65(15).

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