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The Use of Acyclic Monoterpenes in the Preparation of β-pyrones: Synthesis of the Right-hand Fragment of Usneoidone E

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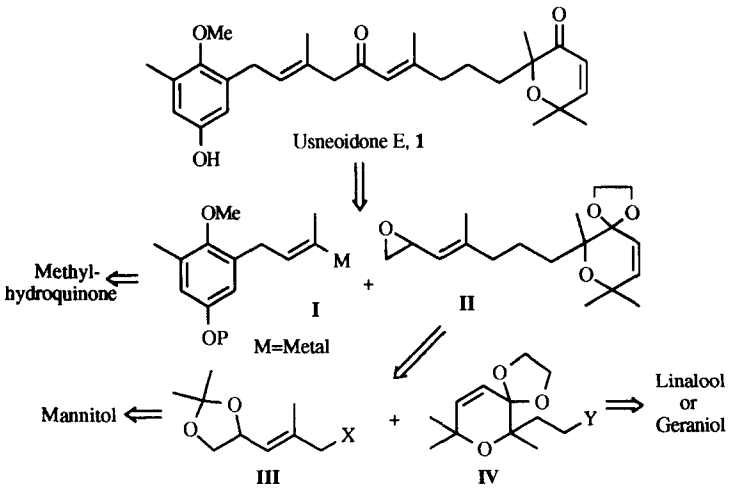
Abstract: The right hand fragment, **36**, of Usneoidone E, **1**, a powerful antiviral and antitumoural agent has been synthesized from the β-pyrone **32**. Using linalool as starting material, a 2,2,6,6-tetrasubstituted dihydropyrane **20**, precursor of **32** and **33**, was prepared. **20** was also synthesized from geranyl acetate through selenide **7**, and is a versatile precursor for the synthesis of tetraprenyltoluquinols. Unambiguous ^{13}C NMR assignment has been done by 2D correlations.

INTRODUCTION

We have recently published the isolation and structure determination of several tetraprenyltoluquinols.[1] Among them, Usneoidone E, **1**, was found to be active against tumour cells and viruses, but also showed a high cytotoxicity level against normal cells. Looking for an improvement in the bioactivity as well as a significant decrease in the cytotoxicity level, the synthesis and structure-activity relationship study of **1** has been undertaken.



Scheme 1. Retrosynthetic analysis

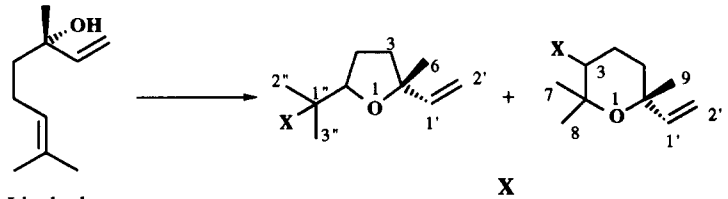
Usneoidone E is a relatively unstable compound due to the reactivity of the aromatic ring and the presence of two Michael acceptors. The disconnections shown in the retrosynthetic analysis are dictated by several factors: preparation of useful synthons in high quantities, stability of the compounds and a total synthesis as convergent as possible[2] (Scheme 1). We report here the preparation of **IV**, an useful intermediate in the synthesis of usneoidones,[1] from linalool or geraniol.

RESULTS AND DISCUSSION

LINALOOL AS STARTING MATERIAL

Usneoidone E possesses one stereogenic centre, therefore use of linalool as starting material will provide useful information about the absolute configuration, and its influence on bioactivity. Moreover cyclization reactions of linalool undergoing tetrahydropyranyl derivatives are well documented in the literature.[3-6]

When linalool is treated with mercuric acetate an unhandly and unseparable mixture of organomercurial derivatives, **2** and **3**, is formed.[3] Treatment of linalool with NBS/CCl_4[4] or PhSeCl[5] led to tetrahydrofuranyl derivatives **4** or **6** respectively. Formation of tetrahydropyranyl derivatives **7** was not achieved (experimental section), even though S. Konstantinovic claimed for it,[5] this result will be discussed later on. However, treatment with MCPBA, followed by epoxide ring-opening led to both tetrahydrofuranyl and tetrahydropyranyl **8** and **9** derivatives as described by D. Felix.[6] (Scheme 2).

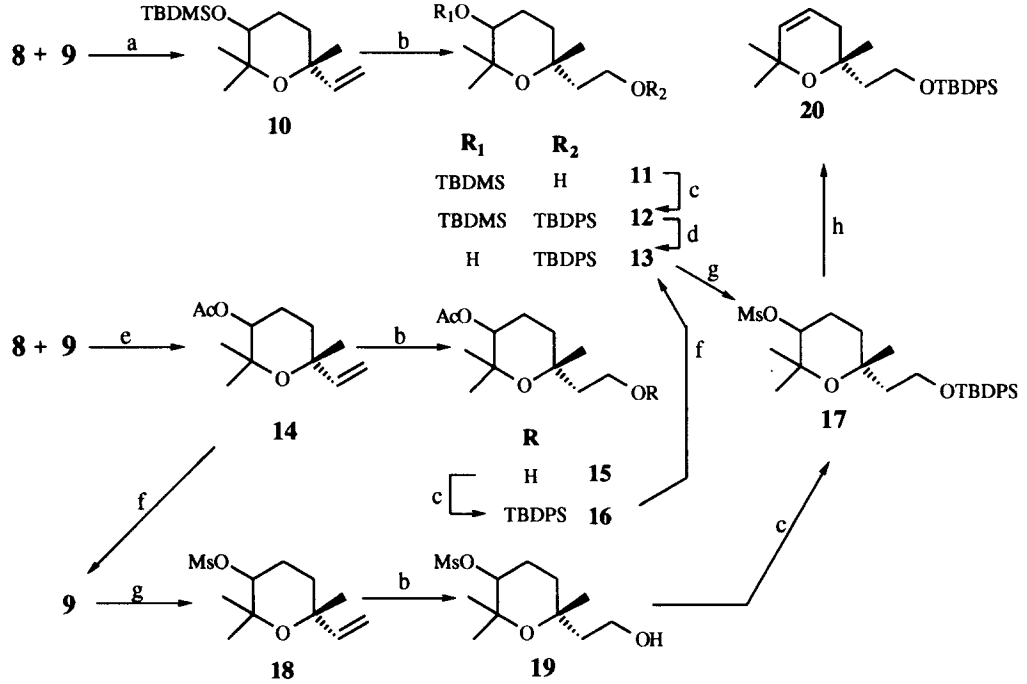


Scheme **2.** Cyclization Reaction of Linaool under different reaction conditions.

Although the tetrahydropyranyl yield was low (15%), it could be a reasonable intermediate to examine the feasibility of this synthesis due to the cheapness of the starting material. Separation of tetrahydropyranyl derivatives from the tetrahydrofuranyl ones, represented a problem, that was overcome, by protection of the secondary alcohol as TBDMS or Ac or by oxidation to ketone. When the tetrahydropyranyl mixture was oxidized, only one of the stereogenic centre was eliminated and both diastereomers afforded the same compound, **21**. Separation of **8** and **9** was achieved by treating the mixture with TBDMSCl[7] to afford unreacted **8** and **10**, easily separable by CC (Scheme 3). Hydroboration and oxidation of the corresponding borane[8] led to alcohols **11**. Protection of the latter with TBDPSCl[9] afforded **12** in good yield. However as selective deprotection of the TBDMS group to afford **13** failed, therefore change of the protecting group was decided.

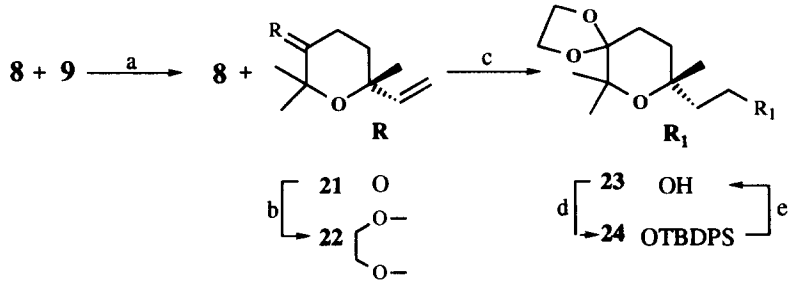
Treatment of **8/9** with Ac_2O/Py afforded again unreacted **8** and the acetoxyderivative **14**, that were separated by CC on silicagel. **14** was easily transformed into **13** following a similar synthetic sequence. When **13** was treated with MsCl[10] gave **17** that was also prepared by inverting the reaction steps (Scheme 3).

Several elimination methods[11] of the mesyl group were attempted, in view of the availability of **17** in good yield (40%) from two different routes, but no good results were met. The best yield in the preparation of the dihydropyrane **20** was achieved with DBU (15%), so a new route for the synthesis of this compound was envisaged.



Scheme 3. a) TBDMSCl; b) 1. BH_3, 2. H_2O_2/OH^-; c) TBDPSCl; d) AcOH/THF/H_2O 4/1/1; e)Ac_2O; f) NaOH/MeOH; g) MsCl; h) DBU.

When the mixture of **8/9** was oxidized with CrO_3/Py,[12] unreacted **8** and ketone **21** were separated. **21** was transformed into 1,3-dioxolane derivative **22** by treatment with ethylene glycol in benzene with TsOH as catalyst.[13] Hydroboration and oxidation of **22** led to **23**, whose protection with TBDPSCl afforded **24**. This route was finally abandoned because selective deprotection of the dioxolane in the presence of the silane protecting group was not achieved giving only **23**, and because of the low yield of the last two steps (Scheme 4); however this route could be used for the synthesis of chiral **20**.

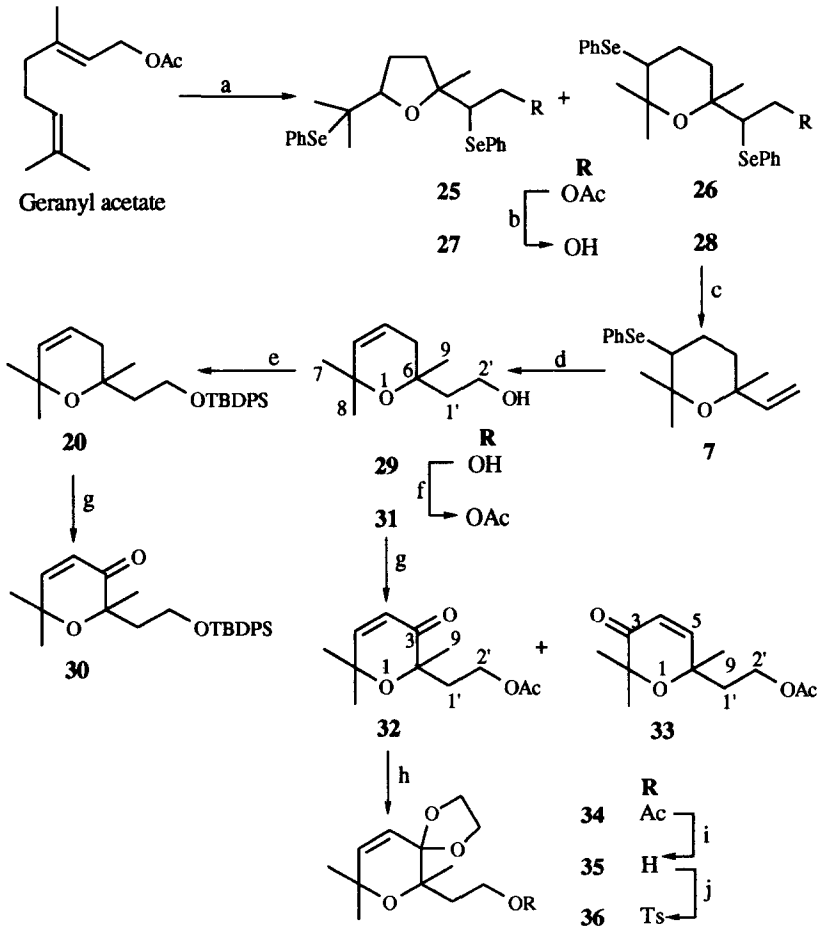


Scheme 4. a) CrO_3/Py; b) Ethylene glycol; c) 1. BH_3, 2. H_2O_2/OH^-; d) TBDPSCl; e) *p*-TsOH

GERANIOL AS STARTING MATERIAL

Several workers had reported on the synthesis of 2,2,6,6–tetrasubstituted tetrahydropyranyl derivatives from geraniol or geranyl derivatives as starting material, Furstoss,[14] prepared all isomers of **9** using a geranyl carbamate; Vidari,[15] using the Sharpless asymmetric epoxidation, prepared a chiral analog of **9** from geraniol. Villiard[16] did the synthesis of non chiral **5**, and Nicolaou[17] prepared racemic **7** using geranylacetate and selenium reagents. Although racemic, Nicolaou's synthetic approach to **7** was chosen because it was easy to scale-up and also a good opportunity to study all the intermediates as well as the cyclization mechanism.[18] In the knowledge that geraniol has been transformed into linalool R or S by several workers.[19]

When geranyl acetate was treated with benzeneselenenic acid (Scheme 5) a mixture of **25** and **26** was formed in a 1:10 ratio. LAH reduction afforded two easily separable compounds **27** and **28**.

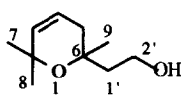


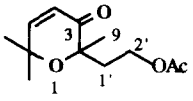
Scheme **5.** a) 1. PheSeSePh / DCM; 2. H_2O_2; 3. $MgSO_4$; 4. Geranyl Acetate; b) $LiAlH_4$; c) $MsCl/Et_3N$; d) 1. BH_3; 2. H_2O_2 / OH^-; e) TBDPSCl; f) Ac_2O; g) Na_2CrO_4/HOAc/NaOAc/Ac_2O/benzene; h) Ethylene glycol / TsOH; i) Na_2CO_3 / MeOH; j) TsC / Et_3N.

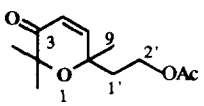
Compound **28** was transformed into **7** by treatment with $MsCl/Et_3N$/DCM. Thus a tetrahydropyranyl derivative with a masked double bond was easily prepared in high quantities. This compound shows in the ^{13}C

NMR spectrum a methine signal at δ 52.8, corresponding to the carbon directly bonded to selenium, that was not observed when linalool was cyclized with PhSeCl, this result demonstrated that the cyclization of linalool gives exclusively tetrahydrofurane **6**. Compound **7** was readily obtained by this method in very good yield, 52% from geranyl acetate. Hydroboration and oxidation with H_2O_2 of the intermediate borane led to alcohol **29** in good yield in a one pot reaction. Unambiguous assignment of ^{13}C NMR resonances was done by 2D correlation experiments (one bond and long-range, Table 1)

Table **1.** ^{1}H-^{13}C (HCCORR). Observed Long Range Correlations for compounds **29**, **32** and **33**.







C	**29**	**32**	**33**
3	7, 8		5
4	2, 5		
5	3, 4, 6	3	
7	2,3	6, 5	2
8	2,3	6, 5	2
9	5, 6, 1'	1', 2, 3	1', 6, 5

Protection of the hydroxyl group of **29** with TBDPSCl led to racemic **20**, that could be obtained from linalool in a chiral form. The allylic oxidation with Na_2CrO_4[20] afforded **30** with 30% yield. When **31,** the acetyl derivative of **29,** was used, its allylic oxidation afforded a mixture of α,β-unsaturated ketones **32** and **33** isomers in good yield.

The 2D experiments (Table 1) indicate that Me-9 correlates with the carbonyl in compound **32**, while **33** shows a correlation between Me-9 and the methine at C-5.

Transformation of **32** into the desired intermediate **36** (IV, X=OTs) was easily achieved by protection of the carbonyl group with ethylene glycol to give **34**, alkaline hydrolysis of the latter afforded **35**, whose tosylation gave **36** (Scheme 5).

An important step in the total synthesis of usneoidone E has been carried out. Now, the coupling between **III** (prepared from mannitol) and **36** as well as the chiral synthesis of **36** are currently under study.

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. ^{1}H 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 ^{1}H 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 in a VG–TS 250 spectrometer at 70 eV ionizing voltage. Mass Spectra are presented as m/z (% rel. int.) Optical Rotations were determined in a

Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether, THF, benzene were distilled from sodium and pyridine and dichloromethane were distilled from calcium hydride under Ar atmosphere.

CYCLIZATION OF LINALOOL WITH NBS[4]

N-Bromosuccinimide (NBS, 1.5 g, 8.2 mmol) was added to linalool (1.1 g, 7.1 mmol) in dry CH_2Cl_2 (10 ml) and the mixture was stirred at room temperature for 48 h. *n*-hexane (10 ml) was added and the mixture filtered and evaporated to afford a crude product (1.7 g) which was chromatographed on silica gel column (40 g) to give **4** (1.4 g, 85%) which was eluted with hexane. MS: 233 (M^+, 9), 231 (4), 205 (27), 189 (6), 153 (11), 135 (32), 109 (19), 93 (21), 81 (100), 68 (46), 59 (81). IR: ν_{max} (film) cm^{-1}: 1654, 1460, 1410, 1380, 1140, 1110, 1020 and 910. ^1H NMR: 6.00 (1H, dd, J=16.6 and 11.1, H-1'); 5.24 (1H, dd, J=16.6 and 1.0, HA-2'); 5.01 (1H, dd, J=11.1 and 1.0, HB-2'); 4.03 (1H, t, J=6.1, H-5); 2.22-1.81 (4H, m, H-3 and H-4); 1.72, 1.75 (3H, s, Me-2" and Me-3"); 1.30 (3H, s, Me-6).

CYCLIZATION OF LINALOOL WITH PhSeCl[5]

Phenylselenium chloride (PhSeCl, 2.7 g, 14.80 mmol) was added to stirred solution of linalool (1.9 g, 12.3 mmol) in dry CH_2Cl_2 (10 ml) at room temperature and stirring was continued for 12 h. Ether was added and the mixture washed with 10% $NaHCO_3$ and brine, dried with Na_2SO_4, filtered and evaporated to afford a crude product (4.3 g), which was chromatographed to give, with hexane/ether 99:1, **6** (1.7 g, 45%). MS: 310 (M^+, 100), 288 (28), 257 (28), 215 (39), 201 (28), 173 (28), 159 (88), 153 (56), 135 (30), 111 (25). IR: ν_{max} (film) cm^{-1}: 1630, 1570, 1470, 1440, 1360, 1300, 1120, 1020 and 910. ^1H NMR: 7.65 (2H, m, Ar); 7.30 (3H, m, Ar); 5.88 (1H, dd, J=17.8 and 11.3, H-1'); 5.21 (1H, dd, J=17.8 and 1.5, HA-2'); 5.00 (1H, dd, J=11.3 and 1.5, HB-2'); 3.99 (1H, t, J=5.9, H-2); 2.90-1.80 (4H, m, H-3 and H-4); 1.37, 1.34 and 1.33 (3H, s, ea, 3Me). ^{13}C NMR: 143.9 (C-1'), 138.6 (2CH-Ar), 131.7 (C-Ar), 128.6 (3CH-Ar), 111.3 (C-2'), 85.9 (C-2), 83.3 (C-5), 49.9 (C-1"), 37.4 (C-3), 27.9, 26.58 and 25.9 (3Me), 26.9 (C-4).

CYCLIZATION OF LINALOOL WITH MCPBA[6]

70% MCPBA (17.9 g, 80.3 mmol) was added to a solution of linalool (10.0 g, 64.9 mmol) in dry CH_2Cl_2 (130 ml) at 0°C and the mixture was maintained under these conditions for 2 h. Ether was added and the mixture washed with 10% $NaHCO_3$ and water, dried with Na_2SO_4, filtered and evaporated to afford a crude product (10.1 g). The crude was dissolved in ether, trichloroacetic acid (0.5 ml) added and stirred for a 12 h at room temperature. When the reaction was judged complete, ether was added and the mixture washed with 10% Na_2CO_3 and brine, dried, filtered and evaporated. The crude product (9.1 g) was chromatographed to give, with hexane/ether 4:1, a mixture of **8/9** (8.9 g, 81%) in a ratio 5:1.

PROTECTION OF **9** WITH TBDMSCl: **10**

A mixture of **8/9** (8.9 g, 52.4 mmol), a catalytic quantity of DMAP, TBDMSCl (1.2 g, 7.8 mmol) and imidazole (3.6 g, 52.3 mmol) were dissolved in the minimum amount of DMF (2 ml) and stirred at room temperature for 3 h. Ether was added and the mixture washed with water and brine, dried with Na_2SO_4, filtered and evaporated. The crude product (10.9 g) was chromatographed (hexane/ether, 4:1) to afford a diastereomeric mixture of **10** (2.2 g, 15%). IR: ν_{max} (film) cm^{-1}: 2920, 2900, 1500, 1260, 1090, 1010, 850 and 790. ^1H NMR: 6.10-5.83 (1H, m, H-1'); 5.08-4.85 (2H, m, H-2'); 3.40 (1H, m, H-3); 1.40-1.20 (3H, s, ea, Me-7, Me-8, Me-9); 0.89 (9H, s, Me_3C-); 0.08 (6H, s, 2Me, -Si-$\underline{Me_2}$).

HYDROBORATION OF **10: 11**

BH_3 (1M in THF, 3.24 ml) was added to a solution of **10** (0.9 g, 3.2 mmol) in dry THF (3ml) at 0°C. The reaction mixture was stirred for 3 h at 0°C and for 1 h at room temperature. Water (0.2 ml), 3 M NaOH (0.6 ml) and 30% H_2O_2 (0.36 ml) were added and the mixture refluxed for 1h. Water was added and the mixture extracted with ether. The combined organic phases were washed with 10% $NaHSO_3$ and brine, dried, filtered and evaporated. The crude product was chromatographed (hexane/ether, 7:3) to give **11** (0.8 g, 80%). IR: ν_{max} (film) cm^{-1}: 3500, 2940, 1480, 1260, 1080, 1000 and 830. ^1H NMR: 3.65 (2H, t, J=7.0 Hz, H-2'); 3.42 (1H, m, H-3); 1.35-1.10 (3H, s, ea, Me-7, Me-8 and Me-9); 0.89 (9H, s, Me_3C-); 0.08 (6H, s, 2Me, -Si-$\underline{Me_2}$). Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.49; H. 11.31.

PROTECTION OF **11** WITH TBDPSCl: **12**

Componud **11** (0.8 g, 2.6 mmol), a catalytic amount of DMAP, TBDPSCl (0.8 ml, 2.8 mmol) and imidazole (0.2 g, 2.6 mmol) were dissolved in DMF (1 ml) and stirred for 12 h at room temperature. Ether was added and the mixture washed with water, dried, filtered and evaporated. Chromatographed (hexane/ether, 9:1) of the crude afforded 12 (1.2 g, 83%). IR: ν_{max} (film) cm^{-1}: 3060, 2980, 2960, 1980, 1920, 1860, 1500, 1450, 1240, 1120, 820, 800 and 710. ^1H NMR: 7.65 (4H, m, Ar); 7.45 (6H, m, Ar); 3.68 (2H, t, J=7.0, H-2'); 3.40 (1H, m, H-3); 1.15 (9H, s, Me_3C-); 1.20-1.05 (3H, s, Me-7, Me-8 and Me-9); 0.89 (9H, s, Me_3C-); 0.03 (6H, s, -Si$\underline{Me_2}$). Anal. Calcd for $C_{32}H_{52}O_3Si_2$: C, 74.94; H, 10.22. Found: C, 74.97; H. 10.19.

SELECTIVE DEPROTECTION OF **12: 13**

HOAc (4 ml), THF (1 ml) and water (1 ml) were added to **12** (1.0 g, 1.9 mmol) and the mixture stirred for 12 h at room temperature. Ether was added and the mixture washed with 10% $NaHCO_3$ and brine, dried, filtered and evaporated. Chromatographed (hexane/ether, 4:1) of the crude product afforded **13** (130 mg, 15%). IR: ν_{max} (film) cm^{-1}: 3300, 1590, 1475, 1430, 1110, 1080 and 820. ^1H NMR: 7.70 (4H, m, Ar); 7.40 (6H, m, Ar); 3.83 (2H, m, H-2'); 3.40 (1H, m, H-3); 1.90-1.60 (6H, m, H-4, H-5 and H-1'); 1.20, 1.15 and 1.10 (3H, s, ea, Me-7, Me-8 and Me-9); 1.06 (9H, s, Me_3C-).

ACETYLATION OF **8/9**: **14**

Ac_2O (5.5 ml, 53.9 mmol) and pyridine (4 ml) were added to a mixture of **8/9** (8.4 g, 49.9 mmol) and stirred at room temperature for 12 h. Ice was added and left for 1 h. The mixture was extracted with ether and washed with 10% HCl, 10% $NaHCO_3$ and brine, dried Na_2SO_4, filtered, evaporated and chromatographed (hexane/ether, 7:3) to give the diastereomeric mixture **14** (1.53, 15%) and unreacted **8** (6.7, 80%). IR: ν_{max} (film) cm^{-1}: 1730, 1640, 1460, 1370, 1250, 910 and 840.^1H NMR: 6.10-5.90 (2H, m, H-1'); 5.10-4.95 (2H, m, H_A-2'); 4.65 (2H, m, H_B-2'); 2.12 (3H, s, -OAc); 2.05 (3H, s, -OAc);1.30-1.15 (3H, s, ea, 6Me).

HYDROBORATION OF **14: 15**

BH_3 (1M in THF, 1ml) was added to **14** (220 mg, 1.00 mmol) at 0°C and stirred for 2 h at 0°C and 1 h at room temperature. The mixture was cooled to 0°C and water (0.2 ml), 3M NaOH (0.6 ml) and 30% H_2O_2 (0.4 ml) were added, and heated to reflux for 1 h. Water was added and the mixture extracted with ether. The organic phase was washed with 10% $NaHSO_3$ and brine, dried, filtred and evaporated. Chromatography of the crude product eluting with hexane/ether 1:1 afforded a diastereomeric mixture **15** (160 mg, 76%). IR: ν_{max} (film) cm^{-1}:

3450, 2940, 1730, 1380, 1240 and 1100. ^{1}H NMR: 4.80-4.60 (2H, m, H-3); 4.00-3.80 (4H, m, H-2'); 2.15 (3H, s, -OAc); 2.10 (3H, s, -OAc); 1.40-1.10 (3H, s, 6Me). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.57; H. 9.62.

PROTECTION OF **15** WITH TBDPSCl: **16**

A catalytic amount of DMAP, TBDPSCl (0.2 ml, 0.8 mmol) and Et_3N (0.1 ml, 0.7 mmol) were added to a solution of **15** (0.15 g, 0.6 mmol) in dry CH_2Cl_2 (4 ml) and the mixture was stirred at room temperature for 30 min. Ether was added and the mixture washed with 5% HCl, 10% $NaHCO_3$ and brine, dried, filtered, evaporated and chromatograped (hexane/ether, 4:1) to afford a diastereoisomeric mixture **16** (270 mg, 91%). IR: ν_{max} (film) cm^{-1}: 1740, 1580,1430,1370,1245 and 820. ^{1}H NMR: 7.70 (20H, m, Ar); 4.65 (2H, m, H-3); 3.81 (4H, m, H-2'); 2.09 (3H, s, OAc); 2.02 (3H, s, OAc), 1.90-1.60 (12H, m, H-4, H-5, H-1'); 1.20, 1.15 and 1.10 (6H, s ea, Me-7, Me-8 and Me-9); 1.04 (18H, s, Me_3C-).

SAPONIFICATION OF **16: 13**

NaOH (0.2 g, 5.0 mmol) in MeOH (3 ml) was added to **16** (0.23 g, 0.5 mmol) and stirred at room temperature for 12 h. MeOH was evaporated, water was added, and the mixture acidified and extracted with ether. The organic layer was washed with 10% $NaHCO_3$, and brine, dried, filtered and evaporated. Chromatography of the crude product (hexane/ether, 7:3) afforded **13** (0.2 g, 92%), already described.

MESYLATION OF **13: 17**

A catalytic amount of DMAP, Et_3N (0.1 ml, 0.71 mmol) and mesyl chloride (24 mg, 0.2 mmol) were added to **13** (76 mg, 0.18 mmol) in dry DCM (2 ml) at 0°C and stirred for 30 min at room temperature. Ether was added and the mixture washed with 10% HCl, 10% $NaHCO_3$, dried, filtered, evaporated and chromatographed (hexane/ether, 4:1) to give **17** (76 mg, 84%). IR: ν_{max} (film) cm^{-1}: 1590, 1475, 1450, 1360, 1180, 1110,950 and 830. ^{1}H NMR: 7.70 (8H, m, Ar); 7.40 (12H, m, Ar); 4.48 (2H, m, H-3); 3.81 (4H, m, H-2'); 3.01 (3H, s, Me-SO_2-); 2.96 (3H, s, Me-SO_2-); 1.90-1.60 (12H, m, H-4, H-5, H-1'); 1.18-1.16 (6H, s, ea, Me-7, Me-8 and Me-9); 1.04 (18H, s,Me_3C-). Anal. Calcd for $C_{27}H_{40}O_5SiS$: C, 64.25; H, 7.99. Found: C, 64.25; H. 8.03.

SAPONIFICATION OF **14: 9**

NaOH (0.75 g, 18.7 mmol) was added to a solution of **14** (0.69 g, 3.3 mmol) in dry MeOH (15 ml). The mixture was stirred for 12 h at room temperature. Usual work-up afforded **9** (440 mg, 80%). IR: ν_{max} (film) cm^{-1}: 3450, 1640, 1380, 1250 and 910. ^{1}H NMR: 5.96 (1H, dd, J=17.5 and 11.6 Hz, H-1'); 4.97 (1H, d, J=17.5, H_A-2'); 4.97 (1H, d, J=11.6, H_B-2'); 3.42 (1H, t, J=7.0, H-3); 2.12 (2H, m, H-4); 1.75 (2H, m, H-5); 1.23-1.15 (3H, s and 6H, s, Me-7, Me-8 and Me-9).

MESYLATION OF **9: 18**

A catalytic amount of DMAP, pyridine (0.61 ml, 7.7 mmol) and mesyl chloride (0.24 ml, 3.1 mmol) were added to a solution of **9** (0.44 g, 2.6 mmol) in dry DCM (5 ml). The mixture was stirred at room temperature for 2 h. Usual work-up afforded **18** (0.53 g, 83%). IR: ν_{max} (film) cm^{-1}: 1650, 1450, 1420, 1350, 1230, 1170, 1080, 1065, 930, 910 and 880. ^{1}H NMR: 5.96 (1H, dd, J=17.5 and 11.6 , H-1'); 5.03 (1H, d, J=11.6, H_A-2');

5.02 (1H, d, J=17.5, HB-2'); 4.50 (1H, dd, J=8.6 and J=6.6, H-3); 3.02 (3H, s, $\underline{Me}SO_3$-R); 2.15-2.00 (4H, m, H-4 and H-5); 1.28, 1.23 and 1.18 (3H, s, ea, Me-7, Me-8 and Me-9).

HYDROBORATION OF **18: 19**

BH_3 (1M in THF, 1ml) was added to **18** (0.10 g, 0.39 mmol) in THF at 0°C. The mixture was stirred for 3 h at 0 °C, warmed up to room temperature with stirring for 1 h. The mixture was cooled again to 0°C and water (0.2 ml), 3M NaOH (0.6 ml) and 30% H_2O_2 (0.4 ml) were added, and heated to reflux for 1 h. Usual work-up afforded **19** (68 mg, 60%). IR: ν_{max} (film) cm^{-1}: 3400, 1454, 1180 and 1120. ^1H NMR: 4.59 (1H, dd, J=5.1 and 2.6, H-3); 3.85 (2H, t, J=5.8, H-2'); 3.08 (3H, s, $\underline{Me}SO_3$-R); 1.33, 1.29 and 1.28 (3H, s, ea, Me-7, Me-8 and Me-9).

PROTECTION OF **19** with TBDPSCl: **17**

Compound **19** (64 mg, 0.23 mmol), a catalytic amount of DMAP and imidazole (63 mg, 0.93 mmol) were dissolved in DMF (1 ml) and TBDPSCl (0.6 ml, 0.28 mmol) added. The reaction mixture was stirred for 1 h at room temperature. Usual work-up and chromatography (hexane/ether, 4:1) afforded **17** (102 mg, 88%).

ELIMINATION WITH DBU OF **17: 20**

DBU (0.15 ml, 0.9 mmol) was added to a solution of **17** (44mg, 0.087 mmol) in toluene (5 ml) and heated to reflux for 48 h. The mixture was diluted with DCM and 10% HCl was added. After that the mixture was extracted with DCM, washed with 10% $NaHCO_3$, dried, filtered, evaporated and chromatographed (hexane/ether, 95:5) to give **20** (6 mg, 15%). IR: ν_{max} (film) cm^{-1}: 1470, 1410, 1390, 1360, 1110, 1010, 810 and 720. ^1H NMR: 7.77 (6H, m, Ar); 7.45 (4H, m, Ar); 5.72 (2H, bs, H-3 and H-4); 3.92 (2H, t, J=6.4, H-2'); 2.20 (1H, d, J=16.6, HA-5); 2.00-1.70 (3H, m, H-1' and HB-5); 1.30, 1.26 and 1.25 (3H, s, ea, Me-7, Me-8 and Me-9); 1.15 (9H, s, Me_3C-). ^{13}C NMR: 135.7, 134.3, 129.6 and 127.7 (CH-Ar), 135.3(C-Ar), 134.2 (C-3), 120.6 (C-4), 71.8 and 71.4 (C-6 and C-2), 60.6 (C-2'), 44.7 (C-1'), 34.4 (C-5), 30.8, 29.9 and 27.2 (C-7, C-8 and C-9), 27.0 (3Me, $\underline{Me_3}C$-), 19.3 ($Me_3\underline{C}$-). Anal. Calcd for $C_{26}H_{36}O_2Si$: C, 76.42; H, 8.88. Found: C, 676.54; H. 8.93. MS: 409 (M^+, 100), 390(30), 369(15), 351(15), 313(98), 269(71), 257(80), 235(40), 199(36), 179(20), 135(15); high-resolution mass spectrum calcd for $C_{26}H_{36}O_2Si$ (M^+): 408.2485, found 408.2485

OXIDATION OF **8/9:21**

To a solution of **8/9** (4.30 g, 25.3 mmol) in pyridine (8 ml) was added CrO_3 (2.51 g, 25.2 mmol). After stirring for 2 h at room temperature, ice and some drops of sulfuric acid were added. The reaction mixture was extracted with ether, washed with 10% HCl, 10% $CuSO_4$, 10% $NaHCO_3$ and water, dried, filtered, evaporated and chromatographed (hexane/ether, 4:1) to give **21** (0.40 g, 9%). IR: ν_{max} (film) cm^{-1}: 1730, 1460, 1450, 1370, 1120, 745 and 740. ^1H NMR: 5.94 (1H, dd, J=17.6 and 10.7 Hz, H-1'); 5.23 (1H, dd, J=17.6 and 1.5 Hz, HA-2'); 5.09 (1H, dd, J=10.7 and 1.5 Hz, HB-2'); 2.50 (2H, m, H-4); 2.15 (2H, m, H-5); 1.35, 1.32, 1.25 (3H, s, ea, Me-7, Me-8 and Me-9). ^{13}C NMR: 214.3 (C-3), 145.1(C-1'), 112.7.2 (C-2'), 80.2 and 73.9 (C-6 and C-2), 33.0 and 31.7 (C-4 and C-5), 29.3, 27.6 and 26.8 (C-7, C-8 and C-9).

PROTECTION OF **21** WITH ETHYLENEGLYCOL: **22**

Compound **21** (0.17 g, 1.0 mmol) was protected with ethyleneglycol (0.11 ml, 2.0 mmol) by treating at reflux of dry benzene (2 ml) with *p*-toluensulfonic acid (traces) in a Dean-Stark trap for 24 h. Usual work-up afforded **22** (0.17 g, 74%). IR: ν_{max} (film) cm^{-1}: 1460, 1380, 1270, 1150, 1100 and 920. ^1H NMR: 6.02 (1H, dd, J=17.5 and 10.7, H-1'), 5.04 (1H, d, J=10.6, HA-2'); 5.00 (1H, d, J=17.5, HB-2'); 3.95 (4H, s, -O-CH_2-CH_2-O-); 2.10-1.90 (4H, m, H-4 and H-5); 1.29, 1.26 and 1.22 (3H, s, ea, Me-7, Me-8 and Me-9).

HYDROBORATION OF **22: 23**

BH_3 (1M in THF, 1ml) was added to a cooled solution (0°C) of **22** (0.16 g, 0.7 mmol) in dry THF (1 ml). The reaction mixture was stirred for 2 h at 0°C and 1 h at room temperature. Water (0.2 ml), 3M NaOH (2 ml) and 30% H_2O_2 (1 ml) were added and the mixture refluxed for 1 h. Usual work-up afforded after chromatography (hexane/ether 1:1) **23** (93 mg, 54%). IR: ν_{max} (film) cm^{-1}: 3400, 1450, 1380, 1140, 1110, 1090 and 1010. ^1H NMR: 3.95 (4H, s, -O-CH_2-CH_2-O-); 3.84 (2H, m, H-2'); 2.10 (2H, m, H-1'), 1.60-1.40 (4H, m, H-4 and H-5); 1.34 and 1.13 (6H, s and 3H, s, Me-7, Me-8 and Me-9).

PROTECTION OF **23** with TBDPSCl: **24**

Compound **23** (33 mg, 0.14 mmol), a catalytic amount of DMAP and imidazole (10 mg, 0.14 mmol) were dissolved in DMF (1 ml) and TBDPSCl (0.05 ml, 0.17 mmol) was added. The reaction mixture was stirred for 12 h at room temperature. Usual work-up and chromatography (hexane/ether, 95:5) afforded **24** (55 mg, 83%). IR: ν_{max} (film) cm^{-1}: 1460, 1420, 1150, 1110, 1080, 1000, 810, 730 and 700. ^1H NMR: 7.73 (4H, m, Ar); 7.41 (6H, m, Ar); 3.97 (4H, s, -O-CH_2-CH_2-O-); 3.84 (2H, m, H-2'); 2.22-1.60 (6H, m, H-1', H-4 and H-5); 1.23, 1.22 and 1.14 (3H, s, ea, Me-7, Me-8 and Me-9); 1.09 (9H, s, Me_3C-).

DEPROTECTION OF **24: 23**

A catalytic amount of *p*-toluensulfonic acid was added to **24** (55 mg, 0.11 mmol) dissolved in dry MeOH, and stirred for 1 h at room temperature. Ether was added and the mixture washed with 10% $NaHCO_3$ and water. Dried, filtered, evaporated and chromatographed (hexane/ether 95:5) to afford **23** (11 mg, 20%).

CYCLIZATION OF GERANYLACETATE

30% H_2O_2 (3.85 ml, 34 mmol) was added to a stirred solution of diphenyl diselenide (10.6 g, 34 mmol) in dry DCM (150 ml) at 0°C. After 30 min a white powder precipitated and $MgSO_4$ (7.5 g) was added and stirred for 30 min at 0°C. A solution of geranyl acetate (5.0 g, 25.5 mmol) in dry DCM was added and stirred at room temperature for 12 h. The reaction mixture was poured in ether (200 ml) and washed with 10% $NaHCO_3$, water and brine. The dried ($MgSO_4$) solvents were removed and the residue was subjected to chromatography (hexane/ether 9:1) affording a mixture of **25:26** (11.3 g, 83%) in a ratio 1:10.

Compound **26**. IR: ν_{max} (film) cm^{-1}: 1730, 1590, 1480, 1450, 1380, 760 and 670. ^1H NMR: 7.55 (6H, m, Ar); 7.27 (4H, m, Ar); 4.61 (1H, dd, J=11.5 and 5.4, HA-2'); 4.32 (1H, dd, J=11.5 and 6.7, HB-2'); 3.20 (1H, dd, J=6.7 and 5.4, H-1'); 3.00 (1H, dd, J=12.1 and 5.4, H-3); 1.91 (3H, s, -OAc); 1.35 y 1.30 (6H, s and 3H, s, Me-7, Me-8 and Me-9); MS: 524 (M^+, 16), 400(8), 309(5), 283(45), 183(8), 157(30), 125(100), 107(26), 81(38).

REDUCTION OF **25/26: 27** and **28**

$LiAlH_4$ (0.6 g, 15.8 mmol) was added to a solution of **25/26** (9.0 g, 17.2 mmol) in dry THF (100 ml). The reaction was stirred por 2 h. at room temperature. After that some drops of water, ether and a mixture of $Na_2SO_4/NaHCO_3$ (1:1, 40g) were added and stirred for 30 min. After filtration, evaporation and chromatography (hexane/ether 8:2) afforded **27** (0.7 g, 9%) and **28** (7.3 g, 88%).

Compound **27**. IR: ν_{max} (film) cm^{-1}: 3460, 3060, 1580, 1480, 1380 and 1120. ^1H NMR: 7.66 (10 H, m, Ar); 4.30-3.80 (3H, m, H-2' y H-5); 3.36 (1H, m, H-1'); 2.30-1.80 (3H, m); 1.34 (6H, s) and 1.30 (3H, s). ^{13}C NMR: 138.6 (2CH, Ar); 134.2 (2CH, Ar) 129.6 (C*ipso*-Ar); 129.4 (2CH, Ar); 128.8 (2CH, Ar); 127.8 (2CH, Ar); 127.3 (C*ipso*-Ar); 86.8 (C-5); 79.0 (C-2); 64.7 (C-2'); 56.4 (C-1'); 48.3 (C-1"); 40.2 (C-4); 27.4 (C-4); 26.0 (Me) 25.9 (Me) and 23.1 (Me).

Compound **28**. IR: ν_{max} (film) cm^{-1}: 3500, 1590, 1480, 1450, 1380, 1130, 1010 and 760. ^1H NMR: 7.40 (6H, m, Ar); 7.30 (4H, m, Ar); 4.10 (1H, dd, J=13.1 and 10.3, HA-2'); 3.80 (1H, dd, J=13.1 and 4.8, HB-2'); 3.20 (1H, dd, J=10.3 and 4.8, H-1'); 3.10 (1H, dd, J=12.4 and 4.8, H-3); 2.20-1.80 (4H, m, H-4 and H-5); 1.43 and 1.40 (3H, s and 6H, s, Me-7, Me-8 and Me-9); MS: 482 (M^+, 7), 283(35), 183(9), 157(21), 125(100), 107(23), 81(60), 69(100).

ELIMINATION REACTION OF **28: 7**

Et_3N (12 ml, 85 mmol) an mesyl chloride (4 ml, 51 mmol) were added to a solution of **28** (8.1 g, 16.7 mmol) in dry DCM (75 ml) at 0°C and stirring was continued for 30 min at room temperature. Some drops of water and ether were added, washed with 10% $NaHCO_3$ and water, dried, filtered, evaporated and chromatographed (hexane/ether, 95:5) to give the diasteroisomeric mixture CIS/TRANS **7** (4.2 g, 81%). IR: ν_{max} (film) cm^{-1}: 1630, 1590, 1480, 1450, 1360, 1230, 1120, 1070, 910 and 750. ^1H NMR, main isomer: 7.60 (3H, m, Ar), 7.30 (2H, m, Ar); 5.89 (1H, dd, J=17.6 and 10.7, H-1'); 5.08 (1H, dd, J=17.6 and 1.5, HA-2'); 4.94 (1H, dd, J=10.7 and 1.5, HB-2'), 3.22 (1H, dd, J=8.8 and 4.4, H-3); 2.20-1.60 (4H, m, H-4 and H-5); 1.43, 1.40, 1.30 (3H, s, ea, Me-7, Me-8 and Me-9). ^{13}C NMR: 147.4 (C-1'), 134.5 (2CH-Ar), 130.5 (C-Ar), 129.1 (2CH-Ar), 127.4 (CH-Ar), 110.5 (C-2'), 75.5 and 73.9 (C-6 and C-2), 52.8 (C-3), 34.1 (C-4), 30.7, 28.0 and 27.7 (C-9, C-8 and C-7), 25.3 (C-5); MS: 310 (M^+, 32), 295 (5), 184 (100), 157 (36), 153 (51), 137 (14), 104 (20), 95 (100), 81 (92), 67 (39).

HIDROBORATION-ELIMINATION REACTION OF **7: 29**

7 (4.2 g, 13.6 mmol) in dry THF (75 ml) was hydroborated (1M BH_3 in THF, 13.5 ml) according to the procedure described. After work-up and chromatography (hexane/ether, 4:1) **29** (1.36g, 60%) was isolated. IR: ν_{max} (film) cm^{-1}: 3400, 1460, 1430, 1390, 1080, 1000 and 710. ^1H NMR: 5.70 (2H, m, H-3 and H-4); 3.85 (2H, t, J=5.0, H-2'); 2.20 (1H, brd, J=16.6, HA-5); 1.82-1.70 (3H, m, H-1' and HB-5), 1.30, 1.28, 1.22 (3H, s, ea, Me-7, Me-8 and Me-9). ^{13}C NMR: 133.6 (C-3), 120.5 (C-4), 74.7 (C-6), 72.2 (C-2), 59.8 (C-2'), 44.3 (C-1'), 33.7 (C-5), 31.5 (C-8), 28.7 (C-9), 26.4 (C-7). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.59; H. 10.59; MS: 170 (M^+, 10), 155 (15), 137 (16), 125 (73), 109 (38), 95 (28), 82 (80), 67 (100), 55 (88); high-resolution mass spectrum calcd for $C_{10}H_{18}O_2$ (M^+): 170.1307, found 170.1304.

PROTECTION OF **29** with TBDPSCl: **20**

29 (0.21 g, 1.23 mmol) was protected with TBDPSCl (0.24 ml, 1.55 mmol) acording to the procedure

already described. Usual work-up and chromatography (hexane/ ether, 4:1) afforded **20** (0.44 g, 86%).

IR: ν_{max} (film) cm^{-1}: 1470, 1410, 1390, 1360, 1110, 1010, 810 and 720. ^1H NMR: 7.77 (6H, m.Ar); 7.45 (4H, m, Ar); 5.72 (2H, bs, H-3 and H-4); 3.92 (2H, t, J=6.4, H-2'); 2.20 (1H, d, J=16.6, HA-5); 2.00-1.70 (3H, m, H-1' and HB-5); 1.30, 1.26 and 1.25 (3H, s, ea, Me-7, Me-8 and Me-9); 1.15 (9H, s, Me_3C-); MS: 409 (M^+, 100), 391 (30), 369 (15), 351 (15), 313 (98), 269 (71), 257 (80), 235 (40), 199 (36), 179 (20), 135 (15).

ALLILIC OXIDATION OF **20** WITH Na_2CrO_4: **30**

Na_2CrO_4 (0.18 g, 1.1 mmol), NaOAc (0.15 g, 18.3 mmol), Ac_2O (1.8 ml, 18.0 mmol) and glacial HOAc (1 ml) were added to a solution of **20** (0.17 g, 0.41 mmol) in dry benzene (2 ml) and stirred at reflux for 24 h. Ice was added and the mixture extracted with ether. The organic layer was washed with 10% $NaHCO_3$ and water, dried, filtered, evaporated and cromatographed (hexane/ether, 95:5) to give **20** (14 mg, 8%) and **30** (46 mg, 25%). IR: ν_{max} (film) cm^{-1}: 1680, 1470, 1420, 1190, 1110, 1020, 820 and 710. ^1H NMR: 7.70 (6H, m, Ar); 7.40 (4H, m, Ar); 6.89 (1H, d, J=10.8, H-5); 5.89 (1H, d, J=10.8, H-4), 3.78 (2H, t, J=5.9, H-2'); 1.93 (2H, m); 1.41, 1.38 and 1.28 (3H, s, ea, Me-7, Me-8 and Me-9), 1.03 (9H, s, Me_3C-). ^{13}C NMR: 199.1 (C-3), 154.7 (C-5), 135.6 (4CH-Ar), 133.7 (2C-Ar), 129.7 (2CH-Ar), 127.7 (4CH-Ar), 121.9 (C-4), 78.3 and 73.1 (C-2 and C-6), 59.9 (C-2'), 45.3 (C-1'), 28.0, 27.8 and 26.9 (C-7, C-8 and C-9), 26.94 (3Me, $\underline{Me}_3C$-), 19.2 (C, $Me_3\underline{C}$-). MS: 423 (M^+, 100), 391 (9), 366 (36), 345 (15), 307 (6), 289 (9), 257 (18), 239 (9), 199 (12), 167 (11), 121 (6); high-resolution mass spectrum calcd for $C_{26}H_{34}O_3Si$ (M^+): 422.2277, found 422.2269.

ALLILIC OXIDATION OF **20** WITH CrO_3 and 3,5-DIMETHYLPYRAZOLE: **30**

To a solution of CrO_3 (220 mg, 2.2 mmol) in dry DCM (2 ml) at -20°C was added 3,5-dimethylpyrazole (211 mg, 2.2 mmol). After 15 min a solution of **20** (44 mg, 0.11mmol) in dry DCM (2 ml) was added. After 1 h at -20°C and 4 h at room temperature, the reaction was quenched with 1M NaOH (2 ml). Extracted with ether, washed with 10% HCl, 10% $NaHCO_3$ and water, dried, filtered and evaporated. After chromatography (hexane/ether 95:5) unreacted **20** (25 mg, 57%) and **30** (14 mg, 30%) were isolated.

ACETYLATION OF **29: 31**

Compound **29** (1.10 g, 6.5 mmol) was acetylated with Ac_2O (2 ml, 19.6 mmol) and pyridine (3 ml). Usual work-up and chromatography (hexane/ether 9:1) afforded **31** (1.18 g, 85%). IR: ν_{max} (film) cm^{-1}: 1745, 1460, 1430, 1390, 1370, 1330, 1240, 1160, 1100 and 710. ^1H NMR: 5.60 (2H, bs, H-3 and H-4); 4.15 (2H, t, J=7.0, H-2'); 1.96 (3H, s, -OAc); 1.80 (4H, m, H-5 and H-1'); 1.17, 1.16 and 1.13 (3H, s, ea, C-7, C-8 and C-9). ^{13}C NMR: 170.9 (-O$\underline{C}$OMe), 134.1 (C-3), 120.2 (C-4), 71.4 and 71.3 (C-2 and C-6), 61.2 (C-2'), 40.6 (C-1'), 34.1 (C-5), 30.7, 29.6 and 26.9 (Me-7, Me-8 and Me-9, respectively), 20.7 (-OCO$\underline{Me}$). MS: 212 (M^+, 16), 197 (40), 153 (30), 137 (74), 125 (74), 109 (41), 95 (51), 82 (100), 67 (80).

ALLILIC OXIDATION OF **31** WITH Na_2CrO_4: **32** AND **33**

31 (0.94 g, 4.4 mmol) in dry benzene was oxidized with Na_2CrO_4 (2.43 g, 15.0 mmol), NaOAc (0.96 g, 9.4mmol), Ac_2O (15 ml) and glacial HOAc (6.5 ml) according to the procedure previously described. Usual work-up and chromatography (hexane/ether 95:5) afforded **32** (0.17 g, 17%). **33** (0.49 g, 65%).

Compound **32**. IR: ν_{max} (film) cm^{-1}: 1740, 1690, 1360, 1240, 1180 and 820. ^1H NMR: 6.82 (1H, d,

J=10.5, H-5); 5.91 (1H, d, J=10.5, H-4); 4.15 (2H, m); 2.30 (1H, dt, J=13.8 and 6.1, HA-1'); 1.96 (3H, s, -OAc); 1.85 (1H, dt, m), 1.44, 1.38 and 1.37 (3H, s, Me-8, Me-7 and Me-9 respectively). ^{13}C NMR: 197.7 (C-3), 170.8 (MeCOO-), 154.7 (C-5), 122.1 (C-4), 78.7 (C-2), 71.7 (C-6), 60.3 (C-2'), 38.3 (C-1'), 28.9 (C-7), 27.7 (C-8), 26.9 (C-9), 20.8 (Me-COO-); MS: 227 (M^+, 15), 167 (12), 145 (36), 126 (47), 108 (25), 96 (82), 81 (52), 69 (83), 55 (100). high-resolution mass spectrum calcd for $C_{12}H_{18}O_4$ (M^+): 226.1205, found 226.1210.

Compound **33.** IR: ν_{max} (film) cm^{-1}: 1740, 1690, 1360, 1240, 1180 and 820. ^1H NMR: 6.74 (1H, d, J=10.5 Hz, H-5); 5.87 (1H, d, J=10.5, H-4); 4.10 (2H, dd, J=13.3 and 6.6, H-2'); 1.92 (3H, s, AcO-); 1.90 (2H, m, H-1'); 1.37, 1.31 and 1.28 (3H, s, ea, Me-9, Me-8 and Me-7 respectively). ^{13}C NMR: 198.5 (C-3), 170.7 (MeCOO-), 153.8 (C-5), 122.6 (C-4), 78.3 (C-6), 72.7 (C-2), 60.4 (C-2'), 41.2 (C-1'), 27.7 (C-9), 27.7 (C-8), 26.7 (C-7), 20.8 (Me-COO-); MS: 227 (M^+, 8), 168(15), 151(13), 139(18), 126(100), 108(64), 96(47), 80(85), 67(23); high-resolution mass spectrum calcd for $C_{12}H_{18}O_4$ (M^+): 226.1205, found 226.1202

PROTECTION OF **32** WITH ETHYLENE GLYCOL: **34**

32 (0.11 g, 0.48 mmol) was protected with ethylene glycol (0.2 ml, 3.6 mmol) according to the procedure already described. Column chromatography (hexane/ether 4:1) of the residue afforded **34** (110 mg, 84%). IR: ν_{max} (film) cm^{-1}: 2980, 1740, 1470, 1360, 1240, 1120, 1010 and 760. ^1H NMR: 5.75 (1H, d, J=12.0, H-5); 5.65 (1H, d, J=12.0, H-4); 4.19 (2H, t, J=8.1, H-2'); 3.96 (4H, m, -O-CH_2-CH_2-O-); 2.00 (3H, s, AcO-); 1.85 (2H, dd, J=13.8 and 8.1, H-1'); 1.29, 1.26 and 1.19 (3H, s, ea, Me-9, Me-8 and Me-7 respectively). ^{13}C NMR: 170.2 (MeCOO-), 133.9 (C-5), 123.6 (C-4), 103.6 (C-3), 77.0 and 71.8 (C-6 and C-2), 64.5 (-O-CH_2-CH_2-O-); 60.5 (C-2'), 40.5 (C-1'), 27.0, 24.4 and 22.6 (C-7, C-8 and C-9 respectively), 20.2 (-OCOMe).

HYDROLISIS OF **34: 35**

10% NaOH in MeOH (1 ml) was added to **34** (70 mg, 0.26 mmol) and stirred for 12 h at room temperature. Usual work-up and chromatography (hexane/ether 1:1) afforded **35** (52 mg, 88%). IR: ν_{max} (film) cm^{-1}: 3500, 2940, 1380, 1140, 1100, 1010 and 760; ^1H NMR: 5.88 (1H, d, J=12.0, H-5); 5.79 (1H, d, J=12.0, H-4); 4.20-3.60 (6H, m, H-2' and -O-CH_2-CH_2-O-); 2.01 (2H, m, H-1'); 1.32, 1.30 and 1.23 (3H, s, ea, Me-7, Me-8 and Me-9 respectively). ^{13}C NMR: 137.1 (C-5), 117.9 (C-4), 102.1 (C-3), 82.4 and 72.2 (C-6 and C-2), 66.4 (C-2'), 62.5 (-O-CH_2-CH_2-O-), 39.0 (C-1'), 31.4, 28.7 and 21.1 (C-7, C-8 and C-9 respectively); MS: 228 (M^+, 30), 213 (5), 167 (25), 140 (21), 96 (100), 84 (28), 71 (46); high-resolution mass spectrum calcd for $C_{12}H_{20}O_4$ (M^+): 228.1362, found 226.1360

TOSYLATION OF **35: 36**

A catalytic amount of DMAP, pyridine (0.05 ml) and tosyl chloride (23 mg, 0.12 mmol) were added to a solution of **35** (20 mg, 0.1 mmol) at 0°C and stirred for 24 h. Then water was added and stirring was continued for 30 min. The reaction mixture was extracted with ether and the organic phase washed with 10% HCl, 10% $NaHCO_3$ and water, dried , filtered and evaporated to give **36** (29 mg, 75%). IR: ν_{max} (film) cm^{-1}: 2870, 1600, 1490, 1120, 910 and 780. ^1H NMR: 7.81 (2H, d, J=8.3, Ar); 7.36 (2H, d, J=8.0 Hz, Ar); 5.97 (1H, d, J=10.6, H-4); 5.82 (1H, d, J=10.6, H-5); 4.15 (2H, m, -O-CH_2-CH_2-O-); 3.81 (2H, m, -O-CH_2-CH_2-O-); 3.71 (2H, t, J=5.1, H-2'); 2.45 (3H, s, Me-Ar); 1.49 and 1.42 (3H and 6H, s, ea, Me-7, Me-8 and Me-9).

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