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The Reactivity of Drimane Unsaturated Dialdehydes Towards Nucleophiles[1]

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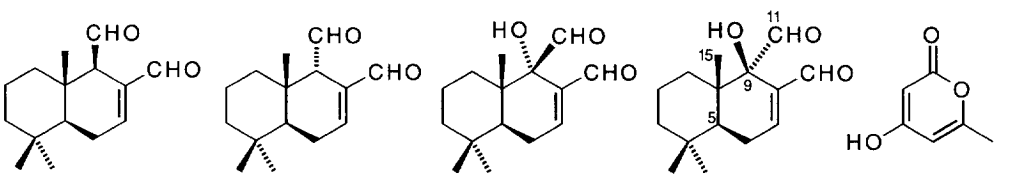
Abstract:. The reactivity of the potent antifeedants and antibiotics (-)-polygodial (**1**) and (-)-warburganal (**3**) [prepared from (-)-**1**] towards amino acids and triacetic acid lactone (**5**) was compared to that of their C-9 epimers **2** and **4** [both prepared from (-)-**1**]. Polygodial (**1**) reacts approximately 10 times faster than warburganal (**3**), which in turn is more reactive that the two epimers. The isolation and characterisation of adducts formed with **5** show that these drimanes react in a similar way as other bioactive sesquiterpenoid unsaturated dialdehydes. Copyright © 1996 Elsevier Science Ltd

Bioactive drimane sesquiterpenes containing an unsaturated 1,4-dialdehyde moiety, for example polygodial (**1**) and warburganal (**3**), have been isolated from various natural sources such as higher plants,[2-5] liverworts,[6] and marine organisms.[7,8] The unsaturated dialdehyde functionality and its reactivity towards biological nucleophiles is considered to be responsible for the general antibiotic activity of these compounds, although other bioactivities (e.g. the affinity for nerve cell receptors) appear to be caused by more selective interactions.[9,10]

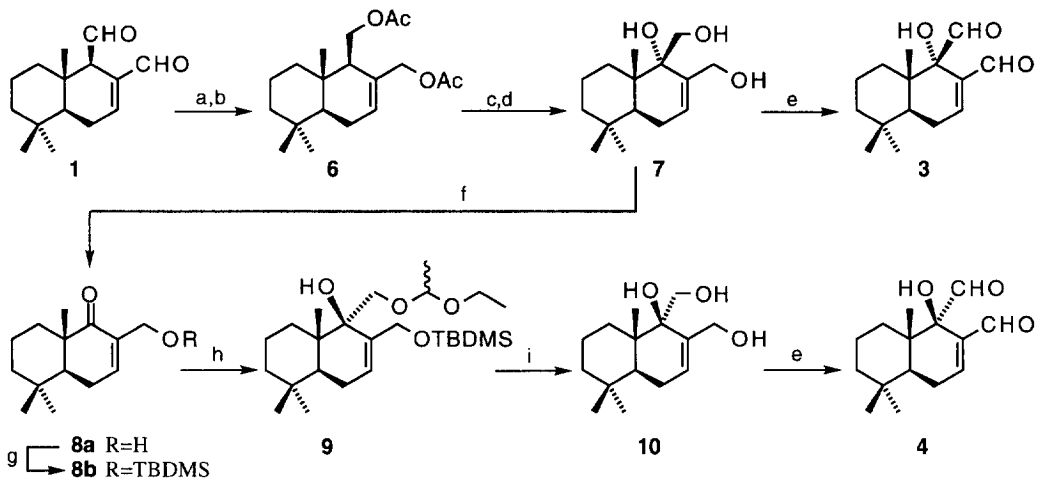


1 **2** **3** **4** **5**

Figure 1

The stereochemistry and the presence of substituents may modulate the reactivity and the bioactivity of the unsaturated dialdehydes considerably. For example, polygodial (**1**) is known to react with primary amines under biomimetic conditions to form pyrroles,[11] a reaction that has been proposed to be responsible for the bioactivities of **1**.[12] Its epimer **2**, which is less bioactive, will not undergo the same reaction, because the formation of a pyrrole is less favoured due to the larger distance between the aldehyde carbons.[11] No pyrrole can be formed with warburganal (**3**), due to the presence of the α-hydroxyl group, but it still reacts rapidly with methyl amine to form a charged azomethine derivative.[11] However, several other reactions with the unsaturated dialdehydes are possible,[13,14] and a deeper understanding of the relationships between structure and activity of the drimane dialdehydes must also take their reactivity as Michael acceptors, for

instance, into consideration. The aim of this study has therefore been to prepare the four drimane dialdehydes **1-4**, and compare their chemical reactivities towards different nucleophiles.



Scheme 1. a) $LiAlH_4$, ether, 0°C→r.t.; b) Ac_2O, pyridine, r.t.; c) SeO_2, dioxan, reflux; d) K_2CO_3, MeOH, r.t.; e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78°C; f) $NaIO_4$, THF/water, r.t.; g) TBDMSCl, imidazole, DMF, r.t.; h) 1-ethoxyethoxymethyllithium, THF, -78°C; i) HOAc/MeOH/water 2:2:1, r.t.

Several total syntheses of both polygodial and warburganal have been developed.[15] While (-)-polygodial (**1**) is readily accessible from natural sources, warburganal is not, and an efficient semisynthetic route from natural (-)-polygodial (**1**) to (-)-warburganal (**3**) would be desirable. The direct oxidation of **1** to **3** was not feasible, but the reduction[16,17] of **1** followed by acetylation to yield **6**, followed by its oxidation via the triol **7** to (-)-warburganal (**3**) using Urones protocol[18] (originally developed by Ley and co-workers[19,20]), gave (-)-warburganal (**3**) in 60 % overall yield. Polygodial (**1**) and its epimer **2** are transformed to each other under slightly basic conditions (approximately 1:2 at equilibrium), and they can be separated from each other by silica gel chromatography (see Experimental section). The warburganal epimer **4** (as a racemate) has previously been reported as a by-product in a total synthesis of (±)-warburganal (**3**).[21] However, we required the pure enantiomer of **4** in order to be able to compare its biological activities with those of the other drimane dialdehydes. Initially, we tried to prepare **4** by the oxidation of the acetylated diol prepared from the polygodial epimer **2** (*vide supra*), but this procedure was unsuccessful presumably due to steric hindrance by the C-10 methyl group. Instead, the homologation of the corresponding ketone to the α-hydroxyaldehyde, for which several procedures have been developed,[22] was considered. The ketone **8a** was obtained by oxidative cleavage of the triol **7** with $NaIO_4$ in THF/water in a nearly quantitative yield. Several routes from **8a** to **4** were investigated, but the only successful was the addition of 1-ethoxyethoxymethyllithium to **8b** (prepared by treatment of **8a** with *t*-butyldimethylsilyl chloride) followed by hydrolysis to the triol **10** and subsequent Swern oxidation to **4**. 1-Ethoxyethoxymethyllithium was prepared according to the Still protocol,[23] and its reaction with ketone **8b** gave the expected product **9** in 83 % isolated yield. The hydrolysis of **9** with HOAc/MeOH/water 2:2:1 proceeded smoothly, affording the triol **10** in 82 % yield, and the overall yield from (-)-polygodial (**1**) to (+)-**4** (nine steps) was 26 %. The spectral data of **4** agree with those reported by Kende *et al.*,[21] and the stereochemistry of **4** was confirmed by a NOESY experiment: Correlations were observed between 5-H and 11-H (but not between 5-H and 9-OH), as well as between 15-H_3 and 9-OH (but not between 15-H_3 and 11-H).

As nucleophiles for the reactivity study, we have chosen the amino acids alanine and lysine, and the

natural triketide triacetic acid lactone (**5**).[24] Lysine contains a primary amino group, and should react more efficiently than alanine at least with polygodial (**1**). Triacetic acid lactone (**5**) is a bi-functional nucleophile that previously has been shown to react exclusively with the α,β-unsaturated aldehyde of marasmane and isolactarane unsaturated dialdehydes, forming pentacyclic pyranone adducts.[14] The reaction rates of the marasmane and isolactarane dialdehydes with **5** in phosphate buffer were strongly correlated with their antibiotic activities, suggesting that their reactivity towards this type of bi-nucleophiles is important for this activity.[14] As the stereo selective control of the addition of a nucleophile can influence the reaction rate, this may explain the differences observed in the biological activities of a given pair of stereo isomers (e.g. **1/2** or **3/4**). The reactivity of the dialdehydes **1**, **2**, **3** and **4** were initially measured towards the amino acids alanine and lysine, and the disappearance of the dialdehydes from a phosphate buffer (pH 7.4) in the absence (= spontaneous degradation) and the presence of alanine or lysine was monitored by HPLC. The half-lifes in hours of the dialdehydes are given in Table 1, and the values were adjusted for the spontaneous degradation in buffer only.

Dialdehyde:	Buffer	Alanine[a]	Lysine[a]
1	260	37	2.6
2	550	830	580
3	200	210	35
4	350	360	280

Table 1. The half-lifes in hours of the dialdehydes **1**, **2**, **3** and **4** (0.2 mM) in the absence and the presence of alanine and lysine (two equiv.) in phosphate buffer (pH 7.4) containing 5 % acetonitrile as a cosolvent, at 37°C.
[a]Spontaneous degradation in buffer (without amino acid) was subtracted.

As expected,[25] the difference between polygodial (**1**) and its epimer **2** is dramatic, polygodial (**1**) reacts rapidly and more than 200 times faster than **2** in the presence of lysine, and reasonably fast also in the presence of alanine. This experiment also demonstrates that the epimerisation of **2** to **1** is slow at pH 7.4, although we have observed that it is substantial under slightly more basic conditions. Warburganal (**3**) reacts faster than its epimer **4** in the presence of lysine (approximately 8 times), but only slightly faster in the presence of alanine. While polygodial (**1**) and warburganal (**3**) react much faster in the presence of lysine than alanine, their epimers do not show the same specificity, and their degradation due to the presence of the amino acids is comparable to their degradation in buffer only. As discussed above, the reaction with primary amines has been suggested to be responsible for the biological activity, e.g. antifeedant activity,[11,12] but this is contradicted by the fact that polygodial (**1**) is more then 10 times more reactive towards lysine compared to warburganal (**3**), which is the more antifeedant of the two.[26]

The reactivity towards triacetic acid lactone (**5**) was investigated in buffer (with 5 % acetonitrile as cosolvent) at 37°C and pH 4.0, 5.6 and 7.4. The reaction is slow at neutral pH, but is catalysed by acid,[14] and a low pH prevents the degradation of the dialdehydes by for example autoxidation.[27] A large excess (20 equivalents) of **5** was used to obtain pseudo-first order kinetics, and the disappearance of the dialdehydes was recorded as described above. The half-lifes (hours) of the four dialdehydes in the presence of **5** are shown in Table 2, and the values were adjusted for the spontaneous degradation in buffer only. The half-life ">2000 h" indicate that the compound does not react with lactone **5** at a measurable rate, and that approximately the same degradation rates were observed in buffer as in buffer containing 20 equivalents **5**.

Dialdehyde:	Buffer only pH: 4.0	5.6	7.4	Buffer + 20 equiv. 5[a] 4.0	5.6	7.4
1	810	980	310	72	180	480
2	980	700	210	820	> 2000	> 2000
3	830	570	100	770	1200	> 2000
4	340	360	67	> 2000	> 2000	> 2000

Table 2. The half-lifes in hours of the dialdehydes **1**, **2**, **3** and **4** (0.2 mM) in buffer at 37 °C and pH 4.0, 5.6 and 7.4 in the absence and the presence of triacetic acid lactone (**5**). [a]Spontaneous degradation in buffer (without lactone **5**) was subtracted.

Again, polygodial (**1**) is the most reactive, and the results resemble those shown for alanine in Table 1. Warburganal (**3**) is slightly more reactive than its epimer **4**, but considerably less reactive compared to polygodial (**1**). In fact, warburganal (**3**), possessing potent bioactivities,[13,26,28,29] is only slightly more reactive than the biologically less active[3,13,29] *epi*-polygodial (**2**), indicating that the bioactivities of warburganal (**3**) mainly depend on other chemical interactions. In order to characterise the adducts formed between the drimane dialdehydes and **5**, the reaction was performed in a preparative scale in refluxing ethyl acetate.[14]

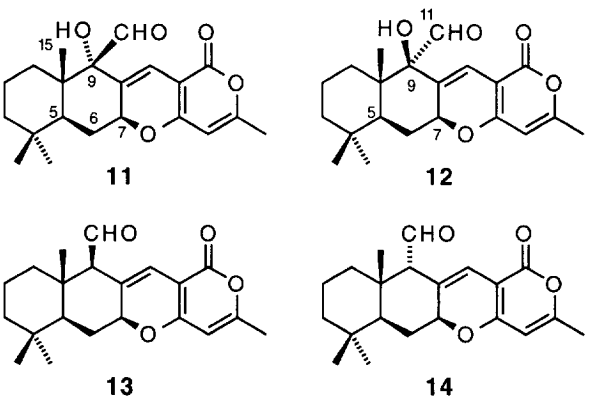


Figure 2

The adducts, shown in Figure 2, correspond to those obtained previously with other dialdehydes.[14] Warburganal (**3**) and its epimer **4** each yielded a single product, **11** and **12**, respectively, and comparison by HPLC showed that the same products were formed in buffer at pH 7.4. For adduct **11**, NOESY correlations were observed between 7-H (5.33 ppm) and 5-H_α (2.18 ppm) as well as 6-H_α (1.84 ppm), and between 6-H_β (1.90 ppm) and 15-H_3 (1.40 ppm), establishing that 7-H has α-orientation. For adduct **12**, NOESY correlations were observed between 7-H (5.44 ppm), 5-H_α (1.74 ppm) and 11-H (9.83 ppm), establishing that 7-H has α-orientation. Both polygodial (**1**) and its epimer **2** gave mixtures of compounds **13** and **14**, which could not be separated from each other and therefore were not fully characterised. Epimerisation of polygodial (**1**) and **2** during the reaction conditions was observed, but it is not clear whether the adducts **13** and **14** also epimerise as they are formed. However, it was possible to identify the signals for **13** as well as **14** in the ^{1}H NMR spectrum of the mixture, by comparison with the corresponding signals in the ^{1}H NMR spectra of compounds **11** and **12**. For instance, the shifts of compound **13** (9.86, 6.09, 5.73, 4.99 and 2.21

ppm) are in accordance with the analogous shifts (10.02, 5.99, 5.74, 5.33 and 2.21 ppm) of **11**. Similarly, the shifts for compound **14** (9.84, 6.17, 5.72, 5.38 and 2.20 ppm) are in accordance with the corresponding shifts (9.83, 6.62, 5.76, 5.44 and 2.23 ppm) for its isomer **12**. The shift for H-9 appears at 2.38 ppm for **13** and at 2.91 ppm for **14**. As the coupling constants for 7-H of **13** and **14** (2, 6 and 11 Hz for both compounds) are similar to those observed for compound **12** (2.4, 6.4 and 11.1 Hz), it is reasonable to assume that 7-H has α-orientation for both these compounds. In a MS analysis of **13/14**, the major fragments [*m/z* : 342 (M^+), 313, 205, 139 and 84] are in good agreement with the major fragments of **11** and **12** [*m/z* : 358 (M^+), 329, 221, 139 and 84], with a difference of 16 (the 9-OH oxygen) for the molecular ion and the two heaviest fragments. Hence, we suggest that compounds **13** and **14** are formed from the reaction of **1** and **2**, respectively, with **5**.

The pyranone adducts are formed as single isomers with equatorial 7-O, and the facial selectivity probably arise from a chair like transition state. The adducts in Figure 2 may be formed by two principal routes; *via* the intermediates formed after a Michael addition of the hydroxyl oxygen of **5** to the β-carbon of the unsaturated aldehyde (followed by an attack of C-2 of **5** on the aldehyde carbon and ring closure), or, more probably, *via* the attack of the nucleophilic C-2 of **5** on the unsaturated aldehyde carbon (followed by an electrocyclic ring-closure).[14,30-32] The influence of the configuration at C-9, as well as the substituent besides the aldehyde group (H or OH), on the reaction of the lactone **5** with the unsaturated aldehyde moiety is interesting, and will be further studied.

When comparing the biological activities of compounds **1-4** (antibiotic and antifeedant activity, affinity for nerve cell receptors, and pungency to human tongue), the two natural products polygodial (**1**) and warburganal (**3**) are approximately equally potent and considerably more active that the epimers **2** and **4** (details about their bioactivities will be reported elsewhere). However, while both **1** and **3** are more reactive towards nucleophiles than the epimers **2** and **4** in this investigation, **1** is nevertheless approximately one order of magnitude more reactive than **3**. This lack of correlation between bioactivity and reactivity for polygodial (**1**) and warburganal (**3**) suggests that the bioactivity of the latter at least to some extent depends on other properties.

EXPERIMENTAL

General Procedures: Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and ether was distilled from sodium/benzophenone ketyl immediately prior to use. Dimethyl sulfoxide (DMSO), CH_2Cl_2, diisopropylamine and triethylamine were distilled from calcium hydride, while N,N-dimethylaniline was distilled from sodium hydroxide prior to use. Dimethylformamide (DMF) and oxalyl chloride were freshly distilled prior to use. Paraformaldehyde was dried over P_2O_5 at 0.01 atm. prior to use. Paraldehyde was washed with water, dried over sodium sulphate and distilled prior to use. α-Chloroethyl ethyl ether was prepared immediately before use according to the method published by Grummit.[33] (Ethoxyethyloxymethyl)tributylstannane was prepared using the Still protocol.[23] Triacetic acid lactone (**5**) was prepared from triacetic acid, according to Collie.[34] (-)-Polygodial (**1**) was purified from an EtOAc-extract of the plant *Polygonum hydropiper*.[35] All reactions involving organometallic reagents or strong bases (e.g. LDA) were conducted under an atmosphere of dry nitrogen or dry argon in oven-dried glassware. TLC analyses were made on "Merck DC-Alufolien Kieselgel 60 F_{254}" SiO_2 plates, visualised by spraying with anisaldehyde/sulphuric acid and warming to 120°C. The EIMS spectrum (direct inlet, 70 eV) was recorded with a JEOL SX102 spectrometer, and the NMR spectra (in $CDCl_3$) with a Bruker ARX 500 spectrometer at 500 MHz (^1H) and 125 MHz (^{13}C), and with a Bruker DRX 400 spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C). The chemical shifts are reported in ppm with the solvent signals (δ_H=7.26 and δ_C=77.0) as reference. The IR spectrum was recorded with a Perkin-Elmer 157G spectrometer, and the UV spectrum with a Varian Cary 219 spectrometer. The melting points (uncorrected) were determined with a Reichert microscope, and the optical rotations were measured with a Perkin-Elmer 141 polarimeter at 24°C. HPLC analyses were performed using an Altex 110A pump, a Merck 50943 LiChroCART 125-4 LiChrospher 100 RP-18 (particle size, 5μm) column, a LDC SpectroMonitor III variable wavelength absorbance detector, a Hewlett Packard HP 3396A integrator, and MeOH/water

mixtures (60 %) as elution solvent with a flow rate of 1 ml/min. The dialdehydes were detected at 231 nm.

Degradation of the dialdehydes in buffer with lysine/alanine: 4 μmol of the dialdehydes were dissolved in CH_3CN (1.00 ml) and added to the PBS buffer (20 ml, pH 7.4). The phosphate buffer saline (PBS) contained: 8.0 mg NaCl, 0.2 g KCl, 1.44 g Na_2HPO_4, 0.24 g KH_2PO_4 and 1000 ml distilled water. The solution was divided into two equal samples, and the amino acid (4 μmol) was added to one of the samples. The mixtures were then stirred at 37°C for a number of days, and samples (0.1 ml) of the reaction mixture were taken at intervals, mixed with 0.1 ml MeOH and analysed by reversed-phase HPLC.

Degradation of the dialdehydes in buffer with triacetic acid lactone (5): 4 μmol of the dialdehydes were dissolved in CH_3CN (1.00 ml) and added to the buffer (20 ml). The following buffers were used: 0.2 M phosphate/0.1 M citric acid buffer (pH 4.0), 0.1 M phosphate buffer (pH 5.6) and 0.1 M phosphate buffer (pH 7.4). The solution was divided into two equal samples, and triacetic acid lactone (**5**) (40 μmol) was added to one of the samples. The mixtures were then stirred at 37°C for a number of weeks, and samples (0.1 ml) of the reaction mixture were taken at intervals, mixed with 0.1 ml MeOH and analysed by reversed-phase HPLC.

(-)-*Epi*-polygodial (2): A mixture of (-)-polygodial (**1**) (1.00 g, 4.27 mmol) and Cs_2CO_3 (3.16 g, 9.70 mmol) in THF (5 ml) was stirred at 55°C for two hours. The mixture was then filtrated through a Celite pad, diluted with ether and washed with saturated NH_4Cl solution followed by brine. The organic phase was dried and concentrated. The residue was purified by chromatography (SiO_2; toluene/MTBE 99/1) yielding (-)-epipolygodial (**2**) (0.536 g, 54 %, higher R_f), and unchanged (-)-polygodial (**1**) (0.409 g, 41 %, lower R_f).

(-)-Warburganal (3): (-)-Polygodial (**1**) (0.887g, 3.79 mmol) was reduced by treatment with $LiAlH_4$ in dry ether according to Peña[17], to afford the corresponding diol (0.776 mg, 86%) as a white solid. The diol was then transferred to (-)-warburganal (**3**), *via* triol **7**, according to Urones *et al.*[18] in 60 % overall yield (5 steps) from (-)-polygodial (**1**). The spectral data for (-)-warburganal (**3**) were identical in all respects with those of the natural product.[20,36-38]

1,4,4a,5,6,7,8,8a-Octahydro-3-hydroxymethyl-5,5,8a-trimethyl-(4a*S*,8a*S*)-naphthalene-1-one (8a): To a stirred solution of $NaIO_4$ (270 mg, 1.26 mmol) in a mixed solvent of THF (0.5 ml) and water (1.5 ml) was added a solution of the triol **7** (227 mg, 0.89 mmol) in THF (1 ml) at room temperature. The reaction was completed in less than 20 min. The reaction solution was extracted with ether (4 x 5 ml) and the combined extracts were washed with brine, dried and concentrated to give a yellowish oil (198 mg). The crude product was purified by chromatography (SiO_2; CH_2Cl_2/EtOAc 20/1) to provide compound **8a** (181 mg, 92%) as a colourless oil. $[\alpha]_D$ -62.4° (*c* 1.00, $CHCl_3$). MS [*m/z* (% rel. int.)]: 222 (M^+, 57), 204 (42), 189 (100), 161 (28), 134 (28), 121 (35), 109 (63), 98 (96), 91 (36), 41 (36). UV (EtOH) λ_{max} (ε): 233 nm (5800). IR (film): 3450, 2920, 1665, 1455, 1390, 1370, 955. ^{1}H NMR: 6.86, dm, *J*=5.8, 1H; 4.21, bd, *J*=5.7, 2H; 2.49, t, *J*=6.5, 1H; 2.41, dm, *J*=19.3, 1H; 2.30, dddd, *J*=19.3, *J*=11.3, *J*=3.9, *J*=1.8, 1H; 1.89, dm, *J*=13.6, 1H; 1.64, dd, *J*=11.3, *J*=4.3, 1H; 1.58, m, 2H; 1.45, dm, 1H; 1.34, m, 1H; 1.18, m, 1H; 1.06, s, H_3; 0.99, s, H_3; 0.91, s, H_3. ^{13}C NMR: 206,5; 145.0; 135.7; 62.2; 49.0; 45.2; 41.5; 33.6; 32.8; 32.3; 24.2; 22.2; 18.0; 17.1.

1,4,4a,5,6,7,8,8a-Octahydro-3-hydroxymethyl-5,5,8a-trimethyl-(4a*S*,8a*S*)-naphthalene-1-one (8b): To a solution of the alcohol **8a** (61 mg, 0.27 mmol) in DMF (5 ml) at 0 °C under argon was added *tert*-butyldimethylsilyl chloride (51 mg, 0.34 mmol) and imidazole (39 mg, 0.57 mmol) and the resulting mixture was stirred over night at room temperature. Dilution with water and work-up gave an oil (92 mg) which was purified by chromatography (SiO_2; heptane/toluene 1/1) to provide the silyl ether **8b** (76 mg, 83%) as a white solid. Recrystallisation (EtOH/water) gave colourless crystals with m.p. 77-79 °C. $[\alpha]_D$ -48.4° (*c* 1.00, $CHCl_3$). MS [*m/z* (% rel. int.)]: 321 (M^+-CH_3, 5), 280 (23), 279 (100), 223 (3), 209 (5), 187 (11), 145 (9), 131 (30), 105 (17), 75 (32). UV (EtOH) λ_{max} (ε): 233 nm (4800). IR (KBr): 2930, 2860, 1665, 1470, 1460, 1400, 1390, 1260, 1125, 1105, 975, 875, 855, 840, 780. ^{1}H NMR: 6.91, m, 1H; 4.30, qm, *J*=13.7, 2H; 2.42, dm, *J*=19.3, 1H; 2.28, dddd, *J*=19.3, *J*=11.2, *J*=5.9, *J*=3.1, 1H; 1.86, dm, *J*=13.7, 1H; 1,60, dd, *J*=11.2, *J*=4.3, 1H; 1.56, m, 2H; 1.43, dm, *J*=13.3, 1H; 1.30, m, 1H; 1.16, m, 1H; 1.04, s, H_3; 0.98, s, H_3; 0.91, m, $4H_3$, 0.06, s, $2H_3$. ^{13}C NMR: 205.0; 141.9; 135.6; 60.5; 49.3; 45.1; 41.6; 33.6; 32.9; 32.3; 25.9[$SiC(CH_3)_3$]; 24.0; 22.2; 18.3, 18.1, 17.1; -5.4; -5.4.

1,4,4a,5,6,7,8,8a-Octahydro-1-hydroxy-5,5,8a-trimethyl-(1*R*,4a*S*,8a*S*)-1,2-naphthalenedimethanol (9): A solution of (ethoxyethyloxymethyl)tributylstannane (50 mg, 0.13 mmol), in 1 ml of anhydrous THF was cooled to -78 °C under nitrogen. The solution was stirred while *n*-butyllithium (100 μl of a 1.14 M hexane solution, 0.114 mmol) was added. After stirring for 5 minutes ketone **3** (31 mg, 0.092 mmol) in THF (0.3 ml) was added dropwise. After stirring the resulting solution for 1 hour at -78 °C, the reaction mixture was diluted with ether, washed with brine, dried and concentrated to afford a colourless oil. Its TLC (toluene) showed only one spot (diastereomeric mixture of **9**) in addition to Bu_4Sn and unconsumed ketone **8b** (caused

by enolisation). The residue was purified by chromatography (SiO_2; toluene, followed by toluene/MTBE), recovering **8b** (9 mg), and yielding the diastereomeric mixture of **9** (40 mg, 58%, but 83% in respect to consumed **8b**) as a colourless oil. MS [*m/z* (% rel. int.)]: 338 (M^+-$CH_3CH_2OCH(CH_3)OCH_2$, 59), 337 (100), 293 (12), 219 (26), 205 (55), 187 (52), 109 (50), 75 (54), 73 (99), 45 (82). ^{1}H NMR: 5.74, m, 2H; 4.70, m, 2H; 4.49, dm, *J*=12.6, 1H; 4.43, dm, *J*=12.9, 1H; 4.11, m, 2H; 3.85, d, *J*=10.0, 1H; 3.78, s, 1H; 3.71, s, 2H; 3.66, m, 2H; 3.59, s, 1H; 3.53, d, *J*=10.0, 1H; 3.49, m, 2H; 2.08, dm, *J*=18.5, 2H; 1.93, ddm, *J*=18.5, *J*=11.2, 2H; 1.70, m, 2H; 1.62-1.37, m, 10H; 1.32, t, $2H_3$; 1.21, bt, $2H_3$; 1.15, dm, *J*=12.4, 2H; 0.96, s, $2H_3$; 0.94, s, $2H_3$; 0.91, m, $6H_3$; 0.87, s, H_3; 0.87, s, H_3; 0.08, s, $2H_3$; 0.08, s, $2H_3$. ^{13}C NMR: 138.4; 138.2; 126.3; 125.8; 100.8; 100.7; 78.5; 78.3; 70.1; 69.2; 65.9; 65.4; 61.5; 61.3; 44.7; 44.6; 42.8; 42.8; 41.5; 41.4; 33.8; 33.7; 33.7; 33.6; 26.4[SiC(CH_3)$_3$]; 26.3[SiC(CH_3)$_3$]; 24.4; 24.3; 22.4; 20.3; 19.0; 19.0; 18.7; 18.7; 15.7; 15.7; 15.5; -4.9; -4.9; -5.0; -5.0. The diastereomeric **9** (36 mg, 0.082 mmol) was stirred in a mixture of HOAc (1 ml), MeOH (1 ml) and water (0.5 ml) at r.t. for 1 hour. The mixture was then diluted with ether. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried and concentrated. The residue was purified by chromatography (SiO_2, CH_2Cl_2/EtOH 19/1) to provide the triol **10** (17 mg, 82%) as a white solid. Recrystallisation (heptane/ether) gave colourless crystals with m.p. 113-115 °C. $[\alpha]_D$ -47.2° (*c* 1.00, $CHCl_3$). MS [*m/z* (% rel. int.)]: 223 (M^+-CH_2OH, 100), 205 (85), 187 (13), 149 (47), 137 (23), 123 (31), 109 (76), 91 (18), 69 (36), 41 (21). IR (KBr): 3500, 3400, 2960, 2920, 1460, 1385, 1200, 1085, 1055, 1000, 945. ^{1}H NMR: 5.80, t, *J*=3.6, 1H; 4.22, d, *J*=11.4, 1H; 4.08, d, *J*=11.4, 1H; 3.94, d, *J*=11.1, 1H; 3.57, d, *J*=11.1, 1H; 3.51, bs, OH; 2.97, bs, OH; 2.11, dm, *J*=18.9, 1H; 1.97, ddd, *J*=19.0, *J*=11.1, *J*=3.1, 1H; 1.67, bs, OH; 1.60, m, 2H; 1.55-1.37, m, 4H; 1.18, m, 1H; 0.99, d, *J*=0.6, H_3; 0.95, s, H_3; 0.88, s, H_3. ^{13}C NMR: 139.6; 130.1; 79.0; 66.1; 65.8; 44.7; 42.6; 41.3; 33.8; 33.5; 32.4; 24.6; 22.4; 18.9; 15.6.

1,4,4a,5,6,7,8,8a-Octahydro-1-hydroxy-5,5,8a-trimethyl-(1*R*,4a*S*,8a*S*)-1,2-naphthalenedicarbaldehyde (4): To a stirring solution of 66 µl (0.76 mmol) of oxalyl chloride in 2 ml of anhydrous CH_2Cl_2, cooled to -78°C, was added dropwise 107 µl (1.51 mmol) of DMSO. After 2 min, a solution of 48 mg (0.19 mmol) of **10** in 0.6 ml of CH_2Cl_2/DMSO (3/1) was added dropwise over 5 min. After an additional 30 min, 0.48 ml (3.45 mmol) of triethylamine was added, and the mixture was allowed to stir at -78 °C for 5 min and then warm to room temperature. The mixture was passed though a plug of silica gel, eluting with heptane/EtOAc (1/1), and the eluent was concentrated to give a yellow oil. The oil was purified by chromatography (SiO_2; cyclohexane/EtOAc 19/1) to provide the dialdehyde **4** (17 mg, 82%) as white crystals. Recrystallisation (heptane) gave colourless crystals with m.p. 61-63 °C. $[\alpha]_D$ -343.5° (*c* 1.00, $CHCl_3$) and $[\alpha]_D$ -320.1° (*c* 0.70, $CHCl_3$). MS [*m/z* (% rel. int.)]: 221.1541 (M^+-CHO, 100 %, calculated for $C_{15}H_{22}O_3$ 221.1531), 203 (5), 189 (3), 149 (12), 133 (13), 109 (35), 105 (21), 81 (16), 69 (25), 55 (17), 41 (19). UV (CH_3CN) λ_{max} (ε): 226 nm (8300). IR (KBr): 3490, 3440, 2960, 2930, 2870, 1730, 1715, 1670, 1635, 1460, 1415, 1385, 1365, 1330, 1210, 1180, 1100, 985, 800. ^{1}H NMR: 9.88, s, 1H; 9.31, s, 1H; 7.15, dd, *J*=4.9, *J*=2.6, 1H; 4.87, s, OH; 2.57, dt, *J*=20.8, *J*=5.0, 1H; 2.32, ddd, *J*=20.8, *J*=11.2, *J*=2.5, 1H; 2.01, dm, *J*=13.0, 1H; 1.71, dd, *J*=11.2, *J*=4.9, 1H; 1.56, m, 1H; 1.47, m, 2H; 1.10, m, 2H; 1.05, s, H_3; 0.98, s, H_3; 0.93, s, H_3. ^{13}C NMR: 204.8; 195.3; 156.7; 139.1; 83.3; 43.5; 42.1; 42.0; 33.4; 33.3; 33.3; 26.2; 22.6; 18.5; 15.3.

11-Hydroxy-3,3,7,10a-tetramethyl-1-oxo-(5a*S*,6a*S*,10a*S*,11*S*)-1*H*,7*H*,8*H*,9*H*,10*H*,10a*H*,11*H*-benzo[*g*]-pyrano[4,3-*b*]chromene-11-carbaldehyde (11). A solution of (-)-warburganal **3** (9.8 mg, 0.039 mmol) and triacetic acid lactone (**5**) (10 mg, 0.078 mmol) in ethyl acetate (3 ml) was refluxed. Substrate **3** was not completely consumed after 52 hours, when the reaction was stopped and the solvent was removed under reduced pressure. The adduct was purified by chromatography in two steps [(SiO_2; EtOAc, followed by CH_2Cl_2/EtOAc (25/1)], yielding **11** as a white solid (2 mg, 14 %). MS [*m/z* (% rel. int.)]: 358.1795 (M^+, $C_{21}H_{26}O_5$ requires 358.1780, 14 %), 329 (28), 221 (100), 220 (49), 191 (14), 109 (16), 84 (20), 69 (16), 55 (16), 43 (17). ^{1}H NMR: 10.02, s, 1H; 5.99, d, *J*=1.9, 1H; 5.74, s, *J*=0.8, 1H; 5.33, m, 1H; 3.58, s, OH; 2.21, s, H_3; 2.18, m, 1H; 2.04, m, 1H; 1.90, dd, *J*=11.3, *J*=13.4, 1H; 1.84, dd, *J*=1.9, *J*=13.4, 1H; 0.87-1.62, m, 5H; 1.40, s, H_3; 0.95, s, $2H_3$. ^{13}C NMR: 204.1; 165.0; 163.6; 162.6; 130.2; 114.1; 100.1; 97.5; 83.4; 77.6; 43.4; 43.1; 41.4; 33.9; 33.8; 33.1; 30.4; 22.6; 20.7; 18.6; 18.4.

11-Hydroxy-3,3,7,10a-tetramethyl-1-oxo-(5a*S*,6a*S*,10a*S*,11*R*)-1*H*,7*H*,8*H*,9*H*,10*H*,10a*H*,11*H*-benzo[*g*]-pyrano[4,3-*b*]chromene-11-carbaldehyde (12). A solution of dialdehyde **4** (9.0 mg, 0.036 mmol) and triacetic acid lactone (**5**) (11 mg, 0.087 mmol) in ethyl acetate (3 ml) was refluxed. After 7 days TLC analysis [heptane/EtOAc (1/1)] showed only one new spot (adduct **12**) in addition to large amounts unconsumed **4** and **5**. The solvent was then removed under reduced pressure, and the adduct was purified by chromatography in two steps [SiO_2; EtOAc, followed by heptane/EtOAc (5/1)], recovering **4** (4.0 mg) and yielding **12** as a white solid (2.3 mg, 18 %, but 32% in respect to consumed **4**). MS [*m/z* (% rel. int.)]: 358.1753 (M^+, $C_{21}H_{26}O_5$ requires 358.1780, 13 %), 330 (26), 329 (100), 221 (73), 220 (18), 191 (22), 176 (16), 163 (14), 139 (20), 43 (30). ^{1}H NMR: 9.83, d, *J*=1.2, 1H; 6.62, d, *J*=2.4, 1H; 5.76, t, *J*=0.8, 1H; 5.44, ddd, *J*=11.1, *J*=6.4, *J*=2.4, 1H; 3.62, d, *J*=1.3, OH; 2.35, m, 1H; 2.23, d, *J*=0.8, H_3; 2.00, m, 1H; 1.78, m, 1H

1.74, dd, J=13.5, J=2.5, 1H; 1.58, m, 1H; 1.28, m, 1H; 1.17, m, 1H; 1.11, d, J=0.5, H_3; 1.01, s, H_3; 0.98, s, H_3; 0.89, m, 2H. ^{13}C NMR: 200.6; 164.4; 163.6; 162.4; 128.6; 115.4; 99.7; 98.6; 86.2; 77.3; 44.9; 44.3; 42.1; 34.7; 34.2; 34.0; 30.5; 22.8; 20.7; 18.7; 15.8.

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