Synthesis of 11,12-Epoxydrim-8,12-en-11-ol, 11,12-Diacetoxydrimane, and Warburganal from (−)-Sclareol

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The first syntheses are reported for recently isolated drimanes 11,12-epoxydrim-8,12-en-11-ol (**2**) and 11,12-diacetoxydrimane (**3**), from (−)-sclareol (**1**). Furthermore, two efficient new routes to the potent bioactive warburganal (**4**) starting also from **1** are described.

Drimanes constitute an important group of sesquiterpenes that occur in a wide range of natural sources. The great variety and strength of the biological activities[1] of these compounds have greatly stimulated the development of general synthetic routes for them.[2]

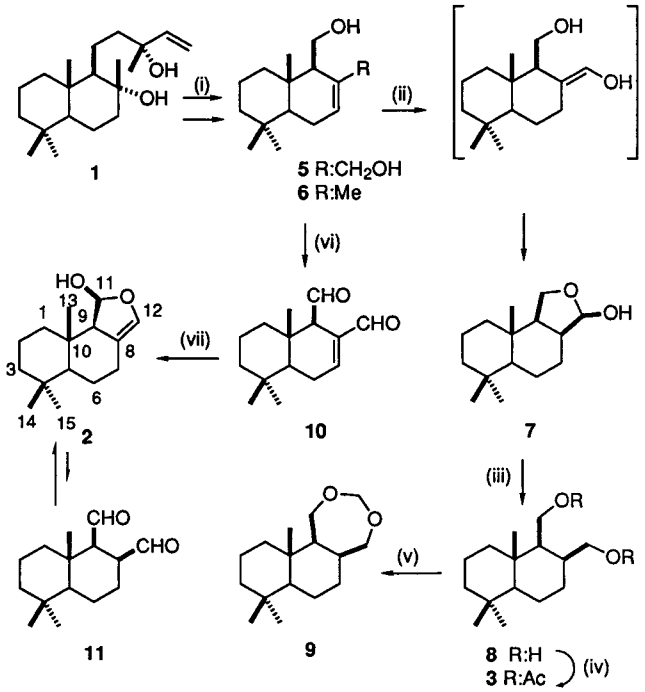
Following the authors' research on the synthesis of bioactive drimanes from (−)-sclareol (**1**)[3,4] and (−)-drimenol (**6**),[5−8] active compounds **2** and **4** have been prepared. 11,12-Epoxydrim-8,12-en-11-ol (**2**) was isolated by Capon et al. from a marine sponge of the genus *Dysidea*,[9] but these authors were unable to fully characterize this drimane due to its considerable instability. The efficient syntheses of **2** from **1** (10 steps, 18% overall yield) and from **6** (6 steps, 28% overall yield) described herein allowed complete characterization with confirmation of the assigned structure and absolute configuration. Moreover, the antitumor activity of **2** has been assayed, which revealed a considerable and selective action. In a parallel route the diacetate **3**, recently isolated from the sponge *Dysidea fusca*,[10] has been synthesized.

Two efficient routes for preparing warburganal (**4**) (11 steps, 25% overall yield and 12 steps, 24% overall yield), which is among the most important drimanes due to its potent biological activity, from (−)-sclareol (**1**) are also described in this paper.

Results and Discussion

Continuing our study of the antitumor structure−activity relationship for this class of compounds the synthesis of the dialdehyde **11**, a saturated analogue of poligodial (**10**), from diol **5** and **6** was planned. **5** was efficiently prepared from **1** through a highly optimized 8-step sequence in 20% overall yield.[4] Hydrogenation of **5** over Pd/C was not stereoselective, affording a 1:1 mixture of **8** and its C-8 epimer. Treatment of **5** with Raney Ni gave the hemiketal **7** as the only product (Scheme 1). The ^{1}H NMR spectrum of this compound showed a doublet (J = 9.1 Hz) at δ 3.84 and a double doublet at 4.00 ppm (J = 9.1, 5.4 Hz), due to H-11 and H-11′ respectively, and a double doublet (J = 6.2, 5.5 Hz) at 5.22 ppm for H-12. C-11 and C-12 appeared at 68.97 and 102.50 ppm in the ^{13}C NMR spectrum. The formation of **7** from **5** might be explained via the isomerization of Δ^7 to $\Delta^{8,12}$ on the surface metal, leading to the enol form of the C-12 aldehyde, which undergoes kinetic protonation on the less hindered α side. Reduction of **7** with $NaBH_4$ gave the diol **8** as the only product. However, the oxidation of **8** to give **11** was unsuccessful under different reaction conditions, affording a complex mixture of compounds in most cases. Treatment of **8** with Swern reagent yielded quantitatively the methylene acetal **9**.[11] **7** was converted into the natural diacetate **3** under standard acetylation conditions. The diacetate obtained showed identical optical rotation and spectroscopic properties to those reported for the natural sesquiterpene.[10]

Scheme 1



(i) Ref. 4. (ii) H_2, Raney Ni, THF, rt, 72h, 85%. (iii) $NaBH_4$,EtOH, rt, 45 min (97%). (iv) Ac_2O, Py, rt, 1h (99%). (v) DMSO/$(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, 15 min (95%). (vi) Ref. 4, 6. (vii) H_2, Raney Ni, THF, rt,1h (95%).

The previous result prompted us to synthesize the unsaturated hemiketal **2**, for which isomerization to **11** had been previously reported,[9] from **10** following a similar procedure. **10** had been previously obtained from **5** (92%)[4] and from **6** (5 steps, 30% overall yield).[6] The treatment of **10** with Raney Ni gave the natural drimane **2** in 95% yield (Scheme 1). The pure compound was isolated as a colorless

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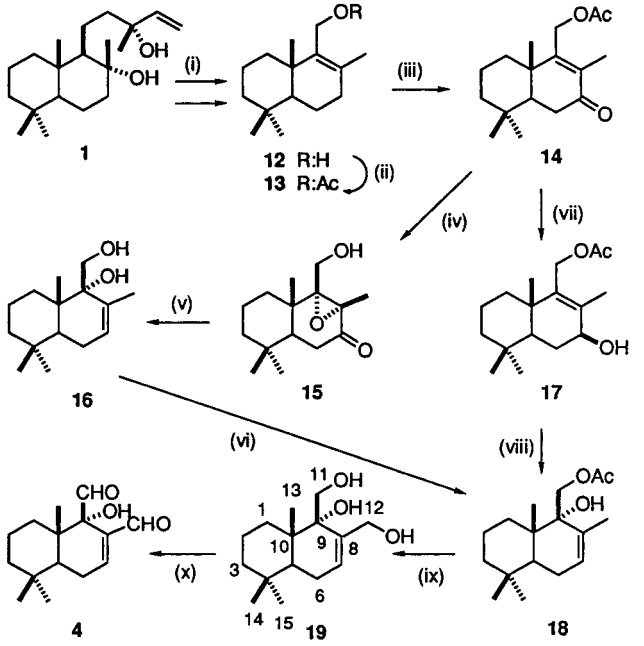
Table 1. Antitumor Activity of Compounds **2** and **10**

compound	IC_{50} (μg/mL)			
	P-388	A-549	HT-29	MEL-28
10	1.20	2.50	2.50	2.50
2	0.50	0.50	1.00	1.00
5-fluorouracil	0.02	0.10	0.10	0.10
adryamycin HCl	0.10	0.025	0.50	0.50
Ametropterin	0.002	0.005	0.01	0.01

Scheme 2



(i) Ref. 4, 12, 13. (ii) Ac_2O, Py, rt, 1h (96%). (iii) Na_2CrO_4, Ac_2O, AcOH, NaOAc, 70°C, 3.5h (91%). (iv) H_2O_2, NaOH, rt, 5h (88%). (v) NH_2NH_2, AcOH, reflux, 30 min (95%). (vi) Ac_2O, Py (92%). (vii) $NaBH_4$, EtOH, 0°C (96%). (viii) MsCl, Et_3N, DMAP, THF, reflux, 1h (81%). (ix) SeO_2, Dioxan, 100°C, 2h; KOH, MeOH, rt, 1h (71%). (x) Ref. 5.

oil after eluting with diethyl ether through a silicagel column. Compound **2** had $[\alpha]_D$ +5 (*c* 1, $CHCl_3$) and in its IR spectrum absorption bands appeared at 959, 1676, 2925, and 3406 cm^{-1}. The HRFABMS showed $[M + H]^+$ at *m/z* 237.185767 (calcd for $C_{15}H_{25}O_2$, 237.185455). The ^1H and ^{13}C NMR data were identical to those assigned in the literature for **2**, which was described as a mixture with the dialdehyde **11**.[9] The ^1H NMR spectra of solutions of **2** in $CDCl_3$, which were kept overnight, showed the appearance of aldehyde protons at δ 9.86 (d, $J = 1.2$ Hz) and 10.12 (s), due to the formation of **11**. Antitumor activity of **2** and **10** was tested against four cell lines. The IC_{50} (mg/mL) values revealed that **2**, which probably acts in the biological medium as dialdehyde **11**, was more active than **10**, showing somewhat selective antitumor activity against P-388 and A-549 cells (Table 1).

Two efficient synthetic routes to warburganal (**4**), through the enone **14** as key intermediate, have been developed. (−)-Sclareol (**1**) was efficiently converted into the allylic alcohol **12** by a previously reported sequence.[4,12,13] The treatment of the acetyl derivative **13** with Na_2CrO_4 and NaOAc in AcOH gave **14** in a high yield (Scheme 2). The 8-en-7-one group of **14** is suitable for transforming into the 7-en-9-ol functionality of warburganal (**4**). This can be achieved by two alternative procedures: via Wharton rearrangement of the ketoepoxyde **15** or through allylic isomerization of the mesylate derived from **17**. The treatment of **14** with alkaline H_2O_2 caused stereoselective epoxidation and simultaneous saponification of the ester group, affording **15** in 88% yield. The α disposition of the epoxy group was established on the basis of the nOe enhancement observed between the Me-12 and Me-15 protons. **15** underwent Wharton rearrangement to give the diol **16**, in almost quantitative yield, when it was refluxed with hydrazine and acetic acid for 30 min. The acetoxy-alcohol **18** was then obtained by standard acetylation conditions. An alternative route to transform the enone **14** into **18** involves stereospecific conversion to the allylic alcohol **17** by treating with $NaBH_4$ at low temperature. This compound is assigned the *S* configuration at C-8 based on the ^1H NMR signal of H-7, which appears as a double doublet ($J = 9.5$ and 7.4 Hz) at 4.09 ppm. When a solution of **17** in THF was refluxed with MsCl, Et_3N and catalytic DMAP, the acetoxyalcohol **18** was obtained in 81% yield. A mixture of acetoxyalcohols was obtained when a solution of **18** in dioxane was heated at 100 °C with SeO_2 for 2 h. The mixture was saponified with KOH-MeOH to give **19** in 71% yield. Compound **19** has previously been converted in high yield into warburganal (**4**) by oxidation with Swern reagent (Scheme 2).[5]

Experimental Section

General Experimental Procedures. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were obtained on Perkin-Elmer model 782 and 983G spectrometers with samples as a thin film between sodium chloride plates or as potassium bromide pellets. ^1H NMR spectra were taken on a Bruker AM 300 (300 MHz), Bruker ARX 400 (400 MHz), and Bruker AMX 500 (500 MHz) spectrometers using $CDCl_3$, and CD_3COCD_3 as solvent and TMS or residual protic solvent $CHCl_3$ (δ_H = 7.25 ppm) as the internal reference, and the multiplicity of a signal is a singlet unless otherwise stated, when the following abbreviations are used: s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; dd, double doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were run either at 75, 100, or 125 MHz on Bruker AM 300, ARX 400, and AMX 500 instruments. Chemical shifts are in ppm (δ scale), and the coupling constants are in Hertz. Carbon substitution was established by DEPT pulse sequence. MS were recorded on a Hewlett-Packard 5988A spectrometer using an ionizing voltage of 70 eV. HRMS were obtained on a trisector WG AutoSpecQ spectrometer. For analytical TLC, Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column chromatography on Merck silica gel 60 (70−230 mesh) and by flash column chromatography on Merck silica gel 60 (230−400 mesh) using hexane−OEt_2 mixtures of increasing polarity unless otherwise stated. Ozonization reactions were carried out with a mixture of ozone-oxygen provided by a Fischer oxygen-feed apparatus (8.3 mmol of O_3 in 10 L of O_2/h). Routinely, dry organic solvents were stored under argon, over freshly activated molecular sieves. Ether, benzene, and THF were dried over sodium benzophenone ketyl, TMEDA from Na, dichloromethane over calcium hydride, and methanol from magnesium methoxide. Where necessary, reactions were carried out in a nitrogen or argon atmosphere.

Synthesis of 11,12-Epoxydriman-12-ol (7). An aqueous suspension of Raney Ni (800 mg) was added to a solution of **5** (300 mg, 1.26 mmol) in THF (10 mL), and the mixture was stirred for 1 h under hydrogen atmosphere. After the solvent was evaporated, column chromatography (hexane/OEt_2 1:1) of crude afforded **7** (253 mg, 85%); $[\alpha]^{25}_D$ +4 (*c* 0.35, $CHCl_3$); IR (film) ν_{max} 3318, 2924, 1458, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.22 (1H, dd, $J = 6.2$, 5.5 Hz, H-12), 4.00 (1H, dd, J = 9.1, 5.4 Hz, H-11), 3.84 (1H, d, $J = 9.1$ Hz, H-11), 2.78 (1H, d, $J = 5.5$ Hz, OH), 2.10 (1H, q, $J = 5.4$ Hz, H-8), 1.95 (1H, bd, $J = 12.8$ Hz), 1.30 (1H, ddd, J= 17.5, 14.5, 3.7 Hz), 0.90 (3H, s, Me-13), 0.88 (3H, s, Me-14), 0.84 (3H, s, Me-15); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 102.5 (t, C-12), 68.9 (t, C-11), 53.9 (d, C-8), 52.4 (d, C-9), 45.9 (d, C-5), 42.2 (t, C-3), 41.2 (t, C-1), 35.2 (s, C-10), 33.5 (q, C-13), 33.0 (s, C-4), 18.5 (t, C-6), 18.3 (t, C-2), 15.6 (q, C-15); CIMS *m/z* 221 [M + H^+ − H_2O] (36), 203 (53), 81 (47), 69 (40), 43 (100); HRFABMS *m/z* [M + H]$^+$ 239.2010 (calcd for $C_{15}H_{27}O_2$, 239.2011).

Synthesis of Drimane-11,12-diol (8). $NaBH_4$ (32 mg, 0.84 mmol) was added to a solution of **7** (100 mg, 0.42 mmol) in EtOH (8 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (3 mL) and extracted with OEt_2 (3 × 100 mL). The organic phase was washed with brine (3 × 50 mL), dried and evaporated to yield **8** (98 mg, 97%) as an oil; $[\alpha]^{25}_D$ +20 (*c* 0.43, $CHCl_3$); IR (film) ν_{max} 3393, 2924, 1458, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (1H, dd, *J* = 10.3, 6.4 Hz, H-11 or H-12), 3.82 (1H, dd, *J* = 11.1, 5.2 Hz, H-11 or H-12), 3.74 (1H, dd, *J* = 11.1, 10.2 Hz, H-11 or H-12), 3.58 (1H, dd, *J* = 10.3, 7.0 Hz, H-11 or H-12), 0.86 (3H, s, Me-13), 0.85 (3H, Me-14), 0.80 (3H, s, Me-15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.2 (t, C-11), 60.7 (t, C-12), 56.5 (d, C-9), 54.5 (d, C-5), 41.9 (t, C-3), 39.5 (t, C-1), 37.8 (d, C-8), 37.5 (s, C-10), 33.6 (q, C-13), 33.2 (s, C-4), 30.2 (t, C-7), 21.6 (q, C-14), 18.4 (t, C-2), 16.5 (q, C-15); HRFABMS *m/z* [M+H]$^+$ 241.2167 (calcd. for $C_{15}H_{29}O_2$, 241.2172).

Synthesis of 11,12-Diacetoxydrimane (3). Pyridine (1 mL) and acetic anhydride (0.5 mL) were added to **8** (60 mg, 0.25 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between OEt_2 (30 mL)−H_2O (5 mL) and the organic phase was washed with saturated $NaHCO_3$ (3 × 10 mL), brine (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to afford **3** (80 mg, 98%) as an oil; $[\alpha]^{25}_D$ +37 (*c* 0.33, $CHCl_3$); IR (film) ν_{max} 2929, 1741, 1239, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (1H, dd, *J* = 11.3, 5.0 Hz, H-11), 4.12 (1H, dd, *J* = 20.9, 10.6 Hz, H-12), 4.05 (2H, m, H-11, H-12), 2.03 (3H, s, OCOMe), 2.02 (3H, s, OCOMe), 0.84 (3H, s, H-15), 0.82 (3H, s, H-13), 0.79 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3 (O*C*OMe), 64.0 (t, C-11), 62.7 (t, C-12), 56.2 (d, C-9), 51.5 (d, C-8), 51.4 (d, C-5), 41.9 (t, C-3), 39.2 (t, C-1), 33.5 (q, C-13), 33.2 (s, C-4), 29.2 (t, C-7), 21.5 (q, C-14), 21.1 (q, OCO*Me*), 18.7 (t, C-6), 17.6 (t, C-2), 16.5 (q, C-15); CIMS *m/z* 325 [M + H^+] (5), 265 (4), 205 (27), 149 (25), 81 (49), 69 (48), 43 (100); HRFABMS *m/z* [M + H]$^+$ 325.2370 (calcd for $C_{19}H_{33}O_4$, 325.2378),

Synthesis of 11,12-Methylenedioxydrimane (9). Dimethyl sulfoxide (1 mL, 14.1 mmol) was added to a solution of $(COCl)_2$ (0.14 mL, 1.68 mmol) in dichloromethane (10 mL) cooled to −78 °C and the mixture was stirred for 15 min. A solution of **8** (100 mg, 0.42 mmol) in dichloromethane (12 mL) was added, and the mixture was stirred for 20 min. The mixture was diluted with OEt_2 (50 mL) and washed with brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give a crude residue which after column chromatography afforded **9** (95 mg, hexane/OEt_2 8:2) as an oil; $[\alpha]^{25}_D$ +15 (*c* 0.65, $CHCl_3$); IR (film) ν_{max} 3402, 1458, 1141, 1124 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.86 (1H, d, *J* = 5.5, OCH_2O), 4.73 (1H, d, *J* = 5.5 Hz, OCH_2O), 3.83 (4H, m, H-11, H-11′, H-12, H-12′), 1.11 (3H, s, Me-13), 0.86 (6H, s, Me-14, Me-15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.3 (t, OCH_2O), 73.3 (t, C-11), 67.6 (t, C-12), 54.2 (d, C-9), 52.9 (d, C-5), 42.2 (t, C-3), 40.4 (t, C-1), 38.2 (d, C-8), 37.6 (s, C-10), 33.6 (q, C-13), 33.2 (s, C-4), 28.0 (t, C-7), 22.0 (q, C-14), 18.4 (t, C-2), 16.3 (q, C-15); HRFABMS *m/z* [M + H]$^+$ 253.2167 (calcd for $C_{16}H_{29}O_2$, 253.2164).

Synthesis of 11,12-Epoxydrim-8,12-en-11-ol (2). A solution of **10** (100 mg, 0.43 mmol) in THF (5 mL) was added to a suspension of Raney Ni in water (0.7 g) and the mixture was stirred at room temperature for 1 h under hydrogen atmosphere. The solid was removed by filtration through a silica gel filter bed and washed several times with OEt_2. Concentration of the combined filtrate afforded 96 mg (95%) of **2** as an oil; $[\alpha]^{25}_D$ +5 (*c* 0.65, $CHCl_3$); IR (film) ν_{max} 3406, 2925, 1676, 959 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.02 (1H, dd, *J* = 1.7, 1.7 Hz, H-12), 5.46 (1H, d, *J* = 1.7 Hz, H-11), 3.46 (1H, bs, 11-OH), 2.44 (1H, ddd, *J* = 13.9, 5.2, 1.8 Hz, H-7), 2.13 (1H, bs, H-9), 1.97 (1H, ddddd, *J* = 13.9, 13.9, 5.2, 1.8, 1.8 Hz, H-7), 1.60−1.70 (2H, m, H-1, H-6), 1.54 (1H, ddddd, *J* = 13.6, 13.6, 13.6, 3.3, 3.3 Hz, H-2), 1.40−1.48 (2H, m, H-2, H-3), 1.24 (1H, dddd, *J* = 12.8, 12.8, 12.8, 5.2 Hz, H-6), 1.14 (1H, ddd, J = 12.8, 12.8, 4.0 Hz, H-1), 0.99 (1H, dd, *J* = 12.8, 2.6 Hz, H-5), 0.86 (3H, s, Me-15), 0.80 (3H, s, Me-14), 0.70 (3H, s, Me-13); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.9 (d, C-12), 114.0 (s, C-8), 100.2 (d, C-11), 66.1 (d, C-9), 53.2 (d, C-5), 42.2 (t, C-3), 39.3 (t, C-1), 33.6 (q, C-13), 33.2 (s, C-4), 23.4 (t, C-7), 22.7 (t, C-6), 21.8 (q, C-14), 18.6 (t, C-2), 14.2 (q, C-15); CIMS *m/z* 237 [M + H^+] (4), 219 [M + H^+ − H_2O] (10), 81 (71), 79 (100), 69 (98); HRFABMS *m/z* [M + H]$^+$ 237.1857 (calcd for $C_{15}H_{25}O_2$, 237.1854).

Synthesis of 11-Acetoxy-8-drimene (13). Acetic anhydride (5 mL) was added to a solution of **12** (700 mg, 3.15 mmol) in pyridine (10 mL) and the mixture was stirred for 1h at room temperature. The reaction mixture was diluted with ether (150 mL) and extracted with 2N HCl (3 × 30 mL) and brine (3 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to give 796 mg of **13** (96%) as an oil; $[\alpha]^{25}_D$ +8.5 (*c* 1.46, $CHCl_3$); IR (film) ν_{max} 2928, 1736, 1673, 1645, 1458, 1365, 1259, 1239, 1075, 1021, 804 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.57 (2H, s, H-11), 2.08 (2H, m, H-7), 2.05 (3H, s, C_8-OCOMe), 1.65 (3H, s, Me-12), 0.96 (3H, s, Me-13), 0.84 (3H, s, Me-14), 0.83 (3H, s, Me-15); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5 (O*C*OMe), 135.5 (s, C-9), 135.3 (s, C-8), 60.7 (t, C-11), 51.4 (d, C-5), 41.6 (t, C-3), 38.0 (s, C-10), 36.3 (t, C-1), 33.8 (t, C-7), 33.3 (s, C-4), 33.3 (q, C-13), 21.6 (q, C-14), 21.3 (q, C-12), 20.7 (OCO*Me*), 19.5 (q, C-15), 18.9 (t, C-2), 18.8 (t, C-6); EIMS *m/z* 264 [M]$^+$ (1), 204 (42), 189 (100), 176 (5), 161 (21), 147 (16), 133 (33), 119 (34), 105 (35); HRFABMS *m/z* 287.1987 (calcd for $C_{17}H_{28}O_2Na$, 287.1987).

Synthesis of 11-Acetoxy-8-drimen-7-one (14). To a solution of **13** (500 mg, 1.89 mmol) in benzene (17 mL) sodium chromate (1.7 g, 3.5 mmol), sodium acetate (1.27 g, 15.4 mmol), acetic anhydride (5 mL), and glacial acetic acid (3 mL) were added, and the mixture was stirred at 70 °C for 3.5h. The reaction mixture was poured into ice and extracted with ether (3 × 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ (3 × 30 mL) and brine (2 × 30 mL). The ethereal phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give a crude residue wich after chromatography (hexane/OEt_2 7:3) yielded **14** (480 mg, 91%) as an oil; $[\alpha]^{25}_D$ +40.0 (*c* 0.73, $CHCl_3$); IR (film) ν_{max} 2931, 1742, 1671, 1376, 1320, 1230, 1027. cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (1H, d, *J* = 12.0, H_A-11), 4.72 (1H, d, *J* = 12.0 Hz, H_B-11), 2.55 (1H, dd, *J* = 13.2, 2.8 Hz, H-6a), 2.41 (1H, dd, *J* = 13.2, 10.7 Hz, H-6b), 2.06 (3H, s, C_8-OCOMe), 1.82 (1H, bd, *J* = 7.9 Hz, H-1a), 1.78 (3H, s, Me-12), 1.73 (1H, dd, *J* = 14.8, 3.8 Hz, H-5), 1.65 (1H, qt, *J* = 13.5, 3.4 Hz, H-2b), 1.46 (1H, ddt, *J* = 16.6, 3.3, 1.4 Hz, H-3a), 1.10 (3H, s, Me-15), 0.90 (3H, s, Me-14) 0.83 (3H, s, Me-13); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.4 (s, C-7), 170.7 (O*C*OMe), 158.2 (s, C-9), 134.5 (s, C-8), 60.0 (t, C-11), 50.1 (d, C-5), 41.1 (t, C-3), 40.0 (s, C-10), 35.4 (t, C-1), 35.3 (t, C-6), 33.1 (s, C-4), 32.5 (q, C-13), 21.2 (q, C-14), 20.9 (OCO*Me*), 18.5 (t, C-2), 18.3 (q, C-12), 11.5 (q, C-15); CIMS *m/z* 279 [M + H]$^+$ (61), 247 (9), 221 (32), 219 (90), 205 (31), 191 (16), 177 (20), 163 (15), 149 (9); HRFABMS *m/z* 301.1778 (calcd for $C_{17}H_{26}O_3Na$, 301.1779).

Synthesis of 11-Hydroxy-8α,9α-epoxydriman-7-one (15). A 6 N solution of NaOH in MeOH (8 mL) was added to a solution of **14** (1 g, 3.6 mmol) in MeOH (15 mL) and the mixture was stirred at room temperature for 15 min. Cold 30% H_2O_2 (8 mL) was added to the solution at 0 °C and the mixture was stirred at room temperature for 6 h. The reaction mixture was partitioned between H_2O (20 mL)−OEt_2 (100 mL) and the organic layer was washed with brine (3 × 30 mL), dried, and evaporated affording a crude residue which after column chromatography (hexane/OEt_2 6:4) gave **15** (800 mg, 88%) as an oil; $[\alpha]^{25}_D$ +2.7 (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 3466, 2930, 1688, 1457, 1436, 1084, 1054, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.96 (1H, d, *J* = 12.1 Hz, H_A-11), 3.85 (1H, d, *J* = 12.1 Hz, H_B-11), 2.47 (1H, dd, *J* = 19.0, 6.8 Hz, H-6a), 2.20 (1H, dd, *J* = 19.0, 12.2 Hz, H-6b), 2.05 (1H, dd, *J* = 12.2, 6.8 Hz, H-5), 1.89 (1H, d, *J* = 11.0 Hz, H-1b), 1.60 (3H, m, H-1b, H-2a, H-2b), 1.49 (3H, s, Me-12), 1.46 (1H, bd, *J* = 12.8 Hz, H-3a), 1.22 (1H, m, H-3b), 1.10 (3H, s, Me-15), 0.90 (3H, s, Me-13),

0.83 (3H, s, Me-14); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.7 (s, C-7), 73.2 (s, C-9), 66.5 (s, C-8), 58.5 (t, C-11), 41.9 (d, C-5), 41.2 (t, C-3), 37.7 (s, C-10), 35.7 (t, C-1), 34.7 (t, C-6), 33.3 (s, C-4), 32.5 (q, C-13), 20.7 (q, C-14), 18.5 (t, C-2), 17.1 (q, C-12), 12.4 (q, C-15); EIMS *m*/*z* 252 [M^+] (83), 221 (6), 209 (60), 191 (13), 149, (44), 179 (9), 163 (14), 149 (44), 135 (25), 123 (35); HRFABMS *m*/*z* 275.1622 (calcd for $C_{15}H_{24}O_3Na$, 275.1623).

Synthesis of 7-Drimen-9α,11-diol (16). Hydrazine hydrate (6.5 mL) and glacial acetic acid (1.5 mL) were succesively added to a solution of **15** (900 mg, 3.6 mmol) in EtOH (20 mL) and the mixture was refluxed for 30 min. The reaction mixture was diluted with H_2O (5 mL) and extracted with OEt_2 (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$ (3 × 30 mL), brine (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to afford a crude residue, which after chromatography (hexane/OEt_2 1:1) gave 800 mg of **16** (95%) as an oil; $[\alpha]^{25}_D$ −35.8 (*c* 0.86, $CHCl_3$); IR (film) ν_{max} 3422, 2924, 1653, 1457, 1365, 1333, 1261, 1189, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.58 (1H, m, H-7), 3.77 (1H, d, J = 11.0, H_A-11), 3.60 (1H, d, J = 11.0 Hz, H_B-11), 2.05 (1H, dt, J = 12.3, 2.3 Hz, H-6), 1.56 (1H, dd, J = 12.1, 4.8 Hz, H-6), 1.50 (2H, m, H-2a, H-2b), 1.40 (1H, bd, J = 12.9 Hz, H-3a), 1.80 (3H, s, Me-12), 0.93 (3H, s, Me-15), 0.89 (3H, s, Me-14), 0.83 (3H, s, Me-13); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.3 (s, C-8), 127.5 (d, C-7), 75.6 (s, C-9), 62.4 (t, C-11), 42.9 (d, C-5), 41.8 (t, C-3), 40.7 (s, C-10), 33.5 (q, C-13), 32.1 (s, C-4), 31.6 (t, C-1), 24.1 (t, C-6), 22.3 (q, C-14), 20.3 (q, C-12), 18.6 (t, C-2), 15.3 (q, C-15); EIMS *m*/*z* 238 [M^+] (1), 204 (42), 189 (100), 176 (5), 161 (21), 147 (16), 133 (33), 119 (34), 105 (35); HRFABMS *m*/*z* 261.1829 (calcd for $C_{15}H_{26}O_2Na$, 261.1811)

Synthesis of 11-Acetoxy-7-drimen-9α-ol (18) from 16. Acetic anhydride (0.5 mL) was added to a solution of **16** (80 mg, 0.33 mmol) in pyridine (2 mL) and the mixture was stirred at room temperature for 1 h. After working up as for acetate **13**, **18** (86 mg, 92%) was obtained as an oil; $[\alpha]^{25}_D$ +14 (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 3510, 2929, 1736, 1672, 1457, 1331, 1239, 1156, 1088 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.62 (1H, m, H-7), 4.20 (1H, d, J = 11.9 Hz, H_A-11), 4.20 (1H, d, J = 11.0 Hz, H_B-11), 2.17 (1H, s, OH), 2.08 (3H, s, C_{11}-OCOMe), 1.74 (3H, s, Me-12), 1.65 (dd, J = 12.0, 4.7 Hz, H-6), 0.93 (3H, s, Me-15), 0.89 (3H, s, Me-14), 0.83 (3H, s, Me-13); CIMS *m*/*z* 263 [M + H − H_2O]$^+$ (100), 240 (14), 231 (9), 202 (20), 167 (16), 139 (19), 71 (24), 55 (25), 43 (20); HRFABMS *m*/*z* [M + H − H_2O]$^+$ 263.2009 (calcd for $C_{17}H_{27}O_2Na$, 263.2011).

Synthesis of 11-Acetoxy-8-drimen-7*β*-ol (17). $NaBH_4$ (300 mg, 8.8 mmol) was added to a solution of **14** (1 g, 3.6 mmol) in EtOH (20 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. Cationic resin (Amberlyst A-15) was added at 0 °C until neutral pH was achieved, followed by H_2O (15 mL), and the mixture was extracted with OEt_2 (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to yield 960 mg (96%) of **17**; $[\alpha]^{25}_D$ +31.9 (*c* 0.7, $CHCl_3$); IR (film) ν_{max} 3446, 2929, 1735, 1457, 1375, 1241, 1141, 1071, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.52 (2H, s, H-11), 4.09 (1H, dd, J = 9.5, 7.4 Hz, H-7), 2.09 (1H, ddd, J = 13.5, 7.4, 1.5 Hz, H-6a), 2.02 (3H, s, OCOMe), 1.72 (3H, s, Me-12), 1.23 (1H, dd, J = 13.5, 1.5 Hz, H-5), 1.00 (3H, s, Me-15), 0.86 (3H, s, Me-14), 0.83 (3H, s, Me-13); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (O*C*OMe), 138.7 (s, C-9), 136.8 (s, C-8), 72.8 (d, C-7), 60.4 (t, C-11), 49.6 (d, C-5), 41.3 (t, C-3), 38.9 (s, C-10), 36.0 (t, C-1), 33.0 (q, C-13), 32.8 (s, C-4), 29.5 (t, C-6), 21.5 (q, C-12), 21.1 (q, C-14), 20.5 (OCO*Me*), 18.6 (t, C-2), 15.0 (q, C-15); EIMS *m*/*z* 280 [M]$^+$ (1), 220 (24), 207 (14), 177 (4), 156 (54), 149 (11), 123 (15), 114 (100); HRFABMS *m*/*z* [M + H − H_2O]$^+$ 263.2013 (calcd for $C_{17}H_{27}O_2Na$, 263.2011).

Synthesis of 11-Acetoxy-7-drimen-9α-ol (18) from 17. To a stirred solution of **17** (120 mg, 0.43 mmol) in anhydrous THF (15 mL), Et_3N (1 mL), MsCl (0.5 mL), and (dimethylamino)pyridine (DMAP) (10 mg) were successively added and the mixture was refluxed for 1 h. The solvent was evaporated and the crude residue was partitioned between OEt_2 (30 mL)−brine (30 mL) and the aqueous layer extracted with OEt_2 (3 × 30 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give a crude residue, which after chromatography (hexane/OEt_2 7:3) yielded 97 mg (81%) of **18**.

Synthesis of 7-Drimen-9α,11,12-triol (19). SeO_2 (235 mg, 2.1 mmol) was added to a solution of **18** (400 mg, 1.8 mmol) in anhydrous EtOH (20 mL), and the mixture was refluxed for 1 h 20 min. H_2O (5 mL) was added, and the mixture extracted with OEt_2 (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give a crude residue which was disolved in MeOH (2 mL) and treated with 2 N KOH in MeOH (2 mL) for 30 min at room temperature. The mixture was diluted with OEt_2 (50 mL) and washed with brine (3 × 30 mL). After drying over anhydrous Na_2SO_4 and removing the solvent, the crude residue was chromatographed (OEt_2/EtOAc 9:1) to give **19** (255 mg, 71%) as an oil; $[\alpha]^{25}_D$ −83 (*c* 0.3, $CHCl_3$); IR (film) ν_{max} 3420, 2925, 1648, 1462, 1375, 1257, 1192, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (1H, dd, J = 4.7, 2.3 Hz, H-7), 4.31 (1H, d, J = 12.2 Hz, H_A-12), 4.13 (1H, d, J = 12.2, H_B-12), 3.75 (1H, d, J = 11.5 Hz, H_A-11), 3.74 (1H, d, J = 11.5 Hz, H_B-11), 0.92 (3H, s, Me-15), 0.90 (3H, s, Me-14), (3H, s, Me-13); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2 (s, C-8), 131.8 (d, C-7), 75.7 (s, C-9), 66.9 (t, C-12), 62.6 (t, C-11), 42.3 (d, C-5), 41.6 (t, C-3), 40.5 (s, C-10), 33.0 (s, C-4), 31.1 (t, C-1), 30.9 (q, C-13), 24.1 (t, C-6), 22.3 (q, C-14), 18.6 (t, C-2), 15.3 (q, C-15); CIMS *m*/*z* 254 [M]$^+$ (36), 278 (25), 261 (78), 246 (62), 218 (80), 202 (95), 81 (66), 69 (100), 55 (60); HRFABMS *m*/*z* 277.1779 (calcd for $C_{15}H_{26}O_3Na$, 277.1779).

Antitumor Activity of 2 and 10. The antitumor activity of **2** and **10** were assayed against P-388 A-549, HT-29, and MEL-28 cells, following the method reported by Bergeron et al.[14] IC_{50} (mg/mL) are shown and compared with standards in Table 1.

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