LANOMYCIN AND GLUCOLANOMYCIN, ANTIFUNGAL AGENTS PRODUCED BY *Pycnidiophora dispersa*

II. STRUCTURE ELUCIDATION

DOUGLAS W. PHILLIPSON†, JOSEPH O'SULLIVAN, JANICE H. JOHNSON††, MARK S. BOLGAR and ALICIA D. KAHLE

Bristol-Myers Squibb Pharmaceutical Research Institute,
P.O. Box 4000, Princeton, N.J. 08543-4000, U.S.A.
†P.O. Box 5100, Wallingford, C.T. 06492-7661, U.S.A.
††Natural Products Sciences Inc.,
420 Chipeta Way, Suite #240, Salt Lake City, Utah, 84108, U.S.A.

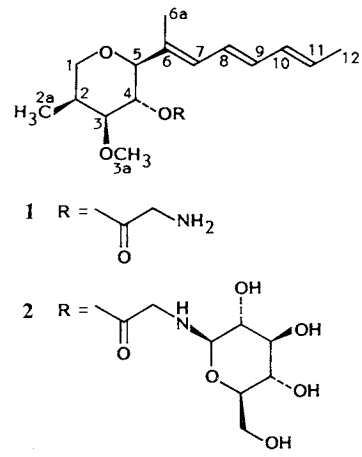
(Received for publication August 19, 1991)

Two novel antifungal agents, lanomycin and glucolanomycin, as well as a biologically inactive degradation product, lanomycinol, were isolated from liquid fermentations of *Pycnidiophora dispersa*. All three compounds share an *E,E,E*-triene appended to a pyran ring. Lanomycin contains a glycine ester and glucolanomycin possesses a glucose unit attached to the glycine nitrogen. The structures, including absolute stereochemistry, were determined by spectroscopic analysis and partial chemical degradation. Both of the glycine containing compounds show activity against several pathogenic fungi *in vitro*.

In the course of our antifungal screening program, two compounds, lanomycin and glucolanomycin, were identified with activity against *Candida* species and dermatophytes. These compounds were found to be inhibitors of the cytochrome P-450 enzyme, lanosterol demethylase. The compounds were isolated from fermentations of a fungus, *Pycnidiophora dispersa*, by ethyl acetate extraction of the whole broth followed by a number of chromatographic steps. Details of the fermentation, taxonomic identification of the producing organism, isolation and biological characterization of these compounds can be found in the preceding paper in this journal.[1]

The physico-chemical data leading to the structure determination of these compounds (Fig. 1) are presented below. The major metabolite, lanomycin (**1**), is probably the same as M5070, a compound disclosed in the Japanese patent literature but whose structure has not been previously described.[2] The characterization of glucolanomycin (**2**) which appears to be, a novel compound, is also presented. The biosynthesis and complete ^{13}C NMR assignment of lanomycin are presented in a separate paper.[3]

Fig. 1. The structures of lanomycin (**1**), glucolanomycin (**2**), and lanomycinol (**3**).



Results and Discussion

The isolation of **1** was accomplished using silica

gel followed by an Ito counter current chromatography step while **2**, because it slowly decomposed under aqueous conditions, required a non-aqueous chromatographic purification using Sephadex LH-20, as described in the preceding paper.[1]

The UV spectra of **1** (with λ_{max} (log ε) at 266 (4.25), 273 (4.37), 284 (4.27)) and **2** were typical of compounds possessing a triene function.[4] The IR spectra were unremarkable except for the presence of a carbonyl absorption in both **1** and **2** and a relatively intense OH stretch in **2** which was not present in **1**. Desorption chemical ionization (DCI) and fast atom bombardment (FAB) mass spectra of the purified compounds suggested molecular weights of 309 and 471 for **1** and **2**, respectively. Accurate mass measurement of the FAB pseudo-molecular ions yielded masses consistent with the formulas $C_{17}H_{27}NO_4$ and $C_{23}H_{37}NO_9$ for non-protonated **1** and **2**, respectively. The ^{13}C NMR spectra of **1** and **2** (see Table 1) were consistent with the formulas suggested by the HR-MS measurements with respect to the number of carbon and hydrogen atoms in the molecules as well as the approximate oxygen content. The 270 MHz ^1H NMR spectra ($CDCl_3$) of both of the natural products showed five olefinic resonances which were assigned to a triene unit, two vinyl methyls (a doublet and a broad singlet), and a third methyl resonating as an upfield doublet, which was shown by ^1H-^1H decoupling, to be coupled to a methine proton resonating at 2.2 ppm. A methoxy methyl and a triplet methine resonating at 5.05 ppm were the other resolvable features in the spectra of these compounds. The remaining signals, appearing between 3 and 4 ppm were not sufficiently resolved to assign.

Table 1. ^{13}C NMR chemical shifts and multiplicities of lanomycin (**1**), glucolanomycin (**2**), lanomycinol (**3**), and D-glucose.*

1	2	D-Glucose	3	Mult.[a]
173.37	173.69	—	—	s
135.36	135.51	—	134.84	d
134.15	134.09	—	135.05	s
133.14	133.20	—	133.32	d
131.16	131.47	—	130.90	d
130.75	130.75	—	130.50	d
126.72	126.72	—	127.10	d
—	91.22	97.4	—	d
86.52	86.55	—	88.68	d
82.69	82.64	—	85.51	d
—	78.72	77.5	—	d
—	78.63	77.4	—	d
—	74.98	75.9	—	d
71.72	71.72	—	71.92	t
—	71.58	71.3	—	d
70.86	70.74	—	68.73	d
—	62.82	62.5	—	t
56.60	56.63	—	56.69	q
43.56	47.53	—	—	t
33.68	33.65	—	33.45	d
18.39	18.48	—	18.39	q
11.91	11.91	—	12.57	q
11.05	11.05	—	11.31	q

[a] From INEPT spectra.
* Chemical shifts in ppm referenced to the center line of the deuteromethanol methyl septet as 49.0 ppm. The spectrum of D-glucose was run in D_2O referenced to external TMS.[7]

Treatment of either **1** or **2** with 1 M sodium carbonate in methanol, yielded an identical triene containing hydrolysis product (**3**). This hydrolysis product, which was also found in and isolated from the ethyl acetate extract of the broth, was much less polar than **1** or **2** and could be purified on silica gel using 15~20% ethyl acetate in hexane. The hydrolysis product showed a molecular weight of 252 by CI-MS. Fifteen of the 17 carbon resonances found in the ^{13}C NMR spectrum of **1** were also present in the spectrum of **3** (see Table 1). The resonances present in **1** but absent in **3** were the carbonyl carbon and the methylene resonance at 43.6 ppm. The ^{13}C NMR and the mass spectral information suggested that a glycine unit was ester linked to the chromophore containing portion of the molecule in **1** but was absent in **3**. The "triplet" methine proton resonating at 5.05 ppm ($CDCl_3$) in **1** was shifted upfield to 3.68 (C_6D_6) in **3** confirming the assumption that hydrolysis produced a de-acylated product. Glycine was shown to be present in the hydrolysis mixture of **1** by co-migration with a standard on normal phase TLC developed with butanol - acetic acid - water, 4 : 1 : 1. Subtraction of the elements C_2H_3NO (glycine) from the formula

Fig. 2. The spin systems (units *a* and *b*) determined for lanomycinol in C_6D_6.

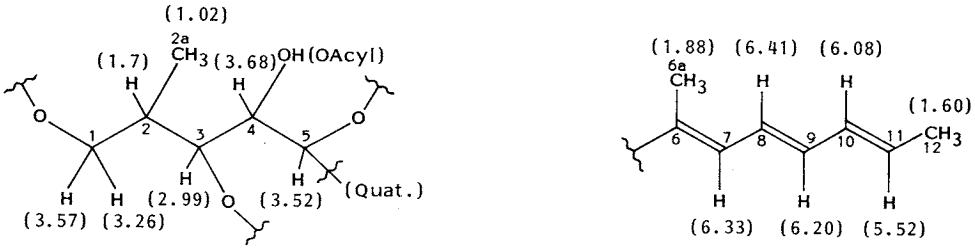


Table 2. 400 MHz ^{1}H NMR of **3** in C_6D_6.

δ	Number of H's	Mult.	Coupling constants	Coupled to:	Assignment
6.41	1	dd	14.0, 11	H's 7, 9	8-H
6.33	1	d (br)	11, (<1)	H's 8, 6	7-H
6.20	1	dd	14.0, 10.5	H's 8, 10	9-H
6.08	1	ddq	14.0, 10.5, 1.6	H's 9, 11	10-H
5.52	1	dq	14.0, 7.0	H's 10, 12	11-H
3.68	1	dd (t)	8.8, 9.4	H's 5, 3	4-H
3.57	1	dd	11.7, 1.8	H's 1β, 2	1-H$_\alpha$
3.52	1	d	9.4	H 4	5-H
3.26	1	dd	11.7, 2.6	H's 1α, 2	1-H$_\beta$
3.09	3	s			3-OCH$_3$
2.99	1	dd	8.8, 5.3	H's 2, 4	3-H
1.88	3	s (br)			6-CH$_3$
1.7	1	m		H's 1α, 1β, 3	2-H
1.60	3	dd	7.0, 1.6	H's 10, 11	12-H
1.02	3	d	7.0	H 2	2-CH$_3$

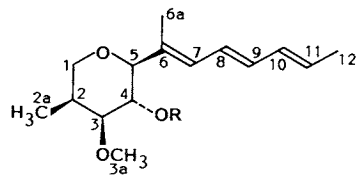
of **1** gave $C_{15}H_{24}O_3$ as the molecular formula of **3**.

The structure of **1** was determined primarily from a detailed examination of the 400 MHz ^{1}H NMR spectrum of **3** run in C_6D_6. In this solvent, resonances corresponding to each of the 23 nonexchangeable hydrogens in **3** could be assigned. Homonuclear decoupling experiments delinated the two spin systems shown in Fig. 2. These two spin systems, plus the methoxy methyl, accounted for all of the carbon atoms and all but one (the hydroxyl proton) of the hydrogens in the molecule. A listing of the proton spectrum and peak assignments of **3**, including coupling information from decoupling and COSY experiments, are detailed in Table 2. The molecular formula of **3** requires a total of four units of unsaturation. The triene accounts for three of these leaving one ring to be formed as a cyclic ether between C-1 and C-3 or C-5, creating either an oxetane or an oxane (pyran) ring system. The oxygen bound to C-4 could not be a part of the cyclic ether because the C-4 proton resonance shifts on acylation. Therefore the C-4 oxygen must be the alcohol oxygen in **3** and the glycine residue must acylate this oxygen in **1**. A pyran ring is compatible with the large vicinal coupling constants observed in unit *a* and the methyl ether could then be assigned to C-3. Units *a* and *b* were joined between C-5 and C-6 to complete the carbon skeleton. Relative stereochemistry of the pyran ring was assigned based on the observation that equatorial-equatorial or equatorial-axial couplings fall in the range of 1 ~ 4 Hz while axial-axial couplings are typically much larger.[5] The geometry of each olefin of unit *b* was also assigned based on coupling constant arguments and the olefinic geometry of the C-6-C-7 olefin was assigned as *E* based on the realization that if the C-12 methyl must be the one at 18.4 ppm the methyl on C-6 (δ 11 or 12) must be *cis* to the carbon chain.[6]

The structure assignment of **2** built on the structure of **1** as we observed that **1** was a decomposition product of **2** in aqueous solvents.[1] The exact mass difference between **1** and **2** corresponds to $C_6H_{10}O_5$ or loss of a sugar. The ^{13}C NMR spectra of **1** and **2** both contain 16 resonances differing insignificantly in their chemical shifts. The only resonance in the spectrum of **1** which differs significantly in the spectrum of **2** is the methylene at δ 43.5 (assigned as the methylene carbon of glycine) in **1** and at 47.5 in **2**. This chemical shift difference was interpreted as the effect of a non hydrogen substituent bound to the glycine amino group. A sugar bound to the nitrogen as an aminal was thought to explain the lability of **2** in aqueous (acidic) solutions. A comparison of the carbon chemical shifts of pyranosides[7] with the six carbon resonances of **2** which were absent in the spectrum of **1**, showed that β-glucopyranoside was the only probable match. The identity of the sugar was confirmed by an high voltage paper electrophoretic comparison of a number of pyranosides with a sample of **2** previously subjected to acidic hydrolysis. The sugar from **2** moved with the same Rf as glucose.

The absolute stereochemistry of lanomycinol (and by conversion, **1** and **2** also) was determined by application of the *O*-methylmandelate ester methodology of TROST *et al.*[8] According to the model the methine hydrogen of the alcohol, the ester carbonyl and the methoxyl group of the methylmandelate all lie in a plane. When viewed in this manner, one observes shielding or an upfield shift of protons proximal to the phenyl group of the ester relative to the chemical shifts of the corresponding protons of the alcohol. In Fig. 4, below, the shielding cone (3/4 circle) of the ester phenyl group is indicated eclipsing the protons closest to it in space.

Fig. 3. The structures of the (*S*)-*O*-methylmandelate ester (**4**), the (*R*)-*O*-methylmandelate ester (**5**) and the acetate (**6**) of lanomycinol.



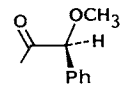
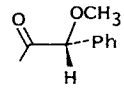
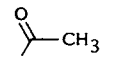
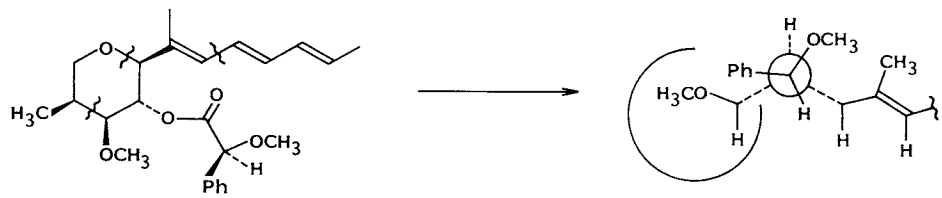
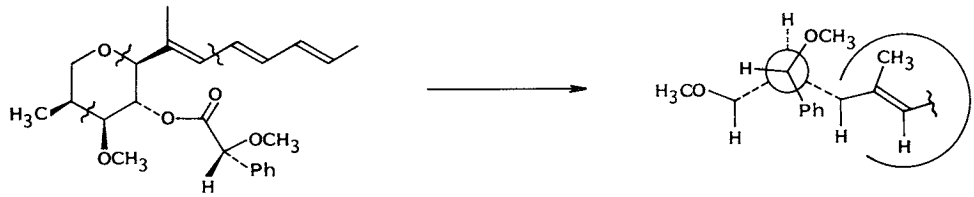
Compound	R
4	
5	
6	

Fig. 4. The aromatic shielding cones created by the mandelate phenyl groups.



(*S*)-*O*-Methylmandelate ester (**4**)



(*R*)-*O*-Methylmandelate ester (**5**)

Table 3. Chemical shifts (δ, $CDCl_3$) and assignments of the resonances of the (*S*)- and (*R*)-*O*-methylmandelate esters, (**4**) and (**5**) and the acetate (**6**) of lanomycinol.

(*S*)-Ester (**4**)	(*R*)-Ester (**5**)	Acetate (**6**)	Assignment*
7.39	7.34	—	(2H, m, mandelate phenyl)
7.28	7.26	—	(3H, m, mandelate phenyl)
6.25~6.0	6.2~5.9	6.3~6.0	(3H, m, 8-H, 9-H, 10-H)
5.93	5.70	5.96	(1H, d, 7-H)
5.72	5.70	5.70	(1H, dq, 11-H)
5.05	5.09	5.00	(1H, [dd]t, 4-H)
4.64	4.69	—	(1H, s, mandelate methine)
3.78	3.77	3.81	(1H, dd, 1-H_α)
3.53	3.53	3.57	(1H, dd, 1-H_β)
3.55	3.50	3.51	(1H, d, 5-H)
3.23	3.34	3.36	(1H, dd, 3-H)
3.33	3.37	3.34	(3H, s, 3-OCH_3)
2.94	3.17	—	(3H, s, mandelate OCH_3)
2.17	2.22	2.25	(1H, m, 2-H)
—	—	1.94	(3H, s, acetate CH_3)
1.78	1.72	1.78	(3H, s, 6-CH_3)
1.77	1.78	1.77	(3H, d, 12-H)
1.05	1.07	1.09	(3H, d, 2-CH_3)

* Coupling constants were similar to those reported for the alcohol in Table 2.

Both the (*S*)-*O*-methylmandelate (**4**), and the (*R*)-*O*-methylmandelate (**5**) esters of lanomycinol (**3**) were synthesized using a slight modification of TROST's DCC coupling methodology.[8] These compounds were examined by ^1H NMR and their resonances were compared with resonances of the corresponding acetate (**6**) in Table 3.

From the data in Table 3, it is apparent that the phenyl group of the *S* ester shielded the C-3 proton and to a lesser extent the C-3 methoxyl, while in the *R* ester, protons assigned to C-5 through C-7 (including the C-6a methyl and especially the C-7 proton) were shielded. The chemical shifts of the acetate are shown for reference. This data is consistent with the views of structures **4** and **5** drawn above and predicts that the absolute stereochemistry of the C-4 carbon is *R*, as drawn.

In the final stages of preparation of this manuscript, we noted the appearance of papers reporting the isolation[9] and structure eleucidation[10] of a compound identical to **1** except for the presence of an *n*-propyl group in palce of the methyl group termination of the triene side chain of **1**.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, or C_6D_6 using Jeol GX-270 or GX-400 spectrometers. Chemical shift values are given in ppm downfield of internal TMS or from the central solvent lines of the deuterated solvents in the ^{13}C NMR spectra. Mass spectra were obtained using a Finnigan TSQ 46 and a direct exposure probe for CI spectra and a VG-ZAB 2F for FAB spectra. IR spectra were obtained using a Perkin-Elmer model 1420 ratio recording infra-red spectrophotometer on ~0.1 M solutions of the compounds dissolved in chloroform. UV spectra were measured using $\sim 10^{-5}$ M methanolic solutions of the analyte in a cuvette having a path length of 1 cm in a Shimadzu UV-260, UV-visible recording spectrophotometer. Optical rotations were determined using a Perkin-Elmer model 241 polarimeter and a 10 cm cell.

(2α,3β,4α,5α)-Tetrahydro-4-methoxy-5-methyl-2-(1-methyl-1,3,5-heptatrienyl)-2*H*-pyran-3-ol, Amino-acetate Ester (**1**)

The fermentation yield of **1** was approximately 10 mg/liter. Slightly yellow oil, $[\alpha]_D$ +121° (*c* 1.0,

MeOH). TLC ($CHCl_3$-CH_3OH, 19:1) Rf 0.45. UV in CH_3OH, λ_{max} nm (log ε), 266 (4.25), 273 (4.37), 284 (4.27). IR ($CHCl_3$) cm^{-1} 2960, 2920, 2840, 1735, 1700, 1610, 1440, 1380, 1110, 1025, 980. ^1H NMR (270 MHz, $CDCl_3$) δ 6.17~5.9 (3H, m), 5.86 (1H, br d, J=10 Hz), 5.63 (1H, dq, J=14 and 7 Hz), 4.96 (1H, t, J=9 Hz), 3.74 (1H, dd, J=11 and 1.8 Hz), 3.55~3.1 (5H, m), 3.25 (3H, s), 2.18 (1H, m), 1.70 (3H, br s), 1.69 (3H, d, J=~6 Hz), 1.02 (3H, d, J=7 Hz). ^{13}C NMR (67 MHz, CD_3OD) see Table 1. MS/HR-MS, positive ion CI {CH_4/N_2O}, m/z 310 $(M+H)^+$, 270, 253, 235, 203. HRFAB vs. PEG measured $(M+H)^+$=310.2025, Calcd for $C_{17}H_{28}NO_4$=310.2018.

(2α,3β,4α,5α)-Tetrahydro-4-methoxy-5-methyl-2-(1-methyl-1,3,5-heptatrienyl)-2*H*-pyran-3-ol, (β-D-Glucopyranosyl Amino)acetate Ester (**2**)

The fermentation yield of **2** was more variable than that of **1** but was as great as 1 mg/liter. Yellow syrup, $[\alpha]_D$ +66.4° (*c* 1.0, MeOH). TLC ($CHCl_3$-CH_3OH, 10:1) Rf 0.15. UV in MeOH, λ_{max} nm (log ε), 266 (4.42), 273 (4.53), 284 (4.43). IR ($CHCl_3$) cm^{-1} 3420 (br), 2980, 2920, 2860, 1740, 1460, 1390, 1115, 1030, 990. ^1H NMR (270 MHz, CD_3OD) δ 6.3~6.0 (3H, m), 5.97 (1H, br d, J=9 Hz), 5.74 (1H, dq, J=14 and 7 Hz), 5.00 (1H, t, J=10 Hz), 3.8~3.0 (13H, m), 3.33 (3H, s), 2.30 (1H, m), 1.76 (3H, d, J=8 Hz), 1.74 (3H, br s), 1.07 (3H, d, J=7 Hz). ^{13}C NMR (67 MHz, CD_3OD) see Table 1. MS/HR-MS positive ion CI {CH_4/N_2O}, m/z 472 $(M+H)^+$, 310, 253, 235. HRFAB vs. PEG, measured $(M+H)^+$=472.2577; Calcd for $C_{23}H_{38}NO_9$=472.2537.

[2*S*(2α,3β,4α,5α)]-Tetrahydro-4-methoxy-5-methyl-2-(1-methyl-1,3,5-heptatrienyl)-2*H*-pyran-3-ol (**3**)

A 670 mg sample of **1** in 10 ml of MeOH was diluted with 10 ml of 1 M Na_2CO_3 and the mixture allowed to stir for 3.5 hours at 25°C. The MeOH was then stripped off and the resulting aqueous suspension was extracted with 3×20 ml of EtOAc. The combined ethyl acetate fraction was washed with 10 ml H_2O, dried over $MgSO_4$, taken to dryness and chromatographed on a 1.5×22 cm silica gel column eluted with $CHCl_3$-MeOH (98:2). Fractions shown to be pure by TLC were pooled and the solvent evaporated yielding 400 mg (73%) **3**. $[\alpha]_D$ +71.3° (*c* 2.5, MeOH). TLC (50% EtOAc-heptane) Rf 0.45. UV in CH_3OH, λ_{max} nm (log ε), 266 (4.42), 273 (4.53), 283 (4.45). IR ($CHCl_3$) cm^{-1} 3640, 3580, 2980, 2940, 2920, 2860, 1680, 1630, 1460, 1390, 1380, 1120, 1100, 1025, 980. ^1H NMR (400 MHz, C_6D_6) see Table 2. ^{13}C NMR (67 MHz, CD_3OD) see Table 1. MS positive ion CI {NH_3}, m/z 270 $(M+NH_4)^+$, 253 $(M+H)^+$, 235.

(2α,3β,4α,5α)-Tetrahydro-4-methoxy-5-methyl-2-(1-methyl-1,3,5-heptatrienyl)-2*H*-pyran-3-ol, (*S*)-(+)-α-Methoxyphenylacetate Ester (**4**)

75 mg (0.3 mmol) of **3**, 166 mg of (*S*)-(+)-α-methoxyphenylacetic acid and 192 mg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, (1 mmol each) and DMAP 10 mg were dissolved in 7 ml freshly distilled THF. After 2 hours, a TLC of the mixture showed that the reaction was complete. The THF was removed and the residue dissolved in 10 ml $MeCl_2$, and shaken with 10 ml portions of 0.1 N HCl, 0.5 N $NaHCO_3$ and water. After chromatography of the residue from the organic layer on a flash[11] silica gel column, and evaporation of the solvent from the pooled fractions containing pure material, 82 mg (70% yield) of **4** was obtained. TLC (30% EtOAc-heptane) Rf 0.43. UV in CH_3OH, λ_{max} nm (log ε) 273 (4.71), 284 (4.61), 263 (sh). IR ($CHCl_3$) cm^{-1} 2980, 2940, 2885, 2860, 2835, 1750, 1450, 1390, 1360, 1175, 1115, 1030, 990. ^1H NMR (270 MHz, $CDCl_3$) see Table 3. ^{13}C NMR (67 MHz, $CDCl_3$) δ 169.6, 136.2, 133.9, 132.7, 131.8, 129.9, 128.3 (3×), 127.2 (2×), 125.6, 85.2, 82.6, 81.6, 70.8, 69.3, 57.6, 56.1, 32.5, 18.2, 11.6, 10.7. MS positive ion CI {NH_3}, m/z 418 $(M+NH_4)^+$, 401 $(M+H)^+$, 293, 235, 203.

(2α,3β,4α,5α)-Tetrahydro-4-methoxy-5-methyl-2-(1-methyl-1,3,5-heptatrienyl)-2*H*-pyran-3-ol, (*R*)-(−)-α-Methoxyphenylacetate Ester (**5**)

Compound **5** was prepared as described above in 53% isolated yield, substituting the (*R*)-(−)-α-methoxyphenylacetic acid for the (*S*) isomer. TLC (30% EtOAc-heptane) Rf 0.40. UV in CH_3OH, λ_{max} nm (log ε) 274 (4.75), 284 (4.66), 264 (sh). IR ($CHCl_3$) cm^{-1} 2975, 2940, 2885, 2860, 2835, 1750, 1450, 1390, 1350, 1175, 1115, 1030, 990. ^1H NMR (270 MHz, $CDCl_3$) see Table 3. ^{13}C NMR (67 MHz, $CDCl_3$) δ 169.8, 136.2, 134.1, 132.3, 131.9, 130.2, 129.8, 128.3 (2×), 128.2, 127.0 (2×), 125.5, 85.0, 82.9, 81.7, 70.7, 69.4, 57.6, 56.2, 32.4, 18.2, 11.6, 10.7. MS positive ion CI {NH_3}, m/z 418 $(M+NH_4)^+$, 401 $(M+H)^+$, 293, 235, 203.

(2α,3β,4α,5α)-Tetrahydro-4-methoxy-5-methyl-2-(1-methyl-1,3,5-heptatrienyl)-2*H*-pyran-3-ol, Acetate Ester (**6**)

To 57 mg (0.23 mmol) of **3** in 5 ml of dry $MeCl_2$, was added 200 μl acetic anhydride, 400 μl pyridine and 10 mg DMAP. This mixture was stirred for 15 hours at 25°C, then the solvent was stipped off and the resulting oil was dried for two hours *in vacuo*. The residue was flash chromatographed on silica gel using 5% EtOAc in petroleum ether as the eluting solvent. The pooled fractions (pure product by TLC) gave 56 mg (83% yield) on removal of solvents. TLC (40% EtOAc-heptane) Rf 0.53. UV in CH_3OH, λ_{max} nm (log ε) 263 (4.25), 273 (4.36), 284 (4.26). IR ($CHCl_3$) cm^{-1} 2970, 2940, 2860, 1735, 1455, 1370, 1115, 1060, 1030, 990. ^1H NMR (270 MHz, $CDCl_3$) see Table 3. ^{13}C NMR (67 MHz, $CDCl_3$) δ 169.8, 133.5, 133.1, 131.9, 129.9, 129.4, 125.9, 85.5, 81.7, 70.8, 68.9, 56.4, 32.5, 20.8, 18.2, 11.7, 10.7. MS positive ion CI $\{NH_3\}$, *m/z* 312 $(M+NH_4)^+$, 295 $(M+H)^+$, 235.

Acknowledgments

The authors would like to thank Dr. A. TYMIAK for her valuable suggestions and encouragement and Mr. P. PRINCIPE, Ms. C. AKLONIS, Mr. R. HUGGILL and Mr. R. SMITH for their excellent technical assistance with the fermentations and broth extractions.

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