1 fs, and the nonbonded integration list was updated every 25 fs. Bond lengths involving hydrogen atoms were kept fixed using the SHAKE[33] algorithm. The initial coordinates for the atoms of 2 and 3 were taken from the X-ray structure. Prior to modeling, two hydrogens (H29 and H30) were removed from the thiazoline ring which was then explicitly aromatized. Typical molecular dynamics simulations involved a 1-ps heating period during which time the system was heated to 300 or 1000 K followed by a 1-ps equilibration period and then 10 ps of dynamics simulation at the appropriate elevated temperature. Energy barrier to rotation was calculated by constraining the valine–proline dihedral to 90° and minimizing. The energy of this structure without constraints less the energy of the unconstrained energy-minimized cis structure is taken as the barrier to rotation.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for tawicyclamide B and tables of HMBC correlation data for compounds 1–4 (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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The Natural Polypropionate-Derived Esters of the Mollusc *Onchidium* sp.

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Eight new polypropionate-derived esters (**5**–**8** and **10**–**13**) have been isolated from pulmonate molluscs of the genus *Onchidium* collected in the South Pacific. The structures of these compounds were determined spectroscopically in particular by one- and two-dimensional NMR and low and high EIMS. The absolute stereochemistry of the seven asymmetric centers was determined by using the Trost–Mosher methodology. Saponification afforded two triols named onchitriol I and II (**4** and **9**, respectively). Compounds **4**–**13** displayed in vitro antitumor activity against several cell lines. Onchitriol I and II had antiviral activity also.

Introduction

The marine mollusc phylum has been the object of intense chemical scrutiny by several research groups. The initial interest was prompted by reports that colorful, shellless molluscs which appear to be highly vulnerable to predation might utilize defensive secretions.[1] The pulmonates of the family Onchidiacea inhabit the rocky intertidal zones of many tropical shorelines and are known to contain epidermal glands described as "repugnatorial". These molluscs have proved to be a rich source of in vitro cytotoxic[2] and in vivo antineoplastic[3] substances of novel molecular types. One of the first examples was onchidal a defensive allomone of *Onchidella binneyi*.[4]

The most interesting compounds isolated from these species have a propionate-based biogenetic origin and posses a linear or cyclic polypropionate carbon skeleton. According to Faulkner, three general classes can be distinguished:[5] the simple polypropionates, such as denticulatin A;[6] the α-pyrones, exemplified by diemenesin;[7] and the γ-pyrones like siphonarins A and B.[8] The γ-pyrones include the polyhydroxylated peroniatriols I and II (**1**, **2**) and ilikonapyrone (**3**), which were isolated from the saponified extracts of *Peronia peronii*[9] and *Onchidium verruculatum*,[10] respectively; these compounds have a linear structure containing two γ-pyrone rings, three hydroxyl groups, and other asymmetric centers.

The general structure and relative stereochemistry of the acetonide of **3** were established by X-ray analysis, and

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Chart I

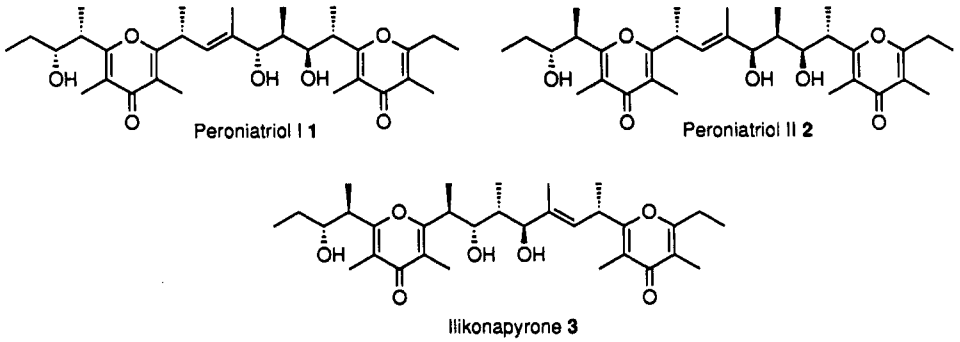
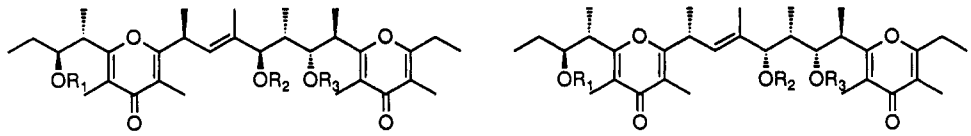


Chart II



Onchitriol I $R_1=R_2=R_3=H$, **4**

Onchitriol I A, $R_1=H$, $R_2=R_3=Ac$, **5**

Onchitriol I B, $R_1=H$, $R_2=(CO)Et$, $R_3=Ac$, **6**

Onchitriol I C, $R_1=H$, $R_2=Ac$, $R_3=(CO)Et$, **7**

Onchitriol I D, $R_1=Ac$, $R_2=R_3=(CO)Et$, **8**

Onchitriol II $R_1=R_2=R_3=H$, **9**

Onchitriol II A, $R_1=R_2=H$, $R_3=Ac$, **10**

Onchitriol II B, $R_1=R_2=H$, $R_3=(CO)Et$, **11**

Onchitriol II C, $R_1=R_2=R_3=Ac$, **12**

Onchitriol II D, $R_1=R_3=Ac$, $R_2=H$, **13**

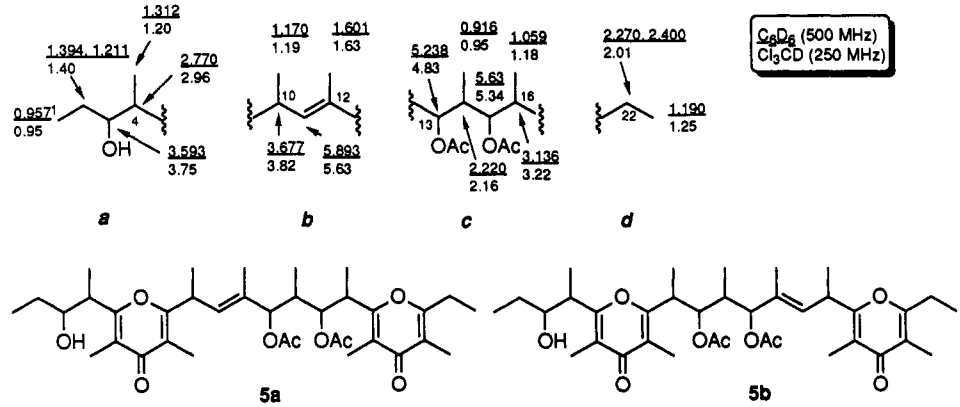


Figure 1. Partial structures of onchitriol I A (**5**).

those of **1** and **2** were originally inferred by comparison of their NMR data with those of **3**; synthesis of the optically active left wing (C1–C10) fragment has recently allowed the correction of the configuration at C4.[11] The absolute stereochemistry of ilikonapyrone (**3**) could not be deduced from its X-ray data, and that of peroniatriols I (**1**) and II (**2**) remain unknown also.

In this paper we describe the isolation and relative and absolute stereochemistry of eight cytotoxic acetates and propionates (**5–8** and **10–13**) isolated from a so far undetermined *Onchidium* sp. Compounds **5–8** are esters of the same triol **4** named onchitriol I while **10–13** are esters of another triol **9** onchitriol II.

Isolation and Characterization

Molluscs of the genus *Onchidium* were collected by scuba diving at Chesterfield atoll in the Mouillage islands, 450 km northwest of New Caledonia. A CH_2Cl_2 extract was obtained and partitioned between aqueous methanolic mixtures and *n*-hexane, CCl_4, CH_2Cl_2, and *n*-BuOH (see Experimental Section). The CCl_4 and CH_2Cl_2 fractions showed cytotoxic activity in vitro against KB human epidermoid carcinoma cells.

Bioassay-directed chromatographic separation of the extracts resulted in the isolation of compounds **5–8** and **9–13**. Flash chromatography on silica gel, followed by reversed-phase HPLC, afforded onchitriol I D (**8**), II C (**12**), and II D (**13**) from the CCl_4 extract; onchitriol I A (**5**), I B (**6**), I C (**7**), II A (**10**), and II B (**11**) were isolated from the CH_2Cl_2 extract.

Compounds 5–8. Onchitriol I A (**5**), the major component of the mixture, was obtained as a colorless amorphous powder. High-resolution EI mass spectral analysis gave the molecular formula $C_{36}H_{52}O_9$ (observed 628.3613, required 628.3611, $\Delta = 0.2$ mmu), indicating 11 degrees of unsaturation. The infrared spectrum of **5** contained hydroxyl (3300 cm^{-1}), ester (1730 cm^{-1}), and dienone (1660 cm^{-1}) bands. ^1H NMR signals in the 2 ppm region indicated that the ester function was due to two acetate groups.

The partial structures **a**, **b**, **c** and **d** (see Figure 1) were deduced from ^1H NMR spin decoupling and Relay COSY experiments. The chemical shifts of the protonated carbons were assigned by a 2D ^1H–^{13}C correlation experiment (HMQC).[12]

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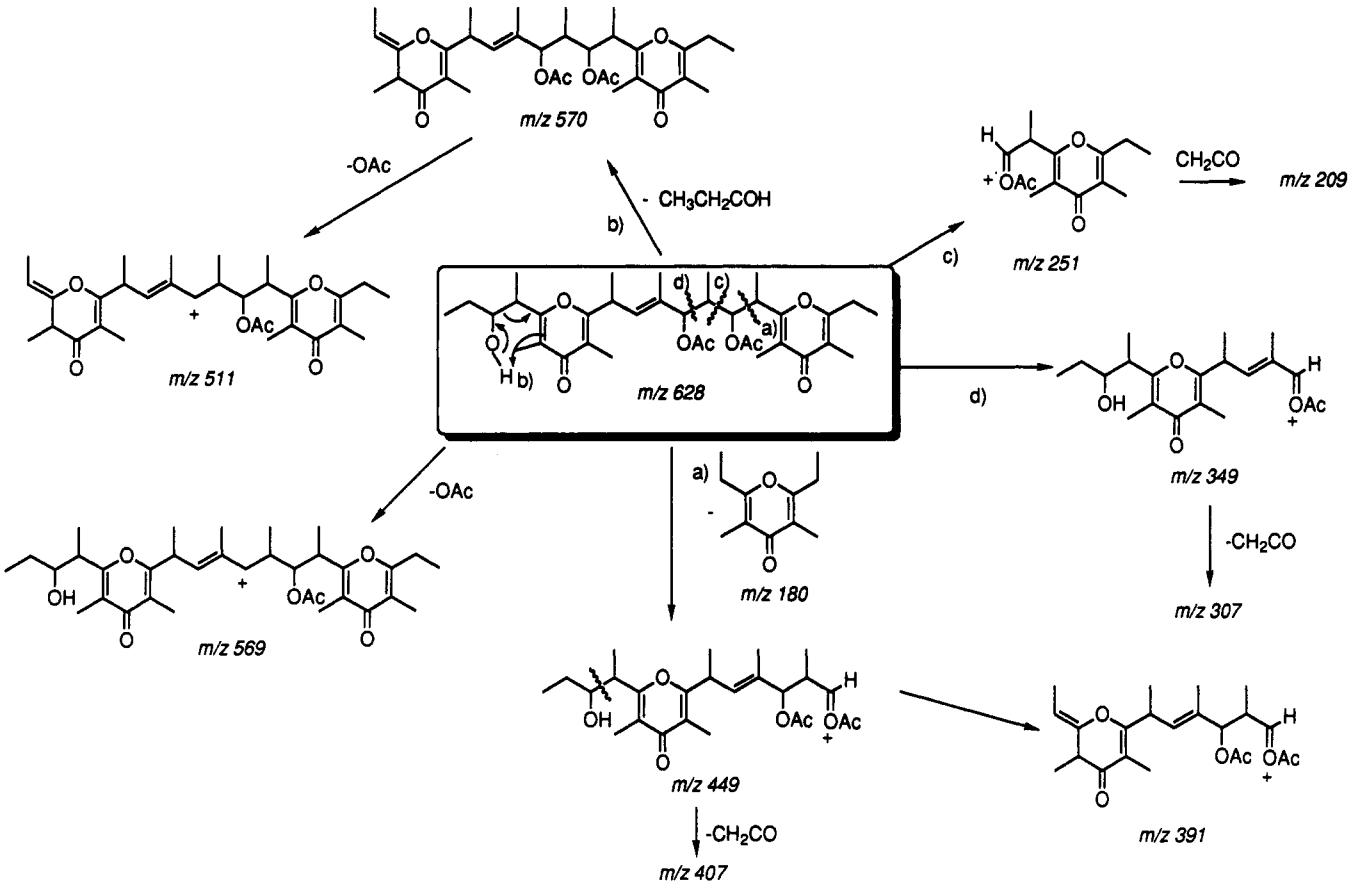
Scheme I



Assignment of the C1–C4 portion (partial structure **a**) was straightforward upon inspection of the ^1H–^1H COSY spectrum, which showed an ethyl group contiguous to a hydroxyl group and a methine proton (both at C3) which in turn are contiguous to a methyl substituent and methine proton at C4.

The structural subunit **b** is characterized by a *E*-double bond and a methylated methine group at C10. The partial structure **c** was shown by the presence of two acetates and signals corresponding to protons H13 and H15 at δ 5.238 (d, J = 10.6 Hz) and δ 5.626 (dd, J = 10.3 and 2.1 Hz) vicinal to another two methines (C14 and C16). Finally, substructure **d** is a normal ethyl moiety.

Examination of long-range homonuclear ^1H–^1H coupling (using the 2D Relay COSY sequence) and long-range heteronuclear ^{13}C–^1H coupling (HMBC sequence)[13] together with NOESY experiments enabled the above spin systems to be put together.

Three-bond coupling of the vinyl proton H11 (δ 5.893) with C13 and between H14 (δ 2.220) and C12 (δ 133.47) permitted us to deduce that subunits **b** and **c** are bound together. The *E* configuration of the double bond was deduced from the NOESY spectrum which shows a NOE cross-peak between the H13 resonance and the vinyl proton H11 and was confirmed by the ^{13}C chemical shift of the vinylic methyl group at δ 11.69.[14]

The highly deshielded protons, H4, H9, H16, and H22 correlate with carbons in the 30–43 ppm region, indicating that they are not bound to oxygen and must thus be vicinal to tetrasubstituted dienones. The quaternary signals at δ 179.02, 161.65, 159.87, 159.06, 119.85, 118.93, 118.01, and 117.39 agree with two fully substituted γ-pyrone rings bearing methyl groups on the β carbons (^1H NMR δ 186, 2.159, 2.070 and 2.046). Thus, the spin systems **a** and **d** are linked to γ-pyrone rings through C4 and C22, respectively.

Fragments **a**–**d** can be connected to give either an ilikonapyrone like structure (**a**–**c**–**b**–**d**) or a peroniatriol-like one (**a**–**b**–**c**–**d**). These two different structures (**5a** and **5b**, see Figure 1) are not easily distinguishable by NMR; the actual arrangement was deduced from the low-resolution mass spectrum (EIMS, see Scheme I), which showed relevant peaks at m/z 449, 407, 349 and 307 that could only be explained as deriving from structure **5a**.

The isomeric onchitriols I B (**6**) and I C (**7**) were also isolated from the CH_2Cl_2 fraction, being obtained as colorless amorphous powders by HPLC on an octadecylsilane column. Their HREIMS spectra afforded the molecular formula $C_{37}H_{54}O_9$ (Δ = 0.7 mmu for **6**, Δ = 0.0 mmu for **7**). Both have have one more CH_2 group than **5**; their ^1H NMR, UV, and IR spectra were almost identical with those of **5**, except for having an additional two-proton quartet (δ 2.22 for **6**, δ 2.07 for **7**) coupled with a high-field triplet at δ 1.06 in **6** and 0.95 in **7**, as confirmed by ^1H–^1H COSY experiments. These data suggested that an acetate group of **5** was replaced by a propionate in **6** and **7**, and since the NMR data for the **a** spin system of **5** are identical to those obtained for **6** and **7**, the acetate and propionate esters must be located at C13 and/or C15. Finally, since the ^1H–^1H NOESY spectrum of **7** showed a cross-peak correlation between the methylene group of the propionate ester (δ 2.17) and both H22 protons (δ 2.62), and since this effect was absent in **6**, compound **7** is the C15 propionate and **6** the C13 propionate.

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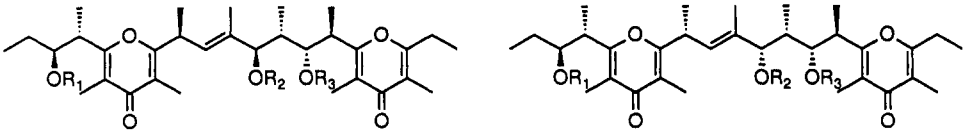
Chart III



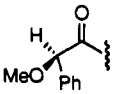
R_1=H, R_2, R_3=Me_2C, **14**

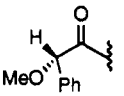
R_1= (+)-MPA, R_2=R_3=OAc, **15**

R_1= (-)-MPA, R_2=R_3=OAc, **16**

R_1=R_2=R_3=(+)-MPA, **17**

R_1=R_2=R_3=(-)-MPA, **18**

R (-) MPA= 

S (+) MPA= 

R_1=H, R_2, R_3=Me_2C, **19**

R_1=R_2=(+)-MPA, R_3=OAc, **20**

R_1=R_2=(-)-MPA, R_3=OAc, **21**

Additional evidence for the locations of the $OCOCH_2CH_3$ group was provided by the low-resolution mass spectra of **6** and **7** showing the production of stable allylic cation fragments by loss of, respectively, 73 ($C_3H_5O_2$) and 59 ($C_2H_3O_2$) mass units from the molecular ion and by peaks due to McLafferty rearrangement of the left-wing pyrone, which loses $OCOCH_2CH_3$ (73) or $OCOCH_3$ (59) (see Scheme I).

Onchitriol I D (**8**) was obtained from the CCl_4 fraction by HPLC. HREIMS showed the molecular ion peak at m/z 698.4040 ($C_{40}H_{58}O_{10}$, Δ = 2.6 mmu). The presence of three ester groups at C3, C13, and C15 was deduced from the deshielding of protons H3, H13, and H15, which were easily identifiable from their multiplicities at δ 5.34 (dd, H15), 5.07 (ddd, H3), and 4.81 (d, H13). The position of each ester was deduced as before from the low-resolution electron impact spectrum, which implied the presence of an acetate group on C3 and two propionates in C13 and C15.

Saponification of compounds **5–8** by stirring in 1% KOH/MeOH gave, in all cases, a single triol named onchitriol I (**4**, $C_{32}H_{48}O_7$, Δ = 0.1 mmu.), whose peroniatriol-type structure was confirmed by HREIMS fragments at m/z 365.2333 and 307.1928 produced by type a and d cleavage, respectively (see Scheme I).

Compounds 10–13. Onchitriol II A (**10**) was obtained from the methylene chloride extract. Its molecular formula was determined by HREIMS as $C_{34}H_{50}O_8$ (m/z 586.3500, Δ = 0.5 mmu), indicating less esterification than in **5–8**. All ^1H NMR signals were corroborated by a ^1H–^1H COSY experiment, and the ^{13}C NMR signals were assigned by comparison with those of **5** and a DEPT experiment; the deshielding of H13 at δ 5.43 (dd, 1 H, J = 10.5 and 1.7 Hz) indicates that the acetate group of **10** is borne by C15.

HREIMS of **11** showed a molecular ion at m/z 600.3676 requiring the molecular formula $C_{35}H_{52}O_8$ (Δ = 0.6 mmu), 14 mass units more than **10**, and since the spectral data of **11** were very similar to those of **10** it was concluded that **11** differed from **10** only in the replacement of the acetate group at C15 by a propionate group.

Onchitriol II C (**12**) has the molecular formula $C_{38}H_{54}O_{10}$ (Δ 0.7 mmu). The proton chemical shifts observed for H3, H13, and H15 (δ 5.07 ddd, δ 4.82 d and 5.34 dd, respectively) are in keeping with its having three acetyl groups; the rest of the protons were assigned by ^1H–^1H COSY (see Table II).

The last compound isolated was onchitriol II D (**13**) which has the molecular formula $C_{36}H_{52}O_9$ (Δ = 0.1 mmu). Its ^1H NMR spectrum showed geminal ester protons at δ 5.58 (dd, J = 10.3 and 1.8 Hz) identified as H13 and δ 5.06 (ddd, J = 9.8, 7.5, and 3.2 Hz) identified as H3, indicating that compound **13** is a C3, C15 diacetylated derivative.

Upon saponification, compounds **10–13** all gave onchitriol II (**9**), molecular formula $C_{32}H_{48}O_7$ (Δ = 0.4 mmu).

Table I. NMR Data of Onchitriol IA (5) from *Onchidium* sp.

C	^{13}C	HMQC connections[a,b]	HMBC connections
1	10.25 q	0.957 t, 7.3	H2
2	28.21 t	1.211 m	H1, H3
		1.394 m	
3	75.03 d	3.593 ddd, 8.5, 8.5, 3.0	H2, H4, H24
4	41.95 d	2.770 dq, 8.5, 7.0	H24
5	159.06 s*		
6	118.01 s$		H25
7	179.02 s		
8	117.39 s$		H26
9	159.87 s*		
10	34.36 d	3.677 dq, 7.0, 8.5	H11, H27
11	132.46 d	5.893 dq, 1.2, 8.5	H10, H27
12	133.48 s		H10, H28
13	78.86 d	5.238 d, 10.6	H11, H28, H29
14	35.14 d	2.220 ddq, 10.6, 2.1, 7.0	H13, H29
15	72.30 d	5.626 dd, 10.3, 2.1	H16, H30
16	37.36 d	3.136 dq, 10.3, 7.0	
17	161.65 s*		
18	119.85 s$		H31
19	179.02 s		
20	118.93 s$		H32
21	161.65 s*		
22	24.65 t	2.270 m	
		2.400 m	
23	19.97 q	1.190 t, 7.6	H22
24	14.06 q	1.312 d, 7.0	H3, H4
25	9.67 q#	2.046 s	
26	9.53 q#	2.159 s	
27	18.90 q	1.170 d, 7.0	H10, H11
28	11.69 q	1.601 d, 1.2	H11, H13
29	8.07 q	0.916 d, 7.0	H13, H15
30	13.32 q	1.059 d, 7.0	H16
31	10.29 q#	2.186 s	
32	9.67 q#	2.070 s	
CO	170.86 s		
CH_3	20.74 q	1.914 s	
CO	169.95 s		
CH_3	19.97 q	1.640 s	

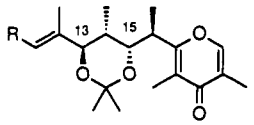
[a] 500 MHz (^1H) and 125 MHz (^{13}C) in C_6D_6. Signals with identical superscripts (*, $, #) within a column may be interchanged. [b] δ_H, multiplicity, J in Hz.

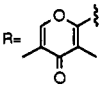
Relative Configuration of Onchitriol I and II. The relative stereochemistry of **4** and **9** was determined by comparison of their NMR data with those of the known compound **1–3**. The agreement between carbon and proton chemical shifts and vicinal J values for the C10–C16 fragment of **4** and those of **1** and of the analogous system of **3** shows that in all three this segment has the same relative stereochemistry, the 1,3 diol unit adopting a hydrogen-bonded chair conformation.[9] Onchitriol II (**9**) has different $J_{H_{13}-H_{14}}$ of 3 Hz, suggesting that H_{13} is now equatorial and the OH axial. Analogously, in both **4** and

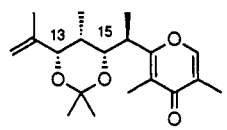
Table II. ^{1}H NMR Data of Onchitriols I (5–8)

H	δ (ppm), multiplicity (J in Hz)			
	5[a]	6[a]	7[a]	8[a]
1	0.95 t, 7.3	0.95 t, 7.3	0.95 t, 7.3	0.83 t, 7.4
2	1.40 m	1.39 m	1.40 m	1.42 m
3	3.75 ddd, 7.9, 7.9, 3.5	3.73 ddd, 7.1, 7.9, 3.3	3.72 ddd, 7.1, 7.9, 3.3	5.07 ddd, 8.2, 8.0, 3.4
4	2.96 dq, 7.1, 7.9	2.97 dq, 7.1, 7.1	2.96 dq, 7.1, 7.1	3.19 dq, 8.2, 7.0
10	3.82 dq, 7.1, 8.6	3.81 dq, 7.1, 8.6	3.82 dq, 7.1, 8.5	3.83 dq, 7.0, 8.9
11	5.63 dq, 1.3, 8.6	5.62 dq, 1.3, 8.6	5.62 dq, 1.2, 8.5	5.62 dq, 1.2, 8.9
13	4.83 d, 10.7	4.84 d, 10.6	4.81 d, 10.7	4.81 d, 10.6
14	2.16 ddq, 10.7, 2.1, 7.0	2.17 ddq, 10.6, 2.0, 7.0	2.15 ddq, 10.6, 2.0, 7.1	2.12 ddq, 9.7, 1.7, 7.0
15	5.34 dd, 10.3, 2.1	5.32 dd, 10.3, 2.0	5.36 dd, 10.3, 2.1	5.34 dd, 10.4, 2.1
16	3.22 dq, 10.3, 7.0	3.22 dq, 10.3, 6.9	3.23 dq, 10.3, 7.0	3.22 dq, 10.4, 6.9
22	2.60 q, 7.3	2.60 m	2.62 m	2.61 m
23	1.25 t, 7.3	1.25 t, 7.1	1.22 t, 7.1	1.23 t, 7.5
24	1.20 d, 7.1	1.23 d, 7.1	1.23 d, 7.1	1.21 d, 7.0
25	1.91 s*	1.96 s*	1.97 s*	1.95 s*
26	1.97 s*	1.95 s*	1.95 s*	1.95 s*
27	1.19 d, 7.1	1.20 d, 7.0	1.22 d, 7.0	1.29, d 7.0
28	1.63 d, 1.3	1.63 d, 1.3	1.62 d, 1.3	1.65 d, 1.32
29	0.92 d, 7.0	0.90 d, 7.0	0.89 d, 7.0	0.89 d, 7.0
30	1.18 d, 7.0	1.19 d, 7.1	1.20 d, 7.0	1.23 d, 7.0
31	1.97 s*	1.91 s*	1.97 s*	1.94 s*
32	1.95 s*	1.79 s*	1.91 s*	1.91 s*
Ac	1.95 s	1.95 s	1.95 s*	2.09 s*
Ac	1.79 s			
Et		2.22 m; 1.06 t, 7.2	2.17 m; 0.95 t, 7.3	2.22–2.00 m; 0.93 t, 7.5
Et				2.37 m; 1.05 t, 7.4

[a] 250 MHz, Cl_3CD. Resonances with * may be interchanged.



	$J_{H13-H14}$	$J_{H14-H15}$	$J_{H15-H16}$	E. (Kcal. mol^{-1})
EXP.(14)	7.0 (147°)	4.0 (57°)	9.6 (152°)	-
CALC.				
R=H	10.2 (152°)	4.3 (57°)	9.8 (152°)	26.4
R= 	10.3 (152°)	3.8 (57°)	9.9 (152°)	23.1
R= 	10.4 (152°)	4.1 (57°)	9.7 (152°)	18.4



	$J_{H13-H14}$	$J_{H14-H15}$	$J_{H15-H16}$	E. (Kcal. mol^{-1})
EXP. (19)	2.3 (54°)	4.6 (57°)	10.8 (157°)*	-
CALC.	1.8 (54°)	3.8 (58°)	9.8 (152°)	36.6

Figure 2. Coupling constants observed experimentally and calculated by molecular mechanics.

9 the C3–C4 fragment must have the same relative spatial orientation as **2** and **3**.[15]

To check the stereochemistry proposed for the 1,3 diol system of **4** and **9** we prepared the corresponding di-

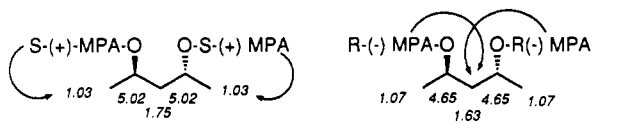


Figure 3. ^{1}H NMR chemical shifts of chiral Bis(*O*-methylmandelates) of 2(*R*),4(*R*)-(−)-pentanediol.

oxolanes (**14** and **19**) and carried out ^{1}H NMR measurements of coupling constants and MM calculations for appropriate models. The results (Figure 2) show good agreement between the *J* values and dihedral angles calculated for the minimum energy conformation and the experimental values.

Absolute Configurations of Onchitriols. The presence of secondary OH groups vicinal to asymmetric centers in compounds **4**–**13** suggested that the absolute stereochemistry of the molecules might be solved by stepwise analysis of the absolute configuration of the hydroxylated carbons and further use of the relative stereochemical relationship with the rest of the centers. This approach was carried out using the well-known Trost–Mosher[16,17] methodology preparing mono-, bis-, or tris(mandelates) of selected compounds. The validity of this method for the 1,3 diol system not studied before was proved with the chiral standard (2*R*,4*R*)-(−)-pentanediol. The ^{1}H NMR spectra of the (*R*)- and (*S*)-*O*-methylmandelate diesters showed chemical shift patterns (see Figure 3) in agreement with the projections where substituents in the vicinity of the aryl group are shielded.

Thus, to determine the absolute stereochemistry of onchitriol I (**4**) and its derivatives **5**–**8** at C-3, compound **5**,

(15) See refs 8 and 9; peroniatriol I (**1**): (500 MHz) H3 (ddd, J = 7, 7, 7 Hz), $J_{H13-H14}$ = 7 Hz, $J_{H14-H15}$ = 1 Hz, $J_{H15-H16}$ = 8 Hz; perioniatriol II (**2**): (500 MHz) H3 (ddd, J = 7, 7, 3 Hz); ilikonapyrone (**3**): (500 MHz) H3 (ddd, J = 7, 7, 3 Hz), $J_{H10-H11}$ = 8 Hz, $J_{H11-H12}$ = 1 Hz, $J_{H12-H13}$ = 7 Hz; onchitriol I (**4**): (250 MHz) H3 (ddd, J = 8, 7, 3 Hz), $J_{H13-H14}$ = 7 Hz, $J_{H14-H15}$ = 2 Hz, $J_{H15-H16}$ = 9 Hz; onchitriol II (**9**): (250 MHz) H3 (ddd, J = 8, 8, 3 Hz), $J_{H13-H14}$ = 3 Hz, $J_{H14-H15}$ = 2 Hz, $J_{H15-H16}$ = 9 Hz.

(16) (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. (b) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929.

(17) Recent examples: (a) Adamczeski, M.; Quiñoá, E.; Crews, P. *J. Org. Chem.* **1990**, *55*, 240. (b) Kustemi, T.; Ohtami, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296. (d) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (e) Finamore, E.; Minale, L.; Riccio, R.; Rinaldo, G.; Zollo, F. *J. Org. Chem.* **1991**, *56*, 1146.

Table III. ^{1}H NMR Data of Onchitriols II (10–13)

H	δ (ppm), multiplicity (J in Hz)			
	10[a]	11[a]	12[a]	13[a]
1	0.95 t, 7.3	0.96 t, 7.5	0.85 t, 7.4	0.90 t, 7.4
2	1.42 m	1.42 m	1.52 m	1.60, 1.90 m
3	3.64 ddd, 8.1, 8.4, 3.0	3.62 ddd, 8.0, 8.5, 3.0	5.07 ddd, 8.1, 8.4, 3.4	5.06 ddd, 9.8, 7.5, 3.2
4	2.99 dq, 8.1, 7.0	2.98 dq, 8.0, 7.0	3.20 dq, 8.1, 7.0	3.20 dq, 7.0, 9.8
10	3.80 dq, 7.1, 9.4	3.81 dq, 6.9, 9.0	3.83 dq, 7.0, 9.1	3.82 dq, 6.9, 8.6
11	5.46 dq, 1.1, 9.4	5.45 dq, 1.1, 9.0	5.65 dq, 1.3, 9.1	5.42 dq, 1.4, 8.8
13	3.53 d, 9.7	3.49 d, 9.7	4.82 d, 10.7	3.63 d, 10.0
14	2.07 ddq, 9.7, 1.7, 7.0	2.10 ddq, 9.7, 1.7, 7.0	2.10 ddd, 9.7, 1.7, 7.0	1.70 ddq, 10.0, 1.8, 7.0
15	5.43 dd, 10.5, 1.7	5.40 dd, 10.5, 1.7	5.34 dd, 10.4, 2.1	5.58 dd, 10.3, 1.8
16	3.31 dq, 10.5, 7.0	3.33 dq, 10.5, 6.9	3.24 dq, 10.4, 6.9	3.30 dq, 10.3, 7.0
22	2.57 q, 7.4	2.57 q, 7.5	2.58 q, 7.5	2.60 m
23	1.19 t, 7.4	1.20 t, 7.5	1.24 t, 7.5	1.22 t, 7.3
24	1.20 d, 7.0	1.20 d, 7.0	1.21 d, 7.0	1.20 d, 7.0
25	2.02 s*	2.02 s*	1.96 s*	1.97 s*
26	1.98 s*	1.98 s*	1.95 s*	1.94 s*
27	1.34 d, 7.1	1.33 d, 7.0	1.31 d, 7.0	1.30 d, 6.9
28	1.51 d, 1.1	1.52 d, 1.1	1.65 d, 1.3	1.62 d, 1.3
29	0.82 d, 7.0	0.81 d, 7.0	0.90 d, 7.0	0.81 d, 7.0
30	1.19 d, 7.1	1.19 d, 7.0	1.23 d, 7.0	1.19 d, 7.0
31	1.95 s*	1.95 s*	1.92 s*	2.01 s*
32	1.93 s*	1.92 s*	1.92 s*	1.98 s*
Ac	1.88 s*		2.09 s*	1.87 s*
Ac			1.95 s*	1.81 s*
Ac		–	1.79 s*	
Et		2.30–2.20 m; 1.20 t, 7.3		

[a] 250 MHz, Cl_3CD. Resonances with * may be interchanged.

Table IV. ^{13}C NMR Data on Onchitriols from Onchidium sp.

C	4[a]	5[a]	6[a]	9[a]	10[a]	13[a]
1	9.6 q	9.5 q	9.5 q	9.7 q	9.5 q	9.6 q
2	27.9 t	28.0 t	28.0 t	27.6 t	27.9 t	24.7 t
3	75.4 d	75.2 d	75.2 d	75.2 d	74.6 d	75.8 d
4	41.4 d	41.5 d	41.5 d	41.8 d	40.9 d	38.7 d
5	164.7 s*	162.4 s*	164.9 s*	165.6 s*	165.1 s*	165.1 s*
6	119.8 s$	118.5 s$	118.7 s$	120.2 s$	119.4 s$	116.9 s$
7	179.8 s#	179.8 s	179.8 s	179.8 s#	179.9 s#	179.9 s
8	118.8 s$	118.5 s$	–	–	–	–
9	164.4 s*	164.4 s*	164.4 s*	164.9 s*	165.0 s*	163.1 s*
10	39.1 d	34.3 d	34.3 d	39.2 d	34.1 d	34.0 d
11	127.3 d	131.7 d	131.4 d	125.5 d	130.1 d	129.0 d
12	137.6 s	133.4 s	133.6 s	137.3 s	138.0 s	137.3 s
13	79.8 d	78.6 d	78.4 d	79.9 d	78.6 d	78.3 d
14	34.4 d	34.9 d	35.1 d	34.3 d	36.5 d	36.5 d
15	72.4 d	72.4 d	72.4 d	73.1 d	74.4 d	74.1 d
16	36.4 d	37.2 d	37.2 d	34.0 d	37.3 d	37.4 d
17	164.3 s*	164.7 s*	162.4 s*	164.5 s*	163.0 s*	163.3 s*
18	118.0 s$	118.5 s$	–	–	–	–
19	179.8 s#	179.8 s	179.8 s	180.0 s#	179.8 s#	179.9 s
20	117.4 s$	118.5 s$	–	–	–	–
21	164.3 s*	164.9 s*	159.2 s*	164.1 s*	165.0 s*	163.1 s*
22	24.7 t	24.7 d	24.7 d	24.5 d	24.7 t	24.7 t
23	11.4 q	13.9 q	10.9 q	10.5 q	10.9 q	11.2 q
24	13.9 q	13.9 q	14.0 q	15.3 q	14.2 q	14.2 q
25	10.1 q	9.3 q	9.4 q	9.5 q	9.2 q	9.2 q
26	9.3 q	9.4 q	9.3 q	9.3 q	9.4 q	14.0 q
27	18.7 q	18.8 q	18.8 q	19.5 q	19.2 q	18.8 q
28	14.4 q	11.8 q	11.9 q	13.6 q	11.2 q	14.2 q
29	9.4 q	8.9 q	9.0 q	9.2 q	9.1 q	8.7 q
30	12.0 q	13.7 q	13.7 q	13.7 q	15.2 q	13.9 q
31	9.1 q	10.1 q	10.1 q	9.7 q	9.8 q	10.6 q
32	9.2 q	9.5 q	9.5 q	9.3 q	9.5 q	9.4 q
CO	–	169.3 s	175.4 s	–	171.6 s	170.5 s
CH_2	–	–	27.6 t	–	–	20.7 t
CH_3	–	21.0 q	8.7 q	–	20.5 q	170.5 s
CO	–	169.8 s	175.4 s	–	–	–
CH_2	–	–	–	–	–	20.4 t
CH_3	–	20.3 q	20.3 q	–	–	170.5 s
CO	–	–	–	–	–	–
CH_3	–	–	–	–	–	20.7 q

[a] 63 MHz Cl_3CD. Signals with identical superscripts (*, $, #) within a column may be interchanged. The multiplicity of the signals was confirmed by DEPT.

Table V. ^{1}H NMR Data for Onchitriol I (4) and Onchitriol II (9)

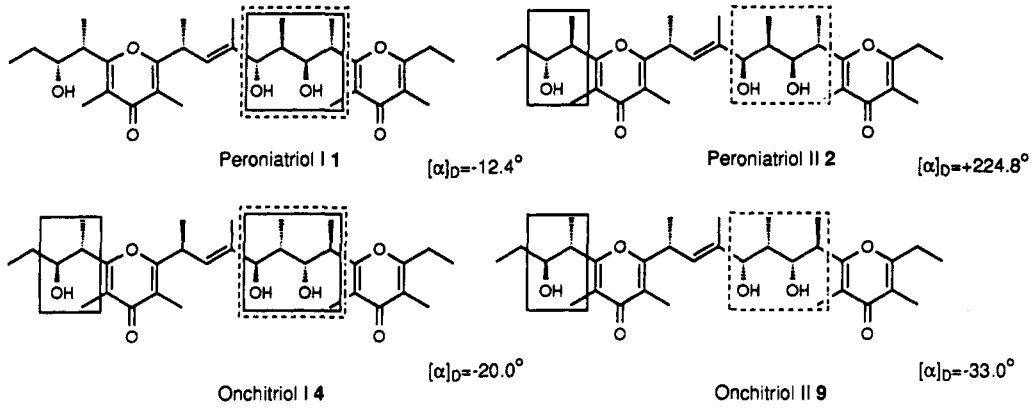
H	δ (ppm), multiplicity (J in Hz)	
	4[a]	9[a]
1	0.95 t, 7.3	0.87 t, 7.3
2	1.43 m; 1.40 m	1.60 m; 1.40 m
3	3.55 ddd 7.2, 8.3, 3.5	3.55 ddd 8.3, 7.9, 3.0
4	2.97 dq 7.2, 7.0	2.79 dq 8.9, 6.9
10	3.90 dq 6.9, 9.2	3.95 dq 6.8, 9.6
11	5.59 dq 1.1, 9.2	5.84 dq 1.2, 9.6
13	4.05 d, 7.4	4.03 d, 3.3
14	1.92 ddq, 7.4, 7.0, 1.9	1.90 ddq, 7.0, 2.0, 3.3
15	4.12 dd, 9.4, 1.9	3.68 dd, 9.7, 2.0
16	3.13 dq, 9.4, 6.9	3.08 dq, 9.7, 7.1
22	2.56 m	2.55 m; 2.24 m
23	1.15 t, 7.5	0.98 t, 7.5
24	1.26 d, 7.0	1.14 d, 6.9
25	1.98s*	1.85s*
26	1.97 s*	1.87 s*
27	1.26, d 7.0	1.31, d 7.1
28	1.70 d, 1.1	1.63 d, 1.2
29	0.92 d, 7.0	1.15 d, 7.1
30	1.14 d, 6.9	1.02 d, 7.1
31	1.95 s*	1.93 s*
32	1.92 s*	2.04 s*

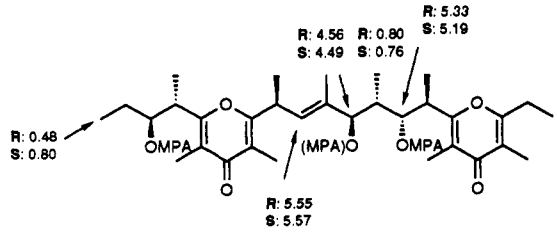
[a] 250 MHz, Cl_3CD. Resonances with * may be interchanged.

the 13,15 diacetate, was converted to the corresponding (+)- and (–)-3-*O*-MPA esters (**15** and **16**, respectively). The ^{1}H NMR data show that in the (*R*)-3-*O*-mandelate **16** the C1 methyl protons resonate at higher field than in the (*S*)-3-*O*-mandelate, the opposite effect being observed for H4 which is shielded in **15**. These shifts implied the presence of a *S* configuration at C3 and hence at C4 (see relative stereochemistry).

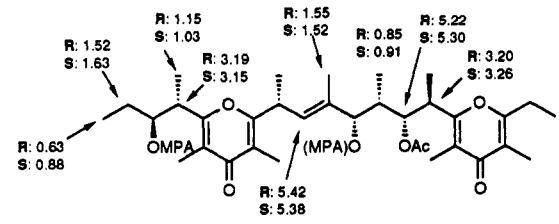
To characterize the rest of the skeleton, **4** was converted into its *S* and *R* 3,13,15-trimandelates **17** and **18**, respectively (see Figure 4). Comparison of NMR spectra showed that in the 3,13,15-(*R*)-trimandelate the C1 methyl group resonates at higher field and H13 and H15 at lower field indicating a 3*S*,13*R*,15*R* configuration. The relative stereochemistry of the remaining centers with respect to the hydroxylated ones, and the perfect agreement between

Chart IV





17 S (+) trimandelate of 4
18 R (-) trimandelate of 4



20 S(+) dimandelate of 10
21 R (-) dimandelate of 10

Figure 4. Selected ^1H NMR data of chiral bis- and tris-(mandelates).

the NMR data for the C10–C16 fragments of **4** and **1**, now imply that compound **4** has the configuration 3*S*,4*S*,10*S*,13*R*,14*R*,15*R*,16*R*.

Similarly, compound **10**, the 15-monoacetate derived from onchitriol II (**9**), was converted to the corresponding (*S*)- and (*R*)-3,13-bis(mandelates) **20** and **21**, respectively. NMR analysis showed that the configuration of **10** is 3*S*,4*S*,13*S*,14*R*,15*R*,16*R*. In contrast to the agreement between **1** and **4** as regards to their NMR data for the C10–C16 skeletal fragment, the chemical shift of C10 in **9** as compared to that in **2** suggests that the C10 substituents of **2** and **9** are differently oriented. Since **9** (3*S*,4*S*,13*S*,14*R*,15*R*,16*R*) and **2** (3*R**,4*R**,10*R**,13*R**,14*S**,15*S**,16*S**) have the same *relative* stereochemistry at 3, 4, 13, 14, 15, and 16 and they are not enantiomers but diastereomers ($[\alpha]_D$ = +224.8 for **2** and $[\alpha]_D$ = −33.0 for **9**), the configuration at C10 must be 10*R* in **9**.

This is the first time that hydroxylated polypropionates of marine origin have been isolated in their natural ester form; previous work was performed on saponified material due to the complexity of the mixture, and although the presence of propionates was clearly established, no acetates were ever identified.

The number and positions of the ester groups in structures **5**–**8** and **10**–**13** do not appear to exhibit any particular pattern. Onchitriol I (**4**) and onchitriol II (**9**) have different configurations at C10 and C13, and are diastereomers of the known peroniatriol I (**1**) and peroniatriol II (**2**). Chart IV shows the stereochemical features (fragments with the same relative stereochemistry are shown framed) and the corresponding α values. These results seems to indicate that diversity at the assymetric centers is a characteristic of this class of metabolites.

Biological Activity. The esters isolated from *Onchidium* sp. were found to be active in vitro against KB human epidermoid carcinoma cells, 90–98% growth inhibition being observed at dosages of 1–10 μg/mL. Compounds **4** and **9** were also tested against P388, A-549, and HT-29 cell lines. IC_{50} values around 10 μg/mL were observed for compound **4** and 20 μg/mL for **9**; both these compounds were also found to possess antiviral activity against type 1 *Herpes simplex* virus (HSV-1) at 10 μg/mL and against *Vesicular stomatitis* virus (VSV) at 20 μg/mL.

From a structural point of view, it is worth noting that onchitriol I and peroniatriol I are both more active than their counterparts onchitriol II and peroniatriol II, which may mean that the central part of the molecules requires a trans 1,3 diol system for maximum activity.

Experimental Section

General Methods. IR and UV spectra were obtained on Perkin-Elmer Model 1420 and Uvikon Model 930 spectrophotometers, respectively, and optical rotations on a Perkin-Elmer Model 141 polarimeter. NMR spectra were recorded on Varian XL500 and Bruker WM250 spectrometers using $CDCl_3$ and C_6D_6 as solvent and internal standard.

The HMQC and HMBC sequences were acquired with a 2K × 128 matrix (zero filled to 512 in 512 in F1) and 128 scans per increment. The delay for polarization transfer was set for an assumed $^1J_{CH}$ of 140 Hz (HMQC) and J_{CH} of 9 Hz (HMBC). The ^1H–^1H COSY and ^1H–^1H NOESY spectra were acquired with a 1K × 128 matrix (zero filled in F1) with 16 or 8 scans per increment. In the NOESY, a mixed time of 200 ms was used.

Mass spectra were obtained on Kratos MS-50 and Hewlet-Packard HP 59970 spectrometers. Fast atom bombardment (FAB) mass spectra were run employing Xe atoms at 7–9 keV and 2-hydroxyethyl disulfide matrix. HPLC separation was performed using a Waters Model 6000A.

Extraction and Isolation. *Onchidium* sp. (3 kg) collected in Juyl 1988 from Chesterfield atoll (Mouillage isles, 450 km NW of New Caledonia) was immediately freeze-dried (600 g dry weight) and then extracted with MeOH. The methanol extract was decanted off and concentrated in vacuo. This was repeated four times, and the total extracts were combined and concentrated again in vacuo. The concentrate was partitioned between 400 mL of 10% aqueous methanol and hexane (2 × 400 mL), the aqueous portion was made 20% aqueous and extracted with CCl_4 (2 × 400 mL), and the aqueous portion was made 40% aqueous and extracted with dichloromethane (3 × 400 mL). The extracts were concentrated in vacuo to obtain 2.9 g of hexane extract (extract

A; cytotoxic to Kb cells at 10 μg/mL: 15% inhibition), 1.2 g of CCl_4 extract (extract B; cytotoxic to Kb cells at 10 μg/mL; 97% inhibition), and 0.68 g of dichloromethane extract (extract C; cytotoxic to Kb cells at 10 μg/mL: 99% inhibition). The CCl_4 extract was flash chromatographed on SiO_2 (Cl_2CH_2 with increasing MeOH) giving five main fractions B1 (inactive), B2 (cytotoxic to Kb cells at 10 μg/mL: 93% inhibition), B3 (inactive), B4 (cytotoxic to Kb cells at 10 μg/mL: 95% inhibition), and B5 (inactive). Fraction B4 was rechromatographed on a SiO_2 flash column (7:9 Et_2O/hexane) afford two active subfractions that under HPLC (μ-Bondapack C_{18}, 77:23 MeOH/H_2O) furnished 4 mg of onchitriol I D (**8**), 4 mg of onchitriol II C (**12**), and 5 mg of onchitriol II D (**13**). Extract C was run on an SiO_2 flash column (CH_2Cl_2 with increasing MeOH), giving four fractions: C1 (inactive), C2 (cytotoxic to Kb cells at 10 μg/mL, 94% inhibition), C3, and C4 (both inactives). Fraction C2 was purified by HPLC (μ-Bondapack C_{18}, 77:23 MeOH/H_2O) affording 8 mg of onchitriol I A (**5**), 4 mg of onchitriol I B (**6**), 4 mg of onchitriol I C (**7**), 6 mg of onchitriol II A (**10**), and 3 mg of onchitriol I D (**9**).

Onchitriol I A (5). $[\alpha]_D$: −11.5° (Cl_2CH_2, c = 0.02). UV (MeOH) λ_{max}: 259 nm. IR ν_{max} (cm^{-1}): 3300, 1730, 1700, 1660, 1370. HREIMS: $C_{36}H_{52}O_9$ calcd 628.3611. Found: 628.3613. EIMS m/z: 628 (27), 585 (2), 571 (18), 570 (54), 569 (35), 511 (30), 459 (10), 451 (15), 449 (10), 407 (5), 391 (5), 360 (3), 349 (8), 291 (5), 289 (7), 259 (9), 251 (8), 238 (10), 231 (11), 209 (17), 193 (14), 180 (100), 179 (32), 151 (17), 109 (10), 83 (11).

Onchitriol I B (6). $[\alpha]_D$: −19.5° (Cl_2CH_2, c = 0.01). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 3350, 1725, 1700, 1660, 1370. HREIMS: $C_{37}H_{54}O_9$ calcd 642.3768. Found: 642.3775. EIMS m/z: 642 (27), 585 (20), 584 (41), 569 (34), 525 (5), 511 (36), 451 (22), 405 (8), 260 (9), 238 (14), 209 (20), 191 (14), 180 (100), 179 (41), 151 (22), 149 (29), 103 (71), 83 (24), 75 (38).

Onchitriol I C (7). $[\alpha]_D$: −18.0° (Cl_2CH_2, c = 0.1). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 3300, 1730, 1660, 1370. HREIMS: $C_{37}H_{54}O_9$ calcd 642.3768. Found: 642.3768. EIMS m/z: 642 (14), 584 (37), 583 (16), 525 (12), 473 (8), 451 (10), 349 (6), 319 (7), 307 (7), 273 (6), 260 (12), 238 (10), 221 (10), 209 (21), 193 (12), 191 (10), 181 (15), 180 (100), 179 (30), 151 (17), 83 (11).

Onchitriol I D (8). $[\alpha]_D$: −25.2° (Cl_2CH_2, c = 0.01). UV (MeOH) γ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 1735, 1660, 1370. HREIMS: $C_{40}H_{58}O_{10}$ calcd 698.4030. Found: 698.4004. EIMS m/z: 698 (7), 641 (3), 639 (3), 625 (47), 582 (43), 551 (17), 492 (16), 463 (2), 405 (8), 390 (3), 280 (15), 180 (100), 151 (22).

Onchitriol II A (10). $[\alpha]_D$: −26.0° (Cl_2CH_2, c = 0.1). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 1733, 1664, 1365. HREIMS: $C_{34}H_{50}O_8$ calcd 586.3505. Found: 586.3500. EIMS m/z: 586 (20), 529 (13), 528 (39), 527 (11), 510 (7), 469 (7), 451 (6), 407 (56), 349 (7), 319 (9), 307 (37), 289 (10), 260 (22), 221 (25), 220 (16), 209 (15), 193 (10), 191 (14), 180 (100), 179 (35), 151 (18), 109 (10), 83 (39).

Onchitriol II B (11). $[\alpha]_D$: −25.2° (Cl_2CH_2, c = 0.01). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 1735, 1660, 1370. HREIMS: $C_{35}H_{52}O_8$ calcd 600.3662. Found: 600.3676. FABMS m/z: 601 (100), 587 (5), 583 (5), 569 (4), 543 (3), 527 (2), 509 (5), 451 (2), 368 (2), 361 (10), 319 (13), 307 (9), 231 (17), 209 (23), 180 (30), 165 (10), 151 (10).

Onchitriol II C (12). $[\alpha]_D$: −26.0° (Cl_2CH_2, c = 0.01). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 1720, 1664, 1365. HREIMS: $C_{38}H_{54}O_{10}$ calcd 670.3717. Found: 670.3722. FABMS m/z: 671 (100), 649 (7), 630 (10), 614 (12), 571 (5), 553 (15), 457 (10), 361 (13), 280 (13), 221 (11), 209 (24), 180 (41), 151 (19).

Onchitriol II D (13). $[\alpha]_D$: −20.0° (Cl_2CH_2, c = 0.1). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 1730, 1660, 1370. HREIMS: $C_{36}H_{52}O_9$ calcd 628.3611. Found: 628.3610. EIMS m/z: 628 (10), 611 (4), 569 (7), 449 (5), 349 (70), 289 (23), 221 (64), 209 (10), 205 (32), 193 (12), 191 (28), 181 (23), 180 (100), 179 (57), 151 (21), 83 (13).

Saponification of 5–9. The ester (1–2 mg) was stirred overnight at room temperature in 1% KOH/MeOH (0.2 mL). Brine (0.3 mL) was added to the reaction and the mixture extracted with dichloromethane (4 × 0.4 mL). Evaporation of the CH_2Cl_2 and purification by HPLC (μ-Bondapack C_{18} column MeOH/H_2O (80:20)) gave the corresponding triol (5 mg of onchitriol I (**4**) were obtained from **5–8** and 4 mg of onchitriol II (**9**) from **10–13**).

Onchitriol I (4). $[\alpha]_D$: −20.0° (Cl_2CH_2, c = 0.01). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 1665, 1620. HREIMS: $C_{32}H_{48}O_7$ calcd 544.3395. Found: 544.3400. EIMS m/z: 544 (7), 515 (2), 486 (6), 459 (4), 365 (10), 319 (7), 307 (23), 248 (34), 219 (13), 191 (16), 180 (100), 179 (54), 151 (20), 123 (16), 97 (17), 83 (34).

Onchitriol II (9). $[\alpha]_D$: −33.0° (Cl_2CH_2, c = 0.01). UV (MeOH) λ_{max}: 260 nm. IR ν_{max} (cm^{-1}): 1660, 1610. HREIMS: [544 (5) $C_{32}H_{48}O_7$ Calcd 544.3395. Found: 544.3399]; [486 (5) $C_{29}H_{42}O_6$ calcd 486.2981. Found: 486.2981]; [365 (10) $C_{21}H_{33}O_5$ calcd 365.2328. Found: 365.2333]; [347 (3) $C_{21}H_{31}O_4$ calcd 347.2222. Found: 347.2215]; [307 (15) $C_{18}H_{27}O_4$ calcd 307.1909. Found: 307.1928]; [289 (5) $C_{18}H_{25}O_3$ calcd 289.1804, found: 289.1861], [248 (10) $C_{15}H_{20}O_3$ calcd 248.1412. Found: 248.1413]; [180 (100) $C_{11}H_{16}O_2$ calcd 180.1150. Found: 180.1154].

Preparation of Dioxolanes 14 and 18 from 4 and 9. 2,2-Dimethoxypropane (1 mL) containing a catalytic amount of *p*-TsOH was added to a 2-mg sample of the triol (**4** or **9**) dissolved in 1 mL of acetone. The reaction mixture was allowed to stand under nitrogen at rt for 24 h. After that, the mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were concentrated to dryness in vacuo to afford, after HPLC purification (μ-Bondapack C_{18} column 90:10 MeOH/H_2O), the corresponding dioxolanes **14** and **18**.

Onchitriol I Dioxolane (14). ^1H NMR (Cl_3CD): 5.53 (dd, 1 H, J = 8.3, 1.1 Hz, H11) 3.96 (dd, 1 H, J = 10.8 and 4.6 Hz, H15), 3.86 (dd, 1 H, J = 8.8 and 6.9 Hz, H10), 3.74 (ddd, 1 H, J = 2.7, 8.2, and 7.0 Hz, H3), 3.61 (d, 1 H, J = 7.1 Hz, H13), 3.09 (dd, 1 H, J = 10.8, 6.8 Hz, H16), 2.99 (dq, 1 H, J = 7.0, 7.0 Hz), 2.61 (q, 2 H, J = 7.3 Hz, H23), 1.99 (s, 3 H), 1.96 (s, 6 H), 1.95 (s, 3 H), 1.92 (m, 1 H, H14), 1.72 (d, 3 H, J = 1.2 Hz, Me28), 1.57 (m, 1 H, H2), 1.48 (m, 1 H, H2), 1.28 (d, 3 H, J = 7.0 Hz, Me24), 1.26 (d, 3 H, J = 6.9 Hz, Me27), 1.25 (t, 3 H, J = 7.4 Hz, Me23), 1.19 (s, 3 H, $Me_{dioxolane}$), 1.13 (d, 3 H, J = 6.8 Hz, Me30), 1.07 (s, 3 H, $Me_{dioxolane}$), 0.96 (t, 3 H, 7.3 Hz, Me1), 0.95 (d, 3 H, J = 6.9 Hz, Me29). HREIMS: $C_{35}H_{52}O_7$ calcd 584.3713. Found: 584.3720. FABMS (+) m/z: 585 (14), 571 (1), 545 (2), 499 (1), 375 (1), 319 (3), 277 (35), 185 (54), 180 (17), 151 (6).

Onchitriol II Dioxolane (18). ^1H NMR (Cl_3CD): 5.53 (dd, 1 H, J = 8.3, 0.8 Hz, H11), 3.95 (dd, 1 H, J = 10.3 and 4.6 Hz, H15), 3.83 (dd, 1 H, J = 8.2 and 7.0 Hz, H10), 3.70 (m, 1 H, H3), 3.66 (d, 1 H, J = 2.3 Hz, H13), 3.20 (m, 1 H, H16), 3.05 (dq, 1 H, J = 7.1 and 7.0 Hz), 2.60 (m, 1 H, H22), 2.42 (m, 1 H, H22), 2.01 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H), 1.93 (s, 3 H), 1.92 (m, 1 H, H14), 1.64 (d, 3 H, J = 0.8 Hz, Me28), 1.60 (m, 1 H, H2), 1.48 (m, 1 H, H2), 1.33 (d, 3 H, J = 7.0 Hz, Me24), 1.26 (d, 3 H, J = 6.9 Hz, Me27), 1.24 (t, 3 H, J = 7.4 Hz, Me23), 1.20 (s, 3 H, $Me_{dioxolane}$), 1.13 (d, 3 H, J = 6.8 Hz, Me30), 1.07 (s, 3 H, $Me_{dioxolane}$), 0.96 (t, 3 H, 7.3 Hz, Me1), 0.87 (d, 3 H, J = 6.9 Hz, Me29). HREIMS: $C_{35}H_{52}O_7$ calcd 584.3713. Found: 584.3720. EIMS m/z: 584 (10), 526 (8), 499 (16), 467 (1), 347 (14), 319 (16), 307 (38), 261 (11), 248 (10), 221 (100), 205 (90), 191 (42), 180 (60), 151 (22).

Standard Procedure for the Preparation of All *O*-Methylmandelate Derivatives. A catalytic amount of 4-(dimethylamino)pyridine was added to a solution of the alcohol, *O*-methylmandelic acid, and dicyclohexylcarbodiimide in CH_2Cl_2. After 24–72 h, the dicyclohexylurea was removed by filtration and the solvent removed in vacuo. The filter cake was washed with Et_2O (three times), and the combined filtrates were washed with cold 1 N HCl (twice), saturated aqueous $NaHCO_3$ (twice), and aqueous NaCl (twice). The organic phase was filtered and the solvent removed to afford a crude product which was purified by reversed-phase HPLC in MeOH/H_2O mixtures.

(*S*)-Tris(*O*-methylmandelate) from (2*R*,4*R*)-(−)-Pentanediol. ^1H NMR (Cl_3CD): 7.39 (m, 10 H, arom), 5.00 (m, 2 H, H2 and H4), 4.73 (s, 2 H, H_α mandel), 3.41 (s, 6 H, OMe mandel), 1.75 (t, 2 H, J = 6.8 Hz, H3), 1.06 (d, 6 H, J = 6.1 Hz, H1 and H5).

(*R*)-Tris(*O*-methylmandelate) from (2*R*,4*R*)-(−)-Pentanediol. ^1H NMR (Cl_3CD): 7.37 (m, 10 H, arom), 4.65 (s, 2 H, H_α mandel), 4.64 (m, 2 H, H2 and H4), 3.37 (s, 6 H, OMe mandel), 1.62 (t, 2 H, J = 6.8 Hz, H3), 1.07 (d, 6 H, J = 6.1 Hz, H1 and H5).

(*S*)-3-*O*-Methylmandelate from Onchitriol I A (15). ^1H NMR (Cl_3CD): 7.30 (m, 5 H, arom), 5.59 (bd, 1 H, J = 8.8 Hz, H11), 5.33 (dd, 1 H, J = 10.2, 2.0 Hz, H15), 5.13 (ddd, 1 H, J = 4.0, 8.3, 9.3, H3), 4.79 (s, 1 H, H_α mandel), 4.74 (d, 1 H, J = 10.7

Hz, H13), 3.76 (dd, 1 H, J = 8.8, 7.0 Hz, H10), 3.54 (s, 3 H, OMe mandel), 3.20 (m, 1 H, H16), 3.04 (dd, 1 H, J = 9.3, 7.0 Hz, H4), 2.60 (q, 2 H, J = 7.4 Hz, H22), 2.10 (m, 1 H, H14), 1.97 (s, 6 H), 1.96 (s, 6 H), 1.87 (s, 3 H), 1.78 (s, 3 H), 1.62 (d, 3 H, J = 1.1 Hz, Me28), 1.42 (m, 2 H, H2), 1.28 (d, 3 H, J = 7.0 Hz, Me27), 1.20 (m, 3 H, Me30), 0.84 (m, 3 H, Me29), 0.82 (d, 3 H, J = 6.9 Hz, Me24), 0.80 (t, 3 H, J = 7.3 Hz, Me1). HREIMS: $C_{45}H_{60}O_{11}$ calcd 776.4135. Found: 776.4153. FABMS (+) m/z: 777 (100), 749 (5), 717 (9), 657 (6), 551 (6), 491 (8), 301 (9), 225 (39), 209 (9), 193 (14), 180 (20), 179 (9), 155 (30), 121 (58).

(*R*)-3-*O*-Methylmandelate from Onchitriol I A (16). ^{1}H NMR (Cl_3CD): 7.31 (m, 5 H, arom), 5.62 (bd, 1 H, J = 8, 8 Hz, H11), 5.34 (dd, 1 H, J = 10.2, 2.0 Hz, H15), 5.11 (ddd, 1 H, J = 4.0, 8.3, 9.3 Hz, H3), 4.78 (s, 1 H, H_α mandel), 4.76 (d, 1 H, J = 10.7 Hz, H13), 3.81 (dd, 1 H, J = 8.8, 7.0 Hz, H10), 3.54 (s, 3 H, OMe mandel), 3.20 (m, 2 H, H16, H4), 2.61 (q, 2 H, J = 7.4 Hz, H22), 2.13 (m, 1 H, H14), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H), 1.94 (s, 3 H), 1.91 (s, 3 H), 1.78 (s, 3 H), 1.64 (d, 3 H, J = 1.1 Hz, Me28), 1.28 (m, 2 H, H2), 1.28 (d, 3 H, J = 7.0 Hz, Me27), 1.20 (d, 3 H, J = 6.9 Hz, Me24), 1.18 (m, 3 H, Me30), 0.84 (m, 3 H, Me29), 0.46 (t, 3 H, J = 7.3 Hz, Me1). HREIMS: $C_{45}H_{60}O_{11}$ calcd 776.4135. Found: 776.4118. FABMS (+) m/z: 777 (100), 749 (3), 717 (6), 657 (4), 551 (2), 491 (6), 301 (7), 225 (37), 209 (7), 193 (12), 180 (19), 179 (9), 155 (30), 121 (58).

(*R*)-3,13,15-Tris(*O*-methylmandelate) from Onchitriol I (18). ^{1}H NMR (Cl_3CD): 7.30 (m, arom), 5.55 (bd, 1 H, J = 8.8 Hz, H11), 5.33 (dd, J = 9.9, 1.8 Hz, H15), 5.13 (m, 1 H, H3), 4.80 (s, 1 H, H_α mandel), 4.71 (s, 1 H, H_α mandel), 4.62 (s, 1 H, H_α mandel), 4.56 (d, 1 H, J = 10.8 Hz, H13), 3.48 (s, 3 H, OMe mandel), 3.43 (s, 3 H, OMe mandel), 3.31 (s, 3 H, OMe mandel), 3.18 (m, 1 H, H16), 3.10 (m, 1 H, H4), 2.57 (m, 2 H, H22), 1.97 (s, 6 H), 1.96 (s, 6 H), 1.86 (s, 3 H), 1.79 (s, 3 H), 0.80 (d, J = 7.0, 3 H, Me29), 0.48 (t, 3 H, J = 7.3 Hz, Me1). HREIMS: $C_{59}H_{72}O_{13}$; calcd 988.4973. Found: 988.5031. EIMS m/z: 988 (1), 823 (2), 657 (1), 577 (1), 491 (2), 251 (5), 221 (4), 180 (5), 151 (3), 121 (100).

(*S*)-3,13,15-Tris(*O*-methylmandelate) from Onchitriol I (17). ^{1}H NMR (Cl_3CD): 7.30 (m, arom), 5.57 (bd, 1 H, J = 8.8 Hz, H11), 5.19 (dd, J = 9.9, 1.8 Hz, H15), 5.07 (m, 1 H, H3), 4.79 (s, 1 H, H_α mandel), 4.69 (s, 1 H, H_α mandel), 4.63 (s, 1 H, H_α mandel), 4.49 (d, 1 H, J = 10.8 Hz, H13), 3.48–3.30 (3 s, 3 OMe mandel), 2.55 (m, 2 H, H22), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 0.80 (t, 3 H, J = 7.3 Hz, Me1), 0.76 (d, J = 7.0, 3 H, Me29), 0.80 (t, 3 H, J = 7.3 Hz, Me1). HREIMS: $C_{59}H_{72}O_{13}$ calcd 988.4973. Found: 988.5029.

(*S*)-3,13-Bis(*O*-methylmandelate) from Onchitriol II A (20). ^{1}H NMR (Cl_3CD): 7.28 (m, 10 H, arom), 5.38 (bd, 1 H, J = 9.4 Hz, H11), 5.29 (dd, 1 H, J = 10.2, 1.6 Hz, H15), 5.14 (m, 1 H, H3), 4.94 (d, 1 H, J = 10.6 Hz, H13), 4.76 (s, 1 H, H_α mandel), 4.65 (s, 1 H, H_α mandel), 3.54 (m, 1 H, H10), 3.25 (m, 1 H, H16), 3.23 (s, 3 H, OMe mandel), 3.15 (m, 1 H, H4), 2.56 (q, 2 H, J = 7.5 Hz, H22), 2.25 (m, 1 H, H14), 1.96 (s, 3 H), 1.92 (s, 3 H), 1.82 (s, 3 H), 1.80 (s, 3 H), 1.63 (m, 2 H, H2), 1.60 (s, 3 H), 1.52 (d, 3 H, J = 1.2 Hz, Me28), 1.22 (d, 3 H, J = 7.0 Hz, Me30), 1.21 (t, 3 H, J = 7.5 Hz, Me23), 1.13 (d, 3 H, J = 6.9 Hz, Me28), 1.03 (d, 3 H, J = 6.9 Hz, Me24), 0.91 (d, 3 H, J = 6.9 Hz, Me29), 0.88 (t, 3 H, J = 7.3 Hz, Me1). HREIMS: $C_{52}H_{66}O_{12}$ calcd 882.4554. Found: 882.4558. FABMS (+) m/z: 883 (53), 805 (15), 791 (7), 717 (15), 657 (19), 491 (9), 209 (12), 180 (21), 179 (11), 151 (10), 121 (100).

(*R*)-3,13-Bis(*O*-methylmandelate) from Onchitriol II A (21). ^{1}H NMR (Cl_3CD): 7.28 (m, 10 H, arom), 5.42 (bd, 1 H, J = 9.4 Hz, H11), 5.22 (dd, 1 H, J = 10.2, 1.6 Hz, H15), 5.07 (m, 1 H, H3), 4.85 (d, 1 H, J = 10.6 Hz, H11), 4.79 (s, 1 H, Hα mandel), 4.60 (s, 1 H, Hα mandel), 3.54 (m, 1 H, H10), 3.52 (s, 3 H, OMe mandel), 3.25 (m, 3 H, H16), 3.24 (m, 3 H, OMe mandel), 3.04 (m, 1 H, H4), 2.60 (q, 2 H, J = 7.4 Hz, H22), 2.25 (m, 1 H, H14), 1.96 (s, 3 H), 1.94 (s, 3 H), 1.93 (s, 3 H), 1.91 (s, 3 H), 1.81 (s, 3 H), 1.76 (s, 3 H), 1.55 (d, 3 H, J = 1.2 Hz Me28), 1.54 (m, 2 H, H2), 1.20 (t, 3 H, J = 7.4 Hz, Me23), 1.15 (d, 6 H, J = 6.9 Hz, Me24, Me30), 1.12 (d, 3 H, J = 7.0 Hz, Me27), 0.85 (d, 3 H, J = 6.9 Hz, Me29), 0.63 (t, 3 H, J = 7.3 Hz, Me1). HREIMS: $C_{52}H_{66}O_{12}$ calcd 882.4554. Found: 882.4561. FABMS (+) m/z: 883 (50), 805 (17), 791 (9), 717 (16), 657 (20), 491 (10), 209 (13), 180 (23), 179 (15), 151 (8), 121 (100).

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Supplementary Material Available: All NMR spectra of **4–14** and **19** (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Intramolecular Photocycloaddition Reactions of 3-(2-Propenoxy)cyclopent-2-en-1-ones and 3-(2-Propenoxy)cyclohex-2-en-1-ones

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The 3-oxa-1,5-hexadienones **4a**, **4b**, **5a**, and **5b** undergo intramolecular [2 + 2] photocycloaddition reactions with quantum yields ranging from 0.2 to 0.002. In general, oxa substitution decreases the quantum yields and favors the formation of crossed closure products in comparison to the alkenyl analogs. Irradiation of stereospecifically deuterated dienones **11a** and **12a** indicate that the intermediate biradical reverts to the starting dienone faster than it proceeds to product. The results are compared with the analogous alkenyl systems. An explanation for changes in regiochemistry, quantum yields, and reversion rates between the two systems is offered.

Enone–alkene [2 + 2] photocycloadditions reactions continue to be the subject of many mechanistic and synthetic studies.[1-4] The utility of this reaction is founded on the predictable manner in which complex ring systems

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