Cyclic Polyketide Peroxides and Acyclic Diol Analogues from the Sponge *Plakortis lita*

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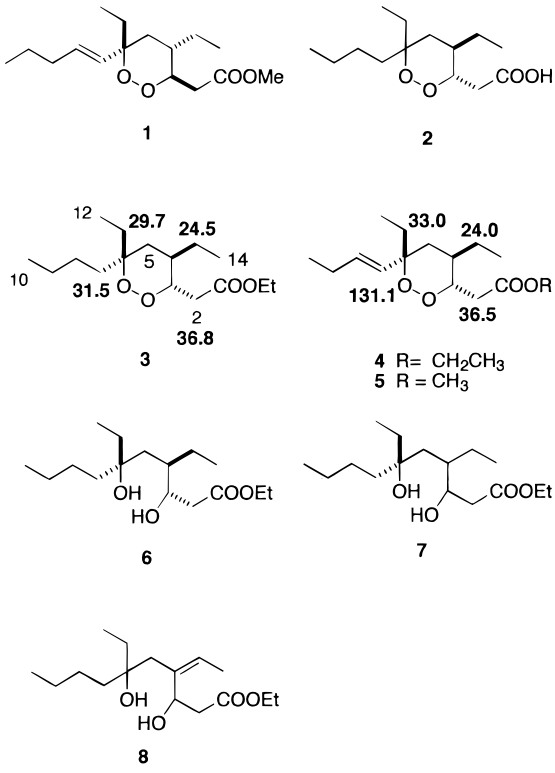
The sponge *Plakortis lita* from Papua New Guinea is a source of three cyclic peroxides—ethyl plakortide Z (**3**), ethyl didehydroplakortide Z (**4**), and methyl didehydroplakortide Z (**5**)—and three acyclic diol analogues—ethyl *seco*-plakortide Z (**6**), *epi*-ethyl *seco*-plakortide Z (**7**), and ethyl didehydro-*seco*-plakortide Z (**8**). The absolute stereochemistry at the three chiral sites of **3** was assigned by preparing **6**, which was investigated using the refined Mosher's method. Compounds **4**, **5**, and **6** were also concluded to have the same absolute stereochemistry as **3**. The cyclic peroxides were generally cytotoxic, while the acyclic analogues were devoid of activity. Compound **3** was equally active *in vitro* against solid tumor and L-1210 leukemia cell lines. Alternatively, **4** was observed *in vitro* to be moderately solid-tumor selective but did not exhibit *in vivo* activity against solid tumors in mice.

A variety of stable cyclic polyketide peroxides, sometimes accompanied by acyclic diol analogues, are usually isolated from *Plakortis* marine sponges. In most cases the 1,2-dioxane ring oxygens are flanked by an HOAc residue and two geminal aliphatic groups.[1] Plakortin, the first such compound, described in 1978, was obtained from a Caribbean *Plakortis halichondrioides*.[2] Subsequently, many related polyketide peroxides, such as plakortin derivatives **1**[3] and **2**,[4] were reported, and the long aliphatic side chain serves as a principal locus for structural variation. Our 1995 publication of plakortolide E,[5] from an Indo-Pacific *Plakortis*, illustrated additional themes on how the peroxide ring substituents can vary while also showing that further discoveries could be made from this genus. Stimulated by the latter discovery we began a chemical study on *Plakortis lita* (family Plakinidae) obtained from Papua New Guinea (PNG). Known constituents of this species, obtained from Truk[6] and Okinawa,[7] consisted of polyketide butenolides, the chondrillins, which are cyclic peroxides related to plakortin, and a series of novel peroxy aliphatic esters related to the chondrillins. Disclosed below are the new metabolites that were present in our collection, including cyclic peroxides [ethyl plakortide *Z* (**3**), ethyl didehydroplakortide *Z* (**4**), and methyl didehydroplakortide *Z* (**5**)] and their ring-opened analogues [ethyl *seco*-plakortide *Z* (**6**), *epi*-ethyl *seco*-plakortide *Z* (**7**), and ethyl didehydro-*seco*-plakortide *Z* (**8**)].

The PNG collection of *P. lita* (1.0 kg wet wt, coll. no. 96178) was preserved according to our standard procedures.[8] The extract afforded an oil that was purified by flash chromatography (gradient of EtOAc−hexane) followed by reversed-phase HPLC (MeOH−H_2O 75:25) to yield compounds **3**−**8**. The structure determination commenced with ethyl plakortide Z (**3**), $[\alpha]^{25}_D$ +58.8°, isolated as a yellow oil whose molecular formula was established as $C_{16}H_{30}O_4$ by HRCIMS. Consistent with prior compounds from this genus were that the two degrees of unsaturation could be ascribed to an ethyl ester carbonyl (δ 170.9) and a 1,2-dioxane ring (δ 83.3 and 82.1). Three additional ethyl groups were evident from sets of triplets in the ^{1}H NMR spectrum (Table 1). Upfield ^{13}C NMR shifts of two methyls (δ 7.4 and 10.8) indicated their attachment to a quaternary and tertiary carbon center, respectively, while the remaining methyl (δ 14.2) had to be the terminus of a chain of three or more methylenes (Table 2). Collectively, these features, along with the additional NMR properties, supported that the gross structure **3** was identical to that of **2**.



A similar approach to that employed above was used to establish the structure of compounds **4** and **5**. The former compound, of formula $C_{16}H_{28}O_4$ and $[\alpha]^{25}_D$ +81.5°, was isolated as a yellow oil. It was presumed to be a dehydro analogue of **3**. Consistent with this was that the ^{1}H NMR data of **4** contained resonances for four 1,2-dioxane substituents each terminating in an ethyl group. In addition, the collective HMBC and ^{1}H−^{1}H COSY data substantiated the location of a *trans*-double bond (δ 5.50, J = 16.5 Hz, H7) as shown in structure **4**.

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Table 1. ^{1}H NMR Assignments for Compounds **3**, **4**, **6**, **7**, and **8** ($CDCl_3$) at 500 MHz

H no.	3	4	6	7	8
2	2.40 dd, 16.0, 8.5 2.63 dd, 16.0, 3.5	2.31. dd, 15.5, 9.5 2.61 dd, 15.5, 3.0	2.40 dd, 16.0, 9.5 2.63 dd, 16.0, 2.5	2.37 dd, 16.5, 1.0 2.60 dd, 16.5, 11.0	2.42 dd, 16.0, 4.0 2.80 dd, 16.0, 9.5
3	4.17 m	4.23 dt, 3.0, 9.5	3.86 ddd, 10.0, 7.5, 2.5	4.19 m	5.05 dd, 9.5, 3.5
4	1.67 m	1.62 m	1.67 m	1.92 m	
5	1.21 t, 13.5 1.81 dd, 13.5, 4.5	1.30 t, 13.0 2.05 dd, 13.0, 4.5	1.50 m 1.69 m	1.40 dd, 2.5, 15.0 1.55 m	2.17 d, 14.0 2.34 d, 14.0
7	1.57 m 1.81 m	5.50 d, 16.5	1.51 m	1.51 m	1.52 m
8	1.15 m 1.33 m	5.53 dt, 16.5, 5.5	1.30 m	1.30 m	1.30 m
9	1.34 m 1.35 m	2.12 dq, 5.5, 7.5	1.31 m	1.23 m 1.30 m	1.30 m
10	0.94 t, 7.5	1.03 t, 7.5	0.92 t, 7.5	0.91 t, 7.5	0.90 t, 7.5
11	1.39 m 1.55 m	1.48 m	1.49 m	1.51 m	1.51 m
12	0.87 t, 7.5	0.85 t, 7.5	0.89 t, 7.5	0.91 q, 7.5	0.91 t, 7.5
13	1.11 m 1.44 m	1.15 m 1.49 m	1.46 m	1.23 m	5.39 q, 7.0
14	0.92 t, 7.5	0.94 t, 7.5	0.91 t, 7.5	0.96 t, 7.5	1.72 d, 7.0
15	4.17 q, 8.0	4.17 q, 7.5	4.18 q, 7.5	4.19 q, 7.5	4.18 q, 7.5
16	1.28 t, 8.0	1.27 t, 7.5	1.28 t, 7.5	1.29 t, 7.5	1.28 t, 7.5

The other compound (**5**), $[\alpha]^{25}_D$ +67.3° and of formula $C_{15}H_{26}O_4$, was clearly the methyl ester analogue of **4**.

The structures of the three diols **6**−**8** were dealt with next. The first of these (**6**), $[\alpha]^{25}_D$ −24.2° and of formula $C_{16}H_{32}O_4$, was concluded to be a diol because two hetero atom protons were deduced to be present from the APT formula of $C_{16}H_{30}$. NMR resonances were observed for the four terminal ethyl groups. This, plus the observation that the ^{13}C NMR shifts of **6** were similar to those of **3**, with the most prominent difference being the two oxygen-bearing carbons C-3 (δ 71.3) and C-6 (δ 73.6), justified the gross structure proposed. Characterization of the remaining two compounds, **7** and **8**, was not straightforward inasmuch as they were obtained as a 1:1 mixture. This was recognized by the LRESIMS data, which displayed two intense $[M + H]^+$ peaks at *m*/*z* 289 and 287, intimating formulas of $C_{16}H_{32}O_4$ and $C_{16}H_{30}O_4$ for **7** and **8**, respectively. The assumption that **6** and **7** were diastereomers was reasonable because they had different HPLC retention times. The NMR resonances ascribed for **7** could be identified in the mixture based on the similarity of its shifts to those of **6**. The remaining signals were ascribed to **8**. In addition, the location and nature of the *Z*-double bond in **8** was established by the NOESY correlations observed from H-5, H-5′ to H-13. Finally, the NMR resonances assigned to **8** were consistent with those in the literature for the cyclic carboxylic acid analogue.[4]

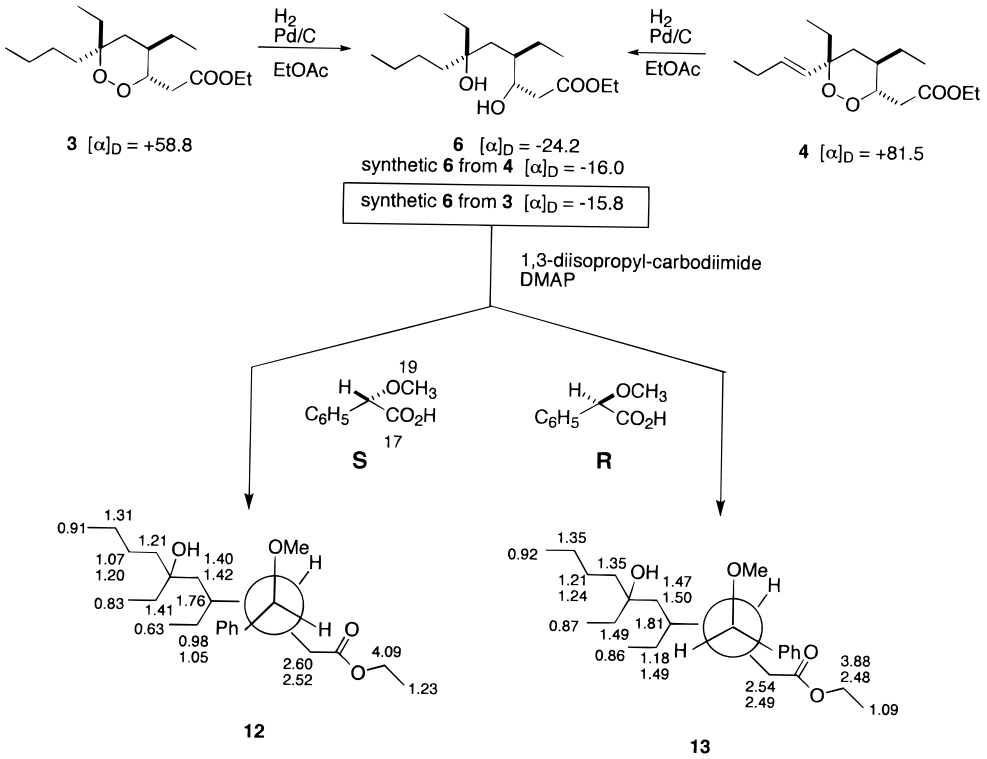
Attention was next shifted to establishing the relative stereochemical features of peroxides **3** and **4**. Proton NMR data was of limited utility because the complex first-order spectra were too convoluted to interpret easily. Considering compound **3** first, equatorial stereochemistry was easily set for the C-13 ethyl group by the H-5 triplet resonance (δ 1.21, J = 13.5 Hz), arising in part due to the axial−axial coupling between H-5 and H-4. Correlating the ^{13}C δs of the $-CH_2-$ positions for each of the ring substituents with values diagnostic of axial−equatorial orientation provided a direct way to assign relative stereochemistry. The equatorial−axial base values were derived from the data of known compounds **9**−**11**,[9] which featured downfield equatorial−upfield axial shift relationships by position as follows [equatorial−axial]: C-2 (δ 37/31), C-7 (δ 36/32), C-11 (δ 30/25), and C-13 (δ 25/−). Thus, in **3** equatorial methylene substituents were assigned at C-2 (δ 36.8), C-11 (δ 29.7), and C-13 (δ 24.5); while an axial residue was proposed at C-7 (δ 31.5). Similarly, in **4** equatorial methylene substituents were assigned at C-2 (δ 36.5), C-11 (δ 33.0), and C-13 (δ 24.0), while an axial residue was proposed at C-7 by default.

Table 2. ^{13}C NMR Assignments for Compounds **3**, **4**, **6**, **7**, and **8** ($CDCl_3$) at 125 MHz

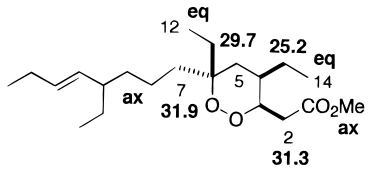
C no.	3	4	6	7	8
1	170.9 s	170.0 s	173.5 s	173.9 s	172.8 s
2	36.8 t	36.5 t	39.6 t	35.8 t	40.7 t
3	82.1 d	82.3 d	71.3 d	70.5 d	65.7 d
4	36.5 d	36.9 d	39.4 d	39.7 d	136.1 s
5	36.3 t	36.0 t	40.3 t	38.6 t	42.3 t
6	83.3 s	84.1 s	73.6 s	73.6 s	74.3 s
7	31.5 t	131.1 d	37.7 t	37.0 t	37.0 t
8	25.6 t	133.0 d	26.2 t	26.1 t	26.7 t
9	23.4 t	25.8 t	23.4 t	23.4 t	23.4 t
10	14.2 q	14.0 q	14.2 q	14.2 q	14.2 q
11	29.7 t	33.0 t	33.2 t	33.0 t	32.4 t
12	7.4 q	7.4 q	8.0 q	8.0 q	8.0 q
13	24.5 t	24.0 t	25.6 t	26.4 t	127.3 d
14	10.8 q	10.6 q	10.5 q	12.6 q	13.5 q
15	60.9 t	60.9 t	60.8 t	60.8 t	60.8 t
16	14.3 q	14.3 q	14.2 q	14.2 q	14.2 q

The absolute stereochemistry of **3**−**6** was determined by employing the refined Mosher's empirical shift correlation method.[10−13] This involved separate conversion of **3** and **4** to **6**, and the latter compound was used to prepare the corresponding *O*-methylmandelate derivatives (Scheme 1). Parallel hydrogenation (palladium on charcoal) of **3** and **4** gave two samples of semisynthetic **6**, which were identical by ^{1}H and ^{13}C NMR to natural **6**. The optical rotation of the reduction products were $[\alpha]^{25}_D$ −15.8° and $[\alpha]^{25}_D$ −16.0°, respectively, which compare closely to that of natural **6** ($[\alpha]^{25}_D$ −24.2°). Standard methods were used to convert **6** to **12** and **13**, respectively. Analysis of the differential ^{1}H NMR resonances of the (*S*)- and (*R*)-*O*-methylmandelic esters **12** and **13** led to the designation of (3*S*)-stereochemistry in **3**, **4**, and **6**. The key observations in support of this conclusion are shown in Scheme 1 and include variations in the chemical shifts between (*S*)-mandelate **12**: δ 2.60/2.52 (H-2/H-2′) and δ 1.76 (H-4) and the (*R*)-mandelate **13**: δ 2.54/2.49 (H-2/H-2′) and δ 1.81 (H-4). The juxtaposition of the (*R*)-mandelate phenyl in proximity to H-2/H-2′ is required to rationalize their relative upfield shifts, which is only possible for (3*S*)-stereochemistry. Based on this assignment and the known

Scheme 1. Formation of *O*-Methylmandelic Esters to Determine Absolute Configuration



relative stereochemistry of **3**, **4**, and **6**, the absolute stereochemistry of all three compounds can be designated as (3*S*), (4*R*), and (6*R*) for **3** and **6** and (3*S*), (4*R*), and (6*S*) for **4**. Furthermore, the absolute stereochemistry of **4** and **5** are presumed to be the same based on their comparable optical rotation data (**4**, $[\alpha]^{25}_D$ +81.5; **5**, $[\alpha]^{25}_D$ +67.3). Finally, it is assumed that the C-6 absolute stereochemistry in **6** is conserved in **7**, because the largest differences in the NMR shifts occurred away from this center and included C-2 (**6**, δ 39.6; **7**, 35.8), H-3 (**6**, δ 3.86; **7**, 4.19), H-4 (**6**, δ 1.67; **7**, 1.92), C-5 (**6**, δ 40.3; **7**, 38.6), H_2-5 (**6**, δ 1.50, 1.69; **7**, 1.40, 1.55), H_2-13 (**6**, δ 1.46; **7**, 1.23), and C-14 (**6**, δ 10.5; **7**, 12.6).



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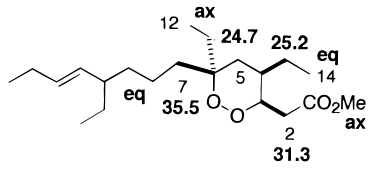

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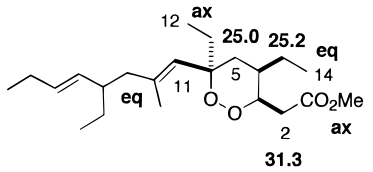

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Initial bioassay studies revealed that the hexane-soluble fraction was slightly tumor selective in the Corbett−Valeriote soft agar disk diffusion assay.[14] Ideally, a zone differential of 250 units between the response of a compound in solid tumor cell lines (such as mouse pancreatic PO3, human colon H-116 or human lung H-125), vs leukemia L-1210 cells, is expected for designation as "solid tumor selective activity." Further fractionation revealed that **3** and **4** were the active constituents. Their relative zone sizes observed in the soft agar assay are as follows (mg/disk: L-1210/PO3/H-116 or H-125): **3** 200: 500/500/410, which indicates equal cytotoxicity; and **4** 180: 360/580/300, which indicates moderate solid-tumor selectivity. The mild tumor selectivity of **4** was the stimulus for a follow-up *in vivo* study. This was conducted over a period of 31 days in mice carrying a PO3 tumor burden and utilized a total dosage of 304.5 mg/kg of **4**. At the end of the trial, however, no antitumor activity was detected. Continuing a trend in which the peroxide functionality is vital to biological activity, the fractions containing the acyclic forms of the peroxides were found to be inactive in the soft agar assay.

Experimental Section

General Experimental Procedures. The NMR spectra ($CDCl_3$) were recorded at 250 or 500 MHz for ^1H and 62.9 or 125.7 MHz for ^{13}C. Multiplicities of ^{13}C NMR were determined using DEPT-135 data. Final NMR assignments were based on 2D NMR data derived from HMQC, HMBC, and $^1H-^1H$ COSY. LRESIMS and HRCIMS were obtained. Flash column chromatography was carried out on Si gel (200−400 mesh). HPLC was performed with a 10-μm ODS column.

Collection and Identification. Scuba was used to gather the sponge (1.0 kg wet wt, coll. no. 96178), from Papua New Guinea at Wongat Island in the Madang

Lagoon at a depth of 30 feet. It was identified as *Plakortis lita* by Dr. M. C. Diaz (UCSC). The morphology was globular, and other features included a tan internal color, brown external color, smooth surface, and dense texture. At the surface it gave off a profuse complex sweet odor that was terpene-like. The skeletal characteristics and species description of the sponge are in accord with those in the literature of *P. lita*.[15,16] A voucher, as well as an underwater photograph,[17] are in the UCSC sponge collection archives and are available from P.C.

Extraction and Isolation. The specimen was initially preserved according to our standard procedure described elsewhere.[5] On prolonged storage in MeOH the specimen completely disintegrated leaving no recognizable tissue, which is a behavior characteristic of this species. The resultant slurry was thus dried and then partially redissolved by successive tritration in MeOH and CH_2Cl_2. The MeOH fraction (7.86 g) was solvent partioned to obtain a hexane partition fraction (3.18 g) that was slightly active against a PO3 line in an in vitro test for diifferential cytotoxity.[14] This oil was then subjected to flash chromatography on Si gel and eluted with hexane−EtOAc of increasing polarity. The resulting flash fractions were then further purified by reversed-phase HPLC (75:25 MeOH−H_2O) to afford 140.6 mg of ethyl plakortide Z (**3**), 74.5 mg of ethyl didehydroplakortide Z (**4**), 3.1 mg of methyl didehydroplakortide Z (**5**), 10.7 mg of ethyl *seco*-plakortide Z (**6**), and a 32.6-mg mixture of *epi*-ethyl *seco*-plakortide Z (**7**) and ethyl didehydro-*seco*-plakortide Z (**8**).

Ethyl plakortide Z (3): yellow oil; $[\alpha]^{25}_D$ +58.8° (*c* 6.8, CH_2Cl_2); IR (neat) ν_{max} 2948, 1740, 1457, 1181 cm^{-1}; LRESIMS, positive ion, *m*/*z* $[M + Na]^+$ 309 (100), 241 (19), 167 (27), 139 (30); ^1H and ^{13}C NMR data, Tables 1 and 2; HRCIMS in methane gas, *m*/*z* 315.2449 $[M + C_2H_5]^+$ (calcd for $C_{18}H_{35}O_4$, 315.2535).

Ethyl didehydroplakortide Z (4): yellow oil; $[\alpha]^{25}_D$ +81.5° (*c* 1.7, CH_2Cl_2); IR (neat) ν_{max} 2948, 1740, 1463, 1175 cm^{-1}; LRESIMS, positive ion, *m*/*z* $[M + Na]^+$ 307 (100), 213 (53), 167 (55), 139 (97); ^1H and ^{13}C NMR data, Tables 1 and 2; HRCIMS in methane gas, *m*/*z* 313.2372 $[M + C_2H_5]^+$ (calcd for $C_{18}H_{33}O_4$, 313.2379).

Methyl didehydroplakortide Z (5): yellow oil; $[\alpha]^{25}_D$ +67.3° (*c* 0.4, CH_2Cl_2); IR (neat) ν_{max} 2948, 1744, 1458, 1181 cm^{-1}; LRCIMS, positive ion, *m*/*z* $[M - H_2O + H]^+$ 253 (21), 225 (55), 199 (100), 167 (76), 151 (62); ^1H and ^{13}C NMR data, identical to **4**, as shown in Tables 1 and 2 except for C-16 (^1H, δ 3.81 s; ^{13}C, 51.9) and the absence of C-15; HRCIMS in methane gas, *m*/*z* 253.1795 $[M - H_2O + H]^+$ (calcd for $C_{15}H_{25}O_3$, 253.1790).

Ethyl *seco*-plakortide Z (6): gold oil; $[\alpha]^{25}_D$ −24.2° (*c* 1.1, CH_2Cl_2); IR (neat) ν_{max} 3340, 2969, 1734, 1450 cm^{-1}; LRCIMS, positive ion in methane gas, *m*/*z* $[M - H_2O + H]^+$ 271 (96), 253 (100), 213 (42), 183 (83); ^1H and ^{13}C NMR data, Tables 1 and 2; HRCIMS in methane gas, *m*/*z* 271.2276 $[M - H_2O + H]^+$ (calcd for $C_{16}H_{31}O_3$, 271.2273).

Ethyl *seco*-plakortide Z (7) and ethyl didehydro-*seco*-plakortide Z (8): a mixture and yellow oil; IR (neat) ν_{max} 3360, 2960, 2349, 1734, 1457, 1170 cm^{-1}; LRESIMS, positive ion, *m*/*z* $[M + H]^+$ 289 (34), $[M + H]^+$ 287 (33), 597 (38), 271 (100); 269 (51), 251 (41); ^1H and ^{13}C NMR data, Tables 1 and 2; HRCIMS in methane gas, *m*/*z* 285.2058 $[M - H]^+$ (calcd for $C_{16}H_{20}O_4$, 285.2066).

Conversion of 3 to 6. Compound **3** (17.3 mg), dissolved in 10 mL of EtOAc, was placed in a round-bottom flask, and a spatula tip of palladium on activated charcoal was added. The flask was then exposed to hydrogen gas and stirred for 24 h. The resulting solution was filtered and extracted with CH_2Cl_2 to give 16.3 mg of **6**, an oil of $[\alpha]^{25}_D$ −15.8 (*c* 1.63, CH_2Cl_2); the ^1H and ^{13}C NMR data were identical to **6**.

Conversion of 4 to 6. Compound **4** (14.0 mg), dissolved in 10 mL of EtOAc, was placed in a round-bottom flask, and a spatula tip of palladium on activated charcoal was added. The flask was then exposed to hydrogen gas and stirred for 24 h. The resulting solution was filtered and extracted with CH_2Cl_2 to give 12.0 mg of **6**, an oil of $[\alpha]^{25}_D$ −16.0° (*c* 1.2, CH_2Cl_2); the ^1H and ^{13}C NMR data were identical to **6**.

Conversion of 6 to Mandelate Esters (*S*)-12 and (*R*)-13. Both *R*-(+) and *S*-(−) mandelic esters **12** and **13** were prepared in the same fashion. Synthetic **6** derived from **3** was dissolved in 0.5 mL of CH_2Cl_2, and spatula-tip amounts of 1,3-diisopropylcarbodiimide, DMAP, and either the (*R*)- or (*S*)-mandelic acid were added. The reaction was stirred for 36 h at room temperature, then filtered and evaporated. The resulting liquid was subjected to reversed-phase HPLC (80:20 MeOH−H_2O) to give pure mandelic esters **12** and **13** (see Scheme 1).

Mandelic ester (*R*)-13: ^1H NMR data in Scheme 1; ^{13}C ($CDCl_3$) δ 170.7 (C-1), 74.6 (C-6), 74.3 (C-3), 60.7 (C-15), 38.8 (C-7), 38.5 (C-4), 37.6 (C-5), 35.0 (C-2), 32.4 (C-11), 26.2 (C-8), 24.0 (C-13), 23.3 (C-9), 14.2 (C-10), 14.1 (C-16), 12.2 (C-14), 8.0 (C-12), also see *O*-methylmandelate for ^{13}C NMR data.

Mandelic ester (*S*)-12: ^1H NMR data in Scheme 1; ^{13}C ($CDCl_3$) δ 170.7 (C-1), 74.4 (C-6), 73.7 (C-3), 60.7 (C-15), 38.4 (C-7), 38.3 (C-4), 37.2 (C-5), 35.3 (C-2), 32.4 (C-11), 26.1 (C-8), 23.6 (C-13), 23.2 (C-9), 14.1 (C-10), 14.1 (C-16), 11.6 (C-14), 7.8 (C-12), also see *O*-methylmandelate for ^{13}C NMR data.

***O*-Methylmandelate (*R*), (*S*):** ^1H NMR ($CDCl_3$) δ 3.42 (3H, s, Me-19), 4.75 (1H, s, H-18), 7.35 (3H, m, H-23), 7.36 (3H, d, J = 7.5 Hz, H-21), 7.37 (3H, d, J = 7.5 Hz, H-25), 7.43 (3H, d, J = 7.5 Hz, H-22), 7.44 (3H, d, J = 7.5 Hz, H-24); ^{13}C NMR δ 57.3 (C-19), 82.5 (C-18), 127.2 (C-22, C-24), 128.6 (C-21, C-25), 128.8 (C-23), 136.3 (C-20), 170.3 (C-17).

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