Stereochemistry and Biosynthesis of Terpestacin, a New Syncytium Formation Inhibitor

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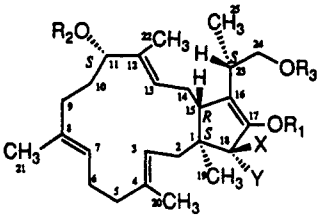
The absolute configuration of terpestacin (1), a fungal metabolite with syncytium formation inhibitory activity, was determined by means of NMR technique and X-ray single-crystal analysis. Its biosynthetic pathway was elucidated by the incorporation experiments of ^{13}C-labeled acetates.

Since AIDS is currently the most serious life-threatening viral infection, the need for effective antiviral agents is even increasing. Research on the disease has indicated that human immunodeficiency virus (HIV) is the major etiological agent of AIDS. The HIV envelope glycoprotein, gp-160, is essential for the viral entry into cells and the gp-120 expressed on HIV-infected cells interacts with CD4, the surface antigen on the target human T cells. This interaction proceeds through a post-binding fusion event mediated by the HIV transmembrane protein gp-41, leading to a multinucleated giant cell called syncytium[1] which results in eventual cell death. From this point of view, syncytium formation inhibitors are potential anti-HIV agents.

In an earlier paper,[2] we reported the taxonomy of the producing organism and the fermentation, isolation, and activity of a new syncytium formation inhibitor, terpestacin (1), isolated from *Arthrinium* sp. FA 1744 (ATCC 74132). The paper also established that 1 belongs to the sesterterpene group of antibiotic having a novel bicyclic 5- and 15-membered ring skeleton. Here, we wish to report the determination of the absolute configuration of 1 by chemical and X-ray experiments. Upon establishment of the absolute configuration, the chirality of C1 and C15 in 1 was found to be opposite to that of the known sesterterpenes, retigeranic acid (16)[3] and variculanol (17).[4] The incorporation of [^{13}C]acetates into 1 was carried out, allowing establishment of its biosynthetic pathway.

Results and Discussion

All carbon and proton signals of 1 in chloroform-*d* were unambiguously assigned by means of ^1H–^1H COSY, ^{13}C–^1H COSY, and ^{13}C–^1H long-range COSY spectra as shown in Table I. Three trisubstituted double bonds (Δ^3, Δ^7, and Δ^{12}) and four asymmetric carbons (C1, C11, C15, and C23) were identified by NMR. The high-field chemical shifts of C20 (δ 15.29), C21 (δ 15.53), and C22 (δ 10.36) in the ^{13}C NMR spectrum established *E* geometry[5] for the three double bonds to which they were attached. ^1H–^1H NOE difference spectroscopy and scalar coupling constants were used to determine the relative configuration at C1 and C15 using Dreiding models. In the ^1H NMR of 1, the signals at δ 2.71 (15-H) and 1.92 (14-H_α) were coupled to each other with J = 11.2 Hz, indicated their trans relationship. Strong NOE between 19-H (δ 1.00) and 14-H_α suggested a trans fusion of the 5- and 15-membered rings.



1 ; R^1=R^2=R^3=H, X,Y=O

3 ; R^1=H, R^2=Me, R^3=H, X,Y=O

7 ; R^1=R^2=H, R^3=Tr, X,Y=O

8a ; R^1=H, R^2=(*R*)-O-Methylmandeloyl, R^3=Tr, X,Y=O

8b ; R^1=H, R^2=(*S*)-O-Methylmandeloyl, R^3=Tr, X,Y=O

12 ; R^1=Me, R^2=R^3=H, X,Y=O,

13a ; R^1=Me, R^2=R^3=H, X=OH, Y=H

13b ; R^1=Me, R^2=R^3=H, X=H, Y=OH

14 ; R^1=Me, R^2=H, R^3=Tr, X=OH, Y=H

15 ; R^1=Me, R^2=*p*-Methoxybenzoyl, R^3=Tr, X=*p*-Methoxybenzoyloxy, Y=H

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(2) Submitted for publication.
(3) Kaneda, M.; Takahashi, R., Iitaka, Y., Shibata, S. *Tetrahedron Lett.* **1972**, 4609.
(4) Singh, S. B.; Reamer, R. A.; Zink, D.; Schmatz, D.; Dombrowski, A.; Goetz, M. A. *J. Org. Chem.* **1991**, *56*, 5618.
(5) Nishino, C.; Bowers, W. S. *Tetrahedron* **1976**, *32*, 2875.

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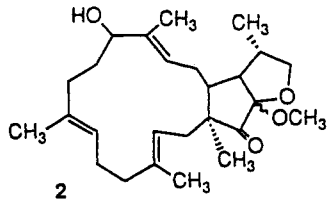
Table I. ^{13}C NMR (100 MHz) and ^{1}H NMR (400 MHz) Assignment of 1 and 4 in $CDCl_3$

	chemical shift (δ, ppm)			
	1		4	
no.	^{13}C	^{1}H (splitting, J, Hz)	^{13}C	^{1}H (spliting, J, Hz)
1	49.02		47.07	
2	39.29	1.72 (dd, J = 7.27, 14.7, Hα), 2.39 (dd, J = 10.7, 14.7, Hβ)	38.19	1.72 (dd, J = 5.53, 14.1, Hα), 2.38 (dd, J = 10.3, 14.1, Hβ)
3	121.57	5.24 (dd, J = 7.27, 10.7)	121.30	5.31 (dd, J = 5.53, 10.3)
4	137.94		138.04	
5	40.29	1.98 (m), 2.28 (m)	40.51	2.08 (m), 2.26 (m)
6	23.82	2.20 (m)	23.83	2.20 (m)
7	124.32	5.13 (m)	124.45	5.19 (m)
8	132.84		132.50	
9	34.88	1.81 (m), 2.08 (m)	36.28	1.86 (m), 1.99 (m)
10	29.77	1.62 (m), 1.81 (m)	21.83	1.57 (m)
11	76.49	4.05 (dd, J = 2.85, 9.95)	35.93	2.11 (m)
12	136.34		142.88	
13	129.02	5.41 (m)	126.73	5.45 (d, J = 7.27)
14	28.79	1.92 (ddd, J = 7.27, 11.2, 17.9, Hα), 2.44 (br d, J = 17.9, Hβ)	78.37	3.68 (dd, J = 7.27, 10.3)
15	49.56	2.71 (dd, J = 2.13, 11.2)	46.80	2.72 (d, J = 10.3)
16	149.66		148.59	
17	146.91		143.61	
18	208.27		207.61	
19	16.24	1.00 (s)	16.21	0.96 (s)
20	15.29	1.63 (s)	15.10	1.65 (s)
21	15.53	1.64 (s)	15.50	1.58 (s)
22	10.36	1.57 (s)	15.47	1.65 (s)
23	37.10	2.64 (m)	30.16	3.10 (dq, J = 3.02, 7.27)
24	65.95	3.82 (dd, J = 5.55, 10.3), 3.88 (dd, J = 5.26, 10.3)	72.15	3.58 (dd, J = 3.02, 11.1, Hα), 3.85 (d, J = 11.1, Hβ)
25	14.33	1.29 (d, J = 7.26)	16.46	1.31 (d, J = 7.27)

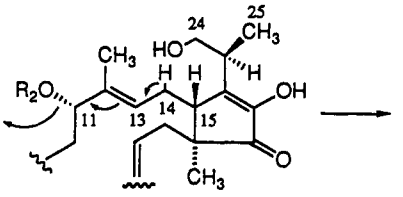
In order to determine the relative configuration at C23 by NMR analysis, preparation of a cyclic compound such as ketal 2 seemed to be useful. Attempts to cyclize 1 using



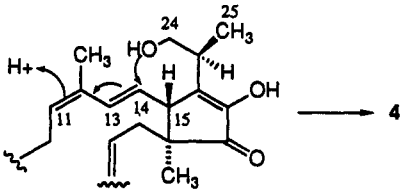
2

hydrochloric acid in methanol did not give 2 but methyl ether 3, whose structure was determined by a comparison of its ^{13}C NMR with that of 1. The presence of a new *O*-methyl signal (δ 55.57) and the lower-field shift of C11 (δ 85.47) in the ^{13}C NMR supported the 11-OMe structure for 3. Further treatment of 3 with *p*-toluenesulfonic acid in methylene chloride yielded a tricyclic ether, 4, which was later found to be produced directly from 1 by *p*-toluenesulfonic acid in methylene chloride. The HR-FAB-MS and ^{13}C NMR of 4 led to the formula $C_{25}H_{36}O_3$, indicating that it was a dehydrated product of 1. However, the presence of the same number of double bonds as those of 1 was seen in the ^{1}H and ^{13}C NMR of 4 (Table I). ^{1}H and ^{13}C NMR of the new compound 4 were very similar to those of the original compounds 1 and 3, except for the remarkable differences in chemical shifts and in coupling patterns of H-C14 and C14 signals. Signals of H-C14 and C14 were strongly shifted downfield to δ 3.68 and 78.37, respectively, compared to those of the parent compounds 1 and 3. Coupling patterns of the adjacent protons H-13 and H-15 showed the presence of only one hydrogen atom at C14. This highly deshielded methine carbon was found to couple to one of protons at C24 (24-H_α, δ 3.85) in the ^{13}C–^{1}H long-range COSY spectrum. The other proton at C24 (24-H_β, δ 3.58, J = 3.02 Hz) was coupled to 23-H (δ 3.10), which in turn coupled to protons of 25-methyl (δ

Scheme I. Proposed Mechanism of Producing 4 from 1 or 3



1 (R_2 = H)
3 (R_2 = CH_3)



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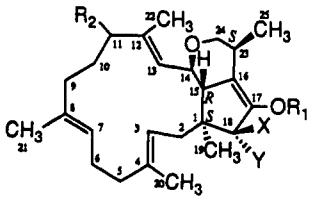
1.31, J = 7.27 Hz). A characteristic W coupling between methyl protons (25-H) and 24-H_α was observed, indicating that they had a rigid conformation. From these results, an ether linkage between C14 and C24 of 1 to form a 6-membered ring was demonstrated for the structure of tricyclic ether 4. NOE from 15-H to 25-H determined by NOESY spectrum established that these protons were on the same side of the ring, thus revealing the relative configuration of three asymmetric carbons (C1, C15, and C23) of 1. As shown in Scheme I, the tricyclic ether 4 was considered to be formed by nucleophilic 1,4-addition of the 24-hydroxyl group to a conjugated diene (Δ^{11} and Δ^{13}) in 5, which was produced from 1 by 1,4-dehydration or from 3 by 1,4-elimination of methanol (Scheme I). In order to clarify the reaction mechanism, 1 was treated with deuterated *p*-toluenesulfonic acid to give deuterium-containing compound 6. In the ^{13}C NMR of 6, C11 was

Table II. ^{1}H NMR (400 MHz) Assignment of 7, 8a, and 8b in DMSO-d_6

no.	chemical shift (δ ppm, splitting J, Hz)		
	tritylate (7)	(*R*)-mandelate (8a)	(*S*)-mandelate (8b)
2	1.68, 2.18 (m)	1.68, 2.20 (m)	1.68, 2.16 (m)
3	5.31 (m)	5.25 (m)	5.23 (m)
5	1.97, 2.25 (m)	1.96, 2.25 (m)	1.96, 2.25 (m)
6	2.09, 2.23 (m)	2.05, 2.26 (m)	2.08, 2.26 (m)
7	5.11 (m)	5.07 (m)	5.09 (m)
9	1.72, 1.98 (m)	1.53, 1.83 (m)	1.76, 2.06 (m)
10	1.58 (m)	1.55 (m)	1.75 (m)
11	3.85 (ddd, J = 8.97, 7.80, 4.70)	5.14 (dd, J = 8.98, 4.70)	5.15 (dd, J = 9.40, 4.28)
13	5.25 (m)	5.43 (m)	5.34 (m)
14	1.80, 2.28 (m)	1.81, 2.21 (m)	1.70, 2.02 (m)
15	2.75 (br d, J = 9.80)	2.70 (br d, J = 11.5)	2.63 (br d, J = 9.83)
19	0.87 (s)	0.82 (s)	0.79 (s)
20	1.60 (s)	1.52 (s)	1.52 (s)
21	1.54 (s)	1.52 (s)	1.60 (s)
22	1.44 (s)	1.46 (s)	1.25 (s)
23	2.58 (m)	2.48 (m)	2.42 (m)
24	3.06 (dd, J = 8.52, 5.99), 3.34 (dd, J = 8.55, 8.52)	3.10 (dd, J = 8.98, 5.13), 3.3[a]	3.09 (dd, J = 8.98, 5.98), 3.3[a]
25	1.15 (d, J = 5.92)	1.10 (d, J = 5.94)	1.08 (d, J = 5.91)

[a] Hidden in DHO.

splitting to a triplet (J = 20 Hz) by coupling to deuterium. Furthermore, three carbons, C11, C10, and C12, were shifted upfield ($\Delta\delta$ 0.38, 0.07, and 0.02, respectively) compared to those of **4**. These results combined with HRFAB-MS indicated **6** to be the 11-monodeuterated derivative of **4**. The incorporation of one deuterium atom in the cyclic ether **6** strongly supported the participation of diene **5** as an intermediate.



4 ; R^1=R^2=H, X,Y=O

6 ; R^1=H, R^2=D, X,Y=O

9 ; R^1=Me, R^2=H, X,Y=O

10a ; R^1=Me, R^2=H, X=OH, Y=H

10b ; R^1=Me, R^2=H, X=H, Y=OH

11 ; R^1=Me, R^2=H, X=Benzoyloxy, Y=H

Attempts to elucidate the relative configuration at C11 of **1** by NMR techniques were fruitless because the 15-membered ring has a flexible conformation. The chirality at C1, C11, C15, and C23 was established as below.

Trost's modification[6] of Dale and Mosher's mandelate method[7] was applied for the determination of the absolute configuration at C11. The 24-hydroxyl group of **1** was tritylated to form **7** and both sets of diastereoisomeric methylmandelates were prepared by reacting **7** with (*R*)- and (*S*)-*O*-methylmandelic acids using DCC and DAMP in methylene chloride. Comparison of ^{1}H NMR (Table II) of C11-(*R*)- and -(*S*)-mandelate derivatives (**8a** and **8b**) revealed significant shielding of the left-hand side of C11 in **8a**, with upfield shifts of the right-hand side in **8b**, reflecting the 11*S* configuration.

The absolute configuration of C1, C15, and C23 was determined by application of the allylic benzoate chirality method.[8] The tricyclic compound **4** was converted to the *O*-methyl derivative **9** using diazomethane. Subsequent reduction with $LiAlH_4$ yielded two epimeric alcohols **10a** (major product) and **10b** (minor one). In ^{1}H–^{1}H NOE difference spectroscopy, a strong NOE between 18-H and 19-H was observed in **10a**, while no NOE was seen between those protons in **10b**, establishing that 18-hydroxyl and 19-methyl had the trans orientation in **10a**. **10a** was then converted to benzoate **11** by treatment with benzoic anhydride and DAMP. The CD spectrum of **11** exhibited a negative exciton chirality (λ_{max} 225 nm, $\Delta\epsilon$ = −22.3), which allowed the assignment of the absolute configuration of 1*S*, 15*R*, 18*S*, and 23*S* in **11**.

The structure of **1** was also elucidated by X-ray single-crystallographic analysis. The crystals were deposited from aqueous methanol. They were monoclinic, space group *C*2, unit cell constants a = 2403.5 (6), b = 6.143 (1), and c = 20.605 (3) Å, β = 110.28 (1)°, V = 1403.5 (6) Å^3, Z = 4, D_x = 1.112 g/cm^3, λ(Cu Kα) = 1.5418 Å. Final R = 0.063 and R_w = 0.071 for 2454 observed reflections. The analysis established the relative configuration of **1**, and the results together with Trost's method and the exciton chirality rule unambiguously established the absolute configuration of **1**. The dibenzoate distance chirality method[8] was applied for the confirmation of the absolute configuration of C11. Methylation of **1** with diazomethane gave **12**, which was reduced with $LiAlH_4$ to afford both epimeric alcohols **13a** and **13b**. The major product **13a** was found to have 18*S* configuration based on the comparative NOE experiments of **13a** and **13b**, because a NOE was observed between 18-H and 19-H only in **13a**. After protecting the 24-hydroxyl group of **13a** with trityl group, tritylate **14** was converted to 11,18-bis-*p*-methoxybenzoate **15**. The CD spectrum of **15** showed a positive

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(7) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(8) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exiton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

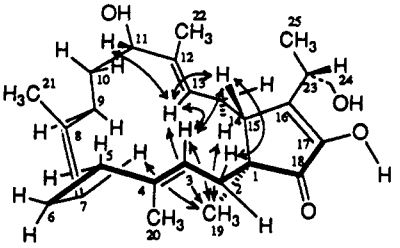


Figure 1. Representation of 1 showing selected NOEs.

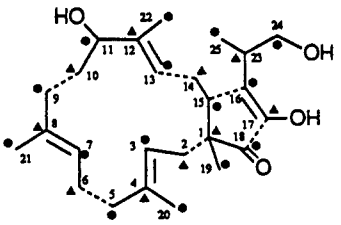


Figure 2. Incorporation of labeled acetates into 1: (●) labeling sites in 1b from [2-^{13}C]acetate; (▲) labeling sites in 1c from [1-^{13}C]-acetate.

exciton chirality (λ_{max} 270 nm, $\Delta\epsilon$ = +2.3, λ_{max} 245 nm, $\Delta\epsilon$ = −14.1) which strongly supported the 11*S* configuration.

The solid-state conformation derived from the X-ray study indicated that the 19-methyl is very close to the three vinyl protons. As the conformation data were consistent with those of NOEs (Figure 1) and scalar coupling constants, the solid-state conformation is considered to be very similar to that in solution.

The sesterterpenoids are a group of pentaprenyl terpenoids whose structures are derivable from geranylfarnesyl pyrophosphate.[9] In order to get insight to the biosynthetic pathway of 1, ^{13}C-labeled acetates were fed to culture of *Arthrinium* sp. FA 1744 (ATCC 74132) and the ^{13}C-enriched antibiotics were isolated. Feeding of [1,2-^{13}C]acetate gave compound **1a** which was highly ^{13}C-enriched in all 25 carbons, indicating that all carbon atoms of 1 originated from acetate. Analysis of the 2D INADEQATE spectrum confirmed the assignment[2] of its ^{13}C chemical shifts in DMSO-d_6. The ^{13}C NMR of the sample obtained by [2-^{13}C]acetate feeding (**1b**) exhibited a clear incorporation in 15 alternating carbons. The feeding of [1-^{13}C]acetate afforded another labeled compound (**1c**) whose ^{13}C NMR indicated incorporation in the 10 carbons adjacent to those of **1b** (Figure 2). The results were consistent with the "head-to-tail" incorporation of acetates and arrangement to the five isoprenoid units.

On ^{13}C-labeled compound **1a** made from [1,2-^{13}C]-acetate, the carbon signals of C-25 were observed that the intencity of a doublet was strong and that of a singlet was weak (Figure 3). However, a weak doublet remaining a strong singlet was recorded on the signals of C24. This observation indicted that stereoselective cyclization of geranylfarnesyl pyrophosphate and the selective hydroxylation at one methyl group (C-24) of the terminal isopropyl. Similar results were observed in signals between C19 and C18, C20 and C5, C21 and C9, and C22 and C13. These results can be explained that the biosynthetic pathway of 1 from mevalonic acid pyrophosphate proceeds stereospecifically as shown in Scheme II.

The absolute configurations at C1 and C15 in 1 are opposite to those of 16, which was produced from lichens

(9) Hanson, R. J. *Nat. Prod. Rep.* **1986**, *3*, 123.

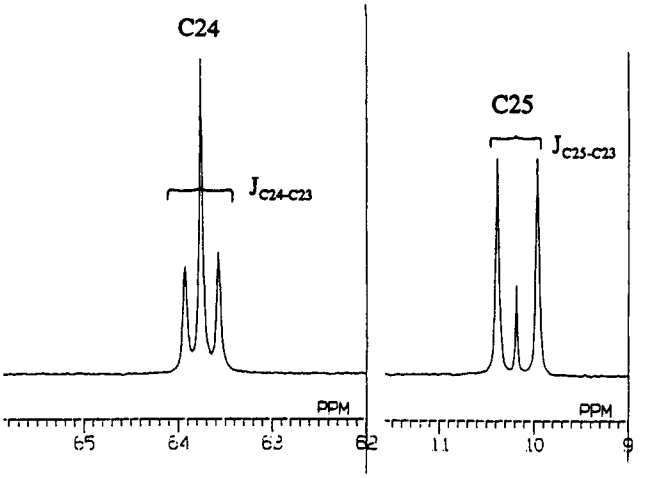
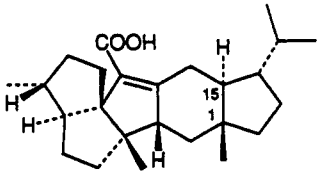
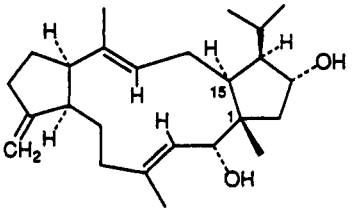


Figure 3. C24 and C25 signals of 1a.



Retigeranic acid (16)

of *Lobaria retigera* group, and 17, a metabolite of *Aspergillus* sp. As *Arthrinium*, the producer of 1, belongs to a genus of *Dematiaceae*, different from *Aspergillus*, 1 may be produced by opposite folding of geranylfarnesyl pyrophosphate and subsequent cyclization compared to the proposed biosynthetic routes[3,4] of 16 and 17.



Variculanol (17)

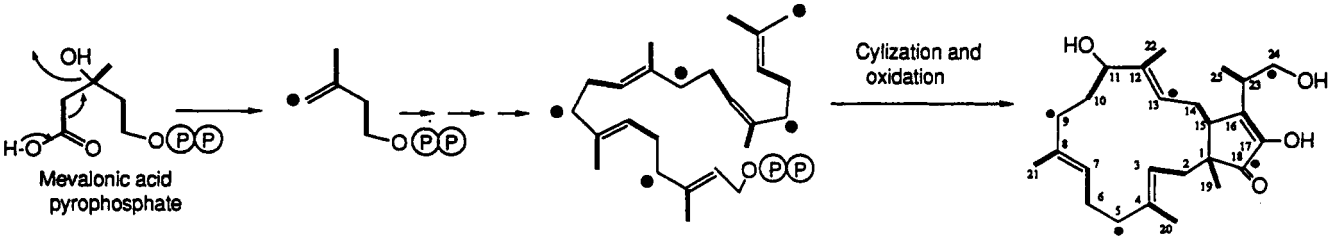
Experimental Section

All the reagents and deuterated solvents were obtained from Aldrich Chemical Company and were used without any purification. E. Merck (Darmstadt) silica gel plates (0.25 mm) were used for preparative or analytical TLC and developed with iodine vapors. Stationary phases used for column chromatography were E. Merck silica gel (230–400 mesh) or Yamamura Chemical Laboratories reversed phase silica gel (60–350 mesh). Melting points are uncorrected.

Spectral Measurements. The IR absorption spectra were obtained in KBr pellet. The UV absorption spectra were measured in MeOH. Mass spectra were obtained in the FAB mode. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless specified otherwise.

11-*O*-Methyl-1 (3). To a solution of 1 (24 mg, 0.06 mmol) in MeOH(3 mL) was added 6 N HCl (0.15 mL), and the mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 (15 mL), washed with water (2 mL), dried over $MgSO_4$, and concentrated. The residual oil was chromatographed on a column of silica gel which was developed with CH_2Cl_2 and 2% MeOH–CH_2Cl_2. The desired fractions were collected and evaporated to give 3 (17 mg): mp >56 °C dec; IR 3400, 1700, 1650 cm^{-1}; UV λ_{max} 264 nm (ϵ 11 400); ^{1}H NMR (DMSO-d_6) δ 0.83 (s, 3 H), 1.16

Scheme II



(d, J = 6.9 Hz, 3 H), 1.41 (s, 3 H), 1.48–1.56 (m, 2 H), 1.58 (s, 6 H), 1.66 (m, 1 H), 1.74 (m, 1 H), 1.87 (m, 1 H), 1.96–2.11 (m, 3 H), 2.13–2.29 (m, 3 H), 2.41 (br d, J = 16.7 Hz, 1 H), 2.53 (m, 1 H), 2.66 (dd, J = 0.8, 9.8 Hz, 1 H), 3.02 (s, 3 H), 3.38 (m, 1 H), 3.49 (dd, J = 7.3, 9.8 Hz, 1 H), 3.61 (dd, J = 7.3, 9.8 Hz, 1 H), 5.10 (m, 1 H), 5.27 (m, 1 H), 5.33 (m, 1 H); ^{13}C NMR δ 49.05 (C1), 39.32 (C2), 121.50 (C3), 138.05 (C4), 40.23 (C5), 23.80 (C6), 123.01 (C7), 132.91 (C8), 34.46 (C9), 31.17 (C10), 85.47 (C11), 134.10 (C12), 130.11 (C13), 28.63 (C14), 49.69 (C15), 149.31 (C16), 146.77 (C17), 208.09 (C18), 16.21 (C19), 15.35 (C20), 15.86 (C21), 10.18 (C22), 37.08 (C23), 66.01 (C24), 14.36 (C25), 55.57 (OCH_3); MS, m/e (relative intensity) 439 (M + Na, 94), 417 (M + H, base peak), 385 (63), 136 (77); HRMS calcd for $C_{26}H_{41}O_4$ (M + H) 417.3005, obsd 417.3012.

Treatment of 3 with *p*-Toluenesulfonic Acid To Give 4. A mixture of 3 (60 mg, 0.12 mmol), *p*-toluenesulfonic acid monohydrate (25 mg), and $MgSO_4$ (50 mg) in CH_2Cl_2 (5 mL) was stirred overnight at room temperature. The mixture was filtered, washed with water, dried over $MgSO_4$, concentrated to a small volume, and chromatographed on a column of silica gel (20 mL), which was developed with CH_2Cl_2 and 0.5% MeOH–CH_2Cl_2. The desired fractions were collected and evaporated to give 4 (36 mg); mp >61 °C dec; IR 3340, 1710, 1700, 1660 cm^{-1}; UV λ_{max} 265 nm (ϵ 9300); for ^{1}H and ^{13}C NMR data, see Table I; MS, m/e (relative intensity) 407 (M + Na, 21), 385 (M + H, 52), 176 (38), 136 (base peak); HRMS calcd for $C_{25}H_{37}O_3$ (M + H) 385.2742, obsd 385.2744.

Treatment of 1 with *p*-Toluenesulfonic Acid To Give 4. A mixture of 1 (106 mg, 0.15 mmol), *p*-toluenesulfonic acid monohydrate (50 mg), and $MgSO_4$ (100 mg) in CH_2Cl_2 (5 mL) was stirred overnight at room temperature. The mixture was filtered, washed with water, dried over $MgSO_4$, concentrated to a small volume, and chromatographed on a column of silica gel (20 mL), which was developed with CH_2Cl_2 and 0.5% MeOH–CH_2Cl_2. The desired fractions were collected and evaporated to give 4 (60 mg).

Treatment of 1 with Deuterated *p*-Toluenesulfonic Acid To Give 6. 1 (60 mg, 0.15 mmol) was dissolved in MeOD (1 mL) and evaporated to dryness, and the residue in MeOD (1 mL) was evaporated. Similarly, *p*-toluenesulfonic acid (300 mg) in D_2O (1 mL) was lyophilized and the residue in D_2O (1 mL) relyophilized. A mixture of the pretreated 1 and *p*-toluenesulfonic acid in CH_2Cl_2 (5 mL) was stirred overnight in the presence of $MgSO_4$ (100 mg) at room temperature. The mixture was filtered, washed with water, dried over $MgSO_4$, concentrated to a small volume, and chromatographed on a column of silica gel (20 mL), which was developed with CH_2Cl_2 and 0.5% MeOH–CH_2Cl_2. The desired fractions were collected and evaporated to give 36 mg of a solid which was further purified with silica gel (10 mL) chromatography to afford a mixture of 6 and 4 (20.8 mg, ca. 1:3 based on the intensity of signals at C10 in the ^{13}C NMR spectrum); IR, UV, ^{1}H NMR and ^{13}C NMR spectral data are almost identical with those of 4, except for the presence of signals of δ 21.79 (C10), 35.59 (t, J = 20 Hz, C11) and 142.88 (C12) in ^{13}C NMR; HRMS calcd for $C_{25}H_{35}DO_3$ (M + H) 386.2822, obsd 386.2805.

Tritylation of 1 To Give 7. A mixture of 1 (62 mg, 0.154 mmol), trityl chloride (94.6 mg, 0.34 mmol), and DAMP (41.4 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) was allowed to stand at 37 °C for 3 days and additional portions of trityl chloride (43 mg, 0.15 mmol) and DAMP (19 mg, 0.15 mmol) were added to the mixture. After 2 days the mixture was washed with 0.1 N HCl (2 × 1 mL), saturated aqueous $NaHCO_3$ (2 × 1 mL), and brine (1 mL), dried over $MgSO_4$, and concentrated. The residual oil was chromatographed on a column of silica gel (20 mL) which was developed in CH_2Cl_2. The desired fractions were collected and evaporated to give 7 (29 mg); mp >92 °C dec; IR 3450, 1695, 1650 cm^{-1}; UV λ_{max} 264 nm (ϵ 10 100); for ^{1}H NMR data, see Table II; ^{13}C NMR (DMSO-d_6) δ 48.67 (C1), 39.08 (C2), 121.88 (C3), 136.82 (C4), 39.81 (C5), 23.27 (C6), 123.17 (C7), 132.46 (C8), 34.38 (C9), 30.28 (C10), 74.19 (C11), 136.69 (C12), 126.81 (C13), 28.28 (C14), 48.02 (C15), 149.40 (C16), 147.48 (C17), 207.08 (C18), 15.97 (C19), 14.88 (C20), 15.64 (C21), 10.21 (C22), 34.48 (C23), 66.21 (C24), 14.22 (C25), 85.58 (CPh_3), 126.90, 127.74 and 128.08 (CPh_3); MS, m/e (relative intensity) 667 (M + Na, 5.3), 645 (M + H, 5.2), 289 (base peak), 273 (46), 259 (99), 241 (99), 215 (98), 183 (98); HRMS calcd for $C_{44}H_{61}O_4$ (M – H) 643.3787, obsd 643.3764.

11-[(*R*)-*O*-Methylmandelate] Ester of 7 (8a). To a stirred mixture of 7 (9.5 mg, 0.015 mmol), (*R*)-*O*-methylmandelic acid (3.3 mg, 0.02 mmol), and DAMP (2.4 mg, 0.02 mmol) in DMF (0.5 mL) was added DCC (4 mg, 0.02 mmol), and the mixture was stirred for 5 h. After evaporation of the mixture, the residue was diluted with CH_2Cl_2 (2 mL) and separated insolubles were removed by filtration. The filtrate was purified by preparative silica gel TLC which was developed with CH_2Cl_2. The desired band was eluted with 1% MeOH–CH_2Cl_2 to give 4.3 mg of 8a: mp >71 °C dec; IR 3350, 1745, 1700, 1655 cm^{-1}; UV λ_{max} 264 nm (ϵ 10 300); for ^{1}H NMR data, see Table II; MS, m/e (relative intensity) 815 (M + Na, 2.1), 649 (1.2), 378 (3.8), 349 (3.1), 259 (21), 243 (base peak), 165 (73); HRMS calcd for $C_{53}H_{60}O_6Na$ (M + Na) 815.4288, obsd 815.4302.

11-[(*S*)-*O*-Methylmandelate] Ester of 7 (8b). 8b (9.2 mg) was obtained with a method similar to that described above, from 7 (19 mg, 0.03 mmol), (*S*)-*O*-methylmandelic acid (6.6 mg, 0.04 mmol), DAMP (4.8 mg, 0.04 mmol), DMF (1 mL), and DCC (8 mg, 0.04 mmol). 8b: mp >71 °C dec; IR 3350, 1745, 1700, 1650 cm^{-1}; UV λ_{max} 263 nm (ϵ 10 700); for ^{1}H NMR data, see Table II; negative MS, m/e (relative intensity) 791 (M – H, 46), 549 (8.3), 274 (6.8), 259 (31), 199 (base peak); HRMS calcd for $C_{53}H_{59}O_6$ (M – H) 791.4311, obsd 791.4290.

17-*O*-Methyl-4 (9). To a solution of 4 (40 mg, 0.1 mmol) in MeOH (1 mL) was added a solution of (trimethylsilyl)diazomethane (ca. 10 equiv) in hexane (1 mL), and the resulting solution was allowed to stand overnight at room temperature. The mixture was evaporated and purified with preparative TLC using silica gel and 1% MeOH–CH_2Cl_2 as eluent. The desired band was eluted with 5% MeOH–CH_2Cl_2. Evaporation of the eluate gave 36 mg of 9 as a viscous oil: IR 1700, 1650 cm^{-1}; UV λ_{max} 256 nm (ϵ 3500); ^{1}H NMR δ 0.89 (s, 3 H), 1.29 (d, J = 7.3 Hz, 3 H), 1.58 (s, 3 H), 1.58–1.64 (m, 2 H), 1.65 (s, 6 H), 1.72 (dd, J = 6.8, 14.1 Hz, 1 H), 1.87 (dt, J = 14.1, 6.8 Hz, 1 H), 1.99 (m, 1 H), 2.02–2.19 (m, 4 H), 2.24–2.30 (m, 2 H), 2.35 (dd, J = 10.3, 14.1 Hz, 1 H), 2.68 (d, J = 10.2 Hz, 1 H), 3.08 (dq, J = 3.0, 7.3 Hz, 1 H), 3.55 (dd, J = 3.0, 11.1 Hz, 1 H), 3.68 (dd, J = 7.7, 10.2 Hz, 1 H), 3.85 (br d, J = 11.1 Hz, 1 H), 3.94 (s, 3 H), 5.19 (m, 1 H), 5.30 (dd, J = 6.8, 10.3 Hz, 1 H), 5.45 (br d, J = 7.7 Hz, 1 H); ^{13}C NMR δ 47.36 (C1), 38.35 (C2), 121.34 (C3), 137.89 (C4), 40.53 (C5), 23.87 (C6), 124.52 (C7), 132.52 (C8), 36.29 (C9), 21.87 (C10), 35.94 (C11), 142.82 (C12), 126.78 (C13), 78.28 (C14), 46.38 (C15), 147.31 (C16), 157.41 (C17), 207.32 (C18), 16.27 (C19), 15.13 (C20), 15.51 (C21), 15.51 (C22), 30.34 (C23), 72.24 (C24), 16.78 (C25), 58.70 (OCH_3); MS m/e (relative intensity) 399 (M + H, base peak), 383 (10), 367 (8.3), 165 (56), 136 (83); HRMS calcd for $C_{26}H_{39}O_3$ (M + H) 399.2899, obsd 399.2900.

Reduction of 9 with $LiAlH_4$ To Give 10a and 10b. To a stirred solution of 9 (27 mg, 0.07 mmol) in dry THF (2 mL) was added $LiAlH_4$ (30 mg, 0.79 mmol) at –30 °C. After 30 min at –30 °C, the mixture was diluted with AcOEt (1 mL), MeOH (1 mL), and water (1 mL) and evaporated to dryness. The residue was

mixed with water (1 mL) and AcOEt (2 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was purified with preparative TLC using a silica gel plate and 1% MeOH–CH_2Cl_2. Each of two bands was eluted with 5% MeOH–CH_2Cl_2. Evaporation of eluate of the less polar band gave 11.8 mg of **10a** as a viscous oil and that of the eluate of polar band yielded 1.5 mg of **10b**. **10a**: IR 3440, 1670 cm^{-1}; UV no maximum band; ^1H NMR δ 0.98 (s, 3 H), 1.19 (d, J = 7.3 Hz, 3 H), 1.56 (s, 3 H), 1.56–1.76 (m, 2 H), 1.61 (s, 3 H), 1.66 (s, 3 H), 1.82–1.96 (m, 2 H), 1.99–2.30 (m, 8 H), 2.61 (dd, J = 2.6, 10.3 Hz, 1 H), 2.77 (dq, J = 3.0, 7.3 Hz, 1 H), 3.41 (dd, J = 3.0, 10.6 Hz, 1 H), 3.62 (dd, J = 6.0, 10.3 Hz, 1 H), 3.71 (d, J = 10.6 Hz, 1 H), 3.77 (s, 3 H), 4.31 (dd, J = 2.6, 7.7 Hz, 1 H, changed to a doublet, J = 2.6 Hz, by D_2O), 5.17 (m, 1 H), 5.37 (m, 2 H); ^{13}C NMR δ 43.04 (C1), 36.44 (C2), 120.99 (C3), 136.27 (C4), 40.31 (C5), 24.05 (C6), 122.92 (C7), 132.78 (C8), 35.96 (C9), 22.39 (C10), 35.01 (C11), 141.09 (C12), 124.84 (C13), 78.15 (C14), 48.19 (C15), 127.57 (C16), 147.85 (C17), 82.96 (C18), 15.96 (C19), 15.09 (C20), 15.96 (C21), 15.46 (C22), 29.46 (C23), 72.59 (C24), 16.68 (C25), 57.50 (OCH_3); MS, m/e (relative intensity) 400 (M, 79), 383 (base peak), 369 (10), 289 (13), 217 (21), 167 (25), 136 (63); HRMS calcd for $C_{26}H_{40}O_3$ (M) 400.2977, obsd 400.2989. **10b**: IR 3440, 1670 cm^{-1}; UV no maximum band; ^1H NMR δ 0.90 (s, 3 H), 1.16 (d, J = 7.3 Hz, 3 H), 1.58 (s, 3 H), 1.61 (s, 3 H), 1.63 (s, 3 H), 1.60–1.75 (m, 2 H), 1.80–2.28 (m, 10 H), 2.47 (d, J = 10.3 Hz, 1 H), 2.76 (dq, J = 3.0, 7.3 Hz, 1 H), 3.52 (dd, J = 3.0, 11.1 Hz, 1 H), 3.69 (dd, J = 7.7, 10.3 Hz, 1 H), 3.73 (d, J = 11.1 Hz, 1 H), 3.75 (s, 3 H), 4.21 (br s, 1 H), 5.22 (m, 1 H), 5.29 (br d, J = 7.7 Hz, 1 H), 5.37 (dd, J = 7.4, 9.0 Hz, 1 H); MS m/e (relative intensity) 401 (M + H, 39), 400 (M, 59), 383 (54), 289 (25), 217 (12), 167 (27), 136 (base peak); HRMS calcd for $C_{26}H_{41}O_3$ (M + H) 401.3033, obsd 401.3055.

Benzoylation of 10a To Give 11. A mixture of **10a** (10 mg, 0.025 mmol), benzoic anhydride (11.3 mg, 0.05 mmol), and DAMP (6.1 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) was stirred overnight at room temperature. The mixture was concentrated to a small volume and chromatographed on a silica gel plate, which was developed in CH_2Cl_2–n-hexane (7:3). The desired band was eluted with CH_2Cl_2 to give **11** (4.1 mg) as a viscous oil: IR 1720 cm^{-1}; UV no maximum band; ^1H NMR δ 1.14 (s, 3 H), 1.24 (d, J = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.56 (s, 3 H), 1.56–1.64 (m, 2 H), 1.68 (s, 3 H), 1.87 (m, 1 H), 2.00–2.08 (m, 4 H), 2.09–2.21 (m, 5 H), 2.74 (dd, J = 2.6, 10.3 Hz, 1 H), 2.83 (dq, J = 3.0, 6.8 Hz, 1 H), 3.45 (dd, J = 3.0, 11.1 Hz, 1 H), 3.64 (s, 3 H), 3.70 (dd, J = 7.3, 10.2 Hz, 1 H), 3.75 (d, J = 11.1 Hz, 1 H), 5.15 (m, 1 H), 5.35 (m, 1 H), 5.41 (br d, J = 6.4 Hz, 1 H), 5.86 (d, J = 2.6 Hz, 1 H), 7.46 (m, 2 H), 7.57 (m, 1 H), 8.09 (m, 2 H); MS, m/e (relative intensity) 504 (M, 2.5), 460(2.7), 383(12), 289(18), 136(base peak); HRMS calcd for $C_{33}H_{44}O_4$ (M) 504.3239, obsd 504.3234.

17-*O*-Methyl-1 (12). To a solution of **1** (70 mg, 0.17 mmol) in MeOH (1 mL) was added a solution of diazomethane (ca. 10 equiv) in ether (2 mL), and the solution was allowed to stand overnight at room temperature. The mixture was evaporated and purified with column chromatography using silica gel (20 mL) and 1% MeOH–CH_2Cl_2 as eluent. Evaporation of the desired fraction gave 65 mg of **12** as a viscous oil: IR 3420, 1700, 1640 cm^{-1}; UV λ_{max} 252nm (ϵ 3700); ^1H NMR δ 0.97 (s, 3 H), 1.24 (d, J = 7.3 Hz, 3 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 1.64 (s, 3 H), 1.65–1.82 (m, 4 H), 1.99 (m, 1 H), 2.01 (m, 1 H), 2.06–2.16 (m, 2 H), 2.22–2.28 (m, 2 H), 2.35 (dd, J = 10.7, 13.6 Hz, 1 H), 2.40 (br d, J = 17.1 Hz, 1 H), 2.64–2.74 (m, 2 H), 3.75 (dd, J = 6.0, 10.2 Hz, 1 H), 3.79 (dd, J = 6.8, 10.2 Hz, 1 H), 3.92 (s, 3 H), 4.05 (dd, J = 3.8, 9.4 Hz, 1 H), 5.14 (m, 1 H), 5.23 (dd, J = 5.1, 10.7 Hz, 1 H), 5.38 (m, 1 H); ^{13}C NMR δ 49.01 (C1), 39.39 (C2), 121.56 (C3), 137.83 (C4), 40.26 (C5), 23.84 (C6), 124.38 (C7), 132.90 (C8), 34.89 (C9), 29.83 (C10), 76.52 (C11), 136.46 (C12), 128.93 (C13), 28.78 (C14), 49.71 (C15), 150.74 (C16), 159.57 (C17), 208.33 (C18), 16.24 (C19), 15.34 (C20), 15.54 (C21), 10.45 (C22), 37.74 (C23), 66.16 (C24), 14.53 (C25), 57.50 (OCH_3); MS m/e (relative intensity) 417 (M + H, 35), 399 (32), 289 (30), 136 (base peak); HRMS calcd for $C_{26}H_{41}O_4$ (M + H) 417.3005, obsd 417.3008.

Reduction of 12 with $LiAlH_4$ To Give 13a and 13b. To a stirred solution of **12** (30 mg, 0.07 mmol) in THF (2 mL) was added $LiAlH_4$ (10 mg, 0.26 mmol) at −80 °C. After 10 min at 0 °C, the mixture was diluted with AcOEt (1 mL), MeOH (1 mL), and water (1 mL) and evaporated to dryness. The residue was mixed with water (1 mL) and CH_2Cl_2 (1 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was purified with preparative TLC using a silica gel plate and 5% MeOH–CH_2Cl_2. Each of two bands was eluted with 10% MeOH–CH_2Cl_2. Evaporation of the eluate of less polar band gave 18 mg of **13a** and that of the eluate of the polar band yielded 7.5 mg of **13b**. **13a**: mp >81 °C dec; IR 3400, 1670 cm^{-1}; UV no maximum band; ^1H NMR δ 1.02 (s, 3 H), 1.12 (d, J = 7.3 Hz, 3 H), 1.56 (s, 3 H), 1.61 (s, 3 H), 1.63 (s, 3 H), 1.64 (m, 1 H), 1.78 (m, 2 H), 1.97 (m, 1 H), 2.02–2.19 (m, 7 H), 2.21–2.36 (m, 2 H), 2.39 (m, 1 H), 3.55 (dd, J = 5.6, 10.7 Hz, 1 H), 3.67 (s, 3 H), 3.70 (dd, J = 5.6, 10.7 Hz, 1 H), 3.95 (dd, J = 4.3, 10.3 Hz, 1 H), 4.37 (d, J = 2.1 Hz, 1 H), 5.02 (m, 1 H), 5.18 (dd, J = 5.6, 6.4 Hz, 1 H), 5.29 (dd, J = 6.4, 7.7 Hz, 1 H); MS, m/e (relative intensity) 441 (M + Na, 17), 418 (M, 23), 401 (67), 383 (52), 369 (17), 183 (base peak), 154 (88), 136 (75); HRMS calcd for $C_{26}H_{42}O_4$ (M) 418.3083, obsd 418.3076. **13b**: IR 3400, 1680 cm^{-1}; UV no maximum band; ^1H NMR δ 1.00 (s, 3 H), 1.13 (d, J = 7.8 Hz, 3 H), 1.58 (s, 3 H), 1.59 (s, 3 H), 1.64 (s, 3 H), 1.66 (m, 1 H), 1.76–1.86 (m, 2 H), 1.96 (m, 1 H), 2.02–2.12 (m, 4 H), 2.13–2.22 (m, 4 H), 2.33 (dd, J = 1.6, 9.7 Hz, 1 H), 2.54 (m, 1 H), 3.62 (dd, J = 7.3, 10.3 Hz, 1 H), 3.66 (dd, J = 6.0, 10.3 Hz, 1 H), 3.73 (s, 3 H), 3.99 (dd, J = 3.9, 8.6 Hz, 1 H), 4.06 (s, 1 H), 5.19 (m, 1 H), 5.24 (m, 1 H), 5.29 (dd, J = 8.1, 7.7 Hz, 1 H); MS m/e (relative intensity) 441 (M + Na, 6.1), 418 (M, 5.2), 401 (21), 383 (16), 183 (27), 136 (base peak); HRMS calcd for $C_{26}H_{42}O_4Na$ (M + Na) 441.2981, obsd 441.2983.

Tritylation of 13a To Give 14. A mixture of **13a** (10 mg, 0.024 mmol), trityl chloride (20 mg, 0.072 mmol), and DAMP (10 mg, 0.082 mmol) in CH_2Cl_2 (1 mL) was allowed to stand at 37 °C for 4 days. The mixture was purified with preparative silica gel TLC which was developed with 10% MeOH–CH_2Cl_2. The desired band was collected and eluted with 15% MeOH–CH_2Cl_2 to give 7 mg of **14**: mp >72 °C dec; IR 3400, 1680 cm^{-1}; UV no maximum band; ^1H NMR δ 1.01 (s, 3 H), 1.12 (d, J = 6.8 Hz, 3 H), 1.26 (m, 1 H), 1.52 (s, 3 H), 1.53 (s, 3 H), 1.63 (s, 3 H), 1.67 (m, 1 H), 1.73–1.82 (m, 2 H), 1.88 (m, 1 H), 1.93–1.99 (m, 2 H), 2.02–2.24 (m, 6 H), 2.41 (m, 1 H), 2.49 (m, 1 H), 3.06 (dd, J = 8.5, 8.6 Hz, 1 H), 3.19 (dd, J = 6.9, 8.5 Hz, 1 H), 3.54 (s, 3 H), 3.97 (dd, J = 2.8, 8.4 Hz, 1 H), 4.46 (br d, J = 6.9 Hz, 1 H), 5.10 (m, 1 H), 5.23 (m, 2 H), 7.22 (m, 3 H), 7.26 (m, 6 H), 7.43 (m, 6 H); MS, m/e (relative intensity) 600 (M, 1.3), 643 (1.2), 425 (4.2), 259 (5.1), 243 (base peak), 165 (19), 136 (18); HRMS calcd for $C_{45}H_{56}O_4$ (M) 660.4179, obsd 660.4197.

***p*-Methoxybenzoylation of 14 To Give 15.** A mixture of **14** (5.1 mg, 0.0077 mmol), *p*-methoxybenzoic acid (15 mg, 0.1 mmol), DCC (20 mg, 0.1 mmol), and DAMP (12 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was stirred overnight at room temperature. The mixture was filtered and the filtrate was chromatographed on a silica gel plate, which was developed in CH_2Cl_2–n-hexane (7:3). The desired band was eluted with CH_2Cl_2 to give **15** (3.1 mg); mp >68 °C dec; IR 1715, 1610 cm^{-1}; UV λ_{max} 257 nm (ϵ 41 500); ^1H NMR δ 1.09 (d, J = 6.8 Hz, 3 H), 1.11 (s, 3 H), 1.45 (s, 3 H), 1.64 (s, 3 H), 1.67 (s, 3 H), 1.81 (m, 1 H), 1.84–2.00 (m, 2 H), 2.02–2.30 (m, 9 H), 2.48 (m, 1 H), 2.62 (m, 1 H), 3.04 (dd, J = 7.6, 8.1 Hz, 1 H), 3.28 (dd, J = 7.7, 8.1 Hz, 1 H), 3.39 (s, 3 H), 3.85 (s, 6 H), 5.14 (m, 1 H), 5.29 (m, 1 H), 5.16 (dd, J = 4.3, 9.4 Hz, 1 H), 5.44 (m, 1 H), 6.03 (d, J = 2.1 Hz, 1 H), 6.89 (m, 4 H), 7.17 (m, 3 H), 7.24 (m, 6 H), 7.45 (m, 6 H), 8.00 (m, 4 H); MS m/e (relative intensity) 928 (M, 2.1), 777 (2.1), 289 (21), 243 (base peak), 217 (15); HRMS calcd for $C_{61}H_{68}O_8$ (M) 928.4915, obsd 928.4930.

Incorporation of Sodium [^{13}C]Acetate into 1. A loopful of well-grown agar slant culture of *Arthrinium* sp. FA1744 was inoculated into a 500-mL Erlenmeyer flask containing 100 mL of a seed medium consisting of soluble starch 2.0%, glucose 0.5%, NZ-case 0.3%, yeast extract 0.2%, fish meat extract 0.5%, and $CaCO_3$, and the pH was adjusted to 7.0 before autoclaving. The inoculated flask was incubated for 4 days at 28 °C and 200 rpm. Five milliliters of the seed culture was transferred into a 500-mL Erlenmeyer flask containing 100 mL of a production medium, which consisted of glucose 2%, sodium glutamate 1.0%, K_2HPO_4 0.1%, and $MgSO_4 \cdot 7H_2O$ 0.02% (pH 7.0). The fermentation was carried out at 28 °C and 200 rpm and [^{13}C]labeled sodium acetate 0.25% was added two times to the flask at 48 and 96 h. The titer of **1a**, **1b**, and **1c** determined by HPLC was 75 μg/mL, 71 μ/mL, and 65 μg/mL, respectively.

Isolation of [^{13}C]Labeled 1. The whole broth (300 mL) fermented in the presence of sodium [1,2-^{13}C]acetate was extracted with BuOH (300 mL) and the extract was evaporated to dryness. The crude solid was chromatographed on a silica gel (20 mL), which was developed with CH_2Cl_2 and 5% MeOH–CH_2Cl_2. The eluate was monitored with TLC, and the desired fractions were collected and evaporated to give 8.8 mg of **1a**. By a similar treatment, 13 mg and 6.5 mg of **1b** and **1c** were obtained. The R_f values on TLC and retention times of HPLC of **1a**, **1b**, and **1c** were identical to those of **1**.

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Supplementary Material Available: ^{1}H NMR spectra of all new compounds described in the Experimental Section (14 pages). This material is contained in 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. The authors have deposited atomic coordinates for terpestacin with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.