Marine Natural Products. XXII.[1] The Absolute Stereostructure of Swinholide A, a Potent Cytotoxic Dimeric Macrolide from the Okinawan Marine Sponge *Theonella swinhoei*

Motomasa KOBAYASHI,[a] Jun-ichi TANAKA,[b] Taketo KATORI,[a] Miki MATSUURA,[a] Megumi YAMASHITA,[a] and Isao KITAGAWA*,[a]

Faculty of Pharmaceutical Sciences, Osaka University,[a] Yamada-oka 1-6, Suita, Osaka 565, Japan and Department of Marine Sciences, University of the Ryukyus,[b] Senbaru 1, Nishihara, Okinawa 903-01, Japan. *Received March 5, 1990*

A potent cytotoxic dimeric macrolide, swinholide A (1), was isolated from the Okinawan marine sponge *Theonella swinhoei*. The absolute stereostructure of 1, having a dimeric dilactone structure with a 44-membered ring, has been determined on the basis of its chemical behavior and an X-ray crystallographic analysis.

Keywords marine sponge; *Theonella swinhoei*; swinholide A; dimeric macrolide; X-ray crystallography; CD exciton coupling; cytotoxicity

Recent investigations on marine sponges have made clear that *Theonella* species are rich sources of bioactive secondary metabolites, *e.g.* theonellapeptolides Ia—e,[2-4] aminobisabolenes,[5] onnamide A,[6] theonellamide F,[7] theonelladines A—D,[8] misakinolide A (bistheonellide A),[9,10] and swinholide A.[11,12] In previous papers, we reported briefly on the dimeric structure[13] and the absolute stereostructure[14] of swinholide A (**1**). This paper presents a full account of the work together with some additional evidence on the structure elucidation of swinholide A (**1**).

In our continuing search for new bioactive substances from Okinawan marine invertebrates, we isolated a potent cytotoxic macrodiolide swinholide A (**1**) from the marine sponge *Theonella swinhoei*. Thus, extraction of the fresh sponge with acetone followed by separation of the ethyl acetate-soluble portion on a silica gel column gave **1** as an amorphous solid together with tridecapeptide lactones named theonellapeptolides Ia, Ib, Ic, Id, and Ie. During the course of the structural study of theonellapeptolides, we have developed a new high-performance liquid chromatographic (HPLC) analysis method for quantitative analysis of their amino acid compositions, including N-methyl amino acids and D-amino acids.[2-4] On the other hand, an Israeli group previously isolated swinholide A as an antibiotic compound from the same kind of marine sponge *Theonella swinhoei* which was collected in the Red Sea,[11,12] and proposed its plain structure as a monomeric macrolide (**3**) mainly based on two dimensional nuclear magnetic resonance (2D-NMR) studies on swinholide A and its tetraformate **4**. Thus, when we first isolated swinholide A (**1**) together with those theonellapeptolides, we anticipated that our study on swinholide A would be terminated by its identification with the authentic compound.

In fact, our swinholide A (**1**) and its formyl derivative **2**, which was obtained by treatment of **1** with formic acid, gave identical spectral data [infrared (IR) and ^{1}H-NMR] with those reported for **3** and **4** by the Israeli group.[11,12] In addition, our compound was found to be identical with swinholide A from the Red Sea sponge by direct comparison in detail of their ^{1}H- and ^{13}C-NMR spectra. The Israeli group reported that their swinholide A gave no molecular ion peak in the mass spectra taken under various conditions even with the fast atom bombardment (FAB) technique. However, we have found that our swinholide A (**1**) and its formate (**2**) gave molecular ion peaks in positive and negative FAB mass spectra (FABMS), at *m/z* 1411 $(M+Na)^+$ and 1388 $(M)^-$ for **1** and at *m/z* 1635 $(M+Na)^+$ for **2**, respectively. It was presumed therefore that swinholide A may have a dimeric dilactone structure rather than the previously proposed structure **3**. In order to verify this, we have conducted a careful investigation on the structure of swinholide A (**1**).

When swinholide A (**1**) was treated with sodium methoxide in methanol, it furnished a monomeric methyl ester **5** as a single product. The methyl ester **5** gave an $(M+H)^+$ ion peak at *m/z* 727 in its FABMS, and the partial plain structures from C_1 to C_{23} and C_{27} to C_{31}-Me in **5** were substantiated by ^{1}H- and ^{13}C-NMR analyses including the homo and hetero correlation spectroscopy (COSY) of **5**.

In order to clarify the connection from C_{23} to C_{27}, the methyl ester **5** was subjected to ozone oxidation in MeOH–pyridine at −78 °C followed by treatment with dimethyl sulfide. The resulting trialdehyde was converted to a trisemicarbazone **7** [δ 7.30 (1H, t, J=5.6 Hz), 7.25 (1H, t, J=5.5 Hz), 7.12 (1H, d, J=7.3 Hz)] by treatment with semicarbazide and NaOAc in MeOH–H_2O and the product was further treated with NaOMe–MeOH under reflux for 2 h to furnish a cyclic semicarbazone **9** in 10% overall yield from **5**. Compound **9** was also obtained *via* another reaction procedure. Acetonidation of **5** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH) gave a 17,19; 21,23-diacetonide (**6**) in 70% yield, and this was ozonolyzed in MeOH–pyridine solution and then treated with semicarbazide as carried out above for **5** to furnish a diacetonide trisemicarbazone **8** in 86% yield. Alkaline degradation of **8** as carried out above for **7** gave an unsaturated semicarbazone **10**, which was then converted to **9** by treatment with 80% aqueous acetic acid at 80 °C for 30 min in 55% yield from **8**. The ^{1}H-NMR spectrum of the cyclic semicarbazone **9** showed a much simpler signal-pattern in the methylene proton region as compared to other derivatives and the COSY-45 of **9** showed six geminal proton cross peaks due to methylene protons at $C_{14,18,25,26,28,30}$, thus proving the connectivity from C_{23} to C_{27}. Furthermore, the location of the lactone linkage in swinholide A (**1**) has been demonstrated to be at C_{21} (and also at $C_{21'}$) by comparison of the ^{1}H-NMR spectra of **1** and **5**. Thus, the signal assignable to 21-H (δ 4.30, d, J=10.1 Hz in C_6D_6) geminal to 21-OH in **5** was observed at higher field than that (δ 5.86, d, J=11.0 Hz in C_6D_6) in **1**.

Although the above physical properties were consistent with the monomeric structure (**3**) reported by the Israeli

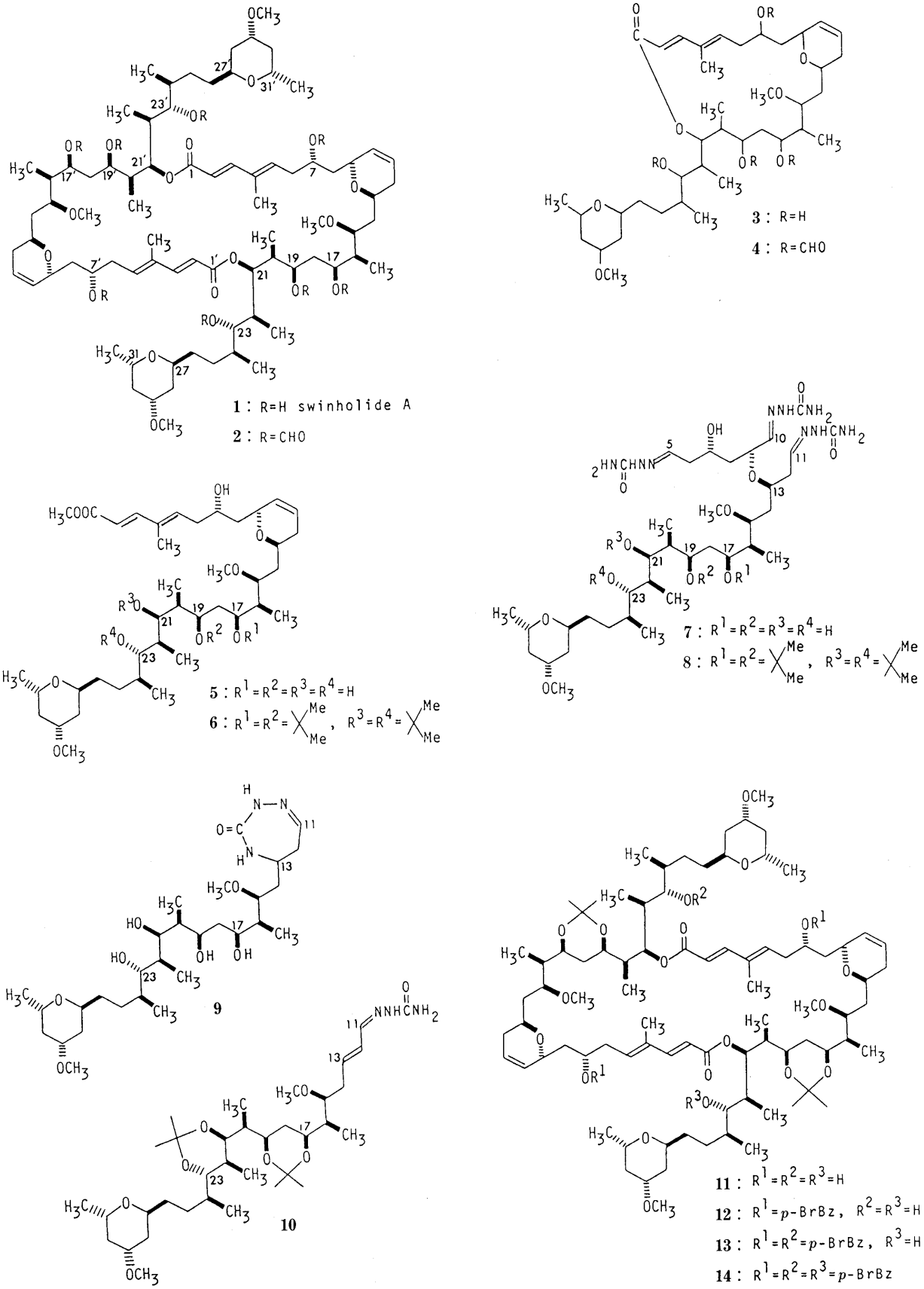


Chart 1

group, the dimeric nature of swinholide A (**1**) has been demonstrated by the following evidence. Swinholide A (**1**) was converted to a diacetonide (**11**) by treatment with 2,2-dimethoxypropane and *p*-TsOH. On treatment with *p*-bromobenzoyl chloride in pyridine at 70 °C for 2 h, **11** provided an asymmetrical tri-*p*-bromobenzoate (**13**) to-

TABLE I. ^{1}H-NMR Data for Swinholide A (**1**), **5**, and **15** in $CDCl_3$

	Swinholide A (**1**)	Methyl ester **5**	Diketone **15**
2	5.79 (d, J=15.8)	5.82 (d, J=15.6)	5.77 (d, J=15.6)
3	7.58 (d, J=15.8)	7.34 (d, J=15.6)	7.23 (d, J=15.6)
4Me	1.83 (s)	1.80 (s)	1.76 (s)
5	6.08 (dd, J=9.6, 5.3)	5.99 (dd, J=7.3, 7.3)	5.93 (dd, J=6.7, 6.7)
6	2.46 (ddd, J=14.7, 9.6, 9.6), 2.18 (br d, J=14.7)	2.47 (ddd, J=15.0, 7.3, 7.3), 2.40 (ddd, J=15.0, 6.7, 6.7)	2.69 (dd, J=6.7, 6.4), 2.69 (dd, J=6.7, 6.4)
7	4.14 (br dd, J=9.7, 9.6)	4.03 (m)	5.37 (m)
8	1.63 (m), 1.58 (m)	1.76 (m), 1.57 (m)	1.98 (m), 1.85 (m)
9	4.51 (br d, J=8.9)	4.52 (br d, J=9.0)	4.28 (m)
10	5.69 (br dd, J=10.4, 1.8)	5.65 (d, J=10.4)	5.67 (d, J=10.1)
11	5.78 (br d, J=10.4)	5.83 (m)	5.84 (m)
12	2.27 (br d, J=16.1), 1.82 (m)	2.19 (br d, J=17.4), 1.92 (m)	2.02 (m), 1.94 (m)
13	3.86 (m)	3.87 (m)	3.61 (m)
14	2.14 (ddd, J=14.0, 10.7, 4.0), 1.46 (ddd, J=14.0, 10.7, 3.4)	2.05 (ddd, J=14.3, 7.3, 7.3), 1.58 (m)	1.87 (m), 1.48 (m)
15	4.01 (m)	3.66 (m)	3.71 (m)
15OMe	3.35 (s)	3.41 (s)	3.28 (s)
16	1.68 (m)	1.92 (m)	1.49 (m)
16Me	0.81 (d, J=7.0)	0.86 (d, J=7.0)	0.80 (d, J=7.0)
17	3.83 (dd, J=9.8, 9.8)	3.87 (m)	3.81 (ddd, J=8.2, 8.2, 5.0)
18	1.69 (m), 1.62 (m)	1.61 (m), 1.61 (m)	1.31 (m), 1.31 (m)
19	3.98 (m)	4.03 (m)	3.86 (dd, J=7.0, 7.0)
20	1.75 (dq, J=10.5, 7.0)	1.98 (m)	1.76 (m)
20Me	0.97 (d, J=7.0)	0.77 (d, J=7.0)	0.95 (d, J=7.0)
21	5.36 (d, J=10.6)	4.03 (m)	5.40 (dd, J=9.7, 2.0)
22	1.95 (m)	1.75 (m)	3.06 (dq, J=2.2, 6.7)
22Me	0.84 (d, J=7.0)	0.89 (d, J=6.7)	1.09 (d, J=6.7)
23	3.12 (d, J=9.5)	3.31 (m)	—
24	1.65 (m)	1.75 (m)	2.84 (ddq, J=7.0, 7.0, 7.0)
24Me	0.99 (d, J=6.7)	1.04 (d, J=7.0)	1.12 (d, J=7.0)
25	1.38 (m), 1.27 (m)	1.70 (m), 1.30 (m)	1.59 (m), 1.41 (m)
26	1.90 (m), 1.30 (m)	1.85 (m), 1.35 (m)	1.69 (m), 1.33 (m)
27	4.02 (m)	4.03 (m)	3.95 (m)
28	1.82 (m), 1.60 (m)	1.84 (m), 1.61 (m)	1.83 (m), 1.50 (m)
29	3.53 (dddd, J=10.0, 10.0, 5.5, 5.5)	3.55 (dddd, J=10.0, 10.0, 4.5, 4.5)	3.51 (m)
29OMe	3.33 (s)	3.35 (s)	3.32 (s)
30	1.96 (m), 1.18 (ddd, J=12.5, 10.4, 10.2)	2.00 (m), 1.22 (m)	1.93 (m), 1.13 (m)
31	3.69 (ddq, J=10.2, 2.9, 6.4)	3.75 (m)	3.69 (m)
31Me	1.20 (d, J=6.4)	1.22 (d, J=6.1)	1.18 (d, J=6.4)

gether with a symmetrical di-*p*-bromobenzoate (**12**) and a tetra-*p*-bromobenzoate (**14**). All *p*-bromobenzoyl derivatives **12**, **13**, and **14**, gave $(M+Na)^+$ ion clusters at m/z 1858, 2041, and 2224 in the FABMS, respectively. The asymmetry in the structure of 7,7',23-tri-*p*-bromobenzoate (**13**) resulted in complex signal patterns in its ^{1}H- and ^{13}C-NMR spectra as compared with those of the symmetrical compounds **12** and **14** (see Experimental).

Finally, an authentic sample of swinholide A (**1**) from the Israeli group[15] did show an $(M+Na)^+$ ion peak at m/z 1411 in the FABMS. Furthermore, the homo and hetero COSY studies of swinholide A (**1**) and the monomeric methyl ester (**5**) have led us assign all proton and carbon signals as shown in Tables I and II. Further confirmation has been supplied by similar spectral analysis in detail of other degradation products. Consequently, the plain structure of swinholide A has been clarified to be a dimeric macrodiolide **1** having a 44-membered ring.

Next, our research has been directed to elucidation of the stereochemistry of swinholide A (**1**). An amorphous solid, swinholide A (**1**) is a dimeric dilactone comprising two monomeric units with 15 asymmetric carbons. It seemed to be very difficult to determine the configurations of all the asymmetric carbons in **1** by NMR analysis, so that we examined the X-ray diffraction method. After many unsuccessful attempts to get a crystalline derivative suitable for the X-ray single crystal analysis, we have found that a dimeric diketone **15** is available for this purpose. Swern oxidation of the di-*p*-bromobenzoate (**12**) furnished in 83% yield a crystalline diketone **15** which gave a molecular ion peak at m/z 1980 $(M+\text{triethanolamine}+H)^+$ on FABMS and showed a signal due to two carbonyl carbons (δ_C 214.4 s) in its ^{13}C-NMR spectrum. The X-ray crystallographic analysis was carried out on a single crystal (mp 100—101 °C) obtained from the methanol–ethyl acetate solution.[16] The final relative structure was obtained as shown in Fig. 1,[14] and the dimeric structure **1** of swinholide A has thus been finally determined.

In the ^{1}H- and ^{13}C-NMR analyses of swinholide A (**1**) and its derivatives (**5**, **15**) (Tables I and II), we have presumed that the diketone **15** in solution possesses a symmetrical structure comprised of two monomeric units with the same conformation. However, it has been shown by the X-ray crystallographic analysis that the diketone **15** in the crystal exists as an asymmetrical pair of two monomeric units with different conformations. Anyway, the relative stereostructure of swinholide A (**1**) except for the relative configurations at C_{23} and $C_{23'}$ has been determined.

Table II. ^{13}C-NMR Data for Swinholide A (**1**), **5**, and **15** in $CDCl_3$

	Swinholide A (**1**)	Methyl ester **5**	Diketone **15**
1	169.6 (s)	167.8 (s)	165.8 (s)
2	113.3 (d)	115.0 (d)	116.4 (d)
3	152.5 (d)	149.5 (d)	149.1 (d)
4	133.9 (s)	134.0 (s)	135.4 (s)
4Me	12.0 (q)	12.1 (q)	12.5 (q)
5	141.2 (d)	138.2 (d)	135.3 (d)
6	37.4 (t)	37.0 (t)	33.7 (t)
7	66.6 (d)	66.8 (d)	71.9 (d)
8	40.4 (t)	40.0 (t)	37.6 (t)
9	66.7 (d)	68.2 (d)	69.4 (d)
10	129.7 (d)	129.6 (d)	128.9 (d)
11	123.1 (d)	123.3 (d)	124.7 (d)
12	30.2 (t)	30.2 (t)	31.0 (t)
13	65.1 (d)	65.0 (d)	64.9 (d)
14	34.6 (t)	34.9 (t)[a]	37.6 (t)
15	75.6 (d)	78.4 (d)	75.7 (d)
15OMe	56.9 (q)	56.9 (q)	57.8 (q)
16	41.4 (d)[a]	40.4 (d)	42.4 (d)
16Me	9.0 (q)[b]	10.4 (q)	7.9 (q)
17	73.5 (d)	74.8 (d)	70.1 (d)
18	38.1 (t)	35.9 (t)[a]	32.4 (t)
19	70.9 (d)	72.1 (d)	67.1 (d)
20	40.7 (d)[a]	39.8 (d)	39.6 (d)
20Me	8.9 (q)[b]	11.4 (q)	9.8 (q)
21	74.1 (d)	74.8 (d)	72.0 (d)
22	37.2 (d)	35.2 (d)[b]	44.4 (d)
22Me	8.8 (q)[b]	10.3 (q)	9.2 (q)
23	75.8 (d)	79.9 (d)	214.4 (s)
24	32.9 (d)	34.7 (d)[b]	44.1 (d)
24Me	17.4 (q)	16.3 (q)	17.3 (q)
25	23.7 (t)	27.9 (t)	28.5 (t)
26	29.0 (t)	28.8 (t)	34.5 (t)
27	70.9 (d)	71.6 (d)	72.4 (d)
28	34.6 (t)	34.5 (t)[a]	34.5 (t)
29	72.9 (d)	73.0 (d)	73.1 (d)
29OMe	54.8 (q)	54.9 (q)	55.2 (q)
30	38.3 (t)	38.2 (t)	39.0 (t)
31	64.3 (d)	64.6 (d)	64.6 (d)
31Me	21.4 (q)	21.4 (q)	21.9 (q)

a, b) Assignments may be interchanged in the same column.

Table III. Comparison of the ^{1}H-NMR Data for the Di-MTPA Esters **16** and **17**[a]

	Di-(+)-(*R*)-MTPA ester **16**	Di-(−)-(*S*)-MTPA ester **17**	$\Delta\delta$ ($S-R$)
2	5.79 (d)	5.85 (d)	+0.06
3	7.26 (d)	7.32 (d)	+0.06
4Me	1.80 (s)	1.80 (s)	0
5	5.95 (dd)	5.96 (dd)	+0.01
6a, 6b	2.70 (dd), 2.70 (dd)	2.70 (dd), 2.70 (dd)	0
7	5.39 (m)	5.39 (m)	0
8a, 8b	1.99 (m), 1.80 (m)	1.99 (m), 1.80 (m)	0, 0
9	4.29 (br d)	4.29 (br d)	0
10	5.67 (br d)	5.67 (br d)	0
11	5.82 (m)	5.84 (m)	+0.02
12a, 12b	1.99 (m), 1.96 (m)	2.01 (m), 1.97 (m)	+0.02, +0.01
13	3.57 (m)	3.58 (m)	+0.01
14a, 14b	1.84 (m), 1.49 (m)	1.86 (m), 1.49 (m)	+0.02, 0
15	3.76 (m)	3.76 (m)	0
15OMe	3.30 (s)	3.32 (s)	+0.02
16	1.43 (m)	1.44 (m)	+0.01
16Me	0.76 (d)	0.78 (d)	+0.02
17	3.73 (m)	3.74 (m)	+0.01
18a, 18b	1.22 (m), 1.22 (m)	1.24 (m), 1.24 (m)	+0.02, +0.02
19	3.51 (m)	3.56 (m)	+0.05
20	1.64 (m)	1.71 (m)	+0.07
20Me	0.81 (d)	0.82 (d)	+0.01
21	5.05 (d)	5.08 (d)	+0.03
22	2.27 (dq)	2.20 (dq)	−0.07
22Me	0.88 (d)	0.94 (d)	+0.06
23	4.93 (dd)	4.89 (dd)	−0.04
24	1.98 (m)	1.82 (m)	−0.16
24Me	0.92 (d)	0.82 (d)	−0.10
25a, 25b	1.3 (m)	1.3 (m)	
26a, 26b	1.84 (m), 1.22 (m)	1.79 (m), 1.08 (m)	−0.05, −0.14
27	3.95 (m)	3.89 (m)	−0.06
28a, 28b	1.77 (m), 1.57 (m)	1.74 (m), 1.54 (m)	−0.03, −0.03
29	3.52 (m)	3.48 (dddd)	−0.04
29OMe	3.33 (s)	3.33 (s)	0
30a, 30b	1.96 (m), 1.18 (m)	1.94 (m), 1.14 (m)	−0.02, −0.04
31	3.66 (m)	3.57 (m)	−0.09
31Me	1.19 (d)	1.16 (d)	−0.03

a) The spectra were taken in $CDCl_3$.

The configurations at $C_{23,23'}$ in the diacetonide **11** have been determined by the ^{1}H-NMR analysis[17,18] of its di-(+)-(*R*)- and di-(−)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetates (MTPA esters) (**16** and **17**). As given in Table III, due to the anisotropic effect of the benzene rings, the signals due to protons attached to the carbons from C_1 to C_{22} (also from $C_{1'}$ to $C_{22'}$) in the di-(+)-(*R*)-MTPA ester (**16**) were observed at higher fields as compared to those of the di-(−)-(*S*)-MTPA ester (**17**), while the signals due to protons from C_{24} to C_{31} (also from $C_{24'}$ to $C_{31'}$) in **16** were observed at lower fields as compared to those of **17**. Consequently, the absolute configurations at C_{23} and $C_{23'}$ in **11** have been elucidated at 23*S* and 23′*S*.

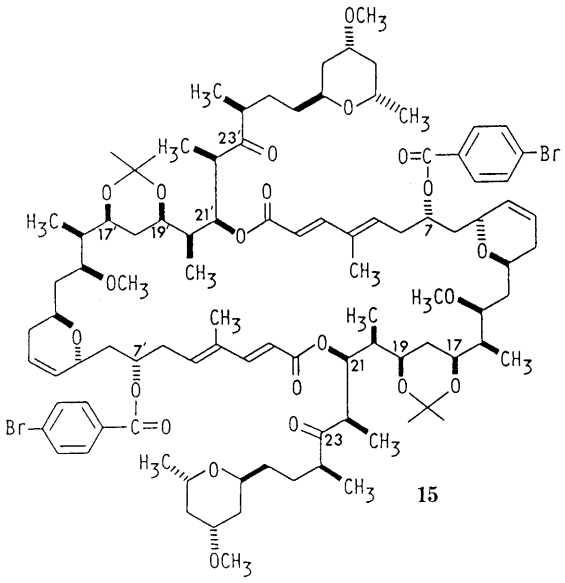
The total absolute stereostructure of **1** has been determined in the following three ways. Firstly, we applied the MTPA method[17,18] to determine the absolute configurations of the C_7 and $C_{7'}$ hydroxyl functions in the diacetonide **11**. Treatment of **11** with (+)-(*R*)- and (−)-(*S*)-MTPA chloride in pyridine at room temperature furnished 7,7′-di-MTPA esters (**18** and **19**), respectively. The comparison of the ^{1}H-NMR data for **18** and **19** (Table IV), as carried out for **16** and **17**, allowed us to determine the absolute configurations at C_7 and $C_{7'}$ in **11** to be 7*S* and 7′*S* as shown.

Table IV. Comparison of the ^{1}H-NMR Data for 7,7′-Di-MTPA Esters **18** and **19**[a]

	7,7′-(+)-(*R*)-MTPA ester **18**	7,7′-(−)-(*S*)-MTPA ester **19**	$\Delta\delta$ ($S-R$)
2	5.85 (d)	5.82 (d)	−0.03
3	7.27 (d)	7.17 (d)	−0.10
4Me	1.80 (s)	1.74 (s)	−0.06
5	5.84 (dd)	5.67 (dd)	−0.17
6a, 6b	2.72 (ddd), 2.68 (ddd)	2.71 (ddd), 2.60 (ddd)	−0.01, −0.08
7	5.34 (m)	5.25 (m)	−0.09
8a, 8b	1.91 (m), 1.71 (m)	1.94 (m), 1.77 (m)	+0.03, +0.06
9	4.13 (br d)	4.26 (br d)	+0.13
10	5.53 (br d)	5.61 (br d)	+0.08
11	5.79 (m)	5.83 (m)	+0.04
12a, 12b	2.00 (m), 1.96 (m)	2.01 (m), 1.98 (m)	+0.01, +0.02
13	3.54 (m)	3.56 (m)	+0.02
14a	1.86 (m)	1.84 (m)	−0.02
14b	1.48 (m)	1.50 (m)	+0.02

a) The spectra were taken in $CDCl_3$.

Secondly, we applied the circular dichroism (CD) exciton chirality method[19] to the 10,11-di-*p*-bromobenzoate (**23**)



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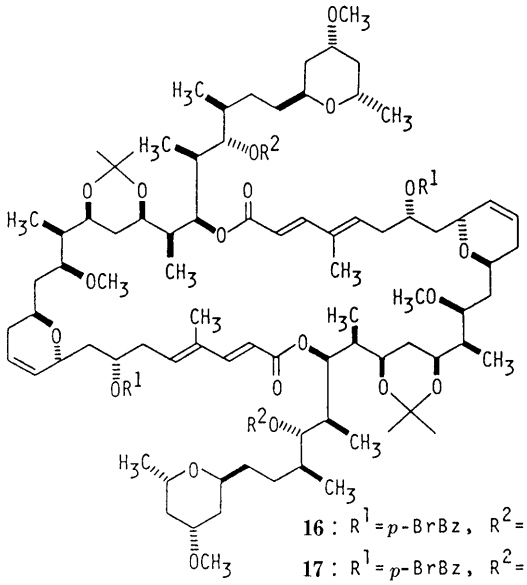
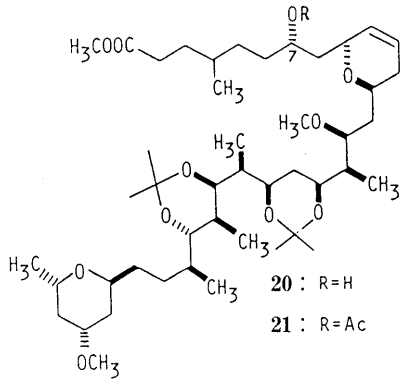
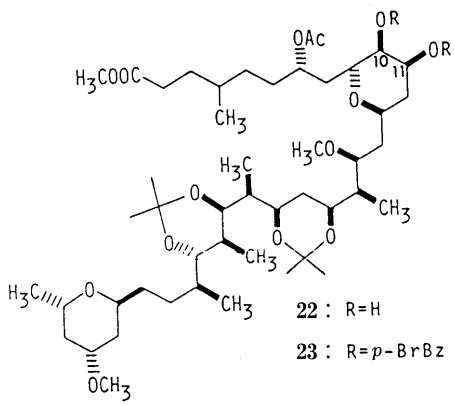


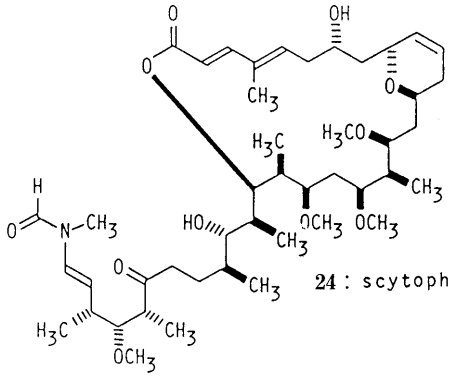
16 : R^1=*p*-BrBz, R^2=(+)-(*R*)-MTPA
17 : R^1=*p*-BrBz, R^2=(-)-(*S*)-MTPA
18 : R^1=(+)-(*R*)-MTPA, R^2=H
19 : R^1=(-)-(*S*)-MTPA, R^2=H



20 : R=H
21 : R=Ac



22 : R=H
23 : R=*p*-BrBz



24 : scytophycin C

Chart 2

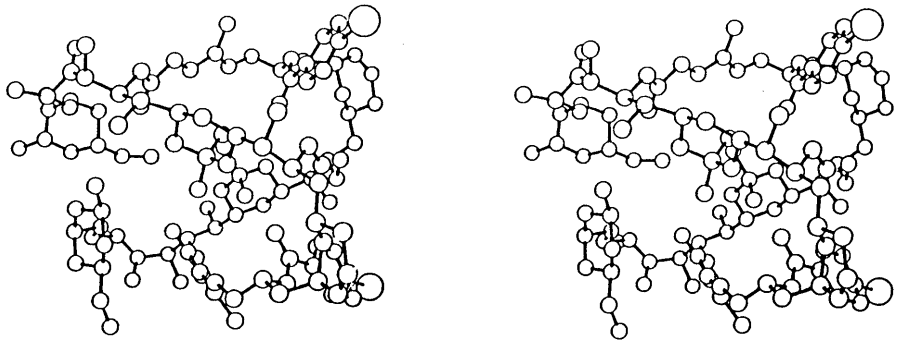


Fig. 1. Computer-Generated Perspective Drawings of the Final X-Ray Model of the Diketone **15**

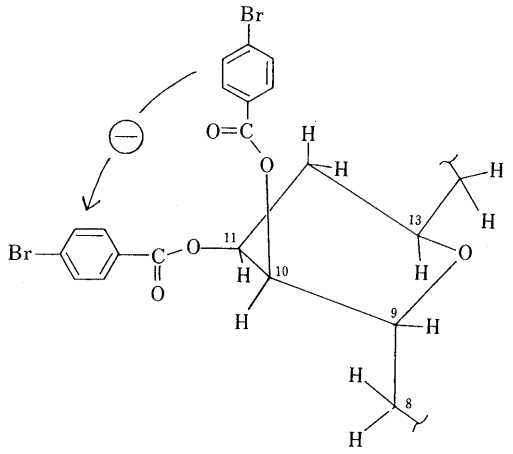


Fig. 2

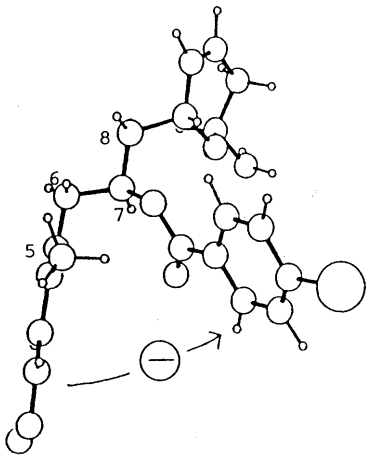


Fig. 3. A Computer-Generated Perspective Drawing of the Partial Structure from C_1 to C_{14} in **15**

which was prepared from the monomeric diacetonide methyl ester **6**. Catalytic hydrogenation over Pd–C of **6** in alkaline methanol solution furnished a 2,3;4,5-tetrahydro derivative (**20**), a diastereomeric mixture of the C_4 configuration. Acetylation of **20** gave the monoacetate **21**, which was subjected to osmium tetroxide oxidation in tetrahydrofuran (THF)–pyridine to provide the 10, 11-diol (**22**). The diol **22** was then further converted to the 10,11-di-*p*-bromobenzoate (**23**). Osmium tetroxide was expected to attack the 10,11-olefin bond in **21** from the opposite side to the neighboring 9β-substituent on the dihydropyran ring.[20] The coupling constants ($J_{9,10}=0$ Hz, $J_{10,11}=2.8$ Hz, $J_{11,12a}=10.2$ Hz, $J_{11,12e}=5.3$ Hz) observed in the ^{1}H-NMR spectrum of **23** indicated that the relative stereochemistry of the tetrahydropyran ring in **23** may be depicted as shown in Fig. 2. The CD spectrum (in methanol) of **23** showed a negative CD maximum ($\Delta\varepsilon-41.5$ at 253 nm), so that the absolute configurations at C_9 and C_{13} in **23** and consequently in **1** have been confirmed as *R* and *S*, respectively.

Thirdly, the diketone **15** showed a typical strongly split CD ($\Delta\varepsilon-76$ at 272 nm, $\Delta\varepsilon+80$ at 241 nm), which may arise from exciton coupling between the 7-*p*-bromobenzoate moiety and the 2,4-dienoate chromophore (and also between the 7′-moiety and the 2′,4′-dienoate). This finding indicates that the chiralities between the 7- and 7′-*p*-bromobenzoate moieties and the 2,4- and 2′,4′-dienoate chromophores respectively through the C_6–C_7 and $C_{6'}$–$C_{7'}$ bonds should be negative.[19] In the ^{1}H-NMR spectrum (in CD_3OD) of **15**, signals due to $H_{6a,6b}$ and H_7 were observed with the respective couplings of $J=6.4$ and 6.4 Hz, so that the dihedral angle between the C_6–C_5 bond and the C_7–OBz moiety (also between $C_{6'}$–$C_{5'}$ and $C_{7'}$–OBz) in **15** in methanolic solution appears to be very similar to those [$-67.3(6)°$ for C_5–C_6–C_7–OBz and -73.1 (7)° for $C_{5'}$–$C_{6'}$–$C_{7'}$–OBz] in the crystal of **15** as shown in Fig. 3. The result thus obtained was consistent with those obtained by the above two methods.

Based on the accumulated evidence mentioned above, the absolute stereostructure of swinholide A has been confirmed to be 7*S*, 7′*S*, 9*R*, 9′*R*, 13*S*, 13′*S*, 15*S*, 15′*S*, 16*S*, 16′*S* 17*S*, 17′*S*, 19*R*, 19′*R*, 20*S*, 20′*S*, 21*S*, 21′*S*, 22*S*, 22′*S*, 23*S*, 23′*S*, 24*S*, 24′*S*, 27*S*, 27′*S*, 29*R*, 29′*R*, 31*S*, 31′*S*, shown as **1**.

Swinholide A (**1**) showed strong cytotoxicity against KB cell lines with an IC_{50} value of 0.04 μg/ml.[13] Moore and his group isolated a cytotoxic monomeric macrolide, scytophycin C (**24**), from the cultured terrestrial blue-green alga *Scytonema pseudohofmanni* and determined the absolute stereochemistry on the basis of X-ray crystallographic analysis.[20] The atomic array in the structure of the monomeric units in swinholide A (**1**) is mostly very similar to that in scytophycin C (**24**) and the configurations at the asymmetric carbons in **1** are the same as those in **24**. These facts may indicate the participation of a symbiotic organism in the biosynthesis of swinholide A (**1**) in our marine sponge *Theonella swinhoei*. By means of electron microscopic analysis, we have recently found a symbiotic blue-green alga inhabiting our marine sponge. We are currently engaged in a cultivation study of this symbiotic alga in order to identify the genuine producer of swinholide A (**1**) in our marine sponge.

Experimental

The instruments used to obtain physical data and the experimental conditions for chromatography were the same as described in our previous paper[1] except that FABMS were recorded with a JEOL JMS-HX100 spectrometer and SIMS with a Hitachi M-80 spectrometer.

Isolation of Swinholide A (1) The marine sponge *Theonella swinhoei* (160 kg, wet) was collected at Kuro Island, Okinawa, in April 1988. The frozen sample was steeped in acetone (250 l), and the filtrate was evaporated *in vacuo* to give an aqueous suspension, which was extracted with ethyl acetate (110 l). The ethyl acetate layer, after evaporation *in vacuo*, gave the extract (2.66 kg), and 600 g of the extract was suspended in a hexane–ethyl acetate mixture (2:1). The precipitate (theonellapeptolide$^{2-4}$) containing fraction) was separated by decantation and the supernatant solution was applied to a silica gel (400 g) column which was then successively eluted with hexane–ethyl acetate (2:1), ethyl acetate, and ethyl acetate–methanol mixtures. Some of the fractions eluted with ethyl acetate and ethyl acetate–methanol mixtures were collected to give crude swinholide A (**1**) (6.35 g) as an off-white amorphous solid. Final purification was carried out by reversed-phase HPLC using aqueous methanol as an eluant. Swinholide A (**1**): A white amorphous solid, $[\alpha]_D^{24}+16°$ ($c=1.3$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3000, 2940, 1675, 1615, 1180, 985. UV ν_{max}^{MeOH} nm (ε): 270 (41400). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: Table I. ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: Table II. FABMS *m/z*: 1411 $(M+Na)^+$, 1388 $(M)^-$. *Anal.* Calcd for $C_{78}H_{132}O_{20}\cdot H_2O$: C, 65.70; H, 9.61. Found: C, 66.00; H, 9.64.

Formylation of Swinholide A (1) to Give the Octaformate 2 A solution of swinholide A (**1**) (134 mg) in formic acid (2 ml) was stirred at room temperature for 3 d. The reaction mixture was poured into a mixture of ethyl acetate and saturated aqueous $NaHCO_3$ solution. The ethyl acetate layer was separated, washed with brine, dried over $MgSO_4$, and then

evaporated *in vacuo* to give the crude product (137 mg), which was purified by HPLC [Cosmosil $5C_{18}$, MeOH–H_2O (10 : 1)] to give the octaformate **2** (31 mg, 22%). The octaformate **2**: A glassy solid, $[\alpha]_D^{24}$ −7.5° (c = 1.6, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2980, 2940, 1720, 1620, 1460, 1380, 1180, 980. UV λ_{max}^{MeOH} nm (ε): 266 (40500). ^{1}H-NMR (500 MHz, C_6D_6) δ: 8.54, 7.96, 7.80, 7.63 (each 2H, s, formate), 7.65 (2H, d, J = 16 Hz, $H_{3,3'}$), 6.07 (2H, d, J = 16 Hz, $H_{2,2'}$), 5.89 (2H, dd, J = 7, 7 Hz, $H_{5,5'}$), 5.61 (2H, m, $H_{11,11'}$), 5.54 (2H, d, J = 10.5 Hz, $H_{21,21'}$), 5.49 (4H, m, $H_{7,7'}$, $H_{17,17'}$), 5.34 (2H, d, J = 10 Hz, $H_{10,10'}$), 5.21 (2H, dd, J = 7, 7 Hz, $H_{19,19'}$), 4.96 (2H, m, $H_{23,23'}$), 4.22 (2H, m, $H_{9,9'}$), 3.85 (2H, m, $H_{27,27'}$), 3.67 (2H, d, J = 10 Hz, $H_{15,15'}$), 3.51 (2H, m, $H_{31,31'}$), 3.28 (2H, m, $H_{29,29'}$), 3.25 (6H, s, $H_{15,15'\text{-OMe}}$), 3.15 (2H, m, $H_{13,13'}$), 3.12 (6H, s, $H_{29,29'\text{-OMe}}$), 2.70 (2H, ddd, J = 14, 7, 7 Hz, $H_{6a,6'a}$), 2.47 (2H, m, $H_{6b,6'b}$), 2.45 (2H, m, $H_{20,20'}$), 2.24 (2H, dq, J = 7, 7 Hz, $H_{22,22'}$), 2.00 (4H, dd, J = 7, 7 Hz, $H_{18,18'}$), 1.91 (2H, m, $H_{24,24'}$), 1.66 (6H, s, $H_{4,4'\text{-Me}}$), 1.18 (6H, d, J = 6 Hz, $H_{31,31'\text{-Me}}$), 1.17 (6H, d, J = 7 Hz, $H_{22,22'\text{-Me}}$), 0.91 (6H, d, J = 7 Hz, $H_{20,20'\text{-Me}}$), 0.84 (6H, d, J = 7 Hz, $H_{16,16'\text{-Me}}$), 0.81 (6H, d, J = 6.5 Hz, $H_{24,24'\text{-Me}}$). ^{13}C-NMR (125 MHz, C_6D_6) δ_C: 166.1 (s, $C_{1,1'}$), 161.0 (d, $C_{17,17'\text{-formyl}}$), 160.9 (d, $C_{23,23'\text{-formyl}}$), 160.7 (d, $C_{7,7'\text{-formyl}}$), 160.3 (d, $C_{19,19'\text{-formyl}}$), 149.0 (d, $C_{3,3'}$), 136.4 (s, $C_{4,4'}$), 134.5 (d, $C_{5,5'}$), 129.6 (d, $C_{10,10'}$), 124.4 (d, $C_{11,11'}$), 117.6 (d, $C_{2,2'}$), 78.6 (d, $C_{23,23'}$), 75.4 (d, $C_{15,15'}$), 73.5 (d, $C_{29,29'}$), 71.5 (d, $C_{21,21'}$), 71.4 (d, $C_{17,17'}$), 70.6 (d, $C_{27,27'}$), 69.9 (d, $C_{19,19'}$), 69.4 (d, $C_{7,7'}$), 68.8 (d, $C_{9,9'}$), 64.8 (d, $C_{31,31'}$), 63.8 (d, $C_{13,13'}$), 56.3 (q, $C_{15,15'\text{-OMe}}$), 55.0 (q, $C_{29,29'\text{-OMe}}$), 40.4 (d, $C_{16,16'}$), 38.8 (t, $C_{30,30'}$), 36.4 (t, $C_{8,8'}$), 35.8 (d, $C_{20,20'}$), 35.6, (2C, t, $C_{14,14'}$, $C_{28,28'}$), 34.0 (t, $C_{18,18'}$), 33.7 (d, $C_{24,24'}$), 33.0 (t, $C_{6,6'}$), 31.6 (t, $C_{12,12'}$), 29.3 (t, $C_{26,26'}$), 26.6 (t, $C_{25,25'}$), 21.9 (q, $C_{31,31'\text{-Me}}$), 17.0 (q, $C_{24,24'\text{-Me}}$), 12.4 (q, $C_{4,4'\text{-Me}}$), 10.3 (q, $C_{22,22'\text{-Me}}$), 9.8 (q, $C_{20,20'\text{-Me}}$), 8.7 (q, $C_{16,16'\text{-Me}}$). FABMS m/z: 1635 $(M+Na)^+$.

Methanolysis of Swinholide A (1) to Give the Methyl Ester 5 A solution of swinholide A (**1**) (1 g) in dry methanol (10 ml) was treated dropwise with a 28% sodium methoxide–methanol solution (2 ml). The reaction mixture was stirred for 1 h at room temperature under a nitrogen atmosphere. The whole was then partitioned into an ethyl acetate–1 N HCl mixture, and the ethyl acetate layer was taken and washed with saturated $NaHCO_3$ solution, then with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give the methyl ester **5** (992 mg, 95%). Methyl ester **5**: A white amorphous powder, $[\alpha]_D^{24}$ −31° (c = 2.8, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 3000, 2930, 1700, 1620, 1455, 1380, 980. UV λ_{max}^{MeOH} nm (ε): 268 (19000). ^{1}H-NMR (500 MHz, C_6D_6) δ: Table I. ^{13}C-NMR (125 MHz, C_6D_6) δ_C: Table II. FABMS m/z: 727 $(M+H)^+$.

Ozonolysis of the Methyl Ester 5 and Preparation of the Trisemicarbazone 7 A solution of the methyl ester (**5**) (60 mg) in methanol (10 ml) and pyridine (0.5 ml) was bubbled with a stream of ozonated O_2 at −78 °C for 1 min. Dimethyl sulfide (3 ml) was added to the reaction mixture, and the mixture was stirred for 1 h while gradually warming to room temperature. Then, a solution of sodium acetate trihydrate (90 mg) and semicarbazide hydrochloride (73 mg) in methanol–water (1 : 1, 1 ml) was added, and the reaction mixture was stirred for 2 h. The whole was partitioned into a mixture of ethyl acetate–butanol (1 : 1) and water, and the organic layer was taken and washed with brine, dried over $MgSO_4$, and then evaporated under reduced pressure. The crude product (66 mg) was purified by HPLC [Shimpac ODS, MeOH–H_2O (3 : 1)] to give the trisemicarbazone **7** (40 mg, 58%). The trisemicarbazone **7**: A white amorphous powder, IR ν_{max}^{neat} cm^{-1}: 3360, 2930, 1675, 1580, 1425, 1380, 965. UV λ_{max}^{MeOH} nm (ε): 231 (31500). ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.30 (1H, t, J = 5.6 Hz), 7.25 (1H, t, J = 5.5 Hz), 7.12 (1H, d, J = 7.3 Hz). FABMS m/z: 834 $(M+H)^+$.

Alkaline Treatment of the Trisemicarbazone 7 to Give the Cyclic Semicarbazone 9 A solution of the trisemicarbazone **7** (186 mg) in dry methanol (3 ml) was treated with 28% sodium methoxide–methanol solution (1 ml), and the whole mixture was refluxed for 2 h. The reaction mixture was then partitioned into a mixture of ethyl acetate–butanol (1 : 1) and water. The organic layer was taken, dried over $MgSO_4$, and evaporated under reduced pressure to provide the crude product (301 mg), which was purified by HPLC [Develosil, MeOH–H_2O (4 : 3)] to furnish the cyclic semicarbazone **9** (26 mg, 17%). The cyclic semicarbazone **9**: $[\alpha]_D^{22}$ +1.3° (c = 0.32, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 2935, 1685, 1565, 1460, 1380, 970. UV ν_{max}^{MeOH} nm (ε): 227 (9800). ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.30 (1H, dd, J = 5.6, 5.6 Hz, H_{11}), 4.25 (1H, ddd, J = 7.5, 5.0, 2.0 Hz, H_{19}), 4.03 (1H, dd, J = 10.0, 1.5 Hz, H_{21}), 3.98 (1H, m, H_{27}), 3.76 (1H, ddq, J = 9.5, 2.5, 7.0 Hz, H_{31}), 3.60 (2H, m, $H_{13,29}$), 3.36, 3.33 (both 3H, s, $H_{15,29\text{-OMe}}$), 3.35 (1H, m, H_{23}), 3.19 (1H, ddd, J = 10, 10, 2.5 Hz, H_{17}), 2.99 (1H, ddd, J = 12.5, 4.5, 1.8 Hz, H_{15}), 2.43 (2H, m, $H_{12a,12b}$), 2.19 (1H, ddd, J = 13, 10.5, 5 Hz, H_{14a}), 1.52 (1H, ddd, J = 12.8, 10.3, 5.5 Hz, H_{28a}), 1.18 (3H, d, J = 7 Hz, $H_{31\text{-Me}}$), 1.10 (1H, ddd, J = 12.5, 10, 9.5 Hz, H_{30b}), 0.95 (3H, d, J = 7.0 Hz, $H_{16\text{-Me}}$), 0.93 (3H, d, J = 7.0 Hz, $H_{24\text{-Me}}$), 0.89 (3H, d, J = 7.0 Hz, $H_{22\text{-Me}}$), 0.77 (3H, d, J = 7.0 Hz, $H_{20\text{-Me}}$). ^{13}C-NMR (125 MHz, CD_3OD) δ_C: 159.8 (s, carbonyl), 144.6 (d, C_{11}), 83.1 (d, C_{15}), 82.3 (d, C_{17}), 80.2 (d, C_{23}), 74.8 (d, C_{13}), 74.5 (d, C_{29}), 73.6 (d, C_{27}), 72.5 (d, C_{21}), 70.9 (d, C_{19}), 66.1 (d, C_{31}), 56.5 (q, $C_{15\text{-OMe}}$), 55.6 (q, $C_{29\text{-OMe}}$), 43.5 (d, C_{16}), 41.2 (d, C_{20}), 40.0 (t, C_{30}), 39.7 (t, C_{12}), 38.4 (t, C_{18}), 37.4 (t, C_{14}), 36.8 (d, C_{22}), 36.3 (d, C_{24}), 35.9 (t, C_{28}), 30.2 (t, C_{26}), 28.2 (t, C_{25}), 22.0 (q, $C_{31\text{-Me}}$), 17.2 (q, $C_{24\text{-Me}}$), 13.2 (q, $C_{16\text{-Me}}$), 10.2 (q, $C_{22\text{-Me}}$), 9.2 (q, $C_{20\text{-Me}}$), SIMS m/z: 596 $(M+Na)^+$, 574 $(M+H)^+$. High-resolution SIMS Found: 574.397. Calcd for $C_{29}H_{56}N_3O_8$: 574.406.

Preparation of the Diacetonide Methyl Ester 6 A solution of swinholide A methyl ester **5** (992 mg) in 2,2-dimethoxypropane (10 ml) was treated with *p*-toluenesulfonic acid monohydrate (*p*-TsOH) (10 mg). The reaction mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then, the mixture was poured into a mixture of ethyl acetate and saturated aqueous $NaHCO_3$. The ethyl acetate layer was taken, washed with brine, dried over $MgSO_4$, and then evaporated under reduced pressure. The crude product (1.02 g) was purified on a silica gel column with benzene–acetone mixture. The fractions eluted with benzene–acetone (7 : 1) were collected and the solvent was evaporated under reduced pressure to give the diacetonide **6** (770 mg, 70%). The diacetonide **6**: A white amorphous powder, $[\alpha]_D^{26}$ −26° (c = 1.3, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 2990, 2840, 1700, 1620, 1455, 1380, 980. UV ν_{max}^{MeOH} nm (ε): 266 (16000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.36 (1H, d, J = 15.8 Hz, H_3), 6.02 (1H, dd, J = 7.3, 7.3 Hz, H_5), 5.82 (1H, d, J = 15.8 Hz, H_2), 5.81 (1H, m, H_{11}), 5.63 (1H, dd, J = 10.4, 1.8 Hz, H_{10}), 4.49 (1H, br d, J = 7.6 Hz, H_9), 3.75 (3H, s, Me ester), 1.80 (3H, s, $H_{4\text{-Me}}$), 1.42, 1.37, 1.32, 1.30 (each 3H, acetonide), 1.20 (3H, d, J = 6.4 Hz, $H_{31\text{-Me}}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 167.6 (s, C_1), 149.3 (d, C_3), 137.7 (d, C_5), 134.3 (s, C_4), 129.5 (d, C_{11}), 123.6 (d, C_{10}), 115.3 (d, C_2), 100.2, 98.2 (each s, acetonide), 57.8 (q, $C_{15\text{-OMe}}$), 55.0 (q, $C_{29\text{-OMe}}$), 51.2 (q, $C_{Me\text{-ester}}$), 30.1, 25.8, 23.4, 19.9 (each q, acetonide). FABMS m/z: 829 $(M+Na)^+$, 807 $(M+H)^+$.

Ozonolysis of the Diacetonide 6 and Preparation of the Trisemicarbazone 8 A solution of diacetonide methyl ester (**6**) (390 mg) in methanol (15 ml) and pyridine (0.75 ml) was bubbled with a stream of ozonated O_2 at −78°C for 10 min. After the removal of excess ozone by bubbling nitrogen, dimethyl sulfide (3 ml) was added, and the whole mixture was stirred for 1 h while warming to room temperature. Then, a solution of sodium acetate trihydrate (520 mg) and semicarbazide hydrochloride (430 mg) in methanol (0.5 ml) and water (0.5 ml) was added, and the mixture was stirred for further 2 h, then partitioned into a mixture of ethyl acetate–butanol (1 : 1) and water. The organic layer was taken and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to provide the crude product (600 mg). The product was purified by HPLC [Shimpac ODS, MeOH–H_2O (10 : 1)] to furnish the trisemicarbazone **8** (380 mg, 86%). The trisemicarbazone **8**: an amorphous powder, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 3420, 2990, 2940, 1690, 1565, 1425, 1380. UV λ_{max}^{MeOH} nm (ε): 232 (33400). ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.29 (1H, t, J = 5.8 Hz, H_5 or H_{11}), 7.24 (1H, t, J = 5.5 Hz, H_5 or H_{11}), 7.09 (1H, d, J = 7.0 Hz, H_{10}). FABMS m/z: 936 $(M+Na)^+$, 914 $(M+H)^+$.

Alkaline Degradation of the Trisemicarbazone 8 A solution of the trisemicarbazone (**8**) (324 mg) in dry methanol (3 ml) was treated with 28% sodium methoxide–methanol solution (0.5 ml). The reaction mixture was refluxed for 2 h, then the whole was partitioned into a mixture of ethyl acetate–butanol (1 : 1) and water. The organic layer was taken and dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a crude product (260 mg), which was purified by HPLC [Shimpac ODS, MeOH–H_2O (20 : 1)] to give the unsaturated semicarbazone **10** (178 mg, 77%). The unsaturated semicarbazone **10**: Amorphous powder, $[\alpha]_D^{24}$ −21° (c = 3.8, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 3420, 2990, 2940, 1690, 1565, 1460, 1380, 980. UV ν_{max}^{MeOH} nm (ε): 266 (24000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.36 (1H, d, J = 9.2 Hz, H_{11}), 6.10 (1H, dd, J = 15.4, 9.2 Hz, H_{12}), 5.90 (1H, ddd, J = 15.4, 7.3, 7.3 Hz, H_{13}), 4.17 (1H, m, H_{19}), 3.91 (1H, m, H_{27}), 3.71 (1H, m, H_{17}), 3.64 (2H, m, $H_{21,31}$), 3.57 (1H, dd, J = 7.3, 7.3 Hz, H_{15}), 3.45 (1H, dddd, J = 10.0, 10.0, 4.5, 4.5 Hz, H_{29}), 3.27 (3H, s, $H_{15\text{-OMe}}$), 3.27 (3H, s, $H_{29\text{-OMe}}$), 3.02 (1H, dd, J = 6.0, 6.0 Hz, H_{23}), 2.45 (1H, ddd, J = 14.1, 7.3, 7.3 Hz, H_{14a}), 2.15 (1H, ddd, J = 14.1, 7.3, 7.3 Hz, H_{14b}), 1.90 (1H, br d, J = 12.8 Hz, H_{30a}), 1.33, 1.28, 1.25, 1.22 (each 3H, s, acetonide), 1.13 (3H, d, J = 6.4 Hz, $H_{31\text{-Me}}$), 0.87 (3H, d, J = 6.7 Hz, $H_{24\text{-Me}}$), 0.78 (3H, d, J = 6.8 Hz, $H_{22\text{-Me}}$), 0.73 (3H, d, J = 6.4 Hz, $H_{16\text{-Me}}$ or $H_{20\text{-Me}}$), 0.70 (3H, d, J = 6.8 Hz, $H_{16\text{-Me}}$ or $H_{20\text{-Me}}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 158.3 (s, carbonyl), 144.1 (d, C_{11}), 138.4 (d, C_{13}), 128.8 (d, C_{12}), 100.4, 98.3 (both s, acetonide), 30.3, 26.0, 23.6, 20.1 (each q, acetonide). FABMS m/z: 654 $(M+H)^+$.

Acid Treatment of 10 to Give the Cyclic Semicarbazone 9 A solution of **10** (100 mg) in 80% aqueous acetic acid (5 ml), was stirred at 80 °C

30 min. After evaporation of the solvent from the reaction mixture under reduced pressure, the resulting residue was separated by HPLC [Develosil, MeOH–H_2O (5 : 1)] to furnish the cyclic semicarbazone **9** (61 mg, 70%). Compound **9** obtained here showed identical spectral data with those of **9** derived from trisemicarbazone **7**.

Preparation of Swinholide A 17,19; 17′,19′-Diacetonide (11) A stirred solution of swinholide A (**1**) (100 mg) in 2,2-dimethoxypropane (2 ml) was treated with *p*-TsOH (5 mg), and the whole was stirred for 1 h under a nitrogen atmosphere at room temperature. The reaction mixture was partitioned into a mixture of ethyl acetate and a saturated $NaHCO_3$ solution. The ethyl acetate layer was taken, washed with brine, dried over $MgSO_4$, and then evaporated *in vacuo*. The crude product (101 mg) was purified by HPLC [Cosmosil $5C_{18}$, MeOH–H_2O (20 : 1)] to furnish the diacetonide (**11**) (75 mg, 71%) as a white amorphous powder. Swinholide A 17,19;17′,19′-diacetonide (**11**): $[\alpha]_D^{24}$ −70° (*c*=5.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 2990, 2945, 1685, 1620, 1460, 1380, 985. UV λ_{max}^{MeOH} nm (ε): 268 (41800). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35 (2H, d, *J*=15.6 Hz, $H_{3,3'}$), 6.01 (2H, dd, *J*=6.8, 6.8 Hz, $H_{5,5'}$), 5.82 (2H, d, *J*=15.6 Hz, $H_{2,2'}$), 5.81 (2H, m, $H_{11,11'}$), 5.64 (2H, dd, *J*=10.4, 2.0 Hz, $H_{10,10'}$), 5.41 (2H, d, *J*=10.4 Hz, $H_{21,21'}$), 4.47 (2H, br d, *J*=8.8 Hz, $H_{9,9'}$), 4.07 (2H, m, $H_{7,7'}$), 4.01 (2H, m, $H_{27,27'}$), 3.88 (2H, m, $H_{19,19'}$), 3.80 (2H, m, $H_{13,13'}$), 3.77 (2H, m, $H_{17,17'}$), 3.71 (2H, m, $H_{15,15'}$), 3.66 (2H, m, $H_{31,31'}$), 3.54 (2H, dddd, *J*=10.2, 10.2, 4.6, 4.6 Hz, $H_{29,29'}$), 3.34, 3.33 (both 6H, s, $H_{15,15'\text{-OMe}}$, $H_{29,29'-\text{OMe}}$), 2.96 (2H, d, *J*=9.8 Hz, $H_{23,23'}$), 2.48 (2H, ddd, *J*=15, 7, 7 Hz, $H_{6a,6'a}$), 2.41 (2H, ddd, *J*=15, 6, 6 Hz, $H_{6b,6'b}$), 2.22 (2H, br d, *J*=17 Hz, $H_{12a,12'a}$), 1.82 (6H, s, $H_{4,4'\text{-Me}}$), 1.31, 1.24 (both 6H, s, acetonide), 1.20 (6H, d, *J*=6.1 Hz, $H_{31,31'\text{-Me}}$), 1.00 (6H, d, *J*=6.7 Hz, $H_{24,24'\text{-Me}}$), 0.90 (6H, d, *J*=7.0 Hz, $H_{20,20'\text{-Me}}$), 0.81 (6H, d, *J*=7.0 Hz, $H_{22,22'\text{-Me}}$), 0.79 (6H, d, *J*=7.0 Hz, $H_{16,16'\text{-Me}}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 168.5 (s, $C_{1,1'}$), 98.6 (s, acetonide), 30.2, 19.6 (both q, acetonide). FABMS *m/z*: 1491 $(M+Na)^+$.

***p*-Bromobenzoylation of 11** A solution of the diacetonide (**11**) (25 mg) in dry pyridine (2 ml) was treated with *p*-bromobenzoyl chloride (155 mg). The reaction mixture was warmed to 70°C and stirred for 2 h under a nitrogen atmosphere. The resulting mixture was partitioned into a mixture of ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The organic layer was taken, washed with brine, dried over $MgSO_4$, and then evaporated *in vacuo* to provide the crude product (72 mg), which was separated by HPLC [Cosmosil $5C_{18}$, MeOH–EtOAc (10 : 3)] to afford three products: the di-*p*-bromobenzoate (**12**) (3 mg, 9%), the tri-*p*-bromobenzoate (**13**) (10 mg, 29%), and the tetra-*p*-bromobenzoate (**14**) (7 mg,. 18%). The di-*p*-bromobenzoate (**12**): A white amorphous powder, $[\alpha]_D^{24}$ −93° (*c*=3.4, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490, 2990, 2945, 1720, 1620, 1590, 1380, 1270, 985. UV λ_{max}^{MeOH} nm (ε): 250 (65900), 267 (sh, 60100). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.87, 7.59 (both 4H, d, *J*=8.5 Hz, benzoate), 7.33 (2H, d, *J*=15.6 Hz, $H_{3,3'}$), 5.97 (2H, dd, *J*=7, 7 Hz, $H_{5,5'}$), 5.84 (2H, d, *J*=15.6 Hz, $H_{2,2'}$), 5.83 (2H, m, $H_{11,11'}$), 5.66 (2H, d, *J*=9.8 Hz, $H_{10,10'}$), 5.41 (2H, d, *J*=10.1 Hz, $H_{21,21'}$), 5.34 (2H, dddd, *J*=6.4, 6.4, 6.4, 6.4 Hz, $H_{7,7'}$), 4.31 (2H, br d, *J*=9.5 Hz, $H_{9,9'}$), 4.01 (2H, m, $H_{27,27'}$), 3.88 (2H, m, $H_{19,19'}$), 3.79 (2H, m, $H_{17,17'}$), 3.70 (4H, m, $H_{15,15'}$ and $H_{31,31'}$), 3.61 (2H, m, $H_{13,13'}$), 3.55 (2H, dddd, *J*=10.4, 10.4, 4.6, 4.6 Hz, $H_{29,29'}$), 3.34, 3.29 (both 6H, s, $H_{15,15'\text{-OMe}}$ and $H_{29,29'\text{-OMe}}$), 2.95 (2H, br d, *J*=7.6 Hz, $H_{23,23'}$), 2.80 (2H, ddd, *J*=15.6, 6.1, 6.1 Hz, $H_{6a,6'a}$), 2.70 (2H, ddd, *J*=15.6, 7.3, 7.3 Hz, $H_{6b,6'b}$), 1.80 (6H, s, $H_{4,4'\text{-Me}}$), 1.33, 1.23 (both 6H, s, acetonide), 1.20 (6H, d, *J*=6.1 Hz, $H_{31,31'\text{-Me}}$), 1.00 (6H, d, *J*=7.0 Hz, $H_{24,24'\text{-Me}}$), 0.90 (6H, d, *J*=7.0 Hz, $H_{20,20'\text{-Me}}$), 0.81 (6H, d, *J*=6.4 Hz, $H_{22,22'\text{-Me}}$), 0.80 (6H, d, *J*=6.7 Hz, $H_{16,16'\text{-Me}}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 168.5 (s, $C_{1,1'}$), 165.3 (s, benzoate carbonyl), 150.0 (d, $C_{3,3'}$), 136.4 (d, $C_{5,5'}$), 135.3 (s, $C_{4,4'}$), 131.9 (2C, d, benzoate), 131.4 (2C, d, benzoate), 129.2 (s, benzoate), 129.1 (d, $C_{10,10'}$), 128.3 (s, benzoate), 124.8 (d, $C_{11,11'}$), 116.0 (d, $C_{2,2'}$), 98.5 (s, acetonide), 76.0 (d, $C_{15,15'}$), 75.9 (d, $C_{23,23'}$), 74.2 (d, $C_{21,21'}$), 73.4 (d, $C_{29,29'}$), 72.7 (d, $C_{27,27'}$), 71.6 (d, $C_{7,7'}$), 70.3 (d, $C_{17,17'}$), 70.0 (d, $C_{9,9'}$), 67.5 (d, $C_{19,19'}$), 65.1 (d, $C_{13,13'}$), 64.6 (d, $C_{31,31'}$), 58.0 (q, $C_{15,15'\text{-OMe}}$), 55.3 (q, $C_{29,29'\text{-OMe}}$), 42.8 (d, $C_{16,16'}$), 39.1 (d, $C_{20,20'}$), 38.9 (t, $C_{30,30'}$), 38.1 (t, $C_{8,8'}$), 37.8 (t, $C_{14,14'}$), 37.3 (d, $C_{22,22'}$), 35.0 (t, $C_{28,28'}$), 33.8 (t, $C_{6,6'}$), 33.0 (d, $C_{24,24'}$), 32.2 (t, $C_{18,18'}$), 31.1 (t, $C_{12,12'}$), 30.2 (q, acetonide), 29.4 (t, $C_{26,26'}$), 24.2 (t, $C_{25,25'}$), 21.9 (q, $C_{31,31'\text{-Me}}$), 19.6 (q, acetonide), 18.0 (q, $C_{24,24'\text{-Me}}$), 12.6 (q, $C_{4,4'\text{-Me}}$), 9.8 (q, $C_{20,20'\text{-Me}}$), 9.2 (q, $C_{22,22'\text{-Me}}$), 8.1 (q, $C_{16,16'\text{-Me}}$). FABMS *m/z*: 1858 $(M+Na)^+$. The tri-*p*-bromobenzoate (**13**): A white amorphous powder, $[\alpha]_D^{29}$ −67° (*c*=0.78, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 2990, 2940, 1710, 1620, 1590, 1270, 980. UV λ_{max}^{MeOH} nm (ε): 247 (88900), 270 (sh, 63300). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.87, 7.86, 7.77, 7.58, 7.57, 7.42 (each 2H, d, *J*=8.6 Hz, benzoate), 7.35 (1H, d, *J*=15.6 Hz, $H_{3'}$), 7.17 (1H, d, *J*=15.6 Hz, H_3), 6.00 (1H, dd, *J*=7, 7 Hz, $H_{5'}$), 5.87 (1H, m, H_5), 5.86 (2H, m, $H_{11,11'}$), 5.84 (1H, d, *J*=15.8 Hz, $H_{2'}$), 5.68 (1H, d, *J*=11.3 Hz, H_{10} or $H_{10'}$), 5.65 (1H, d, *J*=11.8 Hz, H_{10} or $H_{10'}$), 5.62 (1H, d, *J*=15.8 Hz, H_2), 5.40 (2H, m, $H_{21,21'}$), 5.37 (2H, m, $H_{7,7'}$), 4.97 (1H, dd, *J*=7.3, 5.5 Hz, H_{23}), 4.29 (2H, m, $H_{9,9'}$), 3.34 (3H, s), 3.29 (6H, s), 3.27 (3H, s), 2.94 (1H, br d, *J*=9.8 Hz, $H_{23'}$), 1.80 (3H, s, $H_{4'\text{-Me}}$), 1.64 (3H, s, $H_{4\text{-Me}}$), 1.35, 1.32, 1.27, 1.22 (each 3H, s, acetonide), 1.20 (3H, d, *J*=6.5 Hz, $H_{31\text{-Me}}$ or $H_{31'\text{-Me}}$), 1.04 (3H, d, *J*=7.0 Hz), 1.00 (3H, d, *J*=6.1 Hz, $H_{31\text{-Me}}$ or $H_{31'\text{-Me}}$), 0.97 (3H, d, *J*=7.0 Hz), 0.93 (3H, d, *J*=7.0 Hz), 0.87 (3H, d, *J*=7.0 Hz), 0.80 (3H, d, *J*=7.0 Hz), 0.78 (3H, d, *J*=7.0 Hz), 0.76 (3H, d, *J*=7.0 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 168.7 (s), 166.0 (s), 166.0, 165.9, 165.2 (each s, benzoyl carbonyl), 150.1 (d), 148.6 (d), 136.4 (d), 135.4 (d), 135.3 (d), 132.1 (s), 132.0 (s), 131.8 (4C, d, benzoyl), 131.5 (2C, d, benzoyl), 131.4 (2C, d, benzoyl), 131.3 (s), 131.2 (4C, d, benzoyl), 129.4 (s), 129.3 (s), 129.1 (d), 129.1 (d), 128.2 (s), 127.6 (s), 124.8 (d), 124.8 (d), 117.4 (d), 116.0 (d), 98.5 (2C, s, acetonide), 80.7 (d), 75.9 (d), 75.8 (d), 75.7 (d), 74.2 (d), 73.4 (d), 73.3 (d), 72.4 (d), 72.3 (d), 72.2 (d), 71.6 (d), 71.3 (d), 70.2 (d), 70.0 (d), 69.9 (d), 69.7 (d), 67.3 (d), 67.1 (d), 65.1 (d), 64.9 (d), 64.6 (d), 64.5 (d), 58.1 (q), 58.0 (q), 55.3 (q), 55.3 (q), 42.8 (d), 42.7 (d), 40.2 (d), 39.1 (d), 38.9 (t), 38.1 (t), 38.0 (t), 37.9 (t), 37.7 (t), 37.3 (d), 35.2 (d), 35.1 (2C, t), 33.8 (t), 33.7 (d), 33.0 (d), 32.6 (t), 32.3 (t), 31.2 (t), 31.1 (t), 30.3 (2C, q), 30.2 (t), 29.4 (t), 28.3 (t), 28.2 (t), 24.2 (t), 21.9 (q), 21.7 (q), 19.6 (q), 19.6 (q), 18.0 (q), 16.5 (q), 12.6 (q), 12.4 (q), 11.3 (q), 10.0 (q), 9.8 (q), 9.1 (q), 8.0 (2C, q). FABMS *m/z*: 2041 $(M+Na)^+$, 2019 $(M+H)^+$. The tetra-*p*-bromobenzoate (**14**): A white amorphous powder, $[\alpha]_D^{24}$ −47°C (*c*=0.38, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2990, 2930, 1710, 1620, 1590, 1270, 980. UV λ_{max}^{MeOH} nm (ε): 247 (100000), 270 (sh, 56000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.89, 7.78, 7.59, 7.43 (each 4H, d, *J*=8.6 Hz, benzoate), 7.20 (2H, d, *J*=15.7 Hz, $H_{3,3'}$), 5.88 (2H, m, $H_{5,5'}$), 5.86 (2H, m, $H_{11,11'}$), 5.69 (2H, d, *J*=10.1 Hz, $H_{10,10'}$), 5.63 (2H, d, *J*=15.7 Hz, $H_{2,2'}$), 5.42 (2H, d, *J*=9.5 Hz), 5.38 (2H, m), 4.98 (2H, dd, *J*=7, 7 Hz), 4.29 (2H, m, $H_{9,9'}$), 3.90 (2H, m), 3.76 (6H, m), 3.62 (2H, m), 3.51 (2H, m), 3.46 (2H, m), 3.29, 3.27 (both 6H, s, $H_{15,15'\text{-OMe}}$ and $H_{29,29'\text{-OMe}}$), 2.71 (2H, m), 2.29 (2H, m), 1.64 (6H, s, $H_{4,4'\text{-Me}}$), 1.34, 1.25 (each 6H, s, acetonide), 1.04 (6H, d, *J*=7.0 Hz, $H_{22,22'\text{-Me}}$ or $H_{24,24'\text{-Me}}$), 0.99 (6H, d, *J*=6.1 Hz, $H_{31,31'\text{-Me}}$), 0.98 (6H, d, *J*=6.4 Hz, $H_{22,22'\text{-Me}}$ or $H_{24,24'\text{-Me}}$), 0.91, 0.76 (both 6H, d, *J*=7.0 Hz, $H_{16,16'\text{-Me}}$ and $H_{20,20'\text{-Me}}$). FABMS *m/z*: 2224 $(M+Na)^+$, 2202 $(M+H)^+$.

Swern Oxidation of the Di-*p*-bromobenzoate (12) A solution of oxalyl chloride (18 μl) in dry CH_2Cl_2 (0.5 ml) was prepared with stirring at −78 °C under a nitrogen atmosphere. After 2 min, dimethyl sulfoxide (29 μl) was added dropwise, and then a solution of **12** (34 mg) in CH_2Cl_2 (1.5 ml) was further added dropwise. The reaction mixture was then stirred for a further 15 min, and triethylamine (129 μl) was added dropwise. The whole was stirred for 10 min at −78 °C, and then gradually warmed to room temperature while stirring. The reaction mixture was partitioned into a mixture of ethyl acetate and water, and the ethyl acetate layer was taken, washed with brine, dried over $MgSO_4$, and then evaporated *in vacuo*. The crude product (80 mg) was purified by HPLC [Cosmosil $5C_{18}$, MeOH–EtOAc (5 : 1)] to give the dimeric diketone **15** (28 mg, 83%). The dimeric diketone **15**: Colorless plates, mp 100—101 °C (from MeOH–EtOAc). $[\alpha]_D^{26}$ −56° (*c*=0.99, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2990, 2930, 1710, 1620, 1590, 1450, 1380, 1270, 980. UV λ_{max}^{MeOH} nm (ε): 248 (54700). CD (MeOH) Δε: −76 at 272 nm, +80 at 241 nm. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: Table I. ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: Table II. FABMS *m/z*: 1980 (M + triethanolamine + H)$^+$. *Anal.* Calcd for $C_{98}H_{142}Br_2O_{22}\cdot 2CH_3OH$: C, 63.34; H, 7.97; Br, 8.44. Found: C, 63.06; H, 7.80; Br, 8.40.

Preparation of the 23,23′-Di-(+)-(*R*)-MTPA Ester (16) (+)-(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride (90 mg, 30 mol eq) was added dropwise to a solution of the di-*p*-bromobenzoate (**12**) (10.6 mg) in pyridine (0.5 ml). The reaction mixture was warmed to 70 °C and stirring was continued for 3 h under a nitrogen atmosphere. The reaction mixture was then partitioned into a mixture of ethyl acetate and water, and the ethyl acetate layer was taken, washed with brine, dried over $MgSO_4$, and then evaporated *in vacuo*. The crude product (83 mg) was separated by HPLC [Cosmosil $5C_{18}$, MeOH–EtOAc (5 : 1)] to give the 23,23′-di-(+)-(*R*)-MTPA ester (**16**) (3.2 mg, 24%) and recovered starting material **12** (0.5 mg, 5%). The 23,23′-di-(+)-(*R*)-MTPA ester (**16**): A glassy solid, $[\alpha]_D^{27}$ −37° (*c*=0.32, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2930, 1720, 1620, 1590, 1450, 1380, 980. UV λ_{max}^{MeOH} nm (ε): 252 (53800). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: Table III. ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 166.1 (s), 165.9 (s), 165.2 (s), 148.6 (d), 135.5 (s), 135.2 (s), 132.5 (s), 132.0 (s), 131.8 (2C, d), 131.2 (2C, d), 129.4 (d), 129.1 (s), 128.2 (2C, d), 128.2 (d), 128.0 (2C, d), 124.8 (d), 117.1 (d), 98.4 (s, acetonide), 30.1, 19.6 (both q, acetonide). FABMS *m/z*: 2289 $(M+Na)^+$.

Preparation of the 23,23′-Di-(−)-(*S*)-MTPA Ester (17) The di-*p*-

bromobenzoate (**12**) (10.6 mg) was dissolved in pyridine (0.5 ml) and 90 mg of (−)-(*S*)-MTPA chloride (30 mol eq) was added dropwise. The reaction mixture was warmed to 70 °C and stirring was continued for 3 h under a nitrogen atmosphere. Work-up of the mixture in the usual manner furnished the crude product (84 mg), which was separated by HPLC [Cosmosil $5C_{18}$, MeOH–EtOAc (5 : 1)] to provide the 23,23′-di-(−)-(*S*)-MTPA ester (**17**) (3.3 mg, 25%) and recovered starting material **12** (0.5 mg, 5%). The 23,23′-di-(−)-(*S*)-MTPA ester (**17**): A glassy solid, $[\alpha]_D^{26}$ −35° (c=0.32, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2930, 1720, 1620, 1590, 1450, 1380, 980. UV λ_{max}^{MeOH} nm (ε): 252 (57600). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: Table III. ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 166.0 (s), 165.9 (s), 165.2 (s), 148.9 (d), 135.5 (s), 135.3 (d), 132.2 (s), 131.8 (2C, d), 131.2 (2C, d), 129.5 (d), 129.4 (s), 129.1 (d), 128.3 (2C, d), 128.2 (2C, d), 128.1 (s), 124.8 (d), 116.9 (d), 98.5 (s, acetonide), 30.2, 19.6 (both q, acetonide). FABMS m/z: 2289 $(M+Na)^+$.

Preparation of the 7,7′-Di-(+)-(*R*)-MTPA Ester (18) A solution of the diacetonide **11** (59 mg) in dry pyridine (0.5 ml) was treated dropwise with (+)-(*R*)-MTPA chloride (102 mg, 5 mol eq), and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 3 h. The reaction mixture was then worked up in the usual manner. The crude product (135 mg) was purified by HPLC (Cosmosil $5C_{18}$, MeOH) to give the 7,7′-di-(+)-(*R*)-MTPA eater (**18**) (22 mg, 29%). The 7,7′-di-(+)-(*R*)-MTPA ester (**18**): A glassy solid, $[\alpha]_D^{26}$ −38° (c=1.7, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 2940, 1750, 1700, 1625, 1460, 1385, 990. UV λ_{max}^{MeOH} nm (ε): 263 (39000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: Table IV. ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 168.4 (s), 166.3 (s), 149.6 (d), 135.9 (d), 135.5 (s), 132.2 (s), 129.8 (d), 129.0 (d), 128.5 (2C, d), 127.5 (2C, d), 124.7 (d), 116.5 (d), 98.5 (s, acetonide), 30.1; 19.5 (both q, acetonide). FABMS m/z: 1923 $(M+Na)^+$.

Preparation of the 7,7′-Di-(−)-(*S*)-MTPA Ester (19) The diacetonide **11** (53 mg) was dissolved in dry pyridine (0.5 ml), and (−)-(*S*)-MTPA chloride (91 mg, 5 mol eq) was added dropwise. The reaction mixture was stirred for 1 h under a nitrogen atmosphere at room temperature, then worked up in the usual manner to give the crude product (122 mg), which was purified by HPLC (Cosmosil $5C_{18}$, MeOH) to afford the 7,7′-di-(−)-(*S*)-MTPA ester (**19**) (32 mg, 46%). The 7,7′-di-(−)-(*S*)-MTPA ester (**19**): A glassy solid, $[\alpha]_D^{26}$ −80° (c=1.8, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 2940, 1745, 1695, 1620, 1455, 1380, 985. UV λ_{max}^{MeOH} nm (ε): 263 (37000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: Table IV. ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 168.5 (s), 166.3 (s), 150.0 (d), 135.8 (d), 135.2 (s), 132.3 (s), 129.8 (d), 128.9 (d), 128.5 (2C, d), 127.3 (2C, d), 124.9 (d), 116.2 (d), 98.6 (s, acetonide), 30.2, 19.5 (each q, acetonide). FABMS m/z: 1923 $(M+Na)^+$.

Selective Reduction of the Diacetonide Methyl Ester 6 A solution of the diacetonide methyl ester (**6**) (60 mg) in 0.2 N KOH methanol (5 ml) was treated with palladium on carbon (5 mg). The reaction mixture was stirred under a hydrogen atmosphere for 10 min and then filtered through a Celite pad. The resulting filtrate was partitioned into a mixture of ethyl acetate and water. The ethyl acetate layer was taken, washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and then brine, dried over $MgSO_4$, and evaporated under reduced pressure to give the crude product (59 mg), which was purified by HPLC (Cosmosil $5C_{18}$, MeOH) of furnish the tetrahydrodiacetonide **20** (54 mg, 90%). The tetrahydrodiacetonide **20**: A white amorphous powder, ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 5.70 (2H, m), 3.66 (3H, s), 3.35 (6H, s), 1.42, 1.38, 1.32, 1.25 (each 3H, s, acetonide).

Acetylation of the Tetrahydrodiacetonide 20 Followed by Osmium Tetroxide Oxidation Acetic anhydride (2 ml) was added dropwise to solution of **20** (65 mg) in dry pyridine (5 ml). The reaction mixture was stirred for 1.5 h at room temperature and partitioned into a mixture of ethyl acetate and saturated aqueous $NaHCO_3$ solution. The ethyl acetate layer was taken, washed with brine, dried over $MgSO_4$, and then evaporated to give the monoacetate (**21**) (72 mg, >100%). **21** (13 mg) was dissolved in THF (2 ml) and pyridine (0.5 ml), and 50 μl of an osmium tetroxide solution (prepared by dissolving 1 g of OsO_4 in 10 ml of THF) was added dropwise to the reaction mixture. The mixture was stirred for 1 h at room temperature, then 1 ml of saturated aqueous $NaHSO_3$ solution was added dropwise. Stirring was continued for 30 min, then the mixture was partitioned into a mixture of ethyl acetate and water, and the ethyl acetate layer was taken, dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product (21 mg). Purification of the product on a silica gel column with benzene–acetone (4 : 1) gave the 10,11-diol (**22**) (13 mg, 96%). The 10,11-diol (**22**): A white amorphous powder, ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.93 (1H, m), 4.23 (1H, br dd, J=8.1, 4.3 Hz), 3.98 (2H, m), 3.89 (1H, m), 3.82 (1H, m), 3.80 (1H, m), 3.71 (2H, m), 3.66 (3H, s), 3.60 (2H, m), 3.52 (1H, m), 3.34 (3H, s), 3.32 (3H, s), 3.09 (1H, dd, J=6.0, 6.0 Hz), 2.04 (3H, s), 1.42 , 1.36 , 1.32, 1.29 (each 3H, s, acetonide), 1.21 (3H, d, J=6.4 Hz, $H_{31\text{-Me}}$), 0.94 (3H, d, J=6.6 Hz), 0.87 (3H, d, J=6.4 Hz), 0.85 (3H, d, J=6.8 Hz), 0.80 (3H, d, J=7.3 Hz), 0.78 (3H, d, J=7.3 Hz).

Di-*p*-bromobenzoylation of the 10,11-Diol (22) A solution of **22** (13 mg) in dry pyridine (2 ml) was treated with *p*-bromobenzoyl chloride (30 mg) and *N*,*N*-dimethyl aminopyridine (10 mg). The whole mixture was stirred at 60 °C for 1 h under a nitrogen atmosphere. The reaction mixture was then partitioned into a mixture of ethyl acetate and water, and the organic layer was taken, washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and then evaporated *in vacuo*. The crude product (28 mg) was purified by HPLC [μPorasil, hexane–ethyl acetate (3 : 1)] to give the 10,11-di-*p*-bromobenzoate (**23**) (6 mg, 33%). The 10,11-di-*p*-bromobenzoate **23**: A white amorphous powder, CD (MeOH) $\Delta\varepsilon$: −41.5 and 253 nm. ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.92, 7.73, 7.68, 7.55 (each 2H, d, J=8.5 Hz, benzoate), 5.56 (1H, ddd, J=10.2, 5.3, 2.8 Hz, H_{11}), 5.39 (1H, d, J=2.8 Hz, H_{10}), 5.06 (1H, m, H_7), 4.26 (1H, dd, J=7.1, 7.1 Hz, H_{19}), 4.16 (1H, m, H_9), 3.90 (3H, m, $H_{13,17,27}$), 3.82 (1H, m, H_{15}), 3.75 (1H, m, H_{31}), 3.71 (1H, dd, J=10.8, 3.8 Hz, H_{21}), 3.64 (3H, s, methyl ester), 3.36, 3.32 (both 3H, s, $H_{15,29\text{-OMe}}$), 3.15 (1H, dd, J=6.4, 4.9 Hz, H_{23}), 2.33 (3H, m), 2.18 (1H, m, H_{8a}), 2.03 (3H, s, acetate), 1.44, 1.34, 1.30, 1.29 (each 3H, s, acetonide), 1.17 (3H, d, J=6.1 Hz, $H_{31\text{-Me}}$), 0.96 (3H, d, J=7.0 Hz, $H_{24\text{-Me}}$), 0.90 (3H, d, J=6.1 Hz, $H_{4\text{-Me}}$), 0.87 (3H, d, J=6.7 Hz, $H_{22\text{-Me}}$), 0.82 (6H, d, J=7.0 Hz, $H_{16\text{-Me},20\text{-Me}}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 174.3, 170.5, 165.2, 165.0, 132.0 (2C), 131.8 (2C), 131.3 (2C), 131.1 (2C), 128.9, 128.7, 128.6, 128.5, 100.5, 98.4, 79.1, 76.7, 73.4, 73.0, 72.3, 71.2, 70.9, 70.2, 68.9, 68.5, 67.0, 66.4, 64.6, 58.4, 55.3, 51.5, 43.0, 38.9, 38.2, 37.7, 37.0, 35.2, 34.9, 33.5, 32.6, 32.5, 32.1, 31.9, 31.8, 31.7, 30.4, 29.2, 28.2, 26.0, 23.7, 21.9, 21.2, 20.2, 19.1, 16.0, 12.6, 8.5, 8.3. FABMS m/z: 1275 $(M+Na)^+$.

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