

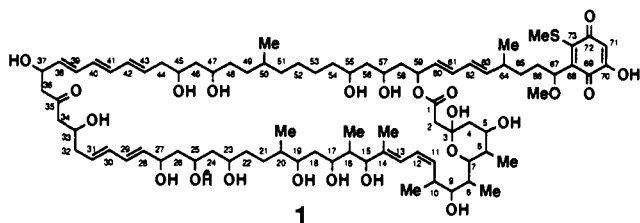
## Structure of a Novel 60-Membered Macrolide, Quinolidomicin A<sub>1</sub>

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In the course of our screening for antitumor antibiotics, we isolated a novel macrolide, quinolidomicin A<sub>1</sub> (**1**), from an actinomycete *Micromonospora* sp.<sup>1</sup> **1** was highly cytotoxic against P388 murine leukemia cells (IC<sub>50</sub> 8 nM).



The MeOH extract of the cultured mycelium (2 L) was subjected to silica gel chromatography, followed by Sephadex LH-20 chromatography and normal-phase HPLC on Aquasil (Senshu Scientific Co.) with CHCl<sub>3</sub>/MeOH (10:1) to give an orange powder of **1** (9 mg).<sup>1,2</sup>

The molecular formula of **1** was determined to be C<sub>83</sub>H<sub>132</sub>O<sub>23</sub>S by HRFABMS [*m/z* 1551.8774 (M + Na)<sup>+</sup>, Δ -0.7 mmu]. The <sup>13</sup>C NMR spectrum confirmed the presence of 83 carbons, and the HSQC<sup>3</sup> spectrum established all one-bond <sup>1</sup>H-<sup>13</sup>C connectivities (Table I).

Phase-sensitive DQF-COSY<sup>4</sup> and HMBC<sup>5</sup> experiments generated partial structures **2-6** (Figure 1). The characteristic UV absorptions<sup>2</sup> at λ<sub>max</sub> 257, 268, and 279 nm indicated the presence of a triene group formed by the connection of C-40 and C-41.

A partial structure including C-47-C-55 presented the most difficult part of the structure determination because of the severe overlap of the methylene signals in the <sup>1</sup>H spectrum and was elucidated by a phase-sensitive HSQC-HOHAHA<sup>3,6</sup> experiment, which showed relayed connectivities from 47-H to C-48 and C-49, from 55-H to C-54, C-53, and C-52, and from 50-CH<sub>3</sub> to C-48, C-49, C-50, C-51, and C-52. The sequence of C-21-C-25 was also assigned on the basis of the relay from 23-H to C-21, C-22, C-24, and C-25, and from 25-H to C-22, C-23, and C-24.

A new technique using phase-sensitive <sup>13</sup>C-decoupled HMBC<sup>7</sup> revealed a correlation between a broad multiplet oxymethine proton (59-H) and an ester carbonyl carbon (C-1) to generate a 60-membered lactone ring. The protons on C-4-C-7 showed large vicinal-coupling constants (*J*<sub>4,5</sub> = 10.5, *J*<sub>5,6</sub> = 10.5, and

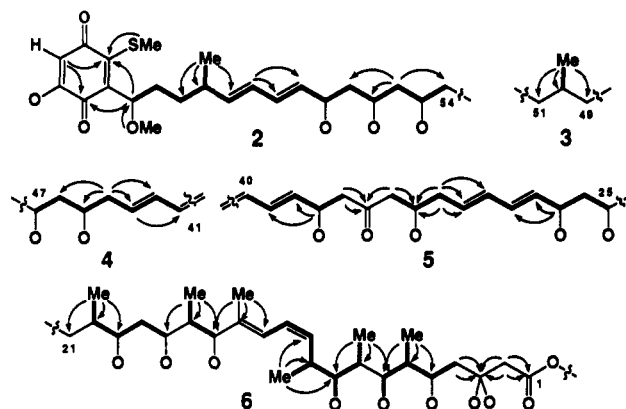


Figure 1. Partial structures of quinolidomicin A<sub>1</sub> with bold lines showing proton spin networks derived from DQF-COSY data and arrows showing <sup>1</sup>H-<sup>13</sup>C long-range correlations derived from HMBC data.

Table I. <sup>13</sup>C and <sup>1</sup>H NMR Data for Quinolidomicin A<sub>1</sub> in CD<sub>3</sub>OD

no.	δ <sub>C</sub>	δ <sub>H</sub>	no.	δ <sub>C</sub>	δ <sub>H</sub>
1	171.7 (s)		43	132.0 (d)	5.75
2	47.8 (t)	2.66, 2.61	44	41.9 (t)	2.29
3	97.5 (s)		45	71.3 (d)	3.82
4	43.9 (t)	2.10, 1.58	46	43.9 (t)	1.58, 1.49
5	70.4 (d)	3.49	47	71.6 (d)	3.71
6	41.3 (d)	1.35	48	35.9 (t)	1.40
7	75.4 (d)	3.63	49	33.4 (t)	1.41, 1.13
8	38.0 (d)	1.70	50	33.8 (d)	1.40
9	79.0 (d)	3.43	51	38.0 (t)	1.33, 1.13
10	35.2 (d)	3.00	52	26.8 (t)	1.42, 1.30
11	134.2 (d)	5.52	53	28.1 (t)	1.32
12	125.0 (d)	6.27	54	38.7 (t)	1.43
13	122.9 (d)	6.42	55	71.4 (d)	3.75
14	140.0 (s)		56	45.3 (t)	1.57
15	81.0 (d)	4.10	57	67.8 (d)	3.83
16	41.2 (d)	1.77	58	43.5 (t)	1.87, 1.62
17	73.5 (d)	3.90	59	73.5 (d)	5.46
18	38.3 (t)	1.62, 1.58	60	130.2 (d)	5.54
19	75.7 (d)	3.55	61	134.5 (d)	6.22
20	40.4 (d)	1.51	62	129.4 (d)	5.98
21	28.8 (t)	1.50, 1.24	63	142.7 (d)	5.57
22	36.4 (t)	1.50	64	38.1 (d)	2.16
23	71.4 (d)	3.72	65	34.3 (t)	1.45, 1.20
24	45.4 (t)	1.58	66	31.7 (t)	1.97, 1.75
25	69.7 (d)	3.85	67	80.1 (d)	4.78
26	45.6 (t)	1.68, 1.59	68	140.0 (s)	
27	71.7 (d)	4.28	69	181.0 (s)	
28	135.6 (d)	5.58	70	150.7 (s)	
29	131.9 (d)	6.21	71	101.1 (d)	5.66
30	133.9 (d)	6.08	72	182.6 (s)	
31	131.1 (d)	5.67	73	154.0 (s)	
32	41.5 (t)	2.28, 2.22	6-Me	12.3 (q)	0.81
33	68.5 (d)	4.10	8-Me	9.2 (q)	0.95
34	51.2 (t)	2.58	10-Me	19.0 (q)	1.02
35	210.1 (s)		14-Me	12.7 (q)	1.71
36	51.8 (t)	2.69, 2.64	16-Me	8.1 (q)	0.93
37	69.3 (d)	4.57	20-Me	15.6 (q)	0.90
38	135.7 (d)	5.67	50-Me	20.3 (q)	0.88
39	131.7 (d)	6.24	64-Me	21.0 (q)	0.98
40	131.7 (d)	6.12	67-OMe	57.4 (q)	3.21
41	134.5 (d)	6.22	73-SMe	19.2 (q)	2.58
42	134.2 (d)	6.13			

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(1) Details of the producing organism, fermentation, and isolation of **1** will be published elsewhere.

(2) **1**: mp 142-147 °C; [α]<sub>D</sub><sup>25</sup> +50° (c 0.1, CHCl<sub>3</sub>/MeOH 1:1); UV λ<sub>max</sub> (ε) 232 (93 500), 257 (42 500), 268 (49 600), 279 (37 900), 365 (6600) nm in MeOH.

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*J*<sub>6,7</sub> = 10.0 Hz) and were required to be in a six-membered ring, thereby showing that C-3 was connected to C-7 with an ether linkage.

The geometrical configurations of the olefinic bonds were established to be 11(*Z*), 28(*E*), 30(*E*), 42(*E*), 60(*E*), and 62(*E*) by their vicinal coupling constants (*J*<sub>11-12</sub> = 11.5, *J*<sub>28-29</sub> = 15.5, *J*<sub>30-31</sub> = 15.0, *J*<sub>38-39</sub> = 15.5, *J*<sub>42-43</sub> = 15.0, *J*<sub>60-61</sub> = 15.0, and *J*<sub>62-63</sub> = 15.0 Hz). The stereochemistry of C-13 was determined to be (*E*) on the basis of a high-field chemical shift for 14-CH<sub>3</sub> (δ 12.7)

and an NOE observed between 12-H and 14-CH<sub>3</sub>. The remaining olefinic bond (C-40) in the triene system was required to have an (*E*) configuration by the <sup>13</sup>C chemical shift similarity of C-38–C-43 to those of the all-(*E*) triene moiety ( $\delta$  132.2, 137.8, 130.7, 135.9, 133.5, and 133.5) of pulvomycin.<sup>8</sup>

The planar structure thus obtained indicates that quinolidomycin A<sub>1</sub> represents a new class of macrolides containing a benzoquinone chromophore and a 60-membered lactone ring, which is far larger than that present in monazomycin,<sup>9</sup> known to have the largest ring in natural products.

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**Supplementary Material Available:** <sup>1</sup>H NMR, <sup>13</sup>C NMR, HSQC, DQF-COSY, HMBC, HSQC-HOHAHA, NOESY, <sup>13</sup>C-decoupled HMBC, and 1-D COSY spectra in CD<sub>3</sub>OD for **1**; pulse sequence for phase-sensitive <sup>13</sup>C-decoupled HMBC; and NMR data summary for **1** (25 pages). Ordering information is given on any current masthead page.

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