While these results demonstrate the potential of allyl sulfones as substrates in molybdenum-catalyzed allylic alkylations, it should be noted that they do have diminished reactivity compared to the corresponding allyl acetates. Agents which coordinate to molybdenum, such as acetonitrile or dioxane solvent and BSA[14] base, inhibit reaction. There is also a significant S_N1 component to the reaction. Tertiary sulfones react faster than the corresponding primary sulfones. Thus, the sulfone isomeric to **3**, prenyl phenyl sulfone, required 4 times as long to produce the same products. The regiochemistry exhibited here is best analyzed as a delicate balance between steric and electronic factors. Sterically demanding nucleophiles attack the intermediate π-allylmolybdenum complex at the least substituted position. Small nucleophiles such as dimethyl malonate, however, react under electronic control and attack at the site of greatest electron deficiency, which is the more substituted allylic terminus. Thus molybdenum catalysis can provide a unique entry into systems containing a quaternary carbon center.

(14) BSA = *O,N*-bis(trimethylsilyl)acetamide.

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute, for their generous support of our programs and the Fannie and John Hertz Foundation for a fellowship for C.A.M. We thank Pressure Chemical Co. for a gift of molybdenum hexacarbonyl.

Registry No. **3**, 72863-20-8; **4**, 74866-35-6; **5**, 43219-18-7; **6**, 97072-44-1; **7**, 124535-79-1; **8**, 124535-80-4; **9**, 124535-81-5; **10**, 124535-82-6; **11**, 124535-83-7; **12**, 124535-84-8; **13**, 97072-36-1; **14**, 97072-43-0; **15** (n = 2), 124535-85-9; **16**, 124535-86-0; **17**, 124535-87-1; **18**, 124535-88-2; **19**, 124535-89-3; **20**, 124535-90-6; **21**, 124535-91-7; **22** (isomer 1), 124561-56-4; **22**, 97072-38-3; **23**, 124535-92-8; **24**, 124535-93-9; **25**, 124535-94-0; $NaCH(CO_2Me)_2$, 18424-76-5; $Mo(CO)_6$, 13939-06-5; $H_2C{=}CHCH_2SO_2Ph$, 16212-05-8; $Br(CH_2)_4Br$, 110-52-1; $Pd(PPh_3)_4$, 14221-01-3; $I(CH_2)_2O(CH_2)_2I$, 34270-90-1; $Cl(CH_2)_2Cl$, 107-06-2; $Br(CH_2)_3Br$, 109-64-8; $H_2C{=}CHCH(CO_2Me)_2$, 40637-56-7; (*E*)-$CH_3CH{=}CHCH_2SO_2Ph$, 72863-24-2; (*Z*)-$MeOCH{=}CHCH_2SO_2Ph$, 124535-95-1; $I(CH_2)_3Cl$, 6940-76-7; 2-(carbomethoxy)cyclopentanone, 10472-24-9.

Supplementary Material Available: Characterization data for **6**, **7**, **9**–**14**, **16**, **17**, **20**, **23**–**25** and sample procedure for alkylation (3 pages). Ordering information is given on any current masthead page.

Synthesis of 16-Membered Macrolide Aglycons, Carbonolide A, Leuconolides, and Maridonolides, via Carbonolide B Type Compounds by Virtue of Completely Stereoselective Epoxidation and Reduction Based on the Conformational Control of Macrolide Rings with Protecting Groups[1]

Noriyuki Nakajima,[†] Kouichi Uoto,[†] Tomohiro Matsushima,[†] Osamu Yonemitsu,*[,†] Hitoshi Goto,[‡] and Eiji Ōsawa[‡]

Faculty of Pharmaceutical Sciences and Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan

Received November 21, 1989

Summary: Carbonolide B type compounds were converted to seven typical 16-membered macrolide aglycons, carbonolide A, EOP aglycon, leuconolide A_1 and A_3, midecanolide A_1, and maridonolide II and I, by virtue of completely stereoselective epoxidation and/or reduction based on the conformational control of macrolide rings with protecting groups. NOE and NOESY measurements and MMP2-CONFLEX2 calculations were employed to predict the conformation of the carbonolide B type compounds.

The 16-membered aglycons of the largest group of macrolide antibiotics represented by carbomycins, leucomycins, and maridomycins are classified into four types, **1**, **2**, **3**, and **4**, according to their oxidation levels[2] and, except for **1**, most of these remain unsynthesized.[3] We recently reported the stereoselective total synthesis of typical macrolide aglycons[4] by virtue of the MPM (methoxyphenylmethyl) protection of hydroxy functions[5] and some stereocontrolled reactions in acyclic systems. This methodology, together with stereoselective epoxidation and reduction on 16-membered lactone rings,[6] is now extended to the first completely stereoselective synthesis of 16-membered macrolide aglycons: carbonolide A (**2b**),[8] leuconolide A_1 (**3a**)[9] and A_3 (josanolide) (**3b**),[10] midecanolide

[†] Faculty of Pharmaceutical Sciences.

[‡] Faculty of Sciences.

(1) Chiral synthesis of polyketide-derived natural products. 28. For part 27, see: Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7.

(2) Omura, S.; Tanaka, H. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984; pp 3–35.

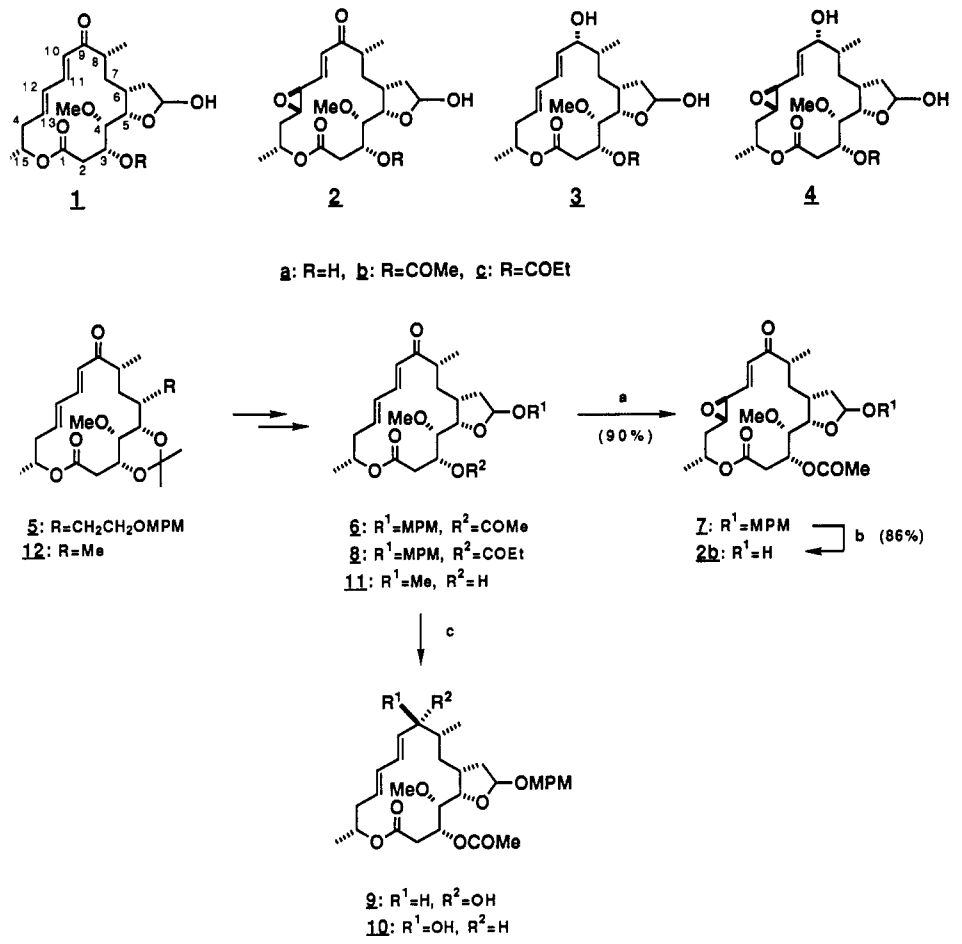
(3) (a) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, Florida, 1984; pp 127–198. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(4) Methynolide: (a) Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647. (b) Tanaka, T.; Nakajima, N.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2203. Pikronolide: (c) Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645. (d) Nakajima, N.; Hamada, T.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2228. Tylonolide: (e) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651. (f) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2209, 2219. Erythronolide A: (g) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569. (h) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1167.

(5) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885, 889. (b) Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393. (c) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397. (d) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021. (e) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

0022-3263/90/1955-1129$02.50/0

Scheme I[a]



[a] (a) MCPBA (4 equiv), $NaHCO_3$, CH_2Cl_2, 20 °C; (b) DDQ, CH_2Cl_2–H_2O (20:1); (c) Bu_4NBH_4 (2 mol), MeOH, room temperature, 1.5 h.

A_1 (**3c**),[11] and maridonolide II (**4b**) and I (**4c**),[12] *etc.*

When the dienone (**6**), synthesized as an intermediate to carbonolide B (**1b**) from D-glucose and L-malic acid via **5**,[13] was oxidized with MCPBA in the presence of $NaHCO_3$, completely regio- and stereoselective epoxidation occurred to give only the expected β-epoxide (**7**),[6,7a,b] which was readily converted to carbonolide A (**2b**) by removal of the MPM group.[5,14]

In order to synthesize the leuconolides and maridonolides, the reduction of **6** and **7** was next examined. When **6** was treated with *n*-Bu_4NBH_4 in MeOH at room temperature, a 1:1.8 mixture of the desired 9*R* alcohol (**9**) and its 9*S* isomer (**10**) was obtained.[7c] Reduction of **7** under the same conditions gave mainly an undesired 9*S* alcohol with 22:1 selectivity. This disappointing selectivity is clearly explained in terms of an unfavorable type A conformation of the dienone portion (Figure 1) on the basis of NOE and NOESY data, which is confirmed by the MMP2 calculation combined with a systematic structure generation algorithm (CONFLEX2).[15,16] As can be seen from the computer drawing (though for **12**, Figure 1), upon reduction of **6**, the reducing agent can attack only from the left-side (arrow) of the A conformer to give **10**, whereas the B conformer can give the expected **9** by the right-side attack of the reductant.[17] If the population of the A conformer is lowered by variation of the protection pattern of C3, C5, and C6″, hydroxy groups, a higher yield of the desired 9*R* (α) alcohol can be expected. According to NOE and NOESY measurements, the 3,5-acetonide (**5**) consists of interconvertible A, B, C, and A′ conformers whose calculated populations are 67.9, 10.5, 10.5, and 8.8%, re-

(6) There are a few precedents of the epoxidation and reduction of similar 16-membered dienones in the tylonolide series. 3-Deoxyrosaranolide[7a] and rosaranolide[7b] were stereoselectively synthesized by the epoxidation of the corresponding dienones with MCPBA, but the reduction of a tylonolide derivative mainly gave an undesired 9*S*-hydroxy compound.[7c]

(7) (a) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. (b) Schlessinger, R. H.; Poss, M. A.; Richardson, S. *J. Am. Chem. Soc.* **1986**, *108*, 3112. (c) Greico, P. A.; Inanaga, J.; Lin, N. H. *J. Org. Chem.* **1983**, *48*, 892.

(8) Carbomycin A: Woodward, R. B.; Weiler, L. S.; Dutter, P. C. *J. Am. Chem. Soc.* **1965**, *87*, 4662.

(9) Leucomycin A_1: Omura, D.; Katagiri, M.; Hata, T. *J. Antibiot.* **1968**, *21*, 199.

(10) Omura, S.; Nakagawa, A.; Suzuki, K.; Hata, T. *J. Antibiot.* **1974**, *27*, 147.

(11) Midecamycin A_1: Inouye, S.; Tsuruoka, T.; Shomura, T.; Omoto, S.; Niida, T. *J. Antibiot.* **1971**, *24*, 460.

(12) Maridomycins: Muroi, M.; Izawa, M.; Asai, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1973**, *26*, 199.

(13) Nakajima, N.; Uoto, K.; Yonemitsu, O. *Heterocycles*, in press.

(14) EOP aglycon (**2c**)[3] was also synthesized from **8** in the same way.

(15) Goto, H.; Ōsawa, E. *J. Am. Chem. Soc.*, in press.

(16) Compound **11** in the same system was calculated to exist mainly in the A conformer (9,10-*s*-*cis*, 11,12-*s*-*trans*) (97.9%) together with the B conformer (9,10-*s*-*cis*, 11,12-*s*-*cis*) (2.0%).

(17) Since in the A conformer the dienone of **6** is almost at right angles to the 16-membered ring plane, the inside of the ring (the right-side of the computer drawing) is completely blocked. The 1:1.8 ratio of **9** and **10** on the reduction of **6** in spite of the 1:49 population ratio of the B and A conformers (interconvertible at room temperature according to the NMR spectrum of **6**) clearly shows that the B conformer was reduced much faster than the A conformer, whose reduction was subject to steric hinderance by the C8 methyl group [the left-side of the B conformer is sterically hindered by the C7 (methylene) group]. Reliable calculation for the epoxide (**7**) are still impossible, but the population of the B conformer must be nearly nil.

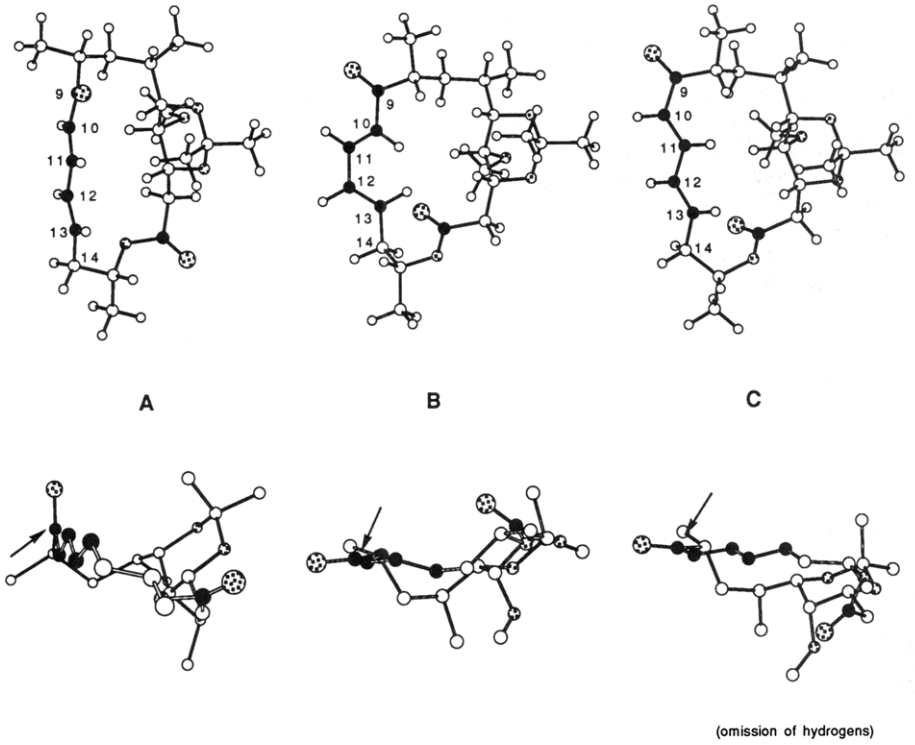
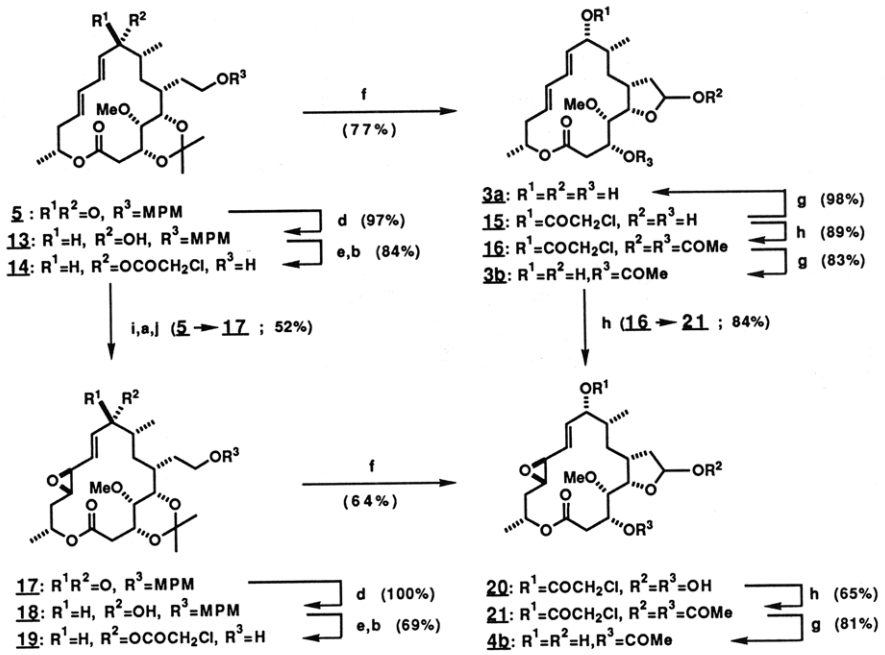


Figure 1.

Scheme II[a]



[a] (d) $NaBH_4$, MeOH, 0 °C, 5 min; (e) $(ClCH_2CO)_2O$ (3 equiv), DMAP (1 equiv), py; (f) $(COCl)_2$ (2 equiv), DMSO (4 equiv), CH_2Cl_2, Et_3N (6 equiv), −78 → 0 °C; then 1 N HCl–THF (1:5); (g) K_2CO_3 (3 equiv), MeOH, 0 °C, 5 min; (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (i) CSA (0.1 equiv), MeOH, 20 °C, 10 min; (j) $Me(MeO)C{=}CH_2$ (5 equiv), PPTS (0.1 equiv), CH_2Cl_2, 20 °C.

spectively.[18] Among them the B, C, and A′ conformers (total population: 29.8%) should be reduced to afford the desired 9*R* alcohol.

When **5** was treated with $NaBH_4$ in MeOH at 0 °C, a rapid stereoselective reduction occurred to give the expected alcohol (**13**) in almost quantitative yield. Protection with a chloroacetyl group followed by DDQ oxidation gave the primary alcohol (**14**), which was oxidized to the aldehyde. The acetonide group was then hydrolyzed to give the hemiacetal (**15**), and finally an alkaline hydrolysis gave leuconolide A_1 (**3a**). Acetylation of **15** gave the diacetate (**16**), which was easily converted to leuconolide A_3 (**3b**).[19] Similarly, midecanolide A_1 (**3c**) was synthesized from **15**.

(18) Data calculated for **12**. C: 9,10-*s-trans*, 11,12-*s-trans*. A′: 9,10-*s-cis*, 11,12-*s-trans*; the dienone portion inside out.

(19) (a) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222.

Oxidation of **5** with MCPBA gave the epoxide (**17**) in poor yield, but a better result was obtained via three conventional reactions. When **17** was reduced with $NaBH_4$, the expected 9*R* alcohol (**18**) was obtained in quantitative yield. This (**18**) was converted to maridonolide II (**4b**) via **19**–**21** as described for **3b**. Compound **4b** was also obtained from **16** via only two reactions: MCPBA oxidation and hydrolysis with K_2CO_3. Similarly, maridonolide I (**4c**) was synthesized from **5**.

The aglycons **2b,c**, **3a–c**, and **4b,c** thus synthesized were identical in all respects (NMR, MS, IR, $[\alpha]_D$) with those derived from natural antibiotics.[20]

Acknowledgment. We thank Yamanouchi Pharmaceutical Co., Dr. K. Hosoi, Meiji Seika, Ltd., and Dr. T. Kishi, Takeda Chemical Industries, Ltd., for kind supplies of josamycin, midecamycin A_1, and maridomycin III, respectively.

Supplementary Material Available: Physical data for compounds **2b,c**, **3a–c**, **4b,c**, **13**, **15**, **17**, and **18** and calculation data (MMP2-CONFLEX2) for **11** and **12** (26 pages). Ordering information is given on any current masthead page.

(20) These aglycons (isomeric mixtures with respect to the hemiacetal positions) except for **3b**[10,19] have never been reported.

Biosynthesis of Furaquinocins A and B

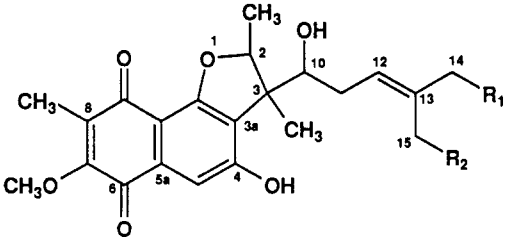
Shinji Funayama, Masami Ishibashi, Kanki Komiyama, and Satoshi Ōmura*

The Kitasato Institute, and School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108, Japan

Received October 9, 1989

Summary: The biosynthetic pathway to furaquinocins was investigated by means of incorporation experiments with [1-^{13}C]acetate, [1,2-$^{13}C_2$]acetate, and [*methyl*-^{13}C]-L-methionine. Furaquinocins are derived from a pentaketide, two mevalonates, and two C_1 units from L-methionine.

The furaquinocins A (**1**) and B (**2**) comprise a novel polyketide antibiotic complex produced by *Streptomyces* sp. KO-3988, which exhibit cytotoxic activity against HeLa S_3 cells but no antimicrobial activity.[1] Extensive spectroscopic analyses have demonstrated that **1** and **2** possess a unique structure, which consists of a naphtho[1,2-*b*]-furan-6,9-dione chromophore with an isoprenoid-like side chain.[2]



1 R_1 = H, R_2 = OH
2 R_1 = OH, R_2 = H

In the present report, we describe studies on the biosynthetic pathway to furaquinocins A and B by means of feeding experiments using ^{13}C-labeled precursors.[3]

Assignment of the ^{13}C NMR signals of **1** and **2** was fully established on the basis of ^{1}H–^{13}C COSY along with LSPD experiments[2] and are presented in Table I. The ^{13}C NMR spectra of furaquinocins A (**1**) and B (**2**) labeled with [1-^{13}C]acetate revealed the enrichment of nine carbon signals (Me-2, C-3, C-4, C-5a, C-7, C-9, C-9b, C-11, and C-13). The intensity ratios of nonlabeled ones are also shown in Table I. In a feeding experiment with [1,2-$^{13}C_2$]acetate, 20 carbons were found to be derived from acetate, of which 11 carbons (C-2, Me-3, C-3a, C-5, C-6, C-8, C-9a, C-10, C-12, C-14, and C-15) arose from C-2 of acetate. The remaining two carbons (MeO-7 and Me-8) were not derived from acetate units. The ^{13}C–^{13}C coupling constants (J_{CC}) of **1** and **2** labeled with [1,2-$^{13}C_2$]acetate are given in Table I. The carbons in the naphthoquinone ring show two kinds of coupling with equal signal intensities. These coupling constants are coincident with those of the adjacent carbons.

Table I. ^{13}C NMR Chemical Shifts, Enrichment Ratio of [1-^{13}C]Acetate-Labeled Furaquinocins, and J_{CC} (in Hz) of [1,2-$^{13}C_2$]Acetate-Labeled Furaquinocins[a]

	1			2		
carbon	δ	enrichmt ratio[b]	*J*	δ	enrichmt ratio[b]	*J*
2	88.9	1.0	38	88.9	1.0	38
Me-2	16.1	5.1	38	16.1	5.2	38
3	52.8	3.3	35	52.4	3.2	34
Me-3	18.9	1.0	35	18.9	0.8	34
3a	124.6	0.4	61, 69	124.5	0.2	61, 70
4	158.9	6.9	69, 67	158.4	5.8	70, 67
5	111.0	0.8	67, 66	110.7	1.0	67, 66
5a	134.0	4.2	66, 54	134.1	4.3	66, 54
6	180.8	0.4	54, 57	180.7	0.3	54, 57
7	156.9	5.3	57, 74	156.9	3.8	57, 74
MeO-7	60.6	0.8	*c*	60.7	0.4	*c*
8	133.6	0.8	74, 52	133.7	0.6	74, 52
Me-8	9.3	1.0	*c*	9.3	0.8	*c*
9	183.8	4.5	52, 60	183.7	4.4	52, 60
9a	108.8	0.3	60, 73	109.2	0.2	60, 73
9b	160.6	4.0	73, 61	160.4	4.8	73, 61
10	71.4	0.8	s[d]	73.0	1.2	s[d]
11	32.4	6.0	43	31.9	7.7	44
12	124.9	0.7	43	120.1	0.9	44
13	138.3	4.0	46	140.0	5.0	43
14	23.2	1.0	s[d]	68.0	0.7	s[d]
15	61.4	0.8	46	14.3	0.8	43

[a] Each sample was dissolved in $CDCl_3$ and chemical shifts were shown with reference to $CDCl_3$ as 77.0 ppm. [b] Enrichment ratios were relative to the C-2 signal as 1.0. [c] Signal for the carbon not incorporated. [d] Signal was singlet, so the carbon had no coupling with others.

(1) Komiyama, K.; Funayama, S.; Anraku, Y.; Ishibashi, M.; Ōmura, S. *J. Antibiot.*, in press.
(2) Funayama, S.; Ishibashi, M.; Anraku, Y.; Komiyama, K.; Ōmura, S. *Tetrahedron Lett.*, in press.
(3) A seed culture of *Streptomyces* sp. KO-3988 was made by the method previously described.[1] The seed culture (1–2 mL) was inoculated into each 500-mL Sakaguchi flask containing 100 mL of medium composed of 2% starch, 1% soy bean meal, and 0.3% NaCl (pH 7.0 before sterilization). ^{13}C-labeled precursors in 2 mL of aqueous solution ([1-^{13}C]- and [1,2-$^{13}C_2$]acetate, 100 mg; [*methyl*-^{13}C]-L-methionine, 50 mg) was added to each flask after 6 h of cultivation and the cultures were then incubated for 66 h at 27 °C. ^{13}C-enriched furaquinocins (2–4 mg) were isolated from the cultured broth (0.5–1 L) by solvent extraction, silica gel chromatography, and Sephadex LH-20 gel filtration as previously reported.[1] ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer in deuteriochloroform.

0022-3263/90/1955-1132$02.50/0