In Vivo Evaluation of Renin Inhibitors. Following the previously described protocol,[28] male and female rhesus monkeys (*Macaca mulatta*) were surgically implanted with chronic arterial vascular access ports for direct monitoring of mean arterial pressure (MAP) and periodic collection of blood samples for determination of plasma renin activity (PRA). Indwelling venous catheters were inserted for intravenous administration of compounds. The monkeys were maintained on a low sodium diet and treated with furosemide the evening before the experiment. The animals were fasted for 18 h before and during the experiment. Compounds were administered intravenously in 0.05% acetic acid/5% dextrose/H_2O 20 min after a control administration of the vehicle. For oral administration, compounds were suspended or dissolved in 0.1 M citric acid/H_2O and delivered by nasogastric catheter. Percent inhibition of PRA and changes in MAP and heart rate were calculated and plotted against time.

Acknowledgment. We thank Drs. Lawrence F. Colwell, Jr., and Jack L. Smith for mass spectral determinations and the laboratory of Mrs. Jane T. Wu for elemental analyses. We are grateful to Mr. Elwood Peterson for the preparation of certain intermediates.

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New Potent Mitomycin Derivatives: Synthesis and Antitumor Activity of 7,7-(Ethylenedioxy)mitomycins

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A series of 6,7-dihydro-7,7-(ethylenedioxy)mitomycins was synthesized and evaluated for antitumor and anticellular activities. These compounds were prepared by basic treatment of 7-methoxymitomycins with ethylene glycol, and were structurally novel mitomycin derivatives containing a masked quinone moiety. 5,6-Enol or 6-chloro derivatives of 6,7-dihydro-7,7-(ethylenedioxy)mitomycins were also prepared and the (allyloxy)carbonyl group at the aziridine nitrogen has proved to be an efficient protecting group in chemical modification of mitomycins. Most of these mitomycin derivatives displayed potent antitumor activity against P388 leukemia in mice and anticellular activity against HeLa S_3 cells.

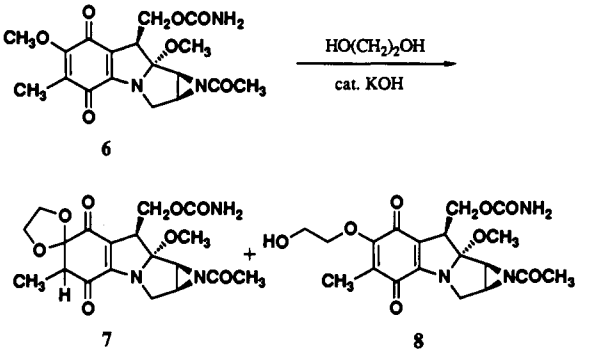
Mitomycin C (1) is one of the most potent antitumor antibiotics which have been clinically used in cancer chemotherapy, but its use is limited by side effects, such as severe bone marrow suppression or gastrointestinal damage.[1,2] Hundreds of compounds targeting less toxicity or more effective activity have been derived from natural mitomycins (Figure 1). Among these derivatives, some of 7-substituted mitomycins[2,3,4] have been reported to possess superior activity to mitomycin C against experimental tumors. On the basis of the recent understanding of detailed mode of action of mitomycins,[5] extensive studies have been underway to develop more useful mitomycin analogues.[3,6,7] Since the reductive activation is believed to be essential for antitumor activity,[5] modification of the quinone might be an interesting approach to develop novel mitomycin analogues which have different chemical and biological property from those of known mitomycin analogues. During the course of our synthesis of 7-substituted mitomycins, we recently reported that a reaction of 1a-acetylmitomycin A (6) with ethylene glycol under basic condition gave 7,7-(ethylenedioxy)mitomycin 7, a novel mitomycin derivative containing an acetal group at the C7 position and lacking the quinone moiety, as a major product along with its isomer 8 (Scheme I).[8a]

In addition to the usefulness of 7 as an intermediate for isotopically labeled mitomycins,[8] we found that this series of compounds showed potent antitumor activity. We now wish to report the synthesis and antitumor activity of these structurally unique mitomycin derivatives.

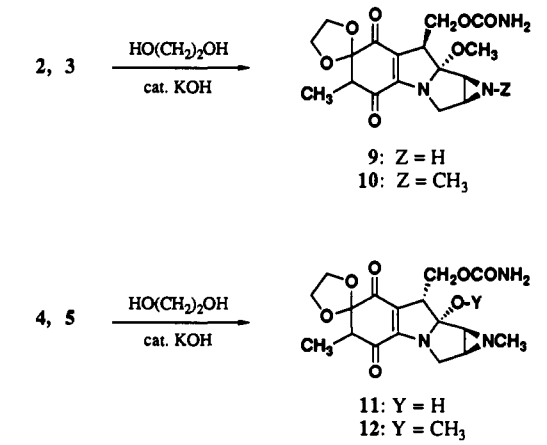
Chemistry

As mentioned above, 7,7-(ethylenedioxy)mitomycins 9-12 were prepared by reactions of natural 7-methoxymitomycins, such as mitomycins A (2), F (3), B (4), and J (5), with ethylene glycol in the presence of KOH in yields

Scheme I



Scheme II



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‡ Pharmaceutical Research Laboratories.

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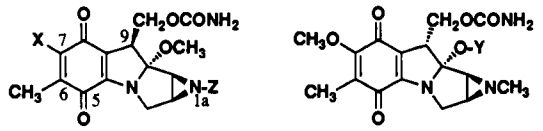
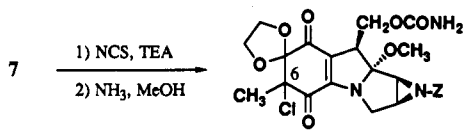


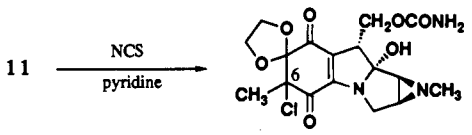
1: X = NH_2, Z = H (mitomycin C) 4: Y = H (mitomycin B)
2: X = OCH_3, Z = H (mitomycin A) 5: Y = CH_3 (mitomycin J)
3: X = OCH_3, Z = CH_3 (mitomycin F)

Figure 1. Structures of some natural mitomycins.

Scheme III



13a: Z = $COCH_3$
13b: Z = H (major isomer at C6)
13c: Z = H (minor isomer at C6)



14 (3:1 mixture at C6)

of 81, 79, 50, and 87%, respectively (Scheme II). It was difficult to separate diastereomers at the C6 position and separation of the diastereomers proved to be inconsequential given that these 7,7-(ethylenedioxy)mitomycins are isomers of 7-(2-hydroxyethoxy)mitomycins,[9] which could be the species having antitumor activity. Therefore we used each respective diastereomeric mixture for biological testing. Among these compounds, **9**, which has mitomycin A type skeleton (9β; 9a, OMe; 1a, NH), showed the most potent antitumor activity, so we chose this compound as a standard compound for further modification. In order to eliminate the complexity caused by the isomeric nature of the above compounds, we next designed those compounds which had no acidic hydrogen at the C6 position. Treatment of 1a-acetyl-7,7-(ethylenedioxy)mitomycin **7** with *N*-chlorosuccinimide in the presence of triethylamine, followed by the deprotection of the 1a-acetyl group with ammonia in methanol, gave 6-chloro-7,7-(ethylenedioxy)mitomycin **13b** (major isomer at the C6 position) in 58% overall yield together with **13c** (minor isomer, 10% yield). Chloride **14** (a 3:1 mixture of diastereomers at the C6 position), which has mitomycin B type skeleton, was also prepared in 54% yield (Scheme III).

5,6-Enol esters and ether were prepared as follows. Enol acetate **15** was prepared by the treatment of **7** with acetic anhydride and triethylamine (39% yield), followed by the deprotection of the 1a-acetyl group with aqueous sodium bicarbonate solution (59% yield). Reactions of **7** with benzoyl chloride or dodecanoyl chloride in the presence of triethylamine and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), followed by the deprotection of the 1a-acetyl group with ammonia, afforded enol benzoate **16** or enol dodecanoate **17**. Enol acetate **18**, which has mitomycin B type skeleton, was also prepared from **11** in a similar manner as that described above in 40% yield. Enol ether **19** was synthesized by the reaction of **7** with dimethyl sulfate in the presence of triethylamine

Table I. Antitumor and Anticellular Activities of 7,7-(Ethylenedioxy)mitomycins

	P388 (ip–ip)[a]		
no.	% ILS_{max}[c]	optimal dose, mg/kg	HeLa S_3:[b] 1 h IC_{50}, μM
9	69 (69)[d]	0.39 (4.0)[e]	0.041
10	53 (69)	2.5 (4.0)	0.60
11	73 (69)	5.0 (4.0)	4.4
12	80 (69)	5.0 (4.0)	3.1
13b	60 (65)	2.5 (6.0)	3.2
13c	73 (65)	2.5 (6.0)	0.59
14	59 (52)	13 (4.0)	50
15	63 (77)	0.50 (6.0)	4.4
16	71 (84)	3.0 (6.0)	0.54
17	67 (84)	0.75 (6.0)	0.094
18	71 (69)	13 (6.0)	4.4
19	41 (52)	3.1 (4.0)	20
21b	72 (72)	1.3 (6.0)	0.074
22b	102 (84)	1.6 (6.0)	0.36
23b	nt[f]	nt	8.1
24b	80 (72)	5.0 (6.0)	0.59
25b	nt	nt	0.87
1 (mitomycin C)	52–84	4.0–6.0	0.81–3.8

[a] $CD2F_1$ mice (five mice/group) were implanted intraperitoneally (ip) with 10^6 cells, and drug was dosed (mg/kg) ip on day 1. [b] In vitro anticellular activities against HeLa S_3 cells. The cells were cultured in 96-well plates on day 0 and treated with drugs for 1 h on day 1. The anticellular activity was determined according to the method described previously (see ref 3b). [c] Maximal increase in life span, calculated $(T/C - 1) \times 100$, where T and C are median survival times of treated and control mice, respectively. [d] ILS_{max}, %, of mitomycin C (control). [e] Optimal dose, mg/kg, of mitomycin C (control). [f] Not tested.

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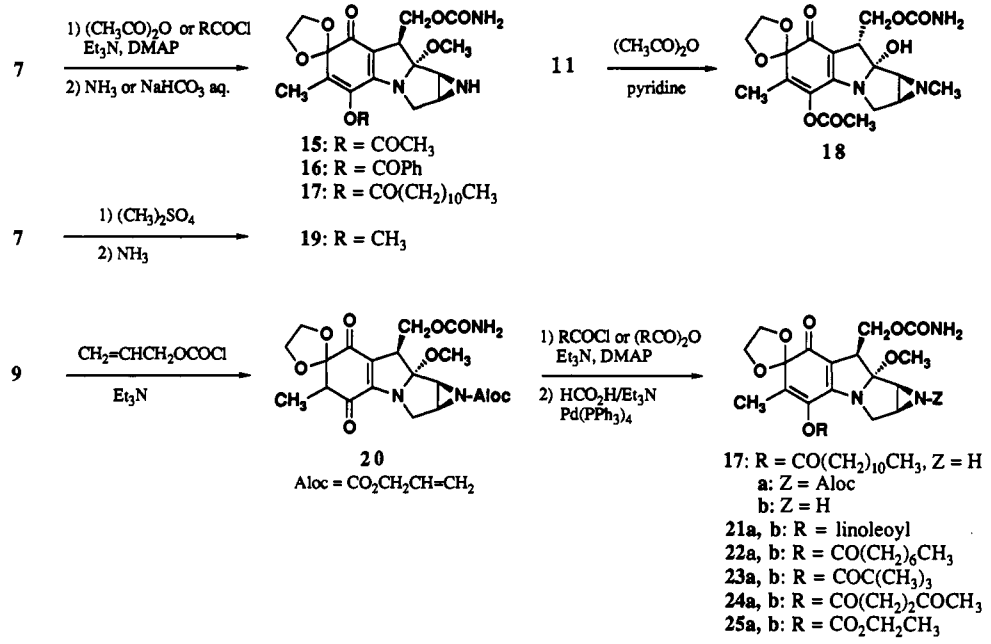
Scheme IV



(33% yield) followed by deprotection of the 1a-acetyl group with ammonia (93% yield). The problem of this method was low selectivity in deprotection of the *N*-acetyl group (Scheme IV).

The fact that some of the enol derivatives showed potent activity prompted us to synthesize more derivatives using a improved method which involved taking advantage of the (allyloxy)carbonyl group as a protecting group[10] of the aziridine nitrogen. 1a-[(Allyloxy)carbonyl]-7,7-(ethylenedioxy)mitomycin **20** was prepared by the reaction of **9** with allyl chloroformate in the presence of triethylamine in 79% yield. Compound **20** was then treated with several acid chlorides or acid anhydrides and triethylamine in the presence of DMAP, followed by the deprotection of the (allyloxy)carbonyl group with triethylamine–formic acid and tetrakis(triphenylphosphine)palladium(0) as a catalyst, to give enol esters **17** and **21b–24b** in good yields (Scheme IV). In the case of preparation of **17**, overall yield from **20** was 72%, whereas the overall yield from **7** was 17%. Enol carbonate **25b** was also prepared in a similar method.

In the deprotection step using the palladium catalyst, neither reduction of quinone nor N-allylation of aziridine was observed. These results have clearly shown that the (allyloxy)carbonyl group should be a suitable protective group for the aziridine nitrogen in the modification of acid- and base-sensitive mitomycins.

Biological Activity and Discussion

Table I shows in vivo antitumor activity of the 7,7-(ethylenedioxy)mitomycins against P388 leukemia in mice and in vitro anticellular activity against HeLa S_3 cells. All compounds were found to show effective increase in life span (ILS) values and most compounds were shown to possess similar activity to mitomycin C (**1**). The most significant conclusion of this assay was that most of these derivatives were quite potent in terms of the optimal dose. For instance, the optimal dose of **9** was only 0.39 mg/kg. In several mitomycin skeletons depicted in Figure 1, mitomycin A type compounds showed stronger activity (**9** vs **10**, **11**, and **12**; **13b**, **13c** vs **14**; **15** vs **18**). Although the biologically active species of these derivatives were supposed to be 7-(2-hydroxyethoxy)mitomycins containing the quinone moiety, 6-chloro or 5,6-enol type compounds (**13b,c**, **14–25b**), which could be considered as masked compounds of the corresponding 7-(2-hydroxyethoxy)mitomycins, also showed potent antitumor activity. In the case of 5,6-enol derivatives, enol esters **17**, **21b**, and **22b**, which have longer hydrophobic side chain at C5, showed strong activity. Enol octanoate **22b** showed the best ILS value in this assay. Enol ether **19** showed less potent activity than the enol esters. The markedly low potencies of the enol ether **19** in comparison to the enol esters may be due to the difficulty of unmasking the quinone from the enol ether in the cell. In addition, each compound generally showed a IC_{50} value that correlated with its potency (Table I).

The results suggest that the length of side chain at C5 and the chemical (or biochemical) reactivity of the enolates might be important factors for the antitumor activity.

Conclusions

A series of 7,7-(ethylenedioxy)mitomycins, which lack a quinone moiety, were prepared and most of them were effective against P388 leukemia in mice and HeLa S_3 cells. Some of these derivatives showed much more potent activity than mitomycin C in terms of optimal dose. It was shown that masking the quinone could be an important approach for designing effective mitomycin analogues. Further detailed studies on antitumor spectra and toxicity of some of these derivatives are in progress.

Experimental Section

Melting points were recorded on a Yanagimoto melting-point apparatus and are uncorrected. Secondary ionization mass spectra (SI-MS) were obtained with a Hitachi M-80B instrument. Fast atom bombardment mass spectra (FAB-MS) were obtained with a JEOL JMS-D300 instrument. IR spectra were obtained with a Nihon Bunko IR-810 instrument. ^1H NMR spectra were obtained with a Bruker AM-400 spectrometer (400 MHz) or a JEOL JNM-GX270 spectrometer (270 MHz) and are reported as ppm relative to TMS. Elemental analyses were performed with a

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Perkin-Elmer 2400 C, H, N analyzer.

7-Demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (9). To a solution of mitomycin A (2) (1.0 g, 2.87 mmol) in THF (15 mL) and ethylene glycol (3 mL) was added a solution of KOH in ethylene glycol (1.6% w/w, 0.5 mL). After being stirred for 5 h at 25 °C, dry ice was added to the reaction mixture. The reaction mixture was poured into brine and extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluted with $CHCl_3$–MeOH (97:3), to give 9 (880 mg, 81% yield, a 4:1 mixture of diastereomers at C6) as a yellow powder: mp 165–170 °C dec; SI-MS m/z 380 (M^+ + H); IR (KBr) 3446, 3296, 2902, 1727, 1720, 1642, 1575, 1447, 1336, 1186, 1068, 964, 855, 757, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 4.80 (2 H, br s), 4.78 (1 H, dd, J = 11, 4.4 Hz), 4.58 (1 H, d, J = 12 Hz), 4.39 (1 H, m), 4.13–3.98 (3 H, m), 3.62 (1 H, dd, J = 11, 4.4 Hz), 3.44 (1 H, dd, J = 12, 1.5 Hz), 3.27 (1 H, q, J = 6.6 Hz), 3.21 (3 H, s), 2.91 (1 H, d, J = 4.4 Hz), 2.80 (1 H, m), 1.18 (3 H, d, J = 6.6 Hz), 0.90 (1 H, br s). Anal. ($C_{17}H_{21}N_3O_7$) C, H, N.

7-Demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin F (10). As described above, mitomycin F (3) (200 mg, 0.55 mmol) was treated with KOH solution (1.6% w/w in ethylene glycol, 0.5 mL) in THF (2 mL) and ethylene glycol (3 mL) to afford 10 (79% yield, a 4:1 mixture of diastereomers at C6) as a yellow powder: mp 88–92 °C dec; SI-MS m/z 394 (M^+ + H); IR (KBr) 3420, 2948, 2900, 1720, 1708, 1650, 1576, 1449, 1340, 1203, 1056, 1031, 972, 950, 846, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 4.78 (1 H, dd, J = 11, 4.4 Hz), 4.72 (2 H, br s), 4.40 (1 H, t, J = 11 Hz), 4.40–3.95 (4 H, m), 3.80 (1 H, d, J = 13 Hz), 3.58 (1 H, dd, J = 11, 4.4 Hz), 3.39 (1 H, dd, J = 13, 2.2 Hz), 3.27 (1 H, q, J = 6.6 Hz), 3.18 (3 H, s), 2.29 (1 H, d, J = 4.7 Hz), 2.25 (3 H, s), 2.22 (1 H, dd, J = 4.7, 2.2 Hz), 1.25 (3 H, d, J = 6.6 Hz); (minor isomer (main peaks)) δ 4.70 (1 H, dd, J = 11, 4.4 Hz), 3.34 (1 H, dd, J = 12, 2.2 Hz), 3.19 (3 H, s), 3.01 (1 H, q, J = 6.9 Hz), 2.26 (1 H, d, J = 13 Hz), 1.25 (3 H, d, J = 6.9 Hz). Anal. ($C_{18}H_{23}N_3O_7 \cdot 0.8H_2O$) C, N; H: calcd, 6.08; found, 5.65.

7-Demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin B (11). As described in the synthesis of 9, mitomycin B (4) (230 mg, 0.66 mmol) was treated with KOH solution (1.6% w/w in ethylene glycol, 0.5 mL) in ethylene glycol (7.2 mL) to give 11 (125 mg, 50% yield, a 4:1 mixture of diastereomers at C6) as a yellow powder: mp 165–170 °C dec; SI-MS m/z 380 (M^+ + H); IR (KBr) 3450, 2960, 2900, 1718, 1702, 1640, 1570, 1455, 1340, 1204, 1063, 951, 847, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 4.73 (1 H, dd, J = 12, 5.6 Hz), 4.67 (1 H, dd, J = 12, 2.0 Hz), 4.40 (1 H, m), 4.15–3.95 (3 H, m), 3.75 (1 H, dd, J = 5.7, 2.0 Hz), 3.72 (1 H, d, J = 13 Hz), 3.38 (1 H, dd, J = 13, 2.0 Hz), 3.23 (1 H, q, J = 6.6 Hz), 2.26 (1 H, d, J = 4.4 Hz), 2.23 (1 H, dd, J = 4.4, 2.0 Hz), 2.23 (3 H, s), 1.18 (3 H, d, J = 6.6 Hz); (minor isomer (main peaks)) δ 3.33 (1 H, br d, J = 12 Hz), 2.98 (1 H, q, J = 7.1 Hz), 1.25 (3 H, d, J = 7.1 Hz). Anal. ($C_{17}H_{21}N_3O_7 \cdot 0.6H_2O$) C, H, N.

7-Demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin J (12). As described above, mitomycin J (5) (160 mg, 0.44 mmol) was treated with KOH solution (1.6% w/w in ethylene glycol, 0.3 mL) in THF (1.0 mL) and ethylene glycol (2.0 mL) to afford 12 (151 mg, 87% yield, a 3:1 mixture of diastereomers at C6) as a yellow powder: mp 83–87 °C; SI-MS m/z 394 (M^+ + H); IR (KBr) 3470, 3370, 2952, 2900, 1715, 1655, 1577, 1461, 1335, 1275, 1200, 1111, 1075, 942, 843, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 4.72 (1 H, dd, J = 11, 3.9 Hz), 4.66 (2 H, br s), 4.48 (1 H, J = 11, 9.1 Hz), 4.40–3.90 (4 H, m), 3.91 (1 H, dd, J = 9.1, 3.9 Hz), 3.64 (1 H, d, J = 13 Hz), 3.51 (1 H, dd, J = 13, 2.2 Hz), 3.30 (3 H, s), 3.17 (1 H, q, J = 6.6 Hz), 2.35 (1 H, dd, J = 4.7, 2.2 Hz), 2.30 (3 H, s), 2.23 (1 H, d, J = 4.7 Hz), 1.19 (3 H, d, J = 6.6 Hz); (minor isomer (main peaks)) δ 4.77 (1 H, dd, J = 11, 3.9 Hz), 4.47 (1 H, dd, J = 11, 9.1 Hz), 3.82 (1 H, d, J = 13 Hz), 3.47 (1 H, dd, J = 13, 2.2 Hz), 3.30 (3 H, s), 3.02 (1 H, q, J = 7.1 Hz), 2.29 (3 H, s), 2.19 (1 H, d, J = 4.7 Hz), 1.23 (3 H, d, J = 7.1 Hz). Anal. ($C_{18}H_{23}N_3O_7$) C, H, N.

6-Chloro-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)-mitomycin A (13). To a solution of 7 (210 mg, 0.50 mmol), prepared from 1a-acetylmitomycin A, as previously reported,[8a] in THF (5 mL) were added sequentially triethylamine (0.5 mL) and *N*-chlorosuccinimide (100 mg, 0.75 mmol). After being stirred at 25 °C for 12 h, the reaction mixture was poured into a phosphate buffer solution (0.1 M, pH 4) and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual crude **13a** was dissolved in MeOH (10 mL), and an NH_3 solution in MeOH (6.8 M, 2 mL) was added to the mixture. After being stirred for 10 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column, eluted with $CHCl_3$–MeOH (96:4), to give **13b** (119 mg, 58% yield) as a yellow powder together with its isomer **13c** at C6 (23 mg, 10% yield).

13b: SI-MS m/z 414 (M^+ + H); IR (KBr) 3380, 2904, 1709, 1653, 1572, 1447, 1378, 1335, 1208, 1057, 994, 948, 855, 822, 778, 755, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (2 H, br s), 4.70 (1 H, dd, J = 11, 4.7 Hz), 4.55 (1 H, t, J = 11 Hz), 4.27–4.13 (4 H, m), 4.10 (1 H, br d, J = 13 Hz), 3.67 (1 H, dd, J = 11, 4.7 Hz), 3.42 (1 H, br d, J = 13 Hz), 3.23 (3 H, s), 2.90 (1 H, br s), 2.82 (1 H, br s), 1.74 (3 H, s), 0.66 (1 H, br s). Anal. ($C_{17}H_{20}ClN_3O_7$) C; H: calcd, 4.87; found, 4.25; N: calcd, 10.15; found, 9.24.

13c: ^1H NMR (100 MHz, $CDCl_3$) δ 4.95 (2 H, br s), 4.86 (1 H, dd, J = 10.5, 4.8 Hz), 4.63 (1 H, t, J = 10.5 Hz), 4.6–4.0 (4 H, m), 3.94 (1 H, d, J = 12 Hz), 3.66 (1 H, dd, J = 10.5, 4.8 Hz), 3.48 (1 H, br d, J = 12 Hz), 3.23 (3 H, s), 3.0–2.8 (2 H, m), 1.71 (3 H, s). Anal. ($C_{17}H_{20}ClN_3O_7$) C, H, N.

6-Chloro-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)-mitomycin B (14). As described in the synthesis of 13, 7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin B (11) (190 mg, 0.50 mmol) was treated with *N*-chlorosuccinimide (110 mg, 0.82 mmol) and triethylamine (0.2 mL) in THF (4 mL) to give 14 (120 mg, 58% yield, a 3:1 mixture of diastereomers at C6): SI-MS m/z 414 (M^+ + H); IR (KBr) 3420, 2950, 1705, 1650, 1562, 1450, 1340, 1205, 1041, 949, 840, 805, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 4.81 (2 H, br s), 4.73 (1 H, dd, J = 11.8, 1.7 Hz), 4.66 (1 H, dd, J = 11.8, 5.7 Hz), 4.31–4.03 (4 H, m), 3.91 (1 H, d, J = 12.8 Hz), 3.72 (1 H, dd, J = 5.7, 1.7 Hz), 3.35 (1 H, dd, J = 12.8, 1.5 Hz), 2.26 (1 H, d, J = 4.7 Hz), 2.23 (1 H, dd, J = 4.7, 1.5 Hz), 2.22 (3 H, s), 1.76 (3 H, s); (minor isomer (main peaks)) δ 4.98 (1 H, br s), 3.83 (1 H, dd, J = 5.8, 2.0 Hz), 3.72 (1 H, d, J = 12.3 Hz), 2.22 (3 H, s), 1.69 (3 H, s). Anal. ($C_{17}H_{20}ClN_3O_7$) C, H, N.

Enol Acetate 15. A mixture of 1a-acetyl-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (7) (400 mg, 0.95 mmol), triethylamine (0.5 mL), and acetic anhydride (0.2 mL, 2.11 mmol) in $CHCl_3$ (5 mL) was stirred at room temperature for 30 h. MeOH (2 mL) was added to the reaction mixture, and the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel, eluted with $CHCl_3$–MeOH (95:5), to give the N-protected enol acetate (170 mg, 39%). The enol acetate obtained above was dissolved in THF (50 mL), and saturated $NaHCO_3$ solution (10 mL) was added. After being stirred for 15 h, the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluted with $CHCl_3$–MeOH (95:5), to afford 15 (92 mg, 59% yield): SI-MS m/z 422 (M^+ + H); IR (KBr) 3450, 1770, 1720, 1671, 1612, 1550, 1490, 1460, 1340, 1190, 1074, 970, 854, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (1 H, dd, J = 11, 4.2 Hz), 4.64 (2 H, br s), 4.56–4.44 (3 H, m), 4.19–4.13 (2 H, m), 3.80 (1 H, d, J = 11 Hz), 3.51 (1 H, dd, J = 11, 4.4 Hz), 3.33 (1 H, br d, J = 12 Hz), 3.16 (3 H, s), 2.88 (1 H, d, J = 4.2 Hz), 2.78 (1 H, br s), 2.29 (3 H, s), 1.72 (3 H, s). Anal. ($C_{19}H_{23}N_3O_8 \cdot 0.6H_2O$) C, H, N.

Enol Benzoate 16. In a similar manner as that described above, 1a-acetyl-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)-mitomycin A (7) (186 mg, 0.44 mmol) was treated with benzoyl chloride (0.1 mL, 0.86 mmol), triethylamine (0.3 mL), and DMAP (1 mg) in $CHCl_3$ (10 mL) to afford the N-protected enol benzoate (136 mg, 59%). The acetyl group at the 1a position was deprotected by the treatment with NH_3 in MeOH (20 mL) for 4 h. Purification by silica gel column chromatography, with $CHCl_3$–MeOH (95:5) as eluent, gave 16 (42 mg, 33% yield): SI-MS m/z 484 (M^+ + H); IR (KBr) 3450, 3350, 2902, 1738, 1716, 1610, 1547, 1482, 1452, 1388, 1321, 1260, 1177, 1070, 1054, 1022, 972, 856, 801, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (2 H, m), 7.69 (1 H, m), 7.55 (2 H, m), 4.70 (2 H, br s), 4.66 (1 H, dd, J = 11, 4.2 Hz), 4.59–4.47 (3 H, m), 4.21–4.16 (2 H, m), 3.78 (1 H, d, J = 12 Hz), 3.54 (1 H, dd, J = 11, 4.2 Hz), 3.19 (3 H, s), 3.13 (1

H, br d, J = 12 Hz), 2.86 (1 H, br d, J = 4.2 Hz), 2.69 (1 H, br s), 1.78 (3 H, s), 0.68 (1 H, br s). Anal. ($C_{24}H_{25}N_3O_8 \cdot 0.3H_2O$) C, H, N.

Enol Dodecanoate 17. As described above, 1a-acetyl-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**7**) (321 mg, 0.763 mmol) was treated with lauroyl chloride (0.176 mL, 0.763 mmol), triethylamine (0.5 mL), and DMAP (5 mg) in $CHCl_3$ (14 mL) to afford the N-protected enol dodecanoate (280 mg, 61%). Deprotection of 1a-acetyl group with NH_3 in MeOH (40 mL) afforded **17** (67 mg, 28% yield): SI-MS m/z 562 (M^+ + H); IR (KBr) 3458, 3350, 3306, 2926, 2854, 1767, 1717, 1610, 1545, 1483, 1454, 1391, 1326, 1181, 1133, 1074, 1013, 972, 936, 893, 857, 801, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (2 H, br s), 4.64 (1 H, dd, J = 11, 4.2 Hz), 4.54–4.44 (3 H, m), 4.19–4.13 (2 H, m), 3.78 (1 H, d, J = 11 Hz), 3.50 (1 H, dd, J = 11, 4.2 Hz), 3.30 (1 H, d, J = 11 Hz), 3.15 (3 H, s), 2.88 (1 H, br s), 2.78 (1 H, br s), 2.53 (2 H, m), 1.72 (2 H, m), 1.71 (3 H, s), 1.68–1.40 (16 H, m), 0.88 (3 H, t, J = 6.6 Hz), 0.73 (1 H, br s). Anal. ($C_{29}H_{43}N_3O_8$) C, H, N.

Enol Acetate 18. In a similar manner as that described for the synthesis of **15**, 7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin B (**11**) (270 mg, 0.71 mmol) was treated with acetic anhydride (0.5 mL, 5.3 mmol) and pyridine (10 mL) to afford **18** (120 mg, 40% yield): SI-MS m/z 424 (M^+ + 3 H); IR (KBr) 3560, 3420, 3184, 2884, 1753, 1706, 1630, 1601, 1533, 1506, 1499, 1459, 1345, 1221, 1210, 1173, 1131, 1067, 1013, 964, 821, 738 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.26 (2 H, br s), 5.54 (1 H, dd, J = 11, 3.7 Hz), 5.08 (1 H, t, J = 11 Hz), 4.60–4.52 (2 H, m), 4.15 (1 H, dd, J = 11, 4.7 Hz), 4.14–4.07 (2 H, m), 3.78 (1 H, d, J = 12 Hz), 3.46 (1 H, dd, J = 12, 2.2 Hz), 2.43 (1 H, d, J = 4.7 Hz), 2.22 (1 H, dd, J = 4.7, 2.2 Hz), 2.19 (3 H, s), 2.07 (3 H, s), 1.78 (3 H, d, J = 0.5 Hz). Anal. ($C_{19}H_{23}N_3O_8 \cdot 1.4H_2O$) C, H, N.

Enol Methyl Ether 19. A mixture of 1a-acetyl-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**7**) (197 mg, 0.47 mmol), dimethyl sulfate (0.2 mL, 2.11 mmol), and K_2CO_3 (300 mg, 2.17 mmol) was stirred for 2 days at room temperature. The reaction mixture was poured into a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluted with $CHCl_3$–MeOH (97:3), to afford the N-protected enol ether (68 mg, 33% yield). Deprotection of acetyl group with NH_3 in MeOH (30 mL) gave **19** (55 mg, 93% yield): SI-MS m/z 394 (M^+ + H); IR (KBr) 3430, 3300, 2940, 2898, 1709, 1659, 1611, 1541, 1474, 1452, 1387, 1332, 1288, 1178, 1137, 1066, 1033, 964, 856, 823, 801, 763, 709, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (2 H, br s), 4.68 (1 H, dd, J = 11, 4.2 Hz), 4.54–4.43 (3 H, m), 4.18–4.13 (2 H, m), 4.09 (1 H, d, J = 12 Hz), 3.65 (3 H, s), 3.51 (1 H, dd, J = 8.9, 4.4 Hz), 3.47 (1 H, br d, J = 12 Hz), 3.21 (3 H, s), 2.89 (1 H, br s), 2.79 (1 H, br s), 1.83 (3 H, s), 0.70 (1 H br s). Anal. ($C_{18}H_{23}N_3O_7 \cdot 0.2H_2O$) C, H; N: calcd, 10.58; found, 10.02.

1a-[(Allyloxy)carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (20). To a solution of 7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**9**) (3.81 g, 10.0 mmol) in $CHCl_3$ (100 mL) and pyridine (1.0 mL) was added dropwise a solution of allyl chloroformate (1.6 mL, 10.9 mmol) in $CHCl_3$ (10 mL) over a period of 15 min at 0 °C. After being stirred for 30 min at 0 °C and another 15 min at room temperature, the reaction mixture was diluted with $CHCl_3$ and washed with a saturated $NaHCO_3$ solution, a saturated NH_4Cl solution, and brine. The mixture was then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 30:1), followed by trituration with $CHCl_3$–n-hexane, to give **20** (3.66 g, a 2.5:1 mixture of diastereomers at C6) as a reddish yellow powder in 79% yield: FAB-MS m/z 464 (M^+ + H); IR (KBr) 3460, 2950, 2900, 1730, 1650, 1580, 1450, 1400, 1330, 1270, 1190, 1090, 1070, 1030 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) (major isomer) δ 7.5–7.3 (2 H, br s), 6.10–5.87 (1 H, m), 5.68 (1 H, dd, J = 11, 4.7 Hz), 5.34 (1 H, dd, J = 17, 1.4 Hz), 5.15 (1 H, dd, J = 11, 1.4 Hz), 4.80 (1 H, t, J = 11 Hz), 4.68 (2 H, d, J = 5.9 Hz), 4.54–3.87 (6 H, m), 3.84 (1 H, d, J = 4.4 Hz), 3.56–3.41 (2 H, m), 3.39 (1 H, q, J = 6.8 Hz), 3.11 (3 H, s), 1.31 (3 H, d, J = 7.0 Hz); (minor isomer (main peaks)) δ 7.5–7.3 (2 H, br s), 6.10–5.87 (1 H, m), 5.68 (1 H, dd, J = 11, 4.7 Hz), 5.29 (1 H, dd, J = 17, 1.6 Hz), 5.09 (1 H, dd, J = 9.5, 1.1 Hz), 4.80 (1 H, t, J = 11 Hz), 4.59 (2 H, d, J = 5.7 Hz), 3.84 (1 H, d, J = 4.4 Hz), 3.15 (3 H, s), 1.29 (3 H, d, J = 7.0 Hz). Anal. ($C_{21}H_{25}N_3O_9 \cdot 0.4H_2O$) C, H, N.

Improved Synthesis of 17. To a solution of 1a-[(allyloxy)carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**20**) (230 mg, 0.495 mmol) in dry CH_3CN (10 mL) and dry triethylamine (1.8 mL) were added lauric anhydride (348 mg, 1.01 mmol) and DMAP (1 mg). After being stirred for 2 h and 10 min at room temperature, the reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, NH_4Cl, and brine. After being dried over Na_2SO_4, the mixture was concentrated under reduced pressure.

The residue was dissolved in THF (10 mL) and triethylammonium formate (0.2 mL), and $Pd(PPh_3)_4$ (135 mg, 0.117 mmol) was added to the mixture. After being stirred for 3 h and 20 min at room temperature under argon atmosphere, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel ($CHCl_3$–MeOH, 30:1) to give **17** (199 mg, 72% yield) as yellow crystals.

Enol Linoleoate 21b. (1) Linoleated Adduct 21a. To a solution of 1a-[(allyloxy)carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**20**) (236 mg, 0.508 mmol) in dry CH_3CN (10 mL) and dry triethylamine (1.8 mL) were added linoleoyl chloride (0.47 mL, 1.46 mmol) and DMAP (5 mg), and the mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with phosphate buffer (0.05 M, pH 7) and extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$, NH_4Cl, and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 50:1) to give a yellow fraction, which was concentrated under reduced pressure. The residue was triturated with ether to afford the desired **21a** (183 mg, 76% yield) as a yellow powder: IR (KBr) 3450, 3350, 3300, 2930, 2860, 1770, 1720, 1610, 1540, 1490, 1460, 1400, 1330, 1180, 1120, 1080 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 7.7–7.3 (2 H, br s), 6.12–5.97 (1 H, m), 5.63 (1 H, dd, J = 10.4, 4.4 Hz), 5.58–5.44 (4 H, m), 5.32 (1 H, dd, J = 17.2, 1.5 Hz), 5.2–5.0 (1 H, m), 4.72 (1 H, t, J = 11.0 Hz), 4.67 (2 H, d, J = 5.9 Hz), 4.72–4.59 (2 H, m), 4.25–4.14 (2 H, m), 4.09 (1 H, d, J = 12.1 Hz), 3.90 (1 H, dd, J = 11.4, 4.4 Hz), 3.85 (1 H, d, J = 4.7 Hz), 3.60 (1 H, dd, J = 4.7, 1.7 Hz), 3.53 (1 H, dd, J = 12.1, 1.7 Hz), 3.10 (3 H, s), 2.93 (2 H, m), 2.77–2.59 (2 H, m), 2.16–2.05 (4 H, m), 1.90 (3 H, s), 1.83–1.63 (2 H, m), 1.45–1.15 (14 H, m), 0.87 (3 H, br t).

(2) Deprotection of 21a. A mixture of linoleated adduct **21a** (270 mg, 0.372 mmol), triethylammonium formate (0.15 mL), and $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) in THF (10 mL) was stirred for 50 min at room temperature under argon. The reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 50:1), followed by trituration with ether, to give **21b** (183 mg, 76% yield) as a yellow powder: FAB-MS m/z 642 (M^+ + H); IR (KBr) 3450, 3350, 3300, 2920, 2850, 1760, 1710, 1610, 1540, 1480, 1450, 1390, 1330, 1070 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 7.7–7.4 (2 H, br s), 5.57–5.40 (4 H, m), 5.43 (1 H, dd, J = 10.3, 4.2 Hz), 5.10 (1 H, br t, J = 11 Hz), 4.71–4.61 (2 H, m), 4.20–4.14 (2 H, m), 3.94 (1 H, d, J = 10.4 Hz), 3.89 (1 H, dd, J = 11.1, 4.2 Hz), 3.48 (1 H, br d, J = 11 Hz), 3.2–3.1 (1 H, m), 3.14 (3 H, s), 2.93 (2 H, m), 2.80 (1 H, br s), 2.66 (2 H, dt, J = 7.3, 3.7 Hz), 2.23–2.07 (5 H, m), 1.88 (3 H, s), 1.83–1.68 (2 H, m), 1.45–1.20 (14 H, m), 0.86 (3 H, t, J = 6.7 Hz). Anal. ($C_{35}H_{43}N_3O_8$) C, H, N.

Improved Synthesis of 21b. A mixture of 1a-[(allyloxy)carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**20**) (90 mg, 0.194 mmol), triethylamine (0.8 mL) linoleic anhydride (0.3 mL, 0.498 mmol), and DMAP (2 mg) in CH_3CN (2 mL) was stirred for 6 h and 20 min at room temperature. The reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was then treated with triethylammonium formate (0.1 mL) and $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) in THF (5 mL) for 1 h and 20 min under an argon atmosphere. A similar workup and purification as those described above gave **21b** (71 mg, 57% yield).

Enol Octanoate 22b. A mixture of 1a-[(allyloxy)carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**20**) (117 mg, 0.253 mmol), triethylamine (0.6 mL), octanoyl chloride (122 mg, 0.749 mmol), and DMAP (5 mg) in CH_3CN (5 mL) was stirred for 8 h at room temperature. The reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residual crude **22a** was treated with triethylammonium formate (0.05 mL) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) in THF (5 mL) under argon at room temperature. After 1 h, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 30:1) to give **22b** (88 mg, 69% yield) as yellow crystals: FAB-MS m/z 506 ($M^+ + H$); IR (KBr) 3450, 3340, 3300, 2920, 2860, 1760, 1710, 1600, 1540, 1480, 1450, 1390, 1330, 1070 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 7.8–7.4 (2 H, br s), 5.43 (1 H, dd J = 10.4, 4.2 Hz), 5.3–5.0 (1 H, m), 4.73–4.63 (2 H, m), 4.24–4.15 (2 H, m), 3.95 (1 H, d, J = 11.4 Hz), 3.89 (1 H, dd, J = 11.2, 4.2 Hz), 3.50 (1 H, dd, J = 11.4, 1.7 Hz), 3.16 (1 H, d, J = 4.3 Hz), 3.14 (3 H, s), 2.82 (1 H, dd, J = 4.3, 1.6 Hz), 2.65 (2 H, m), 2.4–2.0 (1 H, br), 1.88 (3 H, s), 1.78–1.64 (2 H, m), 1.40–1.12 (8 H, m), 0.85 (3 H, t, J = 6.7 Hz). Anal. ($C_{25}H_{35}N_3O_8 \cdot 0.3H_2O$) C, H, N.

Enol Pivalate 23b. A mixture of 1a-[(allyloxy)carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**20**) (118 mg, 0.255 mmol), triethylamine (0.6 mL), trimethylacetyl chloride (59.6 mg, 0.494 mmol), and DMAP (1 mg) in CH_3CN (5 mL) was stirred for 40 min at room temperature. The reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residual crude **23a** was treated with triethylammonium formate (0.10 mL) and $Pd(PPh_3)_4$ (70 mg, 0.061 mmol) in THF (5 mL) under argon at room temperature. After 1 h and 40 min, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 30:1–20:1) to give **23b** (88.7 mg, 75% yield) as yellow crystals: FAB-MS m/z 464 ($M^+ + H$); IR (KBr) 3480, 3350, 3270, 2970, 1740, 1710, 1620, 1540, 1480, 1450, 1390, 1340, 1190, 1110 1070, 970 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 7.8–7.4 (2 H, br s), 5.44 (1 H, dd, J = 10.4, 4.2 Hz), 5.2–5.1 (1 H, overlapped with H_2O), 4.72–4.62 (2 H, m), 4.23–4.14 (2 H, m), 3.89 (1 H, d, J = 11.0 Hz), 3.87 (1 H, dd, J = 11.3, 4.2 Hz), 3.44 (1 H, br d, J = 11 Hz), 3.17 (1 H, br s), 3.13 (3 H, s), 2.83 (1 H, br s), 2.23 (1H, br s), 1.81 (3 H, s), 1.29 (9 H, s). Anal. ($C_{22}H_{29}N_3O_8$) H, N; C: calcd, 57.01; found, 57.51.

Enol 3-Acetylpropionate 24b. To a solution of 1a-[(allyloxy)carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**20**) (95 mg, 0.250 mmol) in CH_3CN (3.5 mL) and triethylamine (0.8 mL) were added DMAP (3 mg) and 3-acetylpropionyl chloride, prepared from 3-acetylpropionic acid (58 mg, 0.50 mmol) and thionyl chloride (0.04 mL) in CH_2Cl_2 (0.50 mL). After 22 h and 30 min, the same amount of the acid chloride was added and the mixture was stirred for additional 30 min. The reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 20:1) to give **24a** (81.7 mg, 56% yield).

A mixture of **24a**, triethylammonium formate (0.1 mL), and $Pd(PPh_3)_4$ (19 mg, 0.016 mmol) in THF (5 mL) was stirred for 10 min at room temperature under an argon atmosphere. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (AcOEt–acetone, 2:1–1:1) to give **24b** (35.1 mg, 52% yield): FAB-MS m/z 478 ($M^+ + H$); IR (KBr) 3450, 2930, 1770, 1720, 1620, 1530, 1490, 1460, 1410, 1340, 1130, 1080 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 7.7–7.3 (2 H, br s), 5.43 (1 H, dd, J = 10.5, 4.1 Hz), 5.10 (1 H, br t, J = 11 Hz), 4.7–4.6 (2 H, m), 4.2–4.1 (2 H, m), 3.93 (1 H, br d, J = 13 Hz), 3.87 (1 H, dd, J = 10.9, 4.1 Hz), 3.70 (1 H, br d, J = 13 Hz), 3.13 (1 H, br s), 3.13 (3 H, s), 3.0–2.8 (4 H, m), 2.77 (1 H, m), 2.13 (1 H, br s), 2.07 (3 H, s), 1.90 (3 H, s). Anal. ($C_{22}H_{27}N_3O_9$) C, H; N: calcd, 8.80; found, 7.49.

Enol Carbonate 25b. A mixture of 1a-[(allyloxy)-carbonyl]-7-demethoxy-6,7-dihydro-7,7-(ethylenedioxy)mitomycin A (**20**) (91.5 mg, 0.197 mmol), triethylamine (0.8 mL), and ethyl chloroformate (0.060 mL, 0.63 mmol) in CH_3CN (2 mL) was stirred for 1 h and 15 min at room temperature. The reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residual crude **25a** was treated with triethylammonium formate (0.10 mL) and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) in THF (5 mL) under argon at room temperature. After 3 h and 20 min, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 20:1) to give **25b** (66.1 mg, 74% yield) as a yellow powder: FAB-MS m/z 452 ($M^+ + H$); IR (KBr) 3450, 2970, 2900, 1770, 1720, 1620, 1550, 1480, 1460, 1340, 1240, 1070 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 7.8–7.3 (2 H, br s), 5.43 (1 H, dd, J = 10.3, 4.3 Hz), 5.09 (1 H, br t, J = 11 Hz), 4.7–4.6 (2 H, m), 4.4–4.2 (2 H, m), 4.2–4.1 (2 H, m), 3.96 (1 H, d, J = 11.9 Hz), 3.90 (1 H, dd, J = 11.4, 4.3 Hz), 3.46 (1 H, br d, J = 12 Hz), 3.15 (1 H, br s), 3.15 (3 H, s), 2.76 (1 H, br s), 2.19 (1 H, br s), 1.90 (3 H, s), 1.22 (3 H, t, J = 7.1 Hz). Anal. ($C_{20}H_{25}N_3O_9$) C, H, N.

Registry No. **2**, 4055-39-4; **3**, 18209-14-8; **4**, 4055-40-7; **5**, 74985-82-3; **7** (isomer 1), 125761-41-3; **7** (isomer 2), 125761-42-4; **9** (isomer 1), 141506-99-2; **9** (isomer 2), 141507-04-2; **10** (isomer 1), 141507-00-8; **10** (isomer 2), 141507-05-3; **11** (isomer 1), 127759-20-0; **11** (isomer 2), 127759-21-1; **12** (isomer 1), 141507-01-9; **12** (isomer 2), 141507-06-4; **13** (Z = H, isomer 1), 141507-02-0; **13** (Z = H, isomer 2), 141507-07-5; **14** (isomer 1), 141437-81-2; **14** (isomer 2), 141507-08-6; **15**, 127678-46-0; **15** N-protected, 127678-45-9; **16**, 127678-49-3; **17**, 127678-50-6; **17** N-protected, 127678-60-8; **18**, 141507-03-1; **19**, 127678-51-7; **19** N-protected, 127678-61-9; **20** (isomer 1), 127678-52-8; **20** (isomer 2), 127759-22-2; **21a**, 141437-82-3; **21b**, 127678-54-0; **22b**, 127678-55-1; **23b**, 127678-56-2; **24a**, 141437-84-5; **24b**, 127678-58-4; **25b**, 141437-83-4; lauroyl chloride, 112-16-3; allyl chloroformate, 2937-50-0; linoleoyl chloride, 7459-33-8; linoleic anhydride, 24909-68-0; octanoyl chloride, 111-64-8; trimethylacetyl chloride, 3282-30-2; 3-acetylpropionyl chloride, 1490-24-0.