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Antiproliferating Polyquinanes. V.[1] Di- and Triquinanes Involving α-Methylene or α-Alkylidene Cyclopentanone, Cyclopentenone, and γ-Lactone Systems

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New analogues related to quadrone (**3**), 3-methylenetricyclo[4.3.2.0^{1,5}]undecan-4-one (**14**), 4-methylenetricyclo[4.3.2.0^{1,5}]undecan-3-one (**15**), and 2-methylenetricyclo[4.3.2.0^{1,5}]undec-4-en-3-one (**16**), and novel propellane- and angular-type triquinanes, 3-methylenetricyclo[3.3.3.0]undecan-2-one (**17**), (*E*)-3-propylidene- and (*E*)-3-(5-carbomethoxy)pentylidenetricyclo[3.3.3.0]undecan-2-ones (**18** and **19**), (*E*)-5-(2-oxotricyclo[3.3.3.0]undecan-3-ylidene)pentyl (*E*)-cinnamate (**20**), 2-methylenetricyclo[3.3.3.0]undecan-3-one (**21**), 4-methylene-2-oxatricyclo[3.3.3.0]undecan-3-one (**22**), and 7-methylenetricyclo[6.3.0.0^{1,5}]undecan-6-one (**23**), were readily synthesized through skeletal transformations, and showed antiproliferating activity. Biomimetic reactions of a model compound of **3**, 2-methylenetricyclo[4.3.2.0^{1,5}]undecan-3-one (**8**), with propanethiol, *etc.* were undertaken. Correlations of the activity of some polyquinanes with second-order rate constants of addition of L-cysteine and with the carbon-13 nuclear magnetic resonance chemical shifts of *exo*-methylene β-carbons are discussed.

Keywords——diquinane; triquinane; α-methylene cyclopentanone; antiproliferating activity; quadrone; cytotoxic functional group; structure–activity relationship; biomimetic reaction; second-order rate constant; ^{13}C-NMR chemical shift

Introduction

The potent cytotoxic action of many terpenoid plant products and their ability to inactivate certain enzymes *in vitro* have been attributed to the presence of the α-methylene γ-butyrolactone moiety.[2] The biological activities of these lactones are apparently derived from the significant chemical affinity of this moiety for thiols and other biological nucleophiles.[3] In particular, interest in α-methylene γ-lactones as medicinal agents has been stimulated by the possibility that some of them might show enough selective toxicity against neoplastic cells to be of therapeutic value as anticancer agents.[3,4] It should be mentioned, however, that the biological activity of α-methylene γ-lactones is not confined to the complex polyfunctional sesquiterpene lactones only. For example, it has been shown that artificial α-methylene γ-lactone derivatives containing no other reactive functional groups can in some instances have growth-inhibitory activity comparable to that of multifunctional natural products.[5]

The structurally related five-membered ring systems, α-methylene cyclopentanone and α-methylene cyclopentenone groups, have also been demonstrated to show intriguing biological activities.[2] Simple representatives of these types (monoquinane: one cyclopentane ring) are sarkomycin (**1**)[6] and methylenomycin B (**2**),[7] possessing antitumor and antimicrobial activities, respectively.

Quadrone (**3**), isolated from the fermentation broth of *Aspergillus terreus* in 1978, was found to display significant activities against KB human epidermoid carcinoma of the nasopharynx *in vitro* and P388 lymphocytic leukemia *in vivo*.[8] The diquinane-type lactone **3** can be classified into the above category, in spite of the absence of functional groups commonly associated with antitumor agents (as described above) in the tetracyclic structure, because the retrolactonization product, terrecyclic acid A (**4**), isolated from the same fungus together with **3**, has been regarded as the carrier of the activities of **3** due to the α-methylene cyclopentanone moiety in **4**.[9] Moreover, as their synthetic analogue, descarboxyquadrone (**5**), having the active center and C-11 geminal methyls on a novel tricyclo[4.3.2.$0^{1,5}$]undecane skeleton, has been synthesized by several groups[10] including ours[11] and found to possess cytotoxicity against HeLa cell at almost the same level as **3**.[10a]

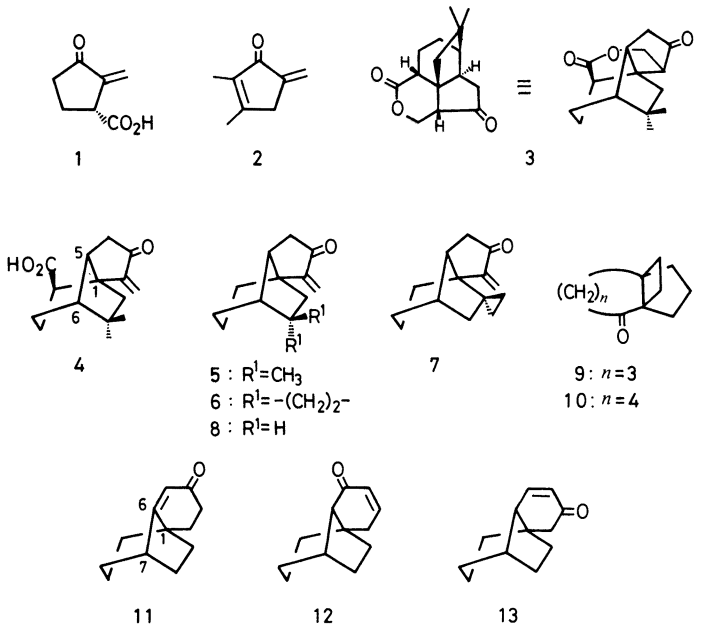


Chart 1

Recently we have reported the synthesis of not only **5**[11] but also some related compounds,[12] 2-methylene-11- and 10-spirocyclopropanotricyclo[4.3.2.$0^{1,5}$]undecan-3-ones (**6** and **7**),[12] and a model compound **8**[11a] by using the unique skeletal transformation of [4.3.2]propellan-2-one (**9**) to this novel framework.[13] As an application of the rearrangement to the higher homologue, [5.3.2]propellan-2-one (**10**), we have also synthesized the tricyclo[5.3.2.$0^{1,6}$]dodecenones **11**, **12**, and **13** containing a cyclohexenone moiety at various positions.[14] In view of the antiproliferating activity of these compounds against P388 and L1210 lymphocytic leukemic cells of mice (also listed in Table I), the results supported the tentative conclusion that, in cell culture as opposed to whole animal assays, the α-methylene cyclopentanone moiety is sufficient to confer cytotoxic properties upon the diquinane structure even in the absence of other functional groups, like the α-methylene γ-lactone system.[5]

On the basis of the above conclusion, in order to elucidate the relationship between cytotoxic activity and the polycyclic structure surrounding the α-methylene cyclopentanone system, and, furthermore, to search for potent cytotoxic functional groups, we describe here the synthesis of the following ten polyquinanes **14**—**23** having an α-methylene or α-alkylidene

carbonyl group and their antiproliferating activities. The diquinanes **14** and **15** with a tricyclo[4.3.2.$0^{1,5}$]undecane framework, the common skeleton of quadrone (**3**) and the related compounds **4**—**8**, possess an α-methylene carbonyl group at different positions from that of **4**—**8**. On the other hand, **16** has an α-methylene cyclopentenone group in place of cyclopentanone in **4**—**8**, and its methylene and carbonyl group are located at the same positions as those of **4**—**8**. These diquinanes **14**—**16** were prepared easily using the skeletal transformations of [4.3.2]propellanone (**9**) as in the cases of **5**—**8**.[11,12] Structurally different triquinane-type α-methylene cyclopentanones **17**, **21**, and **23** were also prepared on the basis of acid-catalyzed rearrangement of [4.3.2]propellanones. Namely, propellane-type triquinanes **17** and **21** were derived from [3.3.3]propellan-2-one (**24**), which was obtained selectively by the rearrangement of **9**.[13a] The oxapropellane **22** having an α-methylene γ-lactone group was also prepared for the purpose of comparison of its activity with that of **21**. The angular-type triquinane **23** was prepared by utilizing the two-step rearrangement method, such as the transformation of **9** to tricyclo[6.3.0.$0^{1,5}$]undecan-5-ol (**25**).[13b,c] In view of our previous results on the biological activities of some α-alkylidene γ-lactones,[15] the propellane-type triquinanes **18**—**20** having an α-alkylidene cyclopentanone group were prepared. The antiproliferating activities of these new polyquinanes would be informative concerning not only the effect of the polycyclic structure and position of the active moiety on the biological activity but also potent cytotoxically active functions.

Next, in order to elucidate the reason for the appearance of the antiproliferating activity of the α-methylene cyclopentanone derivatives, biomimetic reactions of **8** with model compounds of biological nucleophiles are also described herein. Moreover, in an attempt to estimate the magnitude of the cytotoxicity of α-methylene cyclopentanones by chemical methods, comparisons of the activity of some polyquinanes with the reaction rates with L-cysteine and with the carbon-13 nuclear magnetic resonance (^{13}C-NMR) chemical shifts of *exo*-methylene β-carbons are discussed.

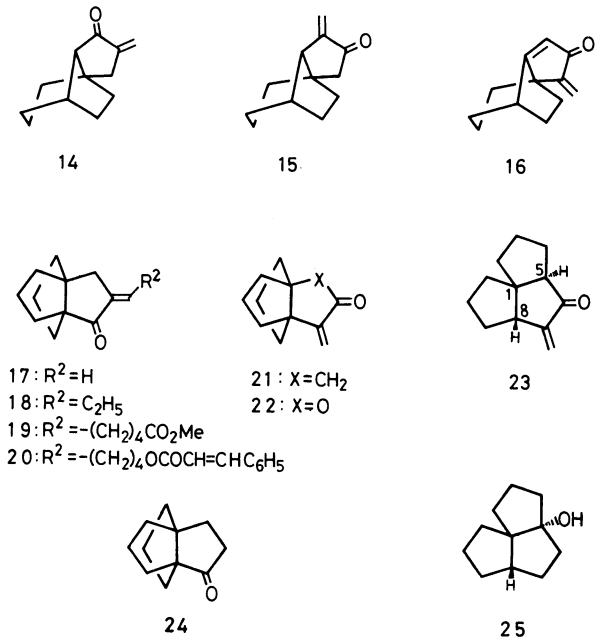


Chart 2

Preparation of Polyquinanes

The diquinanes **14**—**16** were prepared from the synthetic intermediate, tricyclo-[4.3.2.$0^{1,5}$]undec-4-ene (**26**),[11a] used in the synthesis of **8** (Chart 3). The diquinane **14** was obtained in 42% overall yield by hydroboration-oxidation of **26** followed by oxidation and subsequent α-methylenation of the ketone **27**[13b] in the following manner[16]: i) treatment of the enolate of **27** with chlorotrimethylsilane, ii) carbon–carbon bond formation of the silyl enol ether **28** and chloromethyl phenyl sulfide with titanium(IV) chloride ($TiCl_4$), iii) oxidation of the sulfide **29** with *m*-chloroperbenzoic acid (MCPBA), and iv) thermolysis of the sulfoxide **30**. Similarly, α-methylenation of the saturated ketone **32**, which was derived by allylic oxidation of **26** and then hydrogenation of the enone **31**,[11a] gave the diquinane **15** in 21% overall yield along with **8** in 20% overall yield. Dehydration of the alcohol[11a] prepared by hydroxymethylation of **31** *via* the mesylate afforded the diquinane **16** in 70% overall yield.

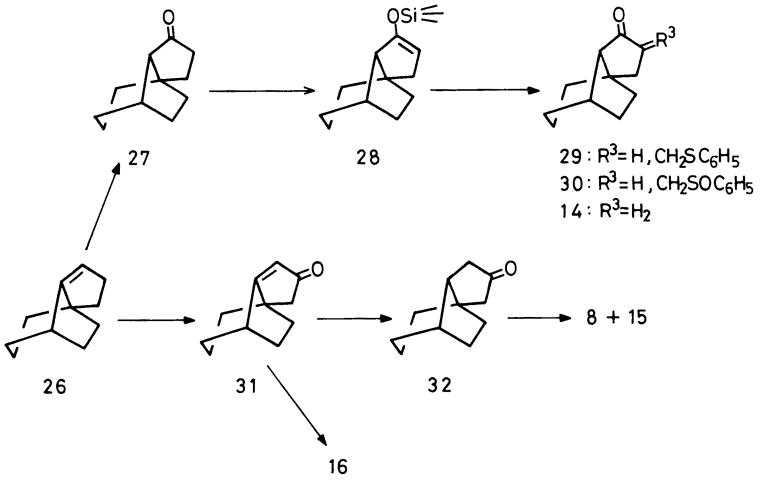


Chart 3

The propellane-type triquinane **17** was produced in 42% overall yield together with a small amount of the dimer (*vide infra*), by α-methylenation of **24** as described for the preparation of **14**. α-Alkylidene cyclopentanones **18**—**20** were synthesized by reaction of the enolate of **24** with the corresponding aldehydes (propionaldehyde, methyl 6-oxohexanoate,[17] and 5-oxopentyl cinnamate) in 71—85% yields. The *E*-geometry of the double bond was deduced from a comparison of the proton nuclear magnetic resonance (^{1}H-NMR) chemical shifts of their vinyl protons (δ, 6.30) with that of (*E*)-2-propylidenecyclopentanone (δ, 6.37).[18] Moreover, under these conditions, products with *E*-geometry are generally obtained.[19] The synthesis of **21** was carried out in two ways starting from **24** (Chart 4). Reaction with methyllithium (MeLi)[20] followed by dehydration of the tertiary alcohol **33** gave the olefin **34** in 86% overall yield. Epoxidation of **34** with MCPBA and the subsequent base-induced isomerization[21] of the epoxide **35** followed by oxidation of the allylic alcohol **36** furnished **21** in 44% overall yield. Alternatively, Wittig olefination of **24** followed by allylic oxidation[22] of the olefin **37** gave **21** in 49% overall yield and **36** in 47% overall yield.

The oxa-analogue of **22** was synthesized by ring contraction[23] of **24** and subsequent transformation to the corresponding γ-lactone **46**[24] followed by α-methylenation (Chart 5). Namely, α-formylation[25] of **24** followed by treatment of the crude **38** with tosyl azide[26] and subsequent UV-irradiation of the diazo ketone **39** in methanol gave methyl [3.3.2]propellane-9-carboxylate (**40**) in 61% overall yield. Saponification of **40** and then reaction of the

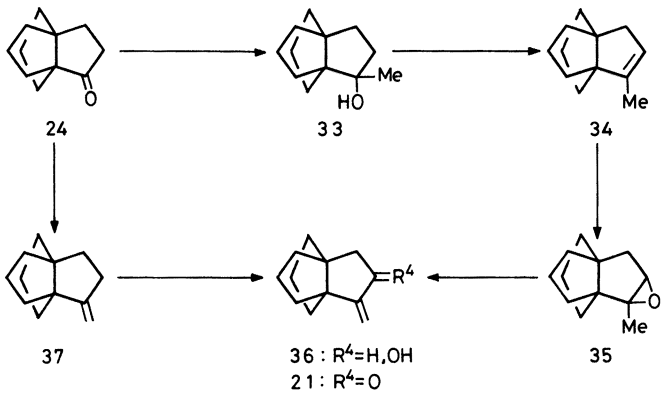


Chart 4

carboxylic acid **41** with MeLi afforded the methyl ketone **42** in 63% overall yield. Baeyer–Villiger oxidation of **42** followed by reduction of the acetate **43** with lithium aluminum hydride ($LiAlH_4$) and then oxidation of the secondary alcohol **44** furnished the cyclobutanone **45**[24] in 78% overall yield. Baeyer–Villiger oxidation[27] of **45** followed by α-methylenation of **46** as described for the preparation of **16** gave the α-methylene γ-lactone **22** in 47% overall yield.

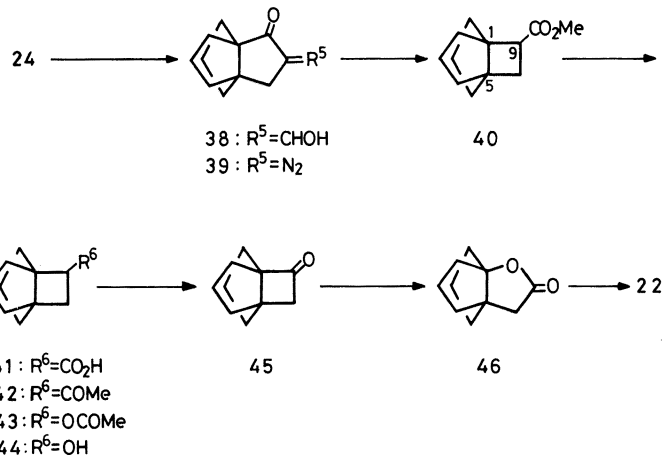


Chart 5

For the synthesis of the angular-type triquinane **23**, the straightforward route from **25** was unsuccessful, because dehydration[13c] of **25** followed by hydroboration-oxidation and subsequent oxidation gave an inseparable mixture of the desired ketone **54** and its isomer, tricyclo[6.3.0.$0^{1,5}$]undecan-4-one,[28] in an approximately 1 : 1 ratio. Therefore, **54** was prepared in a selective manner from [4.3.2]propell-10-en-2-one (**47**)[13b] according to our rearrangement protocol as follows (Chart 6): i) acid-catalyzed rearrangement of **47**, ii) reduction of the chlorohydrin **48** with tributyltin hydride (n-Bu_3SnH), iii) acid-catalyzed rearrangement of the tertiary alcohol **49**, which was confirmed by hydrogenation to give the known saturated alcohol,[13b] iv) chlorination of the allylic alcohol **50**, v) reduction of the

chloride **51** to give the olefin **52**,[29] vi) hydroboration-oxidation of **52** to afford the two epimeric alcohols **53** (3.5 : 1),[29] and vii) oxidation of **53**. Alternatively, we also obtained **54** from **52** and **53** produced by solvolytic rearrangement of *endo*-tricyclo[6.3.0.$0^{1,6}$]undecan-5-yl tosylate (**55**).[29] Finally, α-methylenation of **54** was undertaken by the same procedure as used for **14** to give **23** in 40% overall yield.

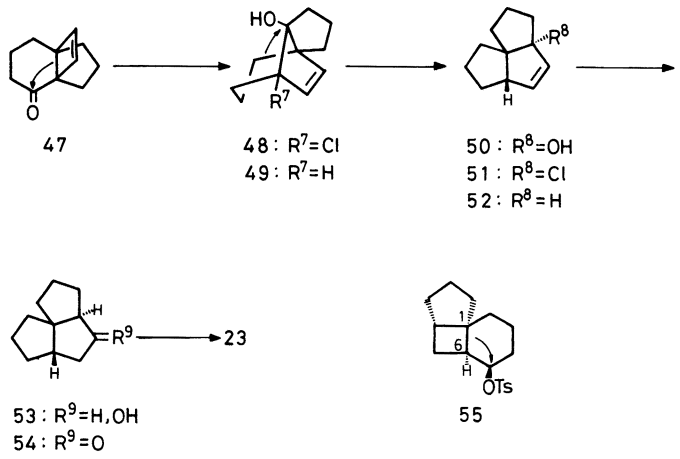


Chart 6

Biological Results and Discussion

The antiproliferating activities of the synthetic compounds **14**—**16** and **18**—**23** against P388, L1210, 3LL, and LY cells in culture are summarized in Table I. The assay procedure is described in the experimental section. The results on quadrone (**3**) and terrecyclic acid A (**4**), which were kindly provided for comparison by Prof. H. Sakai, are also listed in Table I along with those for the other diquinanes **5**—**8** and the cyclohexenones **11**—**13** prepared previously. The propellane-type triquinane **17** was not assayed because of its insolubility in the test media. This may be due to the fact that **17** readily formed the crystalline dimer **56**, when it was allowed to stand at room temperature. The structure of **56** was deduced from the similar dimerization of α-methylene cyclopentanone[30] and was established by spectroscopic and elemental analyses.

In the diquinane series related to quadrone (**3**), **14** showed almost the same level of activity as **3** but was slightly less active than **8**, while **15** was more active than **3** and even slightly more active than **8**, against the leukemic cells. On the other hand, the α-methylene cyclopetenone derivative **16** displayed a lower activity by at least one order of magnitude against P388 cell than the dihydro derivative **8**. These results suggest that the position of the α-methylene carbonyl group in the tricyclic structure has an important effect on the activity, and the α-methylene cyclopentanone group is more effective for inhibition of the cell proliferation than α-methylene cyclopentenone.

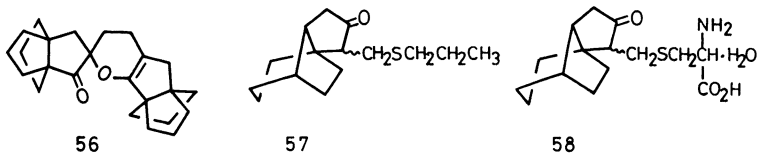
It is of great interest that the variation of tricyclic structure from the diquinane framework to the triquinanes **21** and **23** resulted in enhancement of the activity against almost all cells in the α-methylene cyclopentanone series. In particular, the propellane-type triquinane **21** is the most active of all polyquinanes tested. In contrast, the activity of the α-methylene γ-lactone derivative **22**, an oxa-analogue of **21**, was remarkably depressed. Furthermore, the α-alkylidene cyclopentanone derivatives **18** and **19** had no effect on cell proliferation, like the cyclohexenone derivatives **11**—**13**, whereas **20** having the cinnamyl

TABLE I. Antiproliferating Activity of Di- and Triquinane-Type Compounds[a]

Compound	IC_{50} (μg/ml)			
	P388	L1210	3LL	LY
3	0.19	0.65	0.39	>1.0
4[b]	<1.0	<1.0	<1.0	<1.0
5	0.14	0.06	NT	NT
6	0.17	0.11	0.08	0.26
7	0.42	0.49	0.36	>1.0
8	0.09	0.19	0.07	0.58
11	>1.0	>1.0	>1.0	>1.0
12	>1.0	>1.0	>1.0	>1.0
13	>1.0	>1.0	>1.0	>1.0
14	0.26	0.26	NT	NT
15	0.06	0.05	NT	NT
16	1.05	0.33	NT	NT
18	>1.0	>1.0	NT	NT
19	>1.0	>1.0	NT	NT
20	0.90	>1.0	NT	NT
21	0.02	0.02	0.01	0.08
22	4.00	1.45	NT	NT
23	0.05	0.04	0.08	0.23

a) >1.0 shows no effect on cell proliferation. NT means not tested. *b*) IC_{50} was not determined. The values as % of control at 1 μg/ml for **4** are comparable with those of **8** and were as follows: for **4**, 7.5%, 6.2%, 4.6%, and 10.4%, and for **8**, 6.4%, 3.0%, 1.4%, and 6.6%, against P388, L1210, 3LL, and LY cells, respectively.

moiety, which is inferred to be an active site for antitumor activity,[31] showed very weak activity against P388 cells. These findings indicate that the tricyclic skeleton surrounding the α-methylene carbonyl group plays a significant role in the appearance of the antiproliferating activity, and also demonstrate that the most potent cytotoxic functional group is the α-methylene cyclopentanone group.



56 57 58

Chart 7

In order to confirm that our polyquinane-type compounds serve as Michael acceptors of biological nucleophiles during the appearance of the growth-inhibitory activity, like α-methylene γ-lactones,[5] biomimetic reactions were carried out according to the literature.[32] The reaction conditions and the results are summarized in Table II.

Adenosine as the nucleic acid model compound, and propanethiol, L-cysteine, and L-lysine, and L-serine as the enzyme model compounds were allowed to react with the diquinane-type α-methylene cyclopentanone **8**. The diquinane **8** did not react with adenosine under the conditions employed and was recovered unchanged, as were L-lysine and L-serine. Reactions of **8** with the two compounds containing an SH group, on the other hand, took place smoothly to give adducts **57** and **58** in high yields (82—95%). The structures were established by spectroscopic and elemental analyses. Our biomimetic reactions suggest that the appearance of the activity may be due to irreversible S-alkylation of either L-cysteine,

TABLE II. Biomimetic Reactions of the Diquinane-Type Compound **8** with a Nucleic Acid Model Compound and with Enzyme Model Compounds

Model compound	Solvent system	Product and yield (%)
Adenosine	pH 7.4 potassium phosphate buffer solution–EtOH (1 : 1)	Recovery of **8**
Propanethiol	pH 9.2 borate buffer–THF (2 : 3)	**57**, 95%[a]
L-Cysteine	pH 7.4 potassium phosphate buffer solution–EtOH (1 : 2)	**58**, 82%[b]
L-Lysine	pH 7.4 potassium phosphate buffer solution–EtOH (1 : 1)	Recovery of **8**
L-Serine	pH 7.4 potassium phosphate buffer solution–EtOH (1 : 1)	Recovery of **8**

a) Isolated yield based on **8**. *b*) Isolated yield based on L-cysteine.

TABLE III. Second-Order Rate Constants at 1 °C of Di- and Triquinane-Type Compounds with L-Cysteine at pH 7.4[a]

	5	**8**	**16**	**18**	**19**	**21**
k_2 (l/mol·s)	0.71	0.49	0.24[b]	0.09[b]	0.08[b]	0.83

a) The second-order kinetics for addition of cysteine to polyquinanes were nonlinear. The rate constants were calculated from initial rates. *b*) Extrapolated from Arrhenius plots.

TABLE IV. ^{13}C-NMR Chemical Shifts of *exo*-Methylene β-Carbons of Di- and Triquinane-Type Compounds

Compound	Chemical shift (ppm)
4	116.1[a]
5	114.2[b]
6	112.3[c]
7	112.8[c]
8	112.7[d]
14	117.9
15	115.9
16	113.5
17	117.7
21	117.7
23	117.7

a) Ref. 9. *b*) Ref. 11*b*. *c*) Ref. 12. *d*) Ref. 11*a*.

which is an absolute nutritional requirement for leukemic cells grown in culture,[33] or SH enzymes, as in the case of α-methylene γ-lactones.[3,34]

Based on the above results, it is reasonable to consider that the rate of thiol addition would influence the cytotoxicity. Consequently, the second-order rate constants (Table III) for some synthetic di- and triquinanes with L-cysteine were determined by using the methods of Kupchan *et al.*[3a,34] and Grassetti and Murray.[35] An interesting tendency is apparent from Tables I and III, although only a limited number of our polyquinanes was examined. It seems clear that, in the cases of the simple synthetic compounds, the more active compounds showed faster reaction rates with L-cysteine, though there is no correlation of the rate of cysteine addition with the cytotoxicity of various multifunctional antitumor agents.[3a]

It is a well-accepted view that intramolecular neighboring group participation, such as hydrogen bonding to the carbonyl group of an α,β-unsaturated system, catalyzes the Michael

addition[36] or is a factor enhancing the activity of many antitumor agents.[3] The enhancement is ascribed to the increase in electrophilicity at the *exo*-methylene β-carbon.[3] Therefore, the ^{13}C-NMR chemical shifts of β-carbon which reflect the electrophilicity, *i.e.*, δ^+ nature,[37] were examined for some of our α-methylene cyclopentanone series (Table IV).

Interestingly, a rather wide range ($\Delta\delta = 5.6$) of chemical shifts was found in spite of the absence of functional groups showing neighboring group participation. When these results are compared with the antiproliferating activity (Table I), no rigorous relationship between chemical shift and activity is apparent. It seems interesting, however, that the chemical shifts of **21** and **23**, possessing higher activity, appeared at lower field than those of the diquinanes except for **14**.

Experimental

All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer as liquid films unless otherwise stated. ^{1}H-NMR spectra were obtained on a JEOL JNM-PS-100 spectrometer in CCl_4, and ^{13}C-NMR spectra were taken on a JEOL JNM-FX-60S spectrometer in $CDCl_3$. Chemical shifts are reported as δ-values in parts per million relative to Me_4Si (δ, 0.0) as the internal standard. Mass spectra (MS) were measured with a Hitachi RMU-6E spectrometer and are given in terms of *m/z* (relative intensity) compared with the base peak. Ultraviolet (UV) spectra were recorded on a Hitachi 356 dual-wavelength double-beam spectrometer for kinetic measurement. Analytical gas liquid chromatography (GLC) was carried out on a Hitachi 163 gas chromatograph, and preparative GLC was conducted on a Varian Aerograph 920 gas chromatograph with a 10% FFAP column or a 30% SE-30 column. Column chromatography was performed with Wako C-200 silica gel. Flash chromatography[38] was carried out with Merck Silica gel 60. Yields were calculated based on the consumed starting materials.

Materials——[3.3.3]Propellanone (**24**),[13a] tricyclo[4.3.2.0^{1,5}]undecan-4-one (**27**),[13b] tricyclo[4.3.2.0^{1,5}]undec-4-en-3-one (**31**) and its 2-hydroxymethyl derivatives,[11a] and tricyclo[4.3.2.0]undec-10-en-2-one (**47**),[13b] were prepared as described previously. Adenosine, L-serine, L-lysine·HCl·H_2O, and pH 9.2 borae buffer solution were purchased from Wako Pure Chemical Industries. L-Cysteine was obtained from Sigma Chemical Company. 2,2′-Dipyridyl disulfide and 2-thiopyridone were purchased from Aldrich Chemical Company, Inc. Potassium phosphate buffer solution (pH 7.4) was obtained from Tokyo Kasei Kogyo Co., Ltd.

Diquinane-Type Compound 14——A 1.5 M solution of butyllithium (*n*-BuLi, 7.80 ml, 12.2 mmol) in hexane was added to a stirred solution of diisopropylamine (1.69 ml, 12.2 mmol) in dry tetrahydrofuran (THF, 5 ml) *via* a syringe at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min and cooled to −78 °C. A solution of **27**[13b] (1.00 g, 6.10 mmol) in dry THF (10 ml) was added dropwise during 25 min. The solution was maintained at −78 °C for 30 min and chlorotrimethylsilane (2.41 ml, 18.3 mmol) was added *via* a syringe. The reaction mixture was allowed to warm to room temperature and then stirred for 30 min. The mixture was filtered and the residue was washed with petroleum ether. The combined filtrates were concentrated *in vacuo* to give the residue, which was diluted with petroleum ether. The mixture was filtered again. The filtration was repeated until the residue became a clear solution, to give **28**. IR: 1620 (C=C), 1250 (C–O) cm^{-1}.

A solution of $TiCl_4$ (0.80 ml, 7.32 mmol) in dichloromethane (CH_2Cl_2, 5 ml) was added to a stirred solution of the crude ether **28** and chloromethylphenyl sulfide (1.23 ml, 9.15 mmol) in CH_2Cl_2 (6 ml) *via* a syringe at −23 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1.5 h and then poured into saturated sodium bicarbonate ($NaHCO_3$) solution (30 ml). The resulting mixture was extracted with ether. The combined extract were washed with brine and dried over magnesium sulfate ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give recovered **27** (0.16 g, ether : petroleum ether = 5 : 95) and **29** (1.28 g, 88% yield from **27**, ether : petroleum ether = 3 : 97). IR: 1730 (C=O), 1580 (C_6H_5) cm^{-1}.

A solution of MCPBA (0.91 g, 70%, 4.49 mmol) in chloroform ($CHCl_3$, 15 ml) was added to a stirred solution of the above sulfide **29** in $CHCl_3$ (15 ml) at −15 °C. The reaction mixture was stirred for 2 h and allowed to stand at room temperature overnight. Water was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with saturated sodium bisulfite ($NaHSO_3$) solution, saturated $NaHCO_3$ solution, and brine successively, and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **30**. IR: 1730 (C=O), 1040 (S=O) cm^{-1}.

A solution of the crude sulfoxide **30** in toluene (70 ml) was heated at reflux with stirring for 2 h and then concentrated *in vacuo*. The residue was chromatographed to give **14** (0.52 g, 66% yield from **29**, ether : petroleum ether = 4 : 96). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.25. Found: C, 81.40; H, 9.27. IR: 1725 (C=O), 1635 (C=C) cm^{-1}. ^{1}H-NMR: 1.1—1.9 (11H, m), 2.49 (2H, m, 2-CH_2), 2.66 (1H, m, 5-CH), 5.22 (1H, m, C=CH_2), 5.94 (1H, m, C=CH_2). ^{13}C-NMR: 19.3 (t), 28.6 (t), 32.3 (t), 32.8 (t), 37.1 (d, 6-C), 37.6 (t), 38.5 (t), 45.3 (s, 1-C), 65.0 (d, 5-

C), 117.9 (t, C=$\underline{C}H_2$), 144.7 (s, 3-C), 206.3 (s, 4-C). MS *m/z*: 176 (M^+, 100), 107 (59), 79 (88).

Tricyclo[4.3.2.0^{1,5}]undecan-3-one (32)——A mixture of **31**[11a] (5.15 g, 31.8 mmol) and 10% palladized charcoal (1.00 g) in methanol (MeOH, 80 ml) was stirred at room temperature for 76 h under atmospheric pressure of hydrogen. After filtration, the filtrate was concentrated *in vacuo* and the residue was chromatographed to give **32** (4.84 g, 91% yield, ether : petroleum ether = 4 : 96), which was purified by preparative GLC, mp 40—41 °C. Semicarbazone, recrystallized from MeOH, mp 216 °C (dec.). *Anal.* Calcd for $C_{12}H_{19}N_3O$: C, 65.12; H, 8.65; N, 18.99. Found: C, 64.75; H, 8.66; N, 19.12. IR: 1740 (C=O) cm^{-1}. ^{1}H-NMR: 1.1—2.3 (m). ^{13}C-NMR: 19.2 (t), 28.0 (t), 32.6 (t), 32.8 (t), 37.3 (t), 38.5 (d, 6-C), 40.6 (t), 47.9 (s, 1-C), 49.8 (t), 53.1 (d, 5-C), 217.9 (s, 3-C). MS *m/z*: 164 (M^+, 97), 121 (100), 108 (68), 79 (64).

Diquinane-Type Compound 15——α-Methylenation of **32** (1.01 g, 6.10 mmol) as described for the preparation of **14** gave recovered **32** (0.15 g), **8** (0.23 g, 22% yield, ether : petroleum ether = 4 : 96), and **15** (0.25 g, 23% yield, ether : petroleum ether = 3 : 97) after chromatography. *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.54; H, 9.41. IR: 1725 (C=O), 1640 (C=C) cm^{-1}. ^{1}H-NMR: 1.1—2.0 (10H, m), 2.14 (2H, ABq, J = 17 Hz, 2-CH_2), 2.28 (1H, m, 6-CH), 2.46 (1H, m, 5-CH), 5.06 (1H, m, C=CH_2), 5.88 (1H, m, C=CH_2). ^{13}C-NMR: 19.5 (t), 28.3 (t), 32.4 (t), 33.6 (t), 36.8 (t), 38.6 (d, 6-C), 46.1 (s, 1-C), 48.6 (t, 2-C), 58.4 (d, 5-C), 115.8 (t, C=$\underline{C}H_2$), 147.3 (s, 4-C), 206.7 (s, 3-C). MS *m/z*: 176 (M^+, 100), 148 (90), 119 (86), 91 (100), 79 (81).

Diquinane-Type Compound 16——Methanesulfonyl chloride (5.81 ml, 74.8 mmol) was added dropwise to a stirred solution of the primary alcohol[11a] (4.79 g, 24.9 mmol), derived from **31** by hydroxymethylation, in pyridine (50 ml) *via* a syringe at 0 °C. The reaction mixture was stirred at room temperature for 14 h. Ice-water was added and the mixture was extracted with ether. The combined extracts were washed with two portions of 5% hydrochloric acid (HCl), saturated $NaHCO_3$ solution, and brine successively, and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the mesylate. IR: 1700 (C=O), 1640 (C=C), 1355, 1175 (SO_2) cm^{-1}.

1,8-Diazabicyclo[5.4.0]undec-7-ene (11.2 ml, 74.8 mmol) was added to a stirred solution of the crude mesylate in benzene (50 ml) at room temperature. The reaction mixture was stirred for 21 h and water was added. The mixture was extracted with ether. The combined extracts were washed with two portions of 5% HCl, saturated $NaHCO_3$ solution, and brine successively, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give **16** (3.01 g, 70% yield from the starting alcohol, ether : petroleum ether = 3 : 97). *Anal.* Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.65; H, 8.30. IR: 1700 (C=O), 1630 (C=C) cm^{-1}. ^{1}H-NMR: 1.2—2.2 (10H, m), 3.02 (1H, m, 6-CH), 5.11 (1H, s, C=CH_2), 5.75 (1H, s, 4-CH), 5.81 (1H, s, C=CH_2). ^{13}C-NMR: 18.0 (t), 29.6 (t), 29.7 (t), 31.8 (t), 31.4 (d, 6-C), 39.3 (t), 51.4 (s, 1-C), 113.5 (t, C=$\underline{C}H_2$), 118.0 (d, 4-C), 150.9 (s, 2-C), 188.9 (s, 5-C), 197.6 (s, 3-C). MS *m/z*: 174 (M^+, 48), 146 (100).

Propellane-Type Triquinane Compound 17——α-Methylenation of **24**[13a] (1.50 g, 9.14 mmol) as described for the preparation of **14** gave the dimer **56** (0.10 g, 4% yield), **17** (0.56 g, 42% yield), and recovered **24** (0.26 g) after chromatography (ether : petroleum ether = 3 : 97). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.54; H, 9.33. IR: 1715 (C=O), 1625 (C=C) cm^{-1}. ^{1}H-NMR: 1.3—2.1 (12H, m), 2.49 (2H, t, J = 2.5 Hz, 4-CH_2), 5.16 (1H, m, C=CH_2), 5.80 (1H, m, C=CH_2). ^{13}C-NMR: 26.5 (2C, t), 38.3 (2C, t), 40.9 (t, 4-C), 41.4 (2C, t), 55.9 (s, 5-C), 68.0 (s, 1-C), 117.7 (t, C=$\underline{C}H_2$), 147.0 (s, 3-C), 212.8 (s, 2-C). MS *m/z*: 176 (M^+, 59), 107 (100), 65 (53).

Dimer **56**, mp 72.5—74.0 °C, recrystallized from CH_2Cl_2. *Anal.* Calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.59; H, 9.15. IR (KBr): 1730 (C=O), 1695 (C=C–O) cm^{-1}. ^{1}H-NMR: 1.0—2.4 (m). ^{13}C-NMR: 19.3 (t), 26.0 (t), 26.2 (2C, t), 26.5 (2C, t), 27.6 (t), 36.9 (t), 37.0 (t), 38.2 (t), 38.5 (t), 41.6 (2C, t), 41.9 (t), 44.8 (t), 47.1 (t), 55.6 (s), 57.5 (s), 65.5 (s), 66.8 (s), 84.7 (s, spiro carbon), 104.4 (s, $\underline{C}$=C–O) 150.4 (s, C=$\underline{C}$–O), 218.8 (s, C=O). MS *m/z*: 352 (M^+, 100), 177 (87), 176 (64).

(*E*)-Propylidene Triquinane Compound 18——A solution of **24** (2.76 g, 16.8 mmol) in dry THF (40 ml) was added dropwise to a stirred solution of lithium diisopropylamide (LDA, 26.9 mmol) in dry THF (60 ml) (prepared as described above) at −78 °C during 1 h under a nitrogen atmosphere. The reaction mixture was stirred for 1 h and propionaldehyde (1.23 ml, 16.8 mmol) was added *via* a syringe. After 1 h, the mixture was allowed to warm to room temperature and then stirred for 1 h. Saturated ammonium chloride solution was added and the resulting mixture was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give **18** (2.05 g, 69% yield, ether : petroleum ether = 3 : 97), recovered **24** (0.37 g), and aldols (0.49 g, ether : petroleum ether = 3 : 7). Dehydration of the aldols as described for the preparation of **16** gave **18** (0.13 g, 4% yield from **24**). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.27; H, 10.12. IR: 1710 (C=O), 1640 (C=C) cm^{-1}: ^{1}H-NMR: 1.08 (3H, t, J = 8 Hz, CH_3), 1.3—2.0 (12H, m), 2.14 (2H, qd, J = 8, 2 Hz, $C\underline{H}_2CH_3$), 2.42 (2H, m, 4-CH_2), 6.30 (1H, m, C=CH). ^{13}C-NMR: 12.3 (q, CH_3), 24.4 (t, $\underline{C}H_2CH_3$), 26.1 (2C, t), 37.9 (2C, t), 38.3 (t, 4-C), 41.4 (2C, t), 55.4 (s, 5-C), 67.9 (s, 1-C), 137.7 (d, C=$\underline{C}$H), 138.4 (s, 3-C), 211.6 (s, 2-C). MS *m/z*: 204 (M^+, 100), 175 (50), 96 (57).

(*E*)-Carbomethoxypentylidene Triquinane Compound 19——Methyl 6-oxohexanoate was prepared by using the method of Ballini and Petrini,[17] bp 66—68 °C/3 mmHg (lit.[39] 59—61 °C/1 mmHg). Reaction of **24** (0.50 g, 3.01 mmol) and the aldehyde (0.48 g, 3.35 mmol) as described above gave recovered **24** (0.06 g) and **19** (0.64 g, 85% yield, ether : petroleum ether = 2 : 8) after chromatography. *Anal.* Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.11; H, 9.15. IR: 1740 (C=O), 1710 (C=O), 1640 (C=C), 1165 (O=C–O) cm^{-1}. ^{1}H-NMR: 1.2—1.9 (16H, m),

2.0—2.4 (4H, m), 2.46 (2H, m, 4-CH_2), 3.60 (3H, s, OCH_3), 6.30 (1H, m, C=CH). ^{13}C-NMR: 24.2 (t), 26.1 (2C, t), 27.3 (t), 28.9 (t), 33.2 (t), 38.0 (2C, t), 38.5 (t, 4-C), 41.4 (2C, t), 50.8 (q, OCH_3), 55.5 (s, 5-C), 68.0 (s, 1-C), 135.9 (d, C=CH), 139.4 (s, 3-C), 173.1 (s, O=C–O), 211.7 (s, 2-C). MS *m/z*: 290 (M^+, 100), 203 (60), 79 (51).

5-Oxopentyl (*E*)-Cinnamate——A solution of (*E*)-cinnamoyl chloride (8.01 g, 48.1 mmol) in dry ether (50 ml) was added dropwise to a stirred solution of 1,5-pentanediol (5.00 g, 48.1 mmol) and pyridine (3.89 ml, 48.1 mmol) in dry ether (200 ml) at room temperature during 6 h under a nitrogen atmosphere. The reaction mixture was heated at reflux with stirring for 2 h and water was added to the cooled mixture. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with 10% sulfuric acid (H_2SO_4) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give 5-hydroxypentyl (*E*)-cinnamate (5.61 g, 50% yield, ether : petroleum ether = 7 : 3). IR: 3450 (OH), 1710 (C=O), 1640 (C=C), 1580 (C_6H_5) cm^{-1}.

A solution of pyridine (23.3 ml, 288 mmol) in CH_2Cl_2 (200 ml) was stirred with a mechanical stirrer at 0 °C and anhydrous chromium(VI) oxide (14.4 g, 144 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and then a solution of the above hydroxy ester in CH_2Cl_2 (50 ml) was added. The reaction mixture was stirred for 1 h and decanted from the residue, which was washed with ether. The combined organic solutions were washed with two portions of 10% sodium hydroxide (NaOH) solution, two portions of 5% HCl, saturated $NaHCO_3$ solution, and brine successively, then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give 5-oxopentyl (*E*)-cinnamate (3.32 g, 60% yield, ether : petroleum ether = 15 : 85). IR: 2820, 2720 (CHO), 1725, 1710 (C=O), 1640 (C=C), 1580 (C_6H_5) cm^{-1}. ^{1}H-NMR: 1.4—1.9 (4H, m, CH_2CH_2), 2.43 (2H, m, CH_2CHO), 4.12 (2H, m, OCH_2), 6.33 (1H, d, J = 16 Hz, C=CHC=O), 7.2—7.5 (5H, m, C_6H_5), 7.57 (1H, d, J = 16 Hz, C=CHC$_6$H$_5$), 9.72 (1H, m, CHO). MS *m/z*: 232 (M^+, trace), 132 (100), 103 (54).

(*E*)-[(*E*)-Cinnamyloxy]pentylidene Triquinane Compound 20——Reaction of **24** (0.48 g, 2.93 mmol) and the above aldehyde (0.68 g, 2.93 mmol) as described in the literature[19] gave recovered **24** (0.13 g) and **20** (0.57 g, 71% yield, ether: petroleum ether = 1 : 9) after chromatography, mp 37—38 °C, recrystallized from pentane. *Anal.* Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.03; H, 8.03.IR (KBr): 1710 (C=O), 1655, 1640 (C=C), 1580 (C_6H_5) cm^{-1}. ^{1}H-NMR: 1.3—2.3 (18H, m), 2.40 (2H, m, 4-CH_2), 4.10 (2H, t, J = 6 Hz, OCH_2), 6.30 (1H, m, C=CHCH$_2$), 6.32 (1H, d, J = 16 Hz, C=CHC=O), 7.2—7.5 (5H, m, C_6H_5), 7.57 (1H, d, J = 16 Hz, C=CHC$_6$H$_5$). ^{13}C-NMR: 24.7 (t), 26.4 (2C, t), 28.3 (t), 29.0 (t), 38.3 (2C, t), 38.8 (t, 4-C), 41.7 (2C, t), 55.8 (s, 5-C), 63.9 (t, OCH_2), 68.4 (s, 1-C), 118.0 (d, C=CHC=O), 127.9, 128.8, 130.1, 134.3 (d, d, d, s, C_6H_5), 136.1 (d, C=CHCH$_2$), 139.8 (s, 3-C), 144.5 (d, C=CHC$_6$H$_5$), 166.7 (s, O=C–O), 212.3 (s, 2-C). MS *m/z*: 378 (M^+, 10), 131 (100).

2-Methyltricyclo[3.3.3.0]undecan-2-ol (33)——A 1.2 N solution of MeLi (4.34 ml, 5.20 mmol) in ether was added to a stirred solution of **24** (0.57 g, 3.47 mmol) in dry ether (20 ml) *via* a syringe at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min and then MeOH (0.21 ml, 5.20 mmol) was added *via* a syringe. After 1 min, MeLi (4.34 mmol) was added and the reaction mixture was stirred for 15 min. This procedure was repeated a total of eight times.[20] Water was added and the organic layer was separated. The aqueous layer was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give recovered **24** (0.10 g) and **33** (0.46 g, 89% yield, ether : petroleum ether = 5 : 95), which was purified by preparative GLC, mp 96.5—98.5 °C. *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.68; H, 11.23. IR (KBr): 3450 (OH) cm^{-1}. ^{1}H-NMR: 0.8—2.0 (m, containing s at 1.18). MS *m/z*: 180 (M^+, 11), 109 (59), 108 (100).

2-Methyltricyclo[3.3.3.0]undec-2-ene (34)——Thionyl chloride (0.62 ml, 8.50 mmol) was added to a stirred solution of **33** (0.90 g, 5.00 mmol) and pyridine (2.80 ml, 35.0 mmol) in CH_2Cl_2 (10 ml) *via* a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. Ice-water was carefully added and the resulting mixture was extracted with CH_2Cl_2. The combined extracts were washed with 5% HCl, saturated $NaHCO_3$ solution, and brine successively, and dried ($MgSO_4$). The solvent was carefully removed *in vacuo* and the residue was chromatographed to give **34** (0.78 g, 96% yield, petroleum ether). *Anal.* Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.67; H, 11.44. IR: 3020, 790 (C=C) cm^{-1}. ^{1}H-NMR: 1.2—1.8 (15H, m), 2.14 (2H, m, 4-CH_2), 4.98 (1H, m, 3-CH). MS *m/z*: 162 (M^+, 51), 133 (100).

2-Methyl-3-oxatetracyclo[4.3.3.0.0^{2,4}]dodecane (35)——A solution of MCPBA (1.09 g, 7.68 mmol) in $CHCl_3$ (30 ml) was added to a stirred mixture of **34** (0.78 g, 4.81 mmol) and disodium hydrogen phosphate (1.09 g, 7.68 mmol) in $CHCl_3$ (15 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and then water was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with saturated $NaHSO_3$ solution, saturated $NaHCO_3$ solution, and brine successively, and dried ($MgSO_4$). The solvent was removed *in cacuo* and the subsequent flash chromatography (ether : peptroleum ether = 1 : 9) gave **35** (0.56 g, 65% yield). *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.70; H, 10.40. IR: 3000, 835 (epoxide) cm^{-1}. ^{1}H-NMR: 1.2—2.1 (17H, m, containing s at 1.29), 3.18 (1H, d, J = 2 Hz, 4-CH). MS *m/z*: 178 (M^+, 63), 108 (68), 107 (100).

Propellane-Type Triquinane Compound 21——A 1.5 M solution of *n*-BuLi (15.1 ml, 22.7 mmol) in hexane was added to a stirred solution of diethylamine (2.53 ml, 22.7 mmol) in dry ether (25 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature. A solution of **35** (2.02 g, 11.3 mmol) in dry ether (10 ml) was

added to the above lithium diethylamide solution.[21] The mixture was heated at reflux with stirring for 6 h and then water was added to the cooled mixture. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with 5% HCl, saturated $NaHCO_3$ solution, and brine successively, and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **36**. IR: 3300 (OH), 1660 (C=C) cm^{-1}.

The crude alcohol **36** was oxidized with Collins reagent as described above to give recovered **35** (0.34 g) and **21** (1.12 g, 68% yield from **35**) after flash chromatography (ether : petroleum ether = 15 : 85). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.58; H, 9.38. IR: 1715 (C=O), 1625 (C=C) cm^{-1}. ^{1}H-NMR: 1.2—2.0 (12H, m), 2.31 (2H, s, 4-CH_2), 5.18 (1H, s, C=CH_2), 5.82 (1H, s, C=CH_2). ^{13}C-NMR: 26.0 (2C, t), 42.1 (2C, t), 42.9 (2C, t), 52.4 (t, 4-C), 54.3 (s, 5-C), 62.3 (s, 1-C), 117.7 (t, C=CH_2), 156.3 (s, 2-C), 209.5 (s, 3-C). MS *m/z*: 176 (M^+, 12), 134 (100).

2-Methylenetricyclo[3.3.3.0]undecane (37)——A 2 N solution of sodium *tert*-amylate (30.5 ml, 61.0 mmol) in benzene was added to a stirred mixture of triphenylmethylphosphonium bromide (16.3 g, 45.7 mmol) in dry benzene (50 ml) at room temperature under a nitrogen atmosphere, then a solution of **24** (2.50 g, 15.2 mmol) in dry benzene (20 ml) was further added. The reaction mixture was heated at reflux with stirring for 3 h and then water was added to the cooled mixture. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was carefully removed *in vacuo* and the subsequent flash chromatography (petroleum ether) gave **37** (2.42 g, 98% yield). *Anal.* Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.84; H, 11.31. IR (CCl_4): 3050, 1645 (C=C) cm^{-1}. ^{1}H-NMR: 1.3—1.8 (14H, m), 2.26 (2H, td, J=7, 2 Hz, 3-CH_2), 4.67 (2H, t, J=2 Hz, C=CH_2). MS *m/z*: 162 (M^+, 38), 134 (100).

An Alternative Synthesis of 21——A mixture of selenium(IV) oxide (0.77 g, 7.00 mmol) and 80% *tert*-butylhydroperoxide (3.50 ml, 28 mmol) in CH_2Cl_2 (11 ml) was stirred at 25 °C for 30 min.[22] The mixture was cooled to 0 °C, and **37** (2.26 g, 14.0 mmol) was added. This mixture was stirred at 25 °C for 2 h, then saturated $NaHSO_3$ solution and water were added. The resulting mixture was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give **21** (1.20 g, 49% yield, ether : petroleum ether = 1 : 9) and **36** (1.18 g, 47% yield, ether : petroleum ether = 2 : 8).

Methyl Tricyclo[3.3.2.0]decan-9-carboxylate (40)——A mixture of **24** (5.00 g, 30.5 mmol) and ethyl formate (3.70 ml, 45.7 mmol) was added dropwise to a stirred ice-cooled suspension of sodium hydride (1.47 g, 50%, 30.5 mmol) and ethanol (EtOH, 1.5 ml) in dry ether (90 ml). The mixture was stirred at room temperature for 3 h and then allowed to stand overnight. Water was added and the organic layer was separated and washed with three portions of 10% NaOH solution. The combined aqueous layer was acidified with conc. HCl. The solid that separated was taken up in ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give **38** as a white solid. IR (KBr): 1680, 1600, 1520, 1180 (O=C–C=C–OH) cm^{-1}.

p-Toluenesulfonyl azide (7.40 g, 37.5 mmol) was added dropwise to a stirred solution of the crude hydroxymethylene ketone **38** in triethylamine (9.50 ml, 68.2 mmol) and CH_2Cl_2 (27 ml) cooled in an ice-salt bath. The mixture was stirred at that temperature for 2 h. A solution of potassium hydroxide (KOH, 3.00 g) in water (27 ml) was then added and the whole was stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with KOH solution and two portions of water, and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **39**. IR: 2070 (N_2), 1655 (C=O) cm^{-1}.

A solution of the crude diazoketone **39** in MeOH (300 ml) was irradiated in a Pyrex vessel with a 500 W high-pressure mercury lamp for 36 h. The solvent was removed *in vacuo* and the residue was chromatographed to give **40** (3.62 g, 61% yield from **24**, ether : petroleum ether = 5 : 95). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.58; H, 9.43. IR: 1730 (C=O), 1165 (O=C–O) cm^{-1}. ^{1}H-NMR: 1.1—2.3 (14H, m), 2.63 (1H, dd, J=10, 7 Hz, 9-CH), 3.61 (3H, s, OCH_3). ^{13}C-NMR: 29.5 (t), 30.1 (t), 30.6 (t), 35.0 (t), 38.5 (t), 39.2 (t), 39.8 (t), 41.3 (d, 9-C), 51.2 (q, OCH_3), 53.3 (s, 5-C), 60.1 (s, 1-C), 174.6 (s, C=O). MS *m/z*: 194 (M^+, 2), 108 (100), 80 (56).

9-Acetyltricyclo[3.3.2.0]decane (42)——A mixture of **40** (3.42 g, 17.6 mmol) and KOH (2.50 g) in MeOH (35 ml) was heated at reflux with stirring for 3 h. The solvent was removed *in vacuo* and water was added to the residue. The mixture was extracted with petroleum ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give recovered **40** (0.21 g). The aqueous layer was acidified with 6 N HCl and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give **41**, as a white solid. IR (KBr): 3500—2500 (CO_2H), 1685 (C=O) cm^{-1}.

A 1.2 N solution of MeLi (35.8 ml, 43.0 mmol) in ether was added dropwise to a stirred solution of the crude carboxylic acid **41** in dry ether (70 ml) at 0 °C during 1 h under a nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and then water was carefully added at 0 °C. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give **42** (1.86 g, 63% yield form **40**, ether : petroleum ether = 5 : 95). IR: 1700 (C=O) cm^{-1}. ^{1}H-NMR: 1.1—2.3 (17H, m, containing s at 1.91), 2.68 (1H, dd, J=9, 8 Hz, 9-CH). MS *m/z*: 178 (M^+, 5), 108 (100), 107 (70), 80 (67).

2-Oxatricyclo[3.3.3.0]undecan-3-one (46)[24]——A solution of **42** (1.78 g, 10.0 mmol) and MCPBA (1.96 g, 12.0 mmol) in $CHCl_3$ (50 ml) was stirred at 40 °C for 40 h. The mixture was washed with saturated $NaHSO_3$ solution, saturated $NaHCO_3$ solution, and brine successively, and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **43**. IR: 1735 (C=O), 1240, 1040 (O=C–O) cm^{-1}.

A solution of the crude acetate **43** in dry ether (15 ml) was added to a stirred solution of $LiAlH_4$ (0.95 g, 25.0 mmol) in dry ether (15 ml) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Water was carefully added to the cooled mixture at 0 °C and then 5% HCl was added. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give **44** (1.42 g, 87% yield from **42**, ether : petroleum ether = 15 : 85), which was identical with a sample prepared by an alternative method.[24]

Oxidation of **44** (0.80 g, 5.25 mmol) with Collins reagent as described above gave **45**[24] (0.70 g, 89% yield, ether : petroleum ether = 5 : 95) after chromatography. Baeyer-Villiger oxidation[27] of **45** (4.88 g, 29.3 mmol) with 30% hydrogen peroxide and 9.3 N NaOH in MeOH afforded **46** (4.53 g, 86% yield, ether : petroleum ether = 2 : 8) after chromatography.

Propellane-Type Oxatriquinane Compound 22——α-Hydroxymethylation of **46** (2.00 g, 12.1 mmol) as described previously[11,15] gave recovered **46** (1.23 g) and the primary alcohol (0.65 g, 70% yield, ether : petroleum ether = 8 : 2) after chromatography. IR: 3450 (OH), 1745 (C=O) cm^{-1}. ^{1}H-NMR: 1.3—2.3 (12H, m) 2.53 (1H, t, J = 7 Hz, 4-CH), 2.82 (1H, br s, OH), 3.80 (2H, d, J = 7 Hz, $C\underline{H}_2OH$). Dehydration of the alcohol was carried out as described for the preparation of **16** to give **22** (0.44 g, 78% yield from the alcohol, ether : petroleum ether = 2 : 8) after chromatography. *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.95; H, 8.10. IR: 1745 (C=O), 1650 (C=C) cm^{-1}. ^{1}H-NMR: 1.5—2.2 (12H, m), 5.51 (1H, s, C=CH_2), 6.09 (1H, s, C=CH_2). ^{13}C-NMR: 25.8 (2C, t), 38.3 (2C, t), 41.0 (2C, t), 59.8 (s, 5-C), 102.1 (s, 1-C), 122.2 (t, C=$\underline{C}H_2$), 146.2 (s, 4-C), 171.3 (s, 3-C). MS m/z: 178 (M^+, 80), 150 (100), 122 (89), 79 (84).

5-Hydroxytricyclo[4.3.2.0^{1,5}]undec-10-ene (49)——A solution of **47**[13b] (7.18 g, 44.3 mmol) and conc. HCl (15 ml) in ether (120 ml) was heated at reflux with stirring for 10 h. Water was added and the organic layer was separated. The aqueous layer was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give **48** (6.97 g, 79% yield, ether : petroleum ether = 5 : 95). IR: 3470 (OH), 725 (C=C) cm^{-1}

A solution of n-Bu_3SnH (15.3 g, 52.6 mmol) in cyclohexane (100 ml) was added to a stirred solution of **48** (6.96 g, 35.1 mmol) and 2,2′-azobisisobutyronitrile (1.0 g) in cyclohexane (50 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was heated at reflux with stirring for 9 h. The solvent was removed *in vacuo* and the residue was chromatographed to give **49** (4.71 g, 82% yield, ether : petroleum ether = 2 : 8), which was purified by preparative GLC, mp 42—43 °C. IR (KBr): 3380 (OH), 3030 (C=C), 1120 (C–OH), 725 (C=C) cm^{-1}: 1.0—2.2 (13H, m), 2.50 (1H, m, 6-CH), 5.42 (1H, d, J = 6 Hz, 10-CH), 5.68 (1H, dd, J = 6, 2.5 Hz, 11-CH). ^{13}C-NMR: 17.2 (t), 20.0 (t), 22.8 (t), 24.1 (t), 32.6 (t), 37.3 (t), 47.6 (d, 6-C), 55.9 (s, 1-C), 87.8 (s, 5-C), 131.1, 137.6 (d, d, C-10 and C-11). MS m/z: 164 (M^+, 93), 108 (96), 97 (100). Hydrogenation of **49** (0.25 g, 1.55 mmol) as described above gave a saturated alcohol (0.23 g, 92% yield) which was identical (mp, IR, and ^{13}C-NMR spectra) with the known alcohol.[13b]

Angular-Type Triquinane Compound 23——A solution of **49** (1.00 g, 6.10 mmol) and 50% H_2SO_4 (8 ml) in THF (20 ml) was stirred at *ca.* 60 °C for 24 h. Water was added and the resulting mixture was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give recovered **49** (0.06 g) and **50** (0.21 g, 22% yield, ether : petroleum ether = 1 : 9). IR: 3450 (OH), 3030, 740 (C=C) cm^{-1}.

Thionyl chloride (0.42 ml, 5.79 mmol) was added to a stirred solution of **50** (0.63 g, 3.86 mmol) in dry ether (7 ml) *via* a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and then ice-water was carefully added. The resulting mixture was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed to give **51** (0.37 g, 53% yield, petroleum ether). IR: 3030, 760 (C=C) cm^{-1}.

Reduction of **51** (0.37 g, 2.03 mmol) with n-Bu_3SnH as described above gave **52** (0.24 g, 80% yield, elution with petroleum ether) which was identical (IR and ^{1}H-NMR spectra) with the sample obtained from **55**.[29] The ketone **54** was prepared as reported[29] by hydroboration-oxidation of **52** followed by Collins oxidation of **53** (3.5 : 1, the epimer mixture).

α-Methylenation of **54** (3.11 g, 18.9 mmol) as described for the preparation of **14** gave recovered **54** (0.85 g) and **23** (0.95 g, 40% yield from **54**) after chromatography (ether : petroleum ether = 3 : 97). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.66; H, 9.44. IR: 1715 (C=O), 1625 (C=C) cm^{-1}. ^{1}H-NMR: 1.2—2.1 (12H, m), 2.13 (1H, dd, J = 12, 6 Hz, 5-CH), 2.70 (1H, m, 8-CH), 5.14 (1H, m, C=CH_2), 5.80 (1H, m, C=CH_2). ^{13}C-NMR: 26.2 (t), 26.6 (t), 31.6 (t), 36.1 (t), 40.9 (t), 41.7 (t), 51.3 (d, 8-C), 55.6 (s, 1-C), 59.7 (d, 5-C), 117.7 (t, C=$\underline{C}H_2$), 152.0 (s, 7-C), 217.7 (s, 6-C). MS m/z: 176 (M^+, 100), 148 (49), 119 (45).

Antiproliferation Assay *in Vitro*——The assay was performed according to our previous method[40] with a slight modification. Test murine cells maintained in our laboratory (Toray) were cultured in RPMI 1640 medium containing 2-mercaptoethanol (2×10^{-5} M) for P388 (lymphocytic leukemia) and L1210 (lymphocytic leukemia), RPMI 1640 medium for 3LL (Lewis lung tumor), or Eagle's MEM for LY (subcutaneous tissue). Each medium was supplemented with 10% precolostrum newborn calf serum (Mitsubishi Chemical Industries Ltd., Tokyo). Polyquinanes were dissolved in acetone at a concentration of 10 mg/ml followed by dilution with dimethylsulfoxide

(DMSO) at 1 mg/ml. Alternatively, five test compounds (**3**, **4**, **8**, **12**, and **13**) were directly dissolved in DMSO at 1 mg/ml. These solutions were further diluted with the cell culture medium to appropriate concentrations. Test cells (2×10^4/0.9 ml/well) were seeded into culture plates (24 flat-bottomed wells, Flow Laboratories, Inc., U.S.A.) and sample solutions (0.1 ml/well) were added simultaneously. In the control group, corresponding amounts of the organic solvents were added. After 4 d of culture at 37 °C in a 5% CO_2 incubator (NAPCO, U.S.A.), the cell number was determined with a Coulter counter (model TA II, Coulter Electronics, Inc., U.S.A.). The IC_{50} values (μg/ml) required to produce 50% reduction of cell number *versus* control culture were determined and are summarized in Table I.

Biomimetic Reactions[32]——(1) Treatment of **8** with Adenosine: A solution of **8** (49 mg, 0.28 mmol) and adenosine (91 mg, 0.34 mmol) in a mixture of pH 7.4 potassium phosphate buffer solution (2.5 ml) and EtOH (2.5 ml) was stirred at room temperature for 7 d. Ethanol was removed *in vacuo* and the residue was extracted with ethyl acetate. The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to give recovered **8** (41 mg).

(2) Treatment of **8** with Propanethiol: Propanethiol (0.77 ml, 8.52 mmol) was added *via* a syringe to a stirred solution of **8** (50 mg, 0.28 mmol) in a mixture of pH 9.2 borate buffer solution (1.6 ml) and THF (2.4 ml) at room temperature. The reaction mixture was stirred for 13 h and then water was added. The mixture was extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (ether : petroleum ether = 8 : 92) of the residue gave **57** (68 mg, 95% yield), mp 22—23 °C. *Anal.* Calcd for $C_{15}H_{24}OS$: C, 71.38; H, 9.58. Found: C, 71.33; H, 9.63. IR: 1730 (C=O) cm^{-1}. ^{1}H-NMR: 0.99 (3H, t, J=4 Hz, CH_3), 1.2—2.3 (18H, m), 2.44 (2H, t, J=7 Hz, SCH_2CH_2), 2.88 (1H, t, J=4 Hz, 2-CH). MS *m/z*: 252 (M^+, 34), 177 (100).

(3) Treatment of **8** with L-Cysteine: A solution of L-cysteine (35 mg, 0.29 mmol) in pH 7.4 potassium phosphate buffer solution (0.7 ml) was added to a stirred solution of **8** (53 mg, 0.30 mmol) in EtOH (1.3 ml) at room temperature, with bubbling of nitrogen through the solution. A white precipitate appeared immediately. The mixture was further stirred for 15 min and subjected to filtration to give a white solid. The solid was washed with water, EtOH, and ether successively, to give **58** (74 mg, 82% yield based on L-cysteine), which seemed to be a mixture of diastereomers. We could not determine the ratio or separate them due to their insolubility in organic solvents and only slight solubility in water. Recrystallization from water gave an analytical sample as fine needles, which seemed to be one of the diastereomers, mp 113—115 °C (dec.). *Anal.* Calcd for $C_{15}H_{24}NO_4S$: C, 57.12; H, 7.99; N, 4.44. Found: C, 56.72; H, 7.70; N, 4.34. IR (KBr): 3650—3200 (CO_2H), 1730 (C=O), 1620 (H_2O) cm^{-1}. MS *m/z*: 279 ($M^+ - 2H_2O$, 6), 44 (75), 18 (100).

(4) Treatment of **8** with L-Lysine: Reaction of **8** (50 mg, 0.28 mmol) and L-lysine·HCl·H_2O (57 mg, 0.31 mmol) as described above gave recovered **8** (46 mg).

(5) Treatment of **8** with L-Serine: Reaction of **8** (51 mg, 0.29 mmol) and L-serine (33 mg, 0.31 mmol) as described above gave recovered **8** (47 mg).

Kinetic Measurement——The second-order kinetics for addition of L-cysteine to polyquinanes were measured according to the methods in the literature.[3a,34,35] To determine the quantity of remaining L-cysteine, the λ_{max} (343 nm) and the molar extinction (6.96×10^3, lit.[35] 7.06×10^3) of 2-thiopyridone, which was produced by reaction of L-cysteine and 2,2′-dipyridyl disulfide, were used. Since the second-order kinetics were nonlinear, the rate constants were calculated from initial rates (25—40% reaction),[34] and were the averages of at least three runs at the same sample concentration. In the cases of **16**, **18**, and **19**, the reactions proceeded too slowly at 1 °C to give accurate rate constants. Therefore, these were extrapolated from Arrhenius plots obtained by measurement at different temperatures. The rate constants are as follows: **16**, k_2=0.59 (l/mol·s) at 10 °C, 0.36 at 5 °C; **18**, k_2=0.32 at 10 °C, 0.16 at 5 °C; **19**, k_2=0.51 at 15 °C, 0.27 at 10 °C.

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References and Notes

1) Part I, ref. 11*a*; II, ref. 14; III, ref. 12; IV, ref. 11*b*.
2) For recent reviews, see: S. Kano, S. Shibuya, and T. Ebata, *Heterocycles*, **14**, 661 (1980); H. M. R. Hoffmann and J. Rabe, *Angew. Chem. Int. Ed. Eng.*, **24**, 94 (1985).
3) *a*) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); *b*) E. Fujita and Y. Nagao, *Bioorg. Chem.*, **6**, 287 (1977).
4) K.-H. Lee, E.-S. Huang, C. Pinatadosi, J. S. Pagano, and T. A. Geissmann, *Cancer Res.*, **31**, 1649 (1971); I. H. Hall, K.-H. Lee, C. O. Starnes, S. A. Eigebaly, T. Ikuba, Y.-S. Wu, T. Kimura, and M. Haruna, *J. Pharm. Sci.*, **67**, 1235 (1978) and earlier references cited therein.
5) A. Rosowsky, N. Papathansopoulos, H. Lazarus, G. E. Foley, and E. J. Modest, *J. Med. Chem.*, **17**, 672 (1974); P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *ibid.*, **20**, 71 (1977).

6) H. Umezawa, T. Yamato, T. Takeuchi, T. Osata, Y. Okami, S. Yamaoka, T. Okuda, K. Nitta, K. Yagishita, R. Otahara, and S. Umezawa, *Antibiot. Chemother.*, **4**, 514 (1954).
7) T. Haneishi, N. Kitahara, Y. Takiguchi, and M. Arai, *J. Antibiot.*, **27**, 386 (1974).
8) R. L. Ranieri and G. J. Calton, *Tetrahedron Lett.*, **1978**, 499; G. J. Calton, R. L. Ranieri, and M. A. Espenshade, *J. Antibiot.*, **31**, 38 (1978).
9) M. Nakagawa, A. Hirota, H. Sakai, and A. Isogai, *J. Antibiot.*, **35**, 778, 783 (1982).
10) *a*) A. B. Smith, III, B. A. Wexler, and J. Slade, *Tetrahedron Lett.*, **23**, 1631 (1982); *b*) K. Takeda, Y. Shimono, and E. Yoshii, *J. Am. Chem. Soc.*, **105**, 563 (1983); *c*) G. Mehta, K. Pramod, and D. Subrahmanyam, *J. Chem. Soc., Chem. Commun.*, **1986**, 247; *d*) T. Imanishi, M. Matsui, M. Yamashita, and C. Iwata, *Tetrahedron Lett.*, **27**, 3161 (1986).
11) *a*) K. Kakiuchi, T. Nakao, M. Takeda, Y. Tobe, and Y. Odaira, *Tetrahedron Lett.*, **25**, 557 (1984); *b*) K. Kakiuchi, M. Ue, T. Tadaki, Y. Tobe, and Y. Odaira, *Chem. Lett.*, **1986**, 507.
12) K. Kakiuchi, T. Tadaki, Y. Tobe, and Y. Odaira, *Chem. Lett.*, **1985**, 1565.
13) *a*) K. Kakiuchi, K. Itoga, T. Tsugaru, Y. Hato, Y. Tobe, and Y. Odaira, *J. Org. Chem.*, **49**, 659 (1984); *b*) K. Kakiuchi, T. Tsugaru, M. Takeda, I. Wakaki, Y. Tobe, and Y. Odaira, *ibid.*, **50**, 488 (1985); *c*) A. B. Smith, III, B. A. Wexler, C.-Y. Tu, and J. P. Konopelski, *J. Am. Chem. Soc.*, **107**, 1308 (1985).
14) K. Kakiuchi, M. Takeda, Y. Tobe, and Y. Odaira, *Chem. Lett.*, **1985**, 305.
15) K. Kakiuchi, T. Yonei, Y. Tobe, and Y. Odaira, *Bull. Chem. Soc. Jpn.*, **54**, 2770 (1981).
16) I. Peterson and I. Freming, *Tetrahedron Lett.*, **1979**, 995.
17) R. Ballini and M. Petrini, *Synth. Commun.*, **14**, 827 (1984).
18) E. Lee-Ruft and P. G. Khazanie, *Can. J. Chem.*, **56**, 803 (1978).
19) E. J. Corey and M. M. Mehrotra, *J. Am. Chem. Soc.*, **106**, 3384 (1984).
20) L. A. Paquette and Y.-K. Han, *J. Am. Chem. Soc.*, **103**, 1835 (1981).
21) J. K. Crandall and L. C. Craoley, "Organic Synthesis," Vol. 53, ed. by A. Brossi, John Wiley and Sons, Inc., New York, 1973, p. 17.
22) M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977).
23) J. Meinwald and J. K. Crandall, *J. Am. Chem. Soc.*, **88**, 1292 (1966) and references cited therein.
24) This lactone was also synthesized by an alternative route, see: Y. Tobe, Y. Hayauchi, and Y. Odaira, *J. Org. Chem.*, **46**, 5219 (1981).
25) C. Ainsworth, "Organic Synthesis," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 536.
26) M. Regitz, J. Ruter, and A. Liedhegener, "Organic Synthesis," Vol. 51, ed. by R. E. Benson, John Wiley and Sons, Inc., New York, 1971, p. 86.
27) B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5321 (1973).
28) G. Mehta and K. S. Rao, *Tetrahedron Lett.*, **25**, 3481 (1984).
29) K. Kakiuchi, S. Kumanoya, M. Ue, Y. Tobe, and Y. Odaira, *Chem. Lett.*, **1985**, 989.
30) H. J. Roth, Ch. Schwenke, and G. Dvorak, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **298**, 326 (1965).
31) G. R. Pettit, G. M. Cragg, D. Gust, and P. Brown, *Can. J. Chem.*, **60**, 544 (1982).
32) *a*) E. Fujita, Y. Nagao, K. Kaneko, S. Nakazawa, and H. Kuroda, *Chem. Pharm. Bull.*, **24**, 2118 (1976); *b*) S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore, and R. F. Bryan, *J. Am. Chem. Soc.*, **98**, 2295 (1976).
33) G. E. Foley, E. F. Barell, R. A. Adams, and H. Lazarus, *Exp. Cell Res.*, **57**, 129 (1969).
34) S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 376 (1970).
35) D. R. Grassetti and J. F. Murray, Jr., *Arch. Biochem. Biophys.*, **119**, 41 (1967).
36) S. R. Wilson and H.-T. Chen, *Bioorg. Chem.*, **9**, 212 (1980).
37) *Cf.* E. Fujita, Y. Nagao, T. Kohno, M. Matsuda, and M. Ozaki, *Chem. Pharm. Bull.*, **29**, 3208 (1981).
38) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
39) E. Bosone, P. Farina, G. Guazzi, S. Innocenti, V. Marotta, and U. Valavi, *Synthesis*, **1983**, 942.
40) T. Kataoka, F. Oh-hashi, Y. Sakurai, and N. Ida, *Cancer Chemother. Pharmacol.*, **9**, 75 (1982); N. Ida, N. Uenishi, A. Kajita, and Y. Satoh, *Gann*, **73**, 952 (1982).