Geiparvarin Analogues. 3.[1] Synthesis and Cytostatic Activity of 3(2*H*)-Furanone and 4,5-Dihydro-3(2*H*)-furanone Congeners of Geiparvarin, Containing a Geraniol-like Fragment in the Side Chain

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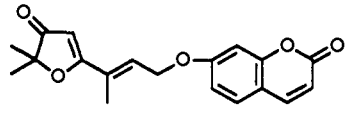
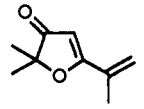
Continuing our study on the structural features of geiparvarin (1), responsible for cytostatic activity, a series of 4,5-dihydro-3(2*H*)-furanones **10a–f** and of 3(2*H*)-furanones **11a–f** as well as 2″,3″-dihydrogeiparvarin (**14**) have been designed and synthesized. Their cytostatic activity was evaluated against proliferation of murine (L1210, FM3A) and human (Raji, Molt/4F, and MT4) tumor cells. Modifications in the region of the olefinic double bond by introduction of the characteristic alkenyl side chain of ascofuranone (compounds **10a–f** and **11a–f**) markedly decreased the cytostatic activity as compared to geiparvarin itself, but this effect does not seem to be correlated to the presence of the furanone moiety linked to the alkenyl chain or to the ability to afford Michael type adducts. Replacement of the coumarin portion by other aromatic rings did not alter the cytostatic activity. The essential inactivity of 2″,3″-dihydrogeiparvarin (**14**) points to the importance of the 3(2*H*)-furanone ring system in the cytostatic activity; consequently, this moiety may be considered as the determinant pharmacophore for antitumor activity, while the side chain plays a rather modulatory role.

Introduction

In the search for antitumor agents of plant origin, a number of natural 3(2*H*)-furanone derivatives with significant antitumor cell activity (geiparvarin (**1**), jatrophone, and eremantholides A, B, C) have been reported.[2,3] The biological activity of these complex natural products appears to be associated with their ability to act as alkylating agents by virtue of conjugate addition of biological nucleophiles to the 3(2*H*)-furanone moiety. The 3(2*H*)-furanone ring system is the most reactive chemical functionality in this class of compounds, and model synthetic derivatives containing the 3(2*H*)-furanone moiety, such as **2**, have recently been shown to possess significant in vitro cytostatic activity.[4]



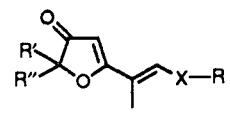
1 (geiparvarin)



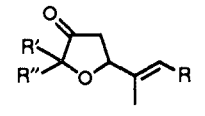
2

Our initial investigations in this area were directed towards the development of structurally simplified geiparvarin analogues containing the pharmacophore 3(2*H*)-furanone ring system.[5,6] Initial attempts to modify the activity by simplifying the structure through the elimination of the alkenyl side chain, resulted in a partial or complete loss of cytostatic activity as compared to the parent geiparvarin. Modifications of the basic 3(2*H*)-furanone ring system, i.e. substitution of alkyl or aryl groups at position 2 (compounds **3a**), provided derivatives at least as active as **1** in inhibiting the proliferation of murine and human tumor cell lines in vitro.

More recently we have synthesized a series of geiparvarin analogues with novel modifications in the region of the olefinic double bond [substitution with a carbamate moiety (compounds **3b**) or an additional double bond] which extend the conjugation of the alkenyl-3(2*H*)-furanone system (compounds **3c**).[7] Among these derivatives only the carbamates showed potent cytostatic activity while the others usually gave compounds which were less active than geiparvarin itself. Taken together, these results point to an important role of the alkenyl side chain in the modulation of the cytostatic activity.



3a–c

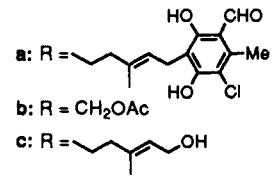


4a–c

a: R′ and R″ are alkyl or aryl residues; X = CH_2O; R = 7-hydroxycoumarinyl

b: R′ = R″ = CH_3; X = CH_2OCONH; R = aryl and cycloalkyl residues

c: R′ = R″ = CH_3; X = *trans* CH=CH; R = aryl residues



As a continuation of this program aimed at clarifying the mechanism of action of the natural compounds containing the 3(2*H*)-furanone moiety we have undertaken a study to identify more potent and selective cytostatic analogues. We now wish to report the synthesis and the cytostatic activity of 2″,3″-dihydrogeiparvarin (**14**) and of a series of geiparvarin analogues **10a–f** and **11a–f** carrying an additional isoprenoid unit in the side chain.

To gain better insight into the mode of action of geiparvarin and related compounds, we wanted to investigate the cytostatic activity of 2″,3″-dihydrogeiparvarin (**14**), a geiparvarin analogue unable to afford Michael-type ad-

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ducts at the furanone moiety. To the best of our knowledge, the cytostatic activity of this type of compound has not been reported although it served as an intermediate in the total synthesis of geiparvarin.[8]

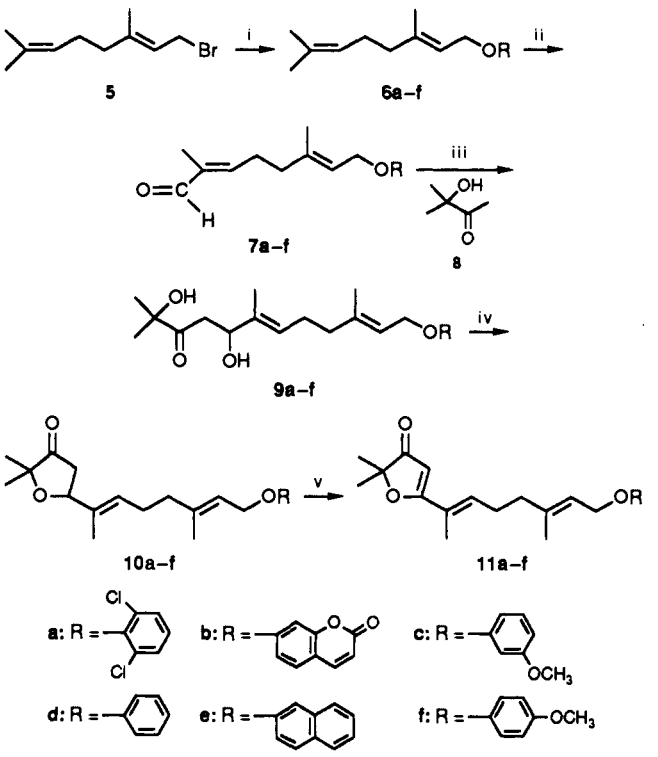
Other modifications that we introduced in geiparvarin were based on antitumor effects on L1210 leukemia by ascofuranone (**4a**), a hypolipidemic antibiotic isolated from the mycelia of *Ascochyta viciae* Libert.[9,10] This compound shows structural similarities to the geiparvarin analogues that we studied and retains marked activity despite the presence of the 4,5-dihydro-3(2*H*)-furanone ring system. Moreover, ascofuranone has a terpenoidal side chain typical of other antitumor agents, for example turbinaric acid, a cytotoxic secosqualene derivative isolated from the brown alga *Tubinaria ornata* which is active against murine melanomas and colon carcinomas.[11] Furthermore, some synthetic retinoids, also a class of compound endowed with potent antitumor activity, possess a geraniol-like fragment.[12]

In this paper we describe the synthesis and the in vitro cytostatic activity of a new series of geiparvarin analogues (**10a–f** and **11a–f**) as well as the synthesis and cytostatic activity of 2″,3″-dihydrogeiparvarin (**14**).

Chemistry

The furanones **10a–f** and **11a–f** were prepared by applying and extending the method recently developed by Mori and co-workers for the total synthesis of ascofuranone.[13] Initial attempts to synthesize the title compounds by etherification of the 4,5-dihydro-3(2*H*)-furanone **4c**, in turn obtained from the corresponding acetyl derivative described by Mori, were unsatisfactory. Only traces of the expected compound, with concomitant disappearance of the starting material, could be recovered. The above-described negative results prompted us to change our strategy and we envisaged the ethers **6a–f** as suitable candidates for an alternative approach (Scheme I). Coupling of the appropriate phenols with commercially available geranyl bromide (**5**) gave rise to a good yield of the ethers **6a–f**, which were transformed (65–33% yield) into the aldehydes **7a–f** by chemo- and stereoselective allylic oxidation utilizing selenium dioxide in ethanol solution followed by PCC oxidation in dichloromethane. Condensation of the dianion derived from 3-hydroxy-3-methyl-2-butanone (**8**) with the aldehydes **7a–f** which contain the complete carbon atom framework of the title compounds. The dianion of 3-hydroxy-3-methyl-2-butanone was obtained by employing $LiN(SiMe_3)_2$ as the base; the yields of **9a–f** were strictly dependent on the reaction condition. The acid-catalyzed cyclization of **9a–f** to the 4,5-dihydro-3(2*H*)-furanones **10a–f** was achieved in 50% yield utilizing catalytic *p*-toluenesulfonic acid in 2-methoxy-1,3-dioxolane and in the presence of a small amount of methanol. Finally, the 3(2*H*)-furanones **11a–f** were

Scheme I[a]



[a] (i) NaH, ROH, DMF; (ii) SeO_2, EtOH, and then PCC, CH_2Cl_2; (iii) *n*-BuLi, $HN(SiMe_3)_2$; (iv) 2-methoxy-1,3-dioxolane, *p*-TsOH, MeOH; (v) DDQ, dioxane.

obtained in high yield by treatment of the dihydrofuranone derivatives **10a–f** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane solution at reflux conditions for 1 h.

Structural assignments for the newly synthesized compounds were inferred by ^1H NMR analysis. The α',β-dihydroxy ketones **9a–f** showed the characteristic signal for the CH_2CO protons, as the ABX system, in the range of 2–3 ppm, and coupling constants were in agreement with the assigned proton system. Ring closure to **10a–f** transformed this signal into a complex multiplet centered at about 2.5 ppm. When compounds **10a–f** were transformed into the corresponding 3(2*H*)-furanones **11a–f**, disappearance of the CH_2CO signal with concomitant appearance of the characteristic furanone (4-H) signal at about 5.5 ppm was observed.

Both geiparvarin and ascofuranone have been synthesized from the commercially available geraniol.[14] The synthetic strategy employed by these authors is based on a chemoselective allylic oxidation and subsequent acid-catalyzed cyclization of the monoepoxide of geraniol to afford in a few steps **4b**, a precursor of the natural compounds.

Retrosynthetic analysis suggested to us that a substituted phenol intermediate like **6**, incorporating the complete carbon atom framework of the target compound **14**, could be the candidate for the construction of the desired dihydrogeiparvarin. This strategy simplifies the previously encountered synthetic problem in the etherification of simple 4,5-dihydro-3(2*H*)-furanones.

One-pot reaction of the ether **12** with selenium dioxide in dioxane, in the presence of camphorsulfonic acid, accomplished chemoselectively the allylic oxidation, followed by acid cyclization (Scheme II). Using this procedure the

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Table I. Inhibitory Effects of Geiparvarin Analogues on the Proliferation of Murine Leukemia L1210, Murine Mammary Carcinoma FM3A, Human B-Lymphoblast Raji, Human T-Lymphoblast Molt/4F, and Human T-Lymphocyte MT-4 Cells

compd	IC_{50}[a] (μg/mL)				
	L1210	FM3A	Raji	Molt/4F	MT-4
10a	58.0 ± 9.9	51.2 ± 7.4	59.9 ± 0.7	50.5 ± 8.5	32.5 ± 1.7
10b	64.5 ± 8.5	54.2 ± 11.0	50.7 ± 1.8	24.2 ± 0.1	42.9 ± 2.5
11a	30.7 ± 0.6	35.3 ± 5.9	26.2 ± 0.1	27.4 ± 1.7	15.5 ± 0.9
11b	39.7 ± 14.5	53.7 ± 18.7	25.2 ± 4.3	28.5 ± 4.7	15.6 ± 2.0
10c	66.5 ± 11.3	68.7 ± 20.1	50.0 ± 9.9	33.8 ± 2.4	51.5 ± 3.5
11c	36.3 ± 0.7	45.9 ± 3.8	45.8 ± 3.5	35.9 ± 0.8	34.0 ± 3.9
10d	64.0 ± 7.1	59.0 ± 13.4	50.7 ± 4.9	27.6 ± 0.4	43.1 ± 0.9
11d	38.7 ± 1.5	44.2 ± 2.7	40.3 ± 7.8	35.2 ± 4.2	29.4 ± 3.4
10e	24.9 ± 2.6	38.4 ± 0.8	47.9 ± 8.8	26.9 ± 3.2	48.8 ± 0.6
11e	47.4 ± 18.5	56.4 ± 22.6	63.2 ± 29.7	51.6 ± 27.4	38.6 ± 15.0
11f	40.2 ± 0.1	43.8 ± 0.5	43.0 ± 0.1	38.6 ± 2.0	33.9 ± 0.1
14	211 ± 15	215 ± 13	226 ± 14	97.5 ± 20.5	107 ± 23
geiparvarin[b]	5.31 ± 0.83	7.87 ± 0.18	8.25 ± 0.21	7.92 ± 0.03	1.64 ± 0.03

[a] Fifty percent inhibitory concentration, or compound concentration required to inhibit tumor cell proliferation by 50%. [b] Data taken from ref 7.

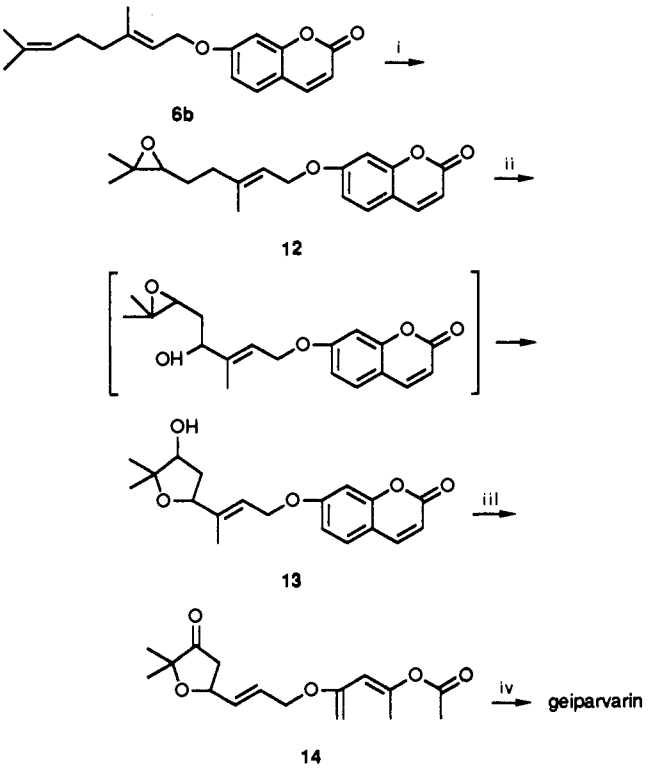
tetrahydrofuran **13** was obtained in 20% yield; subsequent attempts to improve the yield of the preparation were ineffective, but further attempts are currently underway. The final treatment of the alcohol **13** with pyridinium chlorochromate in dichloromethane afforded the 4,5-dihydro-3(2*H*)-furanone **14** in 80% yield. To confirm the structure of the hydrofuranone **14**, this compound was transformed into geiparvarin (**1**) by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane solution at reflux conditions. The analytical and spectral data of the compound thus obtained were identical to those of geiparvarin (as prepared by us previously).

Biological Evaluation

Geiparvarin (**1**), 4,5-dihydro-3(2*H*)-furanones **10a–f**, 3(2*H*)-furanones **11a–f**, and 2″,3″-dihydrogeiparvarin (**14**) were evaluated for their inhibitory effects on the proliferation of murine (L1210, FM3A) and human (Raji, Molt/4F, and MT4) tumor cells (Table I). The 4,5-dihydro-3(2*H*)-furanone derivative **14** of geiparvarin was virtually inactive, which may be related to the inability of this compound to afford Michael-type adducts. The geiparvarin analogues **10a–f** containing the 4,5-dihydro-3(2*H*)-furanone moiety showed a cytostatic activity in the range of 24–69 μg/mL. Similar activity was also shown by the corresponding 3(2*H*)-furanones **11a–f**. All compounds were invariably 10–30-fold less active than geiparvarin. Thus, modifications in the region of the olefinic double bond by introduction of the characteristic alkenyl side chain of ascofuranone (compounds **10a–f** and **11a–f**) markedly decreased the cytostatic activity as compared to geiparvarin itself. Moreover, the cytostatic activity of the geiparvarin analogues does not seem to be correlated to the presence of the furanone moiety linked to the alkenyl chain. In fact, compounds **11a–f** which retain the ability to afford Michael adducts via 1,6-conjugate addition of bionucleophiles have virtually the same activity as the corresponding 4,5-dihydro-3(2*H*)-furanones **10a–f** which are unable to give Michael-type additions. Furthermore, replacement of the coumarin portion by other aromatic rings did not alter the cytostatic activity of the compounds although this modification may have been expected to increase the activity.[15]

The inactivity of **14**, which contrasts with the marked cytostatic activity of 2′,3′-dihydrogeiparvarin, another natural compound extracted from *Geiera parviflora* lindt,[4] points to the importance of the 3(2*H*)-furanone ring system in the cytostatic activity; consequently, this moiety may be considered as the determinant pharmacophore for antitumor activity, while the side chain at position 5 rather plays a modulatory role.

Scheme II[a]



[a] (i) MCPBA, $NaHCO_3$, CH_2Cl_2, H_2O; (ii) SeO_2, camphorsulfonic acid, dioxane; (iii) PCC, CH_2Cl_2; (iv) DDQ, dioxane, reflux.

In conclusion, we have synthesized several 3(2*H*)-furanone and 4,5-dihydro-3(2*H*)-furanone analogues of geiparvarin as a continuation of our investigations on the mode of action of the antitumor agents possessing the 3(2*H*)-furanone ring system. In our current study, some geiparvarin analogues were synthesized that contain structural features common with ascofuranone. One of the aims of this investigation was to identify the functional groups in the geiparvain molecule that are essential for antitumor activity and, in particular, to establish the role of pharmacophores 3(2*H*)-furanone and 4,5-dihydro-3-(2*H*)-furanone in the antitumor activity. Moreover, 2″,3″-dihydrogeiparvarin (**14**) was prepared in view of the

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activity of compounds **10a–f**. Our data clearly point to the necessity of the 3(2*H*)-furanone ring and the modulatory role of the alkenyl side chain in the cytostatic activity in geiparvarin.

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F254 Merck plates. Infrared spectra (IR) were measured on a Perkin Elmer 257 instrument. Nuclear magnetic resonance (^{1}H NMR) spectra were determined for solution in $CDCl_3$ with a Bruker AC-200 spectrometer, and peak positions are given in parts per million downfield from tetramethylsilane as internal standard. Petroleum ether refers to the fractions of boiling range 40–60 °C. Column chromatographies were performed with Merck 60–200 mesh silica gel. All drying operations were performed over anhydrous magnesium sulfate. Column chromatography (medium pressure) was carried out by using the "flash" technique.[16] Microanalysis were in agreement with calculated values within ±0.4%.

Starting Materials. Compounds **6a–7** were prepared by the standard Williamson reaction.[17] Compound **5** is commercially available.

(*E,E*)-2,6-Dimethyl-8-(2,5-dichlorophenoxy)-2,6-octadienal (7a). A suspension of selenium dioxide (2.88 g, 26 mmol) and ether **6a** (5 g, 17 mmol) in ethanol (100 mL) was heated at reflux. When the reaction was complete, as judged by TLC (approximately 2 h), the suspension was cooled to room temperature, filtered through Celite, and concentrated in vacuo. The residue oil was dissolved in dichloromethane (100 mL), cooled to 0 °C, and treated with pyridinium chlorochromate (8.4 g, 39 mmol). The reaction was stirred at room temperature for 12 h, diluted with diethyl ether (200 mL), filtered through Celite, and concentrated in vacuo. Flash-chromatographic purification of the residue oil (1:8 ethyl acetate/petroleum ether) gave **7a** as a colorless oil: 2.32 g, 43.6%; IR (film) 1690, 1630, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 6 H, $(CH_3)_2$), 2.25 (m, 2 H, CH_2C), 2.49 (m, 2 H, CH_2C), 4.63 (d, 2 H, J = 6.6 Hz, CH_2O), 5.66 (m, 1 H, CH=), 6.45 (m, 1 H, CH=), 6.98 (m, 1 H, Ar), 7.27 (m, 2 H, Ar), 9.39 (s, 1 H, CHO). Anal. ($C_{16}H_{18}Cl_2O_2$) C, H.

Compounds **7b–f** were prepared in the same manner as that described for **7a**.

7b: oil, 2.4 g, 46%; IR (film) 1740, 1690, 1620, 1560, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 6 H, $(CH_3)_2$, 2.29 (m, 2 H, CH_2C), 2.51 (m, 2 H, CH_2C), 4.63 (d, 2 H, J = 6.6 Hz, CH_2O), 5.51 (m, 1 H, CH=), 6.28 (d, 1 H, J = 9.3 Hz, coumarin 3-H), 6.48 (m, 1 H, CH=), 6.82 (m, 2 H, coumarin), 7.35 (d, 1 H, J = 8.4 Hz, coumarin), 7.67 (d, 1 H, J = 9.3 Hz, coumarin 4-H), 9.35 (s, 1 H, CHO). Anal. ($C_{19}H_{20}O_4$) C, H.

7c: oil, 2.51 g, 59%; IR (film) 1680, 1640, 1590, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 1.77 (s, 3 H, CH_3), 2.26 (m, 2 H, CH_2C), 2.50 (m, 2 H, CH_2C), 3.78 (s, 3 H, CH_3O), 4.53 (d, 2 H, J = 6.7 Hz, CH_2O), 5.50 (m, 1 H, CH=), 6.48 (m, 4 H, Ar and CH=), 7.17 (m, 1 H, Ar), 9.30 (s, 1 H, CHO). Anal. ($C_{17}H_{22}O_3$) C, H.

7d: oil, 2.6 g, 68%; IR (film) 1700, 1660, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 6 H, $(CH_3)_2$), 2.30 (m, 2 H, CH_2C), 2.50 (m, 2 H, CH_2C), 4.56 (d, 2 H, J = 6.6 Hz, CH_2O), 5.53 (m, 1 H, CH=), 6.45 (m, 1 H, CH=), 6.94 (m, 3 H, Ar), 7.25 (m, 2 H, Ar), 9.45 (s, 1 H, CHO). Anal. ($C_{16}H_{20}O_2$) C, H.

7e: oil, 1.41 g, 34%; IR (film) 1690, 1620, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 1.81 (s, 3 H, CH_3), 2.32 (m, 2 H, CH_2C), 2.51 (m, 2 H, CH_2C), 4.68 (d, 2 H, J = 6.6 Hz, CH_2O), 5.60 (m, 1 H, CH=), 6.45 (m, 1 H, CH=), 7.1–7.39 (m, 4 H, Ar), 7.71 (m, 3 H, Ar), 9.34 (s, 1 H, CHO). Anal. ($C_{20}H_{22}O_2$) C, H.

7f: 2.75, g, 60%; IR (film) 1680, 1640, 1590, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 1.77 (s, 3 H, CH_3), 2.26 (m, 2 H, CH_2C); 2.50 (m, 2 H, CH_2C), 3.78 (s, 3 H, CH_3O), 4.53 (d, 2 H, J = 6.7 Hz, CH_2O), 5.50 (m, 1 H, CH=), 6.48 (m, 4 H, Ar and CH=), 7.17 (m, 1 H, Ar), 9.30 (s, 1 H, CHO). Anal. ($C_{17}C_{22}O_3$) C, H.

(±)-(*E,E*)-12-(2,6-Dichlorophenoxy)-2,5-dihydroxy-2,6,10-trimethyl-6,10-dodecadien-3-one (9a). To a well-stirred solution of $HN(SiMe_3)_2$ (4.3 mL, 20 mmol) at −30 °C was added dropwise 13.8 mL (20 mmol) of a 1.6 M solution of *n*-butyllithium. The temperature was kept at 0 °C for 5 min. The solution was cooled to −40 °C and 3-hydroxy-3-methyl-2-butanone (1.05 g, 10 mmol) in THF (10 mL) was added dropwise in 10 min. The reaction mixture was stirred for 4 h at −30 °C and then at −60 °C for 30 min. A solution of **7a** (1.56 g, 5 mmol) in THF (10 mL) was added. The mixture was stirred for 10 min at −30 °C and then at −60 °C for 1 h. The reaction was diluted with diethyl ether (50 mL) and quenched by the addition of saturated aqueous NH_4Cl (20 mL). To the cooled reaction mixture was added concentrated HCl (5 mL), and the organic layer was separated. The organic solution was washed with brine, dried, and concentrated in vacuo. The residue was flash chromatographed on silica gel (ethyl acetate/petroleum ether 3:7) to give **9a** as an oil: 1.19 g, 57.5%; IR (film) 3400, 1710, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6 H, $(CH_3)_2$), 1.66 (s, 3 H, CH_3C=), 1.72 (s, 3 H, CH_3C=), 2.14 (m, 4 H, CH_2CH_2), 2.56, 2.88 (2 H, ABX system, J = 16.2, 3.1, 9.3 Hz, CH_2CO)), 3.12 (br, 2 H, OH), 4.48 (m, 1 H, CHO), 4.55 (d, 2 H, J = 6.6 Hz, CH_2O), 5.46 (m, 1 H, CH=), 5.60 (m, 1 H, CH=), 6.98 (m, 1 H, Ar), 7.27 (m, 2 H, Ar). Anal. ($C_{21}H_{28}Cl_2O_4$), C, H.

Compounds **9b–f** were prepared in the same manner as described for **9a**.

9b: mp 82–85 °C (diethyl ether/petroleum ether); 1.01 g, 49%; IR (KBr) 3400, 1740, 1710, 1620, 1550, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 6 H, $(CH_3)_2$), 1.65 (s, 3 H, CH_3C=), 1.74 (s, 3 H, CH_3C=), 2.15 (m, 4 H, CH_2CH_2), 2.64, 2.91 (2 H, ABX system, J = 16.4, 3.0, 9.4 Hz, CH_2CO), 3.85 (br, 2 H, OH), 4.49 (m, 1 H, CHO), 4.52 (d, 2 H, J = 6.6 Hz, CH_2O), 5.49 (m, 2 H, CH=), 6.25 (d, 1 H, J = 9.2 Hz, coumarin 3-H), 6.86 (m, 2 H, coumarin), 7.40 (d, 1 H, J = 8.0 Hz, coumarin), 7.65 (d, 1 H, J = 9.2 Hz, coumarin 4-H). Anal. ($C_{24}H_{30}O_6$) C, H.

9c: oil, 0.75 g, 40%; IR (film) 3400, 1700, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 6 H, $(CH_3)_2$, 1.64 (s, 3 H, CH_3C=), 1.74 (s, 3 H, CH_3C=), 2.14 (m, 4 H, CH_2CH_2), 2.55, 2.84 (2 H, ABX system, J = 16.4, 3.0, 9.4 Hz, CH_2CO), 3.13 (br, 2 H, OH), 3.76 (m, 3 H, CH_3O), 4.5 (m, 1 H, CHO), 4.53 (d, 2 H, J = 6.6 Hz, CH_2O), 5.50 (m, 2 H, CH=); 6.52 (m, 3 H, Ar), 7.26 (m, 1 H, Ar). Anal. ($C_{22}H_{32}O_5$) C, H.

9d: mp 47–50 °C (diethyl ether/petroleum ether); 0.66 g, 39%; IR (KBr) 3400, 1710, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6 H, $(CH_3)_2$), 1.68 (s, 3 H, CH_3C=), 1.72 (s, 3 H, CH_3C=), 2.18 (m, 4 H, CH_2CH_2), 2.63, 2.93 (2 H, ABX system, J = 16.4, 3.0, 9.4 Hz, CH_2CO), 3.90 (br, 2 H, OH), 4.48 (m, 1 H, CHO), 4.50 (d, 2 H, J = 6.6 Hz, CH_2O), 5.43 (m, 2 H, CH=), 6.92 (m, 3 H, Ar), 7.27 (m, 2 H, Ar). Anal. ($C_{21}H_{30}O_4$) C, H.

9e: oil, 1.07 g, 51%; IR (film) 3400, 1710, 1620, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6 H, $(CH_3)_2$), 1.69 (s, 3 H, CH_3C=), 1.72 (s, 3 H, CH_3C=), 2.19 (m, 4 H, CH_2CH_2), 2.59, 2.9 (2 H, ABX system, J = 16.4, 3.0, 9.4 Hz, CH_2CO), 3.73 (br, 2 H, OH), 4.45 (m, 1 H, CHO), 4.66 (d, 2 H, J = 6.6 Hz, CH_2O), 5.47 (m, 2 H, CH=), 7.12–7.42 (m, 4 H, Ar), 7.71 (m, 3 H, Ar). Anal. ($C_{25}H_{32}O_4$) C, H.

9f: oil, 0.75 g, 40%; IR (film) 3400, 1710, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 6 H, $(CH_3)_2$), 1.64 (s, 3 H, CH_3C=), 1.72 (s, 3 H, CH_3C=), 2.14 (m, 4 H, CH_2CH_2), 2.55, 2.84 (2 H, ABX system, J = 16.4, 3.0, 9.4 Hz, CH_2CO), 3.25 (br, 2 H, OH), 3.86 (m, 3 H, CH_3O), 4.5 (m, 1 H, CHO), 4.53 (d, 2 H, J = 6.6 Hz, CH_2O), 5.50 (m, 2 H, CH=), 6.89 (s, 4 H, Ar). Anal. ($C_{22}H_{32}O_5$) C, H.

(+)-(*E,E*)-5-[1,5-Dimethyl-7-(2,6-dichlorophenoxy)-1,5-heptadienyl]-2,2-dimethyl-3-tetrahydrofuranone (10a). To a solution of **9a** (0.83 g, 2 mmol) in 2-methoxy-1,3-dioxolane (4 mL) were added *p*-toluenesulfonic acid (traces), and methanol (two drops), and the solution was stirred for 1 h at room temperature. It was then cooled to 0 °C and the reaction was quenched by the addition of water (6 mL) and concentrated HCl (3 mL). The reaction mixture was stirred at this temperature for an additional 10 min; diethyl ether (50 mL) was added, and the organic layer was separated. The organic solution was washed with water, saturated $NaHCO_3$, and brine, and then dried and

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concentrated in vacuo. The residue was flash chromatographed (petroleum ether/ethyl acetate 8:2) to give **10a** as an oil: 0.43 g, 54.4%; IR (film) 1760, 1610, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3 H, CH_3C), 1.31 (s, 3 H, CH_3C), 1.67 (s, 3 H, CH_3C=), 1.71 (s, 3 H, CH_3C=), 2.25 (m, 4 H, CH_2CH_2), 2.48 (m, 2 H, CH_2CO), 4.47 (m, 1 H, CHO), 4.60 (d, 2 H, J = 6.6 Hz, CH_2O), 5.58 (m, 2 H, CH=), 7.02 (m, 1 H, Ar), 7.26 (m, 2 H, Ar). Anal. ($C_{21}H_{26}Cl_2O_3$) C, H.

Compounds **10b–f** were prepared as described for **10a**.

10b: mp 62–5 °C (ethyl acetate/petroleum ether); 0.45 g, 59%; IR (KBr) 1740, 1720, 1660, 1550, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3C), 1.28 (s, 3 H, CH_3C), 1.67 (s, 3 H, CH_3C=), 1.75 (s, 3 H, CH_3C=), 2.12 (m, 4 H, CH_2CH_2), 2.43 (m, 2 H, CH_2CO), 4.57 (m, 1 H, CHO), 4.60 (d, 2 H, J = 6.6 Hz, CH_2O), 5.51 (m, 2 H, CH=), 6.28 (d, 1 H, J = 9.5 Hz, coumarin 3-H), 6.84 (m, 2 H, coumarin), 7.35 (d, 1 H, J = 8.4 Hz, coumarin), 7.63 (d, 1 H, J = 9.5, coumarin 4-H). Anal. ($C_{24}H_{28}O_5$) C, H.

10c: oil, 0.35 g, 50%; IR (film) 1760, 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H, CH_3C), 1.25 (s, 3 H, CH_3C), 1.61 (s, 3 H, CH_3C=), 1.66 (s, 3 H, CH_3C=), 2.19 (m, 4 H, CH_2CH_2), 2.46 (m, 2 H, CH_2CO), 3.78 (s, 3 H, CH_3O), 4.50 (m, 1 H, CHO), 4.53 (d, 2 H, J = 6.6 Hz, CH_2O), 5.56 (m, 2 H, CH=), 6.52 (m, 3 H, Ar), 7.17 (m, 1 H, Ar). Anal. ($C_{22}H_{30}O_4$) C, H.

10d: oil, 0.47 g, 62%; IR (film) 1760, 1610, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3C), 1.29 (s, 3 H, CH_3C), 1.67 (s, 3 H, CH_3C=); 1.74 (s, 3 H, CH_3C=), 2.21 (m, 4 H, CH_2CH_2), 2.45 (m, 2 H, CH_2CO), 4.50 (m, 1 H, CHO), 4.5 (d, 2 H, J = 6.6 Hz, CH_2O), 5.56 (m, 2 H, CH=), 6.93 (m, 3 H, Ar), 7.28 (m, 2 H, Ar). Anal. ($C_{21}H_{28}O_3$) C, H.

10e: oil, 0.38 g, 51%; IR (film) 1760, 1680, 1630, 1600, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 3 H, CH_3C), 1.28 (s, 3 H, CH_3C), 1.66 (s, 3 H, CH_3C=), 1.79 (s, 3 H, CH_3C=), 2.18 (m, 4 H, CH_2CH_2), 2.45 (m, 2 H, CH_2CO), 4.50 (m, 1 H, CHO), 4.65 (d, 2 H, J = 6.6 Hz, CH_2O), 5.56 (m, 2 H, CH=), 7.17–7.41 (m, 4 H, Ar), 7.74 (m, 3 H, Ar). Anal. ($C_{25}H_{30}O_3$) C, H.

10f: oil, 0.35 g, 50%; IR (film) 1760, 1600, 1500 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.24 (s, 3 H, CH_3C), 1.28 (s, 3 H, CH_3C), 1.54 (s, 3 H, CH_3C=), 1.66 (s, 3 H, CH_3C=), 2.23 (m, 4 H, CH_2CH_2), 2.51 (m, 2 H, CH_2CO), 3.72 (s, 3 H, CH_3O), 4.49 (m, 1 H, CHO), 4.53 (d, 2 H, J = 6.6 Hz, CH_2O), 5.5 (m, 2 H, CH=), 6.45 (m, 4 H, Ar). Anal. ($C_{22}H_{30}O_4$) C, H.

(+)-(*E*,*E*)-2,2-Dimethyl-5-[1,5-dimethyl-7-(2,6-dichlorophenoxy)-1,5-heptadienyl]-3(2*H*)-furanone (11a). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.4 g, 1 mmol) was added to a solution of **10a** (0.35 g, 0.9 mmol) in dioxane (10 mL). The mixture was heated at reflux, and the course of the reaction was monitored by TLC. When the reaction was complete, as judged by TLC (approximately 15 min), the suspension was cooled to room temperature, diluted with diethyl ether, filtered through Celite, and concentrated in vacuo. Flash chromatographic purification of the residue oil (1:8 ethyl acetate/petroleum ether) gave the title compound **11a** as a colorless oil: 0.20 g, 57.5%; IR (film) 1700, 1650, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H, $(CH_3)_2$), 1.76 (s, 3 H, CH_3C=), 1.88 (s, 3 H, CH_3C=), 2.26 (m, 2 H, CH_2), 2.34 (m, 2 H, CH_2), 4.55 (d, 2 H, J = 6.4 Hz, CH_2O), 5.50 (s, 1 H, CH=), 5.53 (m, 1 H, furan), 6.55 (m, 1 H, CH=), 7.01 (m, 1 H, Ar), 7.28 (m, 2 H, Ar). Anal. ($C_{21}H_{24}Cl_2O_3$) C, H.

Compounds **11b–f** were prepared in the same manner as described for **11a**.

11b: mp 75–80 °C (ethyl acetate/petroleum ether); 0.19 g, 55%; IR (KBr) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H, $(CH_3)_2$), 1.75 (s, 3 H, CH_3C=), 1.90 (s, 3 H, CH_3C=), 2.26 (m, 2 H, CH_2C=), 2.36 (m, 2 H, CH_2C=), 4.63 (d, 2 H, J = 6.5 Hz, CH_2O), 5.47 (s, 1 H, CH=), 5.50 (m, 1 H, furan), 6.23 (d, 1 H, J = 9.5 Hz, coumarin 3-H), 6.54 (m, 1 H, CH=), 6.81 (m, 2 H, coumarin), 7.35 (d, 1 H, J = 8.4 Hz, coumarin), 7.62 (d, 1 H, J = 9.5 Hz, coumarin 4-H). Anal. ($C_{24}H_{26}O_5$) C, H.

11c: oil, 0.21 g, 61%; IR (film) 1690, 1650, 1600, 1560, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6 H, $(CH_3)_2$), 1.79 (s, 3 H, CH_3C=), 1.89 (s, 3 H, CH_3C=), 2.24 (m, 2 H, CH_2C=), 2.35 (m, 2 H, CH_2C=), 3.88 (s, 3 H, CH_3O), 4.60 (d, 2 H, J = 6.6 Hz, CH_2O), 5.52 (s, 1 H, furan), 5.55 (m, 1 H, CH=), 6.55 (m, 1 H, CH=), 6.54 (m, 3 H, Ar), 7.15 (m, 1 H, Ar). Anal. ($C_{22}H_{28}O_4$) C, H.

11d: oil, 0.15 g, 52%; IR (film) 1690, 1650, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6 H, $(CH_3)_2$), 1.77 (s, 3 H, CH_3C=), 1.89 (s, 3 H, CH_3C=), 2.27 (m, 2 H, CH_2C=), 2.39 (m, 2 H, CH_2C=), 4.56 (d, 2 H, J = 6.4 Hz, CH_2O), 5.51 (s, 1 H, furan), 5.54 (m, 1 H, CH=), 6.58 (m, 1 H, CH=), 6.93 (m, 3 H, Ar), 7.26 (m, 2 H, Ar). Anal. ($C_{21}H_{26}O_3$) C, H.

11e: oil, 0.19 g, 57%; IR (film) 1690, 1650, 1600, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H, $(CH_3)_2$), 1.78 (s, 3 H, CH_3C=), 1.90 (s, 3 H, CH_3C=), 2.25 (m, 2 H, CH_2C=), 2.37 (m, 2 H, CH_2C=), 4.58 (d, 2 H, J = 6.6 Hz, CH_2O), 5.52 (s, 1 H, furan), 5.54 (m, 1 H, CH=), 6.60 (m, 1 H, CH=), 7.14–7.4 (m, 4 H, Ar), 7.74 (m, 3 H, Ar). Anal. ($C_{25}H_{28}O_3$) C, H.

11f: oil, 0.21 g, 60%; IR (film) 1690, 1650, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6 H, $(CH_3)_2$), 1.80 (s, 3 H, CH_3C=), 1.85 (s, 3 H, CH_3C=), 2.31 (m, 2 H, CH_2C=), 2.38 (m, 2 H, CH_2C=), 3.70 (s, 3 H, CH_3O), 4.60 (d, 2 H, J = 6.6 Hz, CH_2O), 5.55 (s, 1 H, furan), 5.59 (m, 1 H, CH=), 6.54 (m, 1 H, CH=), 6.89 (m, 4 H, Ar). Anal. ($C_{22}H_{28}O_4$) C, H.

(+)-(*E*)-7-[[5-(3,3-Dimethyloxiranyl)-3-methyl-2-pentenyl]oxy]-2*H*-1-benzopyran-2-one (12). A solution of sodium bicarbonate (1.76 g, 21 mmol) in water (100 mL) was added at 0 °C to methylene dichloride (100 mL) containing the ether **6b** (3 g, 10 mmol) and *m*-chloroperbenzoic acid (1.81 g, 10 mmol). The two-phase solution was well-stirred at 0 °C for 1 h, and then *m*-chloroperbenzoic acid (0.17 g, 1 mmol) was added. The reaction mixture was stirred for additional 2 h at 0 °C; the organic layer was separated, washed with water, dried, and concentrated in vacuo. The residue was flash-chromatographed on silica gel (diethyl ether/petroleum ether 1:1 containing traces of triethylamine) to give **12** as a solid (2.25 g, 71%): mp 58–60 °C (diethyl ether/petroleum ether); IR (KBr) 1710, 1700, 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H, CH_3C), 1.30 (s, 3 H, CH_3C), 1.71 (m, 2 H, CH_2C), 1.78 (s, 3 H, CH_3C=), 2.23 (m, 2 H, CH_2C), 2.71 (m, 1 H, CHO), 4.62 (d, 2 H, J = 6.6 Hz, CH_2O), 5.52 (m, 1 H, CHC=), 6.24 (d, 1 H, J = 9.4 Hz, coumarin H-3), 6.81 (m, 2 H, coumarin), 7.37 (d, 1 H, J = 8.2 Hz, coumarin), 7.62 (d, 1 H, J = 9.4 Hz, coumarin H-4). Anal. ($C_{19}H_{22}O_4$) C, H.

(+)-(*E*)-7-[[3-(Tetrahydro-5,5-dimethyl-4-hydroxy-2-furanyl)-2-butenyl]oxy]-2*H*-1-benzopyran-2-one (13). To a solution of the epoxide **12** (1.57 g, 5 mmol) in dioxane (15 mL) were added selenium dioxide (0.55 g, 5 mmol) and traces of camphorsulfonic acid. The reaction mixture was warmed up to 55 °C and stirred vigorously until the reaction was complete, as judged by TLC (1.5 h). The solution was cooled and concentrated in vacuo, and the residue dissolved in ethyl acetate was washed with saturated sodium bicarbonate and brine. The dried organic extracts were evaporated in vacuo and the residue was flash chromatographed on silica gel (ethyl acetate/petroleum ether 9:1) to give **13** as an oil (0.32 g, 20%): IR (film) 1715, 1700, 1615, 1550, 1500 cm^{-1}. Anal. ($C_{19}H_{21}O_5$) C, H.

(±)-(*E*)-7-[[3-(Tetrahydro-5,5-dimethyl-4-oxo-2-furanyl)-2-butenyl]oxy]-2*H*-1-benzopyran-2-one (14). The alcohol **13** (0.32 g, 1 mmol) was dissolved in dichloromethane (50 mL), cooled to 0 °C, and treated with pyridinium chlorochromate (0.64 g, 3 mmol). The reaction mixture was stirred at room temperature for 12 h, diluted with diethyl ether (50 mL), filtered through Celite, and concentrated in vacuo. Flash-chromatographic purification of the oily residue (1:8 ethyl acetate/petroleum ether) gave the title compound as a solid (0.25 g, 80%): mp 114–116 °C (ethyl acetate/petroleum ether); IR (KBr) 1760, 1735, 1620, 1560, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3C), 1.33 (s, 3 H, CH_3C), 1.81 (s, 3 H, CH_3C=), 2.45–2.62 (ABX system, 2 H, J = 18.1, 10.1, 6.1 Hz, CH_2CO), 4.60 (m, 1 H, CHO), 4.68 (d, 2 H, J = 6.2 Hz, CH_2O), 5.91 (m, 1 H, CHC=), 6.26 (d, 1 H, J = 9.4 Hz, coumarin 3-), 6.86 (m, 2 H, coumarin), 7.38 (d, 1 H, J = 8.4 Hz, coumarin), 7.65 (d, 1 H, J = 9.4 Hz, coumarin 4-H). Anal. ($C_{19}H_{20}O_5$) C, H.

Cytostatic Activity of Test Compounds. The methods for evaluating the cytostatic activity of the test compounds against murine leukemia (L1210) and mammary carcinoma (FM3A), and human B-lymphoblast Raji, T-lymphoblast Molt/4F, and T-lymphocyte MT-4 cells have been described previously.[18,19]

(18) Balzarini, J.; De Clercq, E.; Torrence, P. F.; Mertens, M. P.; Park, J. S.; Schmidt, C. L.; Shugar, D.; Barr, P. J.; Jones, A. S.; Verhelst, G.; Walker, R. T. Role of thymidine kinase in the inhibitory activity of 5-substituted-2'-deoxyuridines on the growth of human and murine tumor cell lines. *Biochem. Pharmacol.* 1982, *31*, 1089–1095.

Briefly, 5×10^4 L1210 and FM3A, or 7.5×10^4 Raji, Molt/4, and MT-4 cells were suspended in growth medium and added to microplate wells in the presence of varying concentrations of the test compounds. The cells were then allowed to proliferate for 48 h (L1210 and FM3A), 72 h (Raji and Molt/4F), or 120 h (MT-4) at 37 °C in a humidified CO_2-controlled atmosphere. At the end of the incubation period, the cells were counted in a Coulter counter (L1210, FM3A, Raji, Molt/4F). Cell viability was determined by the trypan blue dye exclusion method. The IC_{50} value was determined as the concentration of test compound required to inhibit tumor cell proliferation by 50%.

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Registry No. 1, 36413-91-9; **5**, 6138-90-5; **6a**, 139870-94-3; **6b**, 495-02-3; **6c**, 57782-96-4; **6d**, 35266-82-1; **6e**, 40267-83-2; **6f**, 57782-99-7; **7a**, 139870-95-4; **7b**, 30825-46-8; **7c**, 139871-03-7; **7d**, 139372-91-1; **7e**, 139871-10-6; **7f**, 139871-14-0; **8**, 115-22-0; (±)-**9a**, 139870-96-5; (±)-**9b**, 139871-01-5; (±)-**9c**, 139871-05-9; (±)-**9d**, 139871-08-2; (±)-**9e**, 139871-12-8; (±)-**9f**, 139871-16-2; (±)-**10a**, 139870-97-6; (±)-**10b**, 139871-02-6; (±)-**10c**, 139871-06-0; (±)-**10d**, 139871-09-3; (±)-**10e**, 139871-13-9; (±)-**10f**, 139871-17-3; **11a**, 139870-98-7; **11b**, 139871-00-4; **11c**, 139871-04-8; **11d**, 139871-07-1; **11e**, 139871-11-7; **11f**, 139871-15-1; (±)-**12**, 31946-92-6; **13**, 139870-99-8; (±)-14, 98066-12-7; 2,6-dichlorophenol, 87-65-0; 7-hydroxy-2*H*-1-benzopyran-2-one, 93-35-6; 3-methoxyphenol, 150-19-6; phenol, 108-95-2; 2-naphthol, 135-19-3; 4-methoxyphenol, 150-76-5.

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Synthesis and Anti-HIV Activity of 9-[*c*-4,*t*-5-Bis(hydroxymethyl)cyclopent-2-en-*r*-1-yl]-9*H*-adenine[1]

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The synthesis and in vitro anti-HIV activity of two new racemic nucleoside analogues are described; namely, 9-[*c*-4,*t*-5-bis(hydroxymethyl)cyclopent-2-en-*r*-1-yl]-9*H*-adenine (**12**) and its guanine analogue **18**. While the latter (**18**) showed no activity, the therapeutic index of the former (**12**) was 200 and comparable to that (400) of carbovir. One enantiomer of **12** may be viewed as an analogue of carbocyclic oxetanocin and the other as an analogue of carbovir. Hence, these results indicate that one or both of the individual enantiomers of **12** could serve as candidates or lead compounds for the development of anti-AIDS agents.

Introduction

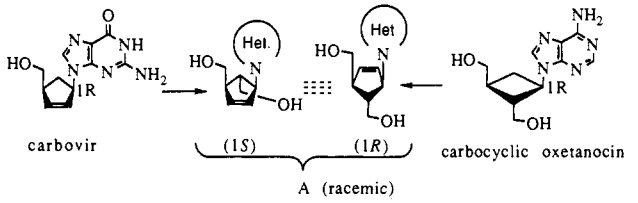
The identification of a retrovirus, referred to as human immunodeficiency virus (HIV), as the etiological agent of human acquired immunodeficiency syndrome (AIDS),[2] has aroused much interest in creating drugs for the treatment of this lethal disease. Although several nucleoside derivatives have been reported to exhibit in vitro anti-HIV activity, to the best of our knowledge, only 3′-azido-3′-deoxythymidine (AZT) and 2′,3′-dideoxyinosine (DDI) have been used clinically. However, clinical studies have indicated substantial toxicities associated with the administration of these two compounds.[3]

In order to create new drugs, we chose as the lead compounds, carbovir[4] and carbocyclic oxetanocin,[5] which were previously reported to exhibit significant anti-HIV activity. The former was pursued as a prospective chemotherapeutic agent against AIDS. From this standpoint, we have chosen the racemic compounds of the 5′-hydroxymethyl derivative of carbovir (A: Het. = 9-adenyl) and its analogue (A: Het. = 9-guanyl) as the target molecules. One enantiomer of A can be regarded as an analogue of carbovir, while the other can be regarded as an analogue of carbocyclic oxetanocin (Scheme I).

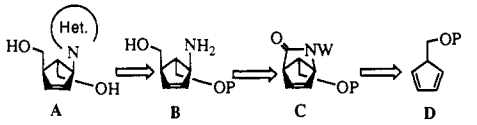
Chemistry

We have previously elaborated the shortest synthetic route to *cis*-4-(hydroxymethyl)cyclopent-2-enylamine from the bicycloamide prepared from the Diels–Alder reactions of cyclopentadiene with either tosyl cyanide[6] or chloro-

Scheme I



Scheme II



W : an electron-withdrawing group
P : a protecting group

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(1) Part XXIII of Synthesis of Nucleosides and Related Compounds. For Part XXII: Katagiri, N.; Nomura, M.; Muto, M.; Kaneko, C. Synthesis of Nucleosides and Related Compounds. XXII. Carbocyclic Analogues of Thymidine and Related Compounds from 2-Azabicyclo[2.2.1]hept-5-en-3-ones. *Chem. Pharm. Bull.* 1991, *39*, 1682–1688.
(2) Popovic, M.; Sarngadharan, M. G.; Read, E.; Gallo, R. C. Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS. *Science* 1984, *224*, 497–500 and references cited therein.

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