°C); and *p*-methoxydiphenyliodonium bromide, mp 183-184 °C (lit.[40] mp 185 °C) were all prepared by the method reported by Beringer.[40]

m-Bromodiphenyliodonium iodide was prepared from the reaction of *m*-bromoiodobenzene dichloride (6 g, 0.017 mol) with diphenylmercury (10 g, 0.028 mol) to give the required product (6 g, 0.012 mol, 74%), mp 133-134 °C (lit.[41] mp 133-134 °C). Anal. Calcd for $C_{12}H_9BrI_2$: C, 29.60; H, 1.86. Found: C, 29.52; H, 1.86.

m-Methoxydiphenyliodonium iodide was prepared from the reaction of *m*-methoxyiodobenzene dichloride (8 g, 0.026 mol) and diphenylmercury (8.6 g, 0.026 mol) to give the required product (6.1 g, 0.014 mol, 53%), mp 164-165 °C (lit.[40] mp 166 °C).

3-Formyldiphenyliodonium iodide was prepared from the reaction of 3-formyliodobenzene dichloride (10 g, 0.023 mol) with diphenylmercury (15 g, 0.042 mol) to give the product (10 g, 0.020 mol, 87%), mp 142-142.5 °C. Anal. Calcd for $C_{13}H_{10}I_2O$: C, 35.81; H, 2.31. Found: C, 35.68; H, 2.29.

m-(Trifluoromethyl)diphenyliodonium iodide was prepared from the reaction of the corresponding iodobenzene dichloride (5 g, 0.015 mol) with diphenylmercury (10 g, 0.025 mol) to give the product (6 g, 0.013 mol, 86%), mp 159-161 °C. Anal. Calcd for $C_{13}H_9F_3I_2$: C, 32.80; H, 1.91. Found: C, 32.77; H, 1.90.

Phenylazotriphenylmethane (Eastman Organic Chemicals) was sublimed before use, mp 109-111 °C (lit.[42] mp 109-111 °C).

Phenol (Aldrich Chemical Co.), bp 180-182 °C (lit.[43] mp 181 °C); 2,6-di-*tert*-butylphenol (Aldrich Chemical Co.), mp 68 °C (lit.[44] mp 69.4 °C); and di-*tert*-butyl nitroxide (Eastman Organic Chemicals), bp 74-75 °C (35 mm) (lit.[45] mp 73-75 °C (35 mm)) were distilled before use.

Procedure for the Reaction of Aryl Iodides with PAT. Mixtures of an aryl iodide (14.8 mmol), carbon tetrachloride (10.4 mmol), and phenylazotriphenylmethane (PAT) (2.1×10^{-1} mmol) were placed in Pyrex ampules that were degassed, sealed, and thermostated at 60 ± 0.1 °C for 18 h. The reaction mixtures were cooled (-80 °C), the ampules opened, and the samples subjected to analysis by GLC (with either a $^1/_8$ in. × 10 ft, 20% FFAP on Chromosorb PAW 60-80 mesh stainless steel column or a $^1/_8$ in. × 20 ft, 3% OV-101 on Chromosorb WAW/DMCS 80-100 mesh stainless steel column). The relative concentrations of products were calculated from the integrated (HP 5840A integrator) GLC area ratios of the products by using a calibration factor determined from known mixtures of authentic materials.

Reaction of Iodonium Salts with Sodium Phenoxide and Sodium 2,6-Di-*tert*-butylphenoxide. Aqueous solutions of the iodonium salts (5×10^{-4} M) and the appropriate sodium phenoxide (5×10^{-4} M), prepared by mixing equimolar amounts of sodium hydroxide and the phenol, were placed in Pyrex ampules that were degassed, sealed, and thermostated at 60.0 ± 1 °C for 36-100 h, depending on a given substrate's proclivity to reaction.

The ampules were cooled (-80 °C) and opened, and the product mixture was dissolved in acetonitrile containing standard amounts of 1,2,4,5-tetramethylbenzene.

Quantitative analysis of the reaction mixtures was carried out by HPLC with a Perkin-Elmer Series 2 chromatograph fitted with a Waters RCM-100 Radical-Pak compressor and a C_{18} reverse-phase radial-Pak compressor and a C_{18} reverse-phase radial-pak column or a C_8 reverse-phase radial-pak column, with a 50:50 water to acetonitrile solvent mixture. A Perkin-Elmer LC-55B UV detector was used. The relative concentrations of products were calculated from the integrated (HP 3380A integrator) area ratios to the products with use of a calibration factor determined from known mixtures of authentic materials.

Reaction of Iodonium Salts with Di-*tert*-butyl Nitroxide. Aqueous solutions of the iodonium salt (0.2 M) and di-*tert*-butyl nitroxide (0.1 M) were placed in Pyrex ampules that were degassed, sealed, and thermostated at 60 ± 0.1 °C for periods ranging from 18 to 60 h. For reactions requiring light, a 500-W incandescent lamp was used to irradiate the reaction mixtures.

The ampules were cooled (-80 °C) and opened, and the mixture was dissolved in acetonitrile containing standard amounts of 1,2,4,5-tetramethylbenzene. The relative concentrations of products were calculated from the integrated (HP 3380A integrator) area ratios of the products and standard with use of a calibration factor determined from known mixtures of authentic materials.

Acknowledgment. We thank the National Research Council of Canada and the University of Alberta for their generous support of this work. We also thank Professor J. Hooz for suggesting that the reduction by phenylate anion might be an alternate method of generating the 9-I-2 intermediate.

Registry No. *m*-$O_2NC_6H_4I$, 645-00-1; *p*-$O_2NC_6H_4I$, 636-98-6; *p*-NCC_6H_4I, 3058-39-7; *m*-BrC_6H_4I, 591-18-4; *m*-$CH_3COC_6H_4I$, 14452-30-3; *p*-BrC_6H_4I, 589-87-7; *m*-$CH_3OC_6H_4I$, 766-85-8; *m*-$CH_3C_6H_4I$, 625-95-6; *p*-$C_6H_5C_6H_4I$, 1591-31-7; *p*-$CH_3C_6H_4I$, 624-31-7; *p*-$CH_3OC_6H_4I$, 696-62-8; *m*-NCC_6H_4I, 69113-59-3; *p*-$OHCC_6H_4I$, 15164-44-0; *m*-$F_3CC_6H_4I$, 401-81-0; *m*-$OHCC_6H_4I$, 696-41-3; *m*-$CH_3OCOC_6H_4I$, 618-91-7; *p*-$CH_3OCOC_6H_4I$, 619-44-3; *p*-$CH_3COC_6H_4I$, 13329-40-3; *m*-$H_2NC_6H_4I$, 626-01-7; *p*-$H_2NC_6H_4I$, 540-37-4; *p*-$CH_3C_6H_4I^+Ph\cdot Cl^-$, 56530-34-8; *m*-$O_2NC_6H_4I^+Ph\cdot Br^-$, 23351-89-5; *m*-$CH_3C_6H_4I^+Ph\cdot Cl^-$, 81447-67-8; *m*-$CH_3OC_6H_4I^+Ph\cdot I^-$, 81447-68-9; *p*-$BrC_6H_4I^+Ph\cdot Br^-$, 59696-27-4; *m*-$OHCC_6H_4I^+Ph\cdot I^-$, 81447-69-0; *m*-$NCC_6H_4I^+Ph\cdot I^-$, 81447-70-3; *m*-$BrC_6H_4I^+Ph\cdot I^-$, 81447-71-7; *m*-$F_3CC_6H_4I^+Ph\cdot I^-$, 81447-72-5; *p*-$CH_3OC_6H_4I^+Ph\cdot Br^-$, 2665-61-4; *p*-$NCC_6H_4I^+Ph$, 81447-73-6; *p*-$O_2NC_6H_4I^+Ph$, 46734-23-0; phenyl radical, 2396-01-2; sodium 2,6-di-*tert*-butylphenoxide, 7175-96-4; sodium phenoxide, 139-02-6; di-*tert*-butyl nitroxide, 2406-25-9.

(41) C. Willgerodt and P. Lenino, *J. Prakt. Chem.*, **69**, 321 (1904).
(42) V. W. Allen and A. Kolliker, *Liebigs Ann. Chem.*, **227**, 110 (1885).
(43) J. Cappelli, *Gazz. Chim. Ital.*, **48**, ii, 107 (1918).
(44) E. Bamberger, *Ber. Dtsch. Chem. Ges.*, **36**, 2036 (1903).
(45) A. K. Hoffmann, A. M. Gelblum, and W. G. Hodgson, *J. Am. Chem. Soc.*, **86**, 639 (1964).

Stereoselective, Biogenetically Patterned Synthesis of (±)-Aplysistatin

James D. White,*[1] Takeshi Nishiguchi, and Richard W. Skeean

Contribution from the Department of Chemistry, Oregon State University, Corvallis, Oregon 97331. *Received December 3, 1981*

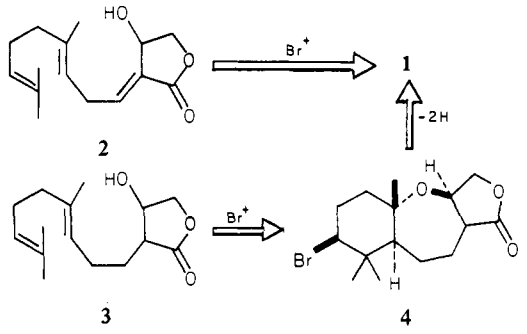
Abstract: A synthesis of (±)-aplysistatin (**1**) from geraniol is described, in which the key step is a biogenetically modeled cyclization of **24** to **26**. Methyl (*E*)-homogeranylacetate (**5c**) was converted to the tetronic acid **10c** via chloroacetylation of the derived ketene acetal **7c**, and **10c** was sulfenylated and reduced to give **24**. Cyclization of the latter with mercuric trifluoroacetate, followed by brominative substitution of mercury, yielded **26** with high stereoselectivity. Oxidation of **26** and thermal elimination of the sulfoxide **28** gave (±)-**1**.

The isolation of aplysistatin (**1**) by Pettit et al. from the sea hare *Aplysia angasi* brought to light a novel, brominated sesquiterpene skeleton (aplysistane) containing an oxepane ring.[2] Interest in **1** was further heightened by the report that it shows significant inhibition of murine lymphocytic leukemia, with a T/C of 175 at 400 mg/kg in the National Cancer Institute's P-388 screen.[3]

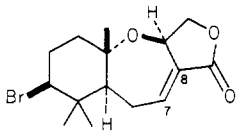
(1) National Institutes of Health Research Career Development Awardee, 1976-1981.
(2) Pettit, G. R.; Herald, C. L.; Allen, M. S.; Von Dreele, R. P.; Vanell, L. D.; Kao, J. P. Y.; Blake, W. *J. Am. Chem. Soc.* **1977**, *99*, 262.
(3) Pettit, G. R.; Herald, C. L.; Judd, G. F.; Bolliger, G.; Thayer, P. S. *J. Pharm. Sci.* **1975**, *64*, 2023.

0002-7863/82/1504-3923$01.25/0

Scheme I



The structure and relative configuration of aplysistatin was established by X-ray crystallographic analysis and revealed that, in addition to the 1-bromo-2,2,4-trimethylcyclohexane moiety common to numerous other marine metabolites,[4] **1** also contained an exo α,β-unsaturated γ-lactone.[5] Recently, Hoye and Kurth described a total synthesis of (±)-aplysistatin, in which construction of the A and B rings was accomplished via mercuric ion-catalyzed cyclization of an acyclic dienol, followed by replacement of the mercury substitutent with bromine.[6]



1

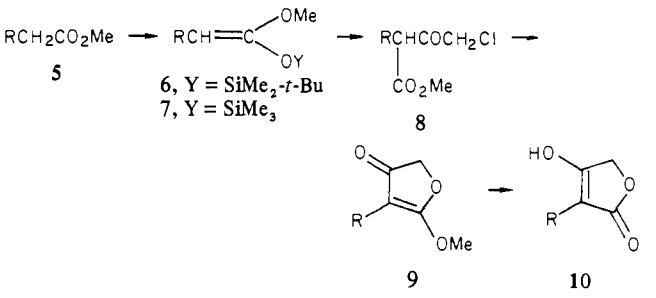
Biogenetic reasoning suggests that **1** arises in nature by means of a "brominative cyclization" of a dienol precursor, e.g., **2** or **3**, in which bromonium ion (or a biological equivalent) serves as the initiating electrophile. The ensuing cyclization, especially its stereochemical outcome, has extensive precedent in the studies of Lewis acid catalyzed polyolefin cyclizations.[7] In practice, attempts to bring about in vitro brominative cyclization of substances analogous to **2** or **3** have led to diasppointing results, with optimized yields no better than ca. 20%.[8] The alternative, indirect incorporation of bromine, exemplified by the tandem mercuration–bromination of Hoye, appears to be somewhat superior and has the advantage of permitting stereospecific synthesis of either equatorial or axial bromide.[9]

In order to provide a firm basis for comparing methods of brominative cyclization, both direct and indirect, we undertook a study of this transformation on a single substrate, intending that this conversion should provide the cornerstone for an improved synthesis of aplysistatin. Of the two options represented in Scheme I, that depicted as **3** → **4** → **1** appeared to be the more practicable. This, however, assumed that a convenient means for introduction of the 7,8 double bond after cyclization could be found. We describe herein a synthesis of (±)-**1**, based upon cyclization of a reduced homogeranyltetronic acid system similar to **3**, from which the four chiral centers emerge in a highly stereoselective fashion. In addition, the 7,8 double bond of aplysistatin is introduced regiospecifically.

Results

Tetronic Acid Synthesis. Our planned approach to a substrate for brominative cyclization was based on the supposition that a 2-homogeranyl-3-hydroxy γ-lactone similar to **3** would be accessible from the corresponding 2-alkyltetronic acid. However, although numerous methods exist for the preparation of tetronic acids,[10] none appeared well suited to the case at hand. We therefore set out to devise a new method for the synthesis of 2-alkyltetronic acids which could be adapted to our plan for aplysistatin.[11]

Scheme II



a, R = $PhCH_2$; b, R = $Me_2C{=}CHCH_2CH_2C(Me){=}CHCH_2$; c, R = $Me_2C{=}CHCH_2CH_2C(Me){=}CHCH_2CH_2$

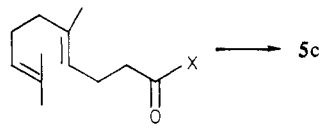
A report by Rathke and Sullivan that (*tert*-butyldimethylsilyl)ketene acetals (**6**), prepared from acetic esters (**5**), undergo acylation to yield β-keto esters[12] suggested that an analogous acylation with α-chloroacetyl chloride could lead to a tetronic acid (Scheme II). However, when the (*tert*-butyldimethylsilyl)ketene acetal **6a**, derived from methyl 3-phenylpropanoate (**5a**), was treated with either acetyl chloride or α-chloroacetyl chloride, no tractable product could be obtained. On the other hand, when the (trimethylsilyl)ketene acetal **7a**, prepared from **5a** by the procedure of Ainsworth,[13] was exposed to α-chloroacetyl chloride in the presence of triethylamine, smooth acylation occurred to give the unstable chloro ketone **8a** in good yield. The disadvantage which accrues from contamination of **7a** by a small quantity of the C-silylated ester (<5%) is compensated by the fact that lithium diisopropylamide in THF can be used for the preparation of **7** as contrasted with lithium isopropylcyclohexylamide in HMPA needed for **6**. The failure of **6a** to undergo acylation may perhaps be ascribed to steric impediments (the successful cases reported by Rathke and Sullivan were less hindered),[14] but this point was not confirmed.

As expected, the γ-chloro β-keto ester **8a** underwent elimination in triethylamine in benzene at reflux to give the dihydrofuranone **9a**.[15] The latter, upon hydrolysis in sulfuric acid, yielded the tetronic acid **10a** which, from the broad band at ca. 2500 cm^{-1} and a carbonyl stretching frequency of 1740 cm^{-1} in its infrared spectrum, was judged to consist predominantly of the enol tautomer.

A similar sequence starting from methyl geranylacetate **5b** was carried forward to tetronic acid **10b**, in this case by using 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) for conversion of **8b** to **9b**. The ester **5b** was obtained from geranyl chloride (prepared from geometrically pure (*E*)-geraniol) by alkylation with diethyl sodiomalonate,[16] followed by saponification, decarboxylation to **11**, and esterification with diazomethane. Finally, the homologous ester **5c** was acquired by a photochemical Arndt–Eistert synthesis[17] from geranylacetic acid **11**, via the chloride **12** and diazo ketone **13**. Application of the sequence in Scheme II to **5c** led to the crystalline tetronic acid **10c** in 32% overall yield.

The tetronic acid synthesis exemplified in the preparation of **10a–c** has the virtue that it avoids reagents (Lewis acids, halogens)

(4) Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421 and references cited.
(5) The prevalence of this structural unit among cytotoxic sesquiterpenes has been noted (Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147).
(6) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065.
(7) Faulkner, D. J. *Pure Appl. Chem.* **1976**, *48*, 25.
(8) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978**, *43*, 3693.
(9) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461.
(10) Haynes, L. J.; Plimmer, J. R. *Q. Rev., Chem. Soc.* **1960**, *14*, 292.
(11) A synthesis of 2-alkyltetronic acids was reported while this work was in progress (Damon, R. E.; Luo, T.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, 2749).
(12) Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, 1297.
(13) Ainsworth, C.; Kuo, Y. *J. Organomet. Chem.* **1972**, *46*, 73.
(14) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.
(15) Mulholland, T. P. C.; Foster, R.; Haydock, D. B. *J. Chem. Soc., Perkin Trans. 1* 1972, 1225.
(16) Barnard, D.; Bateman, L. *J. Chem. Soc.* **1950**, 926.
(17) Bachmann, W. E.; Struve, W. S. *Org. React.* **1942**, *1*, 38.

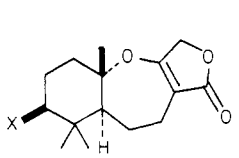


11, X = OH
12, X = Cl
13, X = CHN_2

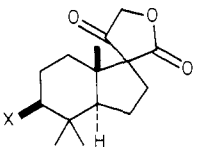
employed in alternative protocols[18] which could destroy the unsaturation in **10b** and **10c**. Moreover, the intermediate 4-alkyl-2,3-dihydrofuran-3-ones (**9**) are potentially valuable synthons, complementary to the O-methylation products formed from tetronic acids at the ketone oxygen.[19]

Cyclization Studies. With tetronic acid **10c** in hand, its conversion to a derivative suitable for transformation to aplysistatin was the next issue. At first, it was hoped that **10c** itself might serve this purpose, since brominative cyclization of the dominant enol tautomer was expected to lead to isoaplysistatin (**14**), from which **1** could perhaps be acquired by isomerization of the 8,12 double bond to the 7,8-position. Accordingly, cyclization of homogeranyltetronic acid **10c** was investigated under a variety of conditions.

The results summarized in Table I show that tricyclic products are formed in low yield from **10c** and that closure at C2 of the tetronic acid to give a spiroindan structure competes with cyclization to an oxepane. Unexpectedly, when **10c** was treated with bromine in the presence of either silver tetrafluoroborate or the hexafluorophosphate, no bromine-containing products were formed. The crystalline desbromoisoaplysistatin (**15**) was iden-



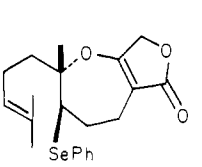
14, X = Br
15, X = H
17, X = SePh



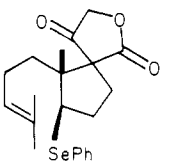
16, X = H
18, X = SePh
22, X = Br

tified from its infrared spectrum, which showed a carbonyl band at 1760 cm^{-1} and C=C stretching at 1675 cm^{-1}, and from its NMR spectrum, which displayed three methyl singlets (δ 0.80, 1.00, and 1.35) in close agreement with the corresponding signals observed for **1**. In contrast, the indan **16** exhibited two discrete carbonyl bands in its infrared spectrum and a group of three saturated methyl peaks in the NMR spectrum which did not include the downfield singlet observed with **15**. The failure to obtain brominated materials from these experiments implies that, in spite of the rigorously anhydrous conditions employed, proton-initiated cyclization supercedes closure mediated by the softer bromonium electrophile. The tetronic acid is assumed to be the proton source in this process.

Cyclization of **10c** in the presence of phenylselenyl hexafluorophosphate again afforded a mixture of oxepane **17** and spiroindan **18**,[20] but in this case, the selenium substitutent was incorporated into the two structures. As with **15**, the crystalline **17** was readily identified by spectral methods. A different mode of cyclization of **10c** took place with phenylselenyl chloride in the presence of triethylamine to give two products tentatively identified as the bicyclic compounds **19** and **20**. These structures, formed by selenium-initiated cyclization at the central double bond, are supported by means of their distinctive NMR spectra, which displayed two vinylic methyl groups and one saturated methyl signal in addition to a single olefinic proton. The cyclopentane **20** consisted of two stereoisomers, but configurational assignments



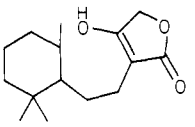
19



20

for these could not be adduced. The formation of **19** and **20** in relatively high yield (57%) upon the addition of triethylamine to the reaction medium could be due to alteration of the conformation of **10c** to one in which the central double bond is more exposed to electrophilic attack or, possibly, to a change in the structure of the electrophile.

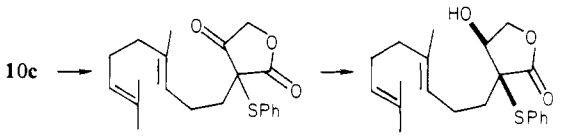
Attempts to effect cyclization of **10c** with mercuric trifluoroacetate appeared, at first, more promising.[21] Reduction of the resultant cycloalkylmercuric complex with sodium borohydride afforded a low yield of desbromoisoaplysistatin (**15**), which was accompanied by significant quantities of **21** in the reduction



21

mixture, indicating that cyclization had been interrupted after a single ring closure. However, when the mercury complex was exposed to bromine in the presence of potassium bromide, only the spiroindan **22** could be isolated.

At this juncture, there appeared to be clear advantage to a cyclization substrate in which the tetronic acid moiety was modified by the inclusion of a substitutent at C2. This substituent would not only prohibit the previously encountered cyclization at carbon but would also serve to isolate the ketone and lactone carbonyl groups, thereby permitting selective reduction of the former. However, the principal attribute to this plan was the prospect that the 7,8 double bond of **1** could be introduced by a direct, regioselective elimination after cyclization. The phenylthio substituent was selected for this purpose in the expectation that thermal elimination of the corresponding sulfoxide would be the final step of an aplysistatin synthesis. Accordingly, **10c** was reacted

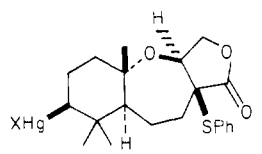


23 **24**

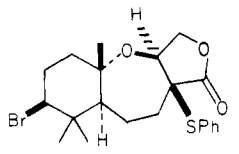
with *N*-thiophenylsuccinimide[22] in the presence of triethylamine to give **23** in 83% yield. Reduction of **23** with sodium borohydride in 2-propanol afforded the crystalline hydroxy lactone **24** as a single epimer in 79% yield. The configuration of this product is assumed to be as shown on the basis of a sterically determined approach by the hydride reagent from the side of the ketone opposite the bulky phenylthio substituent.

Guided by our experience with intramolecular oxymercuration in other systems[23] and by the studies of the Moscow group in this area,[21] we decided to investigate the cyclization of **24** by using the mecuric ion in nitromethane. This tactic was immediately rewarding, for both mercuric nitrate and the trifluoroacetate were found to give a cyclized mercuric complex **25a,b**. Upon treatment with aqueous potassium bromide, both of these yielded **25c**, which was promptly converted to the crystalline bromide **26** when reacted with bromine and lithium chloride in pyridine.[9] A minor, crystalline isomer **27** was also produced in this reaction (**26**:**27** = 3.6:1).

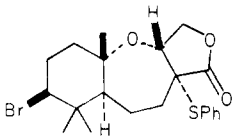
(18) Wegand, F.; Bestmann, H. J. *Angew. Chem.* **1960**, *72*, 535.
(19) Bloomer, J. L.; Kappler, F. E. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1485.
(20) Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1173.
(21) Kurbanov, M.; Semenovsky, A. V.; Smit, W. A.; Shmelev, L. V.; Kucherov, V. F. *Tetrahedron Lett.* **1972**, 2175.
(22) Behforouz, M.; Kerwood, J. E. *J. Org. Chem.* **1969**, *34*, 51.
(23) Sheldon, B. G. Ph.D. Dissertation, Oregon State University, 1981.



25a, X = NO_3
b, X = $OCOCF_3$
c, X = Br



26

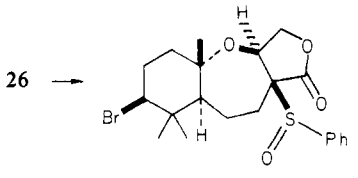


27

The results summarized in Table I indicate that, under optimal conditions, the isolated yield of pure **26** is ca. 23% via the mercuration–bromination route. Attempts to effect direct brominative cyclization of **24** by treatment with a variety of brominating systems, including 2,4,4′,6-tetrabromocyclohexadienone,[24] were without success.

Although our expectation, based upon a conformational analysis of **24** and the analogous Lewis acid catalyzed polyolefin cyclizations, was for a product with the stereochemistry of **26**, this point was not established unambiguously until the latter was converted to aplysistatin. However, it was clear from the absence of olefinic protons and a hydroxyl group in **26**, as well as the appearance of three sharp methyl singlets (δ 1.00, 1.20, and 1.46), that a fully cyclic structure had been produced. In addition, the chemical shift of the C*H*Br proton (δ 3.86 (double doublet)) was in good agreement with an axial orientation and hence an equatorial bromine substituent.[25] With this prerequisite, the favored conformation for **26** is that shown in Figure 1 and, in accord with this, the C11 and C12 hydrogens form an ABX triad having J_{AB} = 10 Hz, J_{AX} = 7.5 Hz, and J_{BX} = 8.5 Hz. These couplings agree with predicted values on the basis of dihedral angles estimated from a Dreiding model of **26**.[26]

Oxidation of **26** with *m*-chloroperbenzoic acid in dichloromethane afforded the crystalline sulfoxide **28** in quantitative yield. The latter, upon heating in benzene at reflux, gave (±)-aplysistatin (**1**, 68%), which was in all respects identical with a sample of (±)-**1** provided by Professor Hoye. *rac*-**1**, in turn, has been correlated with natural aplysistatin isolated by Pettit et al.[2] This identification not only confirmed that the cyclization of **24** had followed the anticipated trans,anti stereochemical pathway but also demonstrated that an electrophilically initiated polyolefin cyclization can proceed with reasonable efficiency (and high stereoselectivity) in the presence of potentially interfering groups such as hydroxyl and sulfide. This assumes particular significance in the context of in vivo olefin cyclization where, in certain instances, functionalization of the acyclic, isoprenoid precursor probably occurs prior to the enzyme-mediated ring closure.



28

In summary, the direct brominative cyclization route to aplysistatin remains an elusive goal, and thus a true biomimetic synthesis must await either a superior brominating system or a substrate of improved design. In the meantime, the tandem process of mercurative cyclization, followed by bromination, as exemplified in Hoyes synthesis and our own, remains a viable alternative.[27]

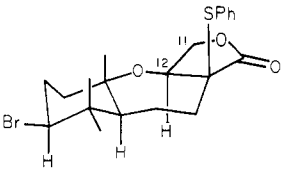


Figure 1. Conformation of **26**.

Experimental Section

General Data. Melting points were determined on a Büchi capillary melting point apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were obtained with a Perkin-Elmer 137 or 727B spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian EM-360A, HA-100, or FT-80A spectrometer; chemical shifts are reported in parts per million downfield from tetramethylsilane as internal standard (δ = 0). Coupling constants (J) are given in hertz with the following abbreviations for splitting patterns: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Exact mass determinations were made by using a CEC-110B spectrometer by the peak match technique. All thin-layer chromatography (TLC) was performed on Merck precoated silica plates (60F-254). Triethylamine, pyridine, and diisopropylamine were dried by distillation from barium oxide. Ether and tetrahydrofuran were dried by distillation from sodium benzophenone ketyl. Methylene chloride and pentane were washed with sulfuric acid followed by water and then distilled from phosphorus pentoxide. Unless otherwise noted, organic solutions resulting from workup of reaction mixtures were dried by being stirred briefly over anhydrous magnesium sulfate and then filtered.

1-Methoxy-1-(trimethylsiloxy)-3-phenyl-1-propene (7a). To a flame-dried, 25-mL two-neck flask equipped with a magnetic stirrer and addition funnel and swept with nitrogen was added dry tetrahydrofuran (7.5 mL) followed by *n*-butyllithium (0.45 mL of 2.4 M solution in hexane, 1.1 mmol). The resultant solution was cooled by being stirred in an ice bath, and dry diisopropylamine (0.15 mL, 110 mg, 1.1 mmol) was added dropwise. After addition was complete, the mixture was stirred at 0 °C for 10 min and the ice-bath was replaced with a bath of Dry Ice–acetone. The mixture was stirred for 5 min and methyl hydrocinnamate (**5a**, 164 mg, 0.01 mmol) was added dropwise. The solution was stirred at −70 °C for 0.5 h, and trimethylchlorosilane (2.5 mL, 25 mmol) was added dropwise. The mixture was stirred briefly at − 70 °C and at room temperature for 0.5 h and was diluted with an equal volume of dry pentane. The mixture was filtered and evaporated at reduced pressure, and the residue was taken up in pentane, filtered, and evaporated again. The residue was distilled in vacuo to give **7a** (184 mg, 88%): bp 69–79 °C (0.6 torr); IR (film) 2970, 2940, 2860, 1680, 750, 700 cm^{-1}; NMR (CCl_4) δ 0.35 (9 H, 2s), 3.75 (3 H, s), 3.0–4.2 (3 H, m), 7.4 (5 H, br s).

Methyl 2-(Chloroacetyl)-3-phenylpropanoate (8a). To a stirred solution of chloroacetyl chloride (0.35 mL, 0.49 g, 4.3 mmol) in dry tetrahydrofuran (5 mL) cooled in an ice bath under nitrogen was added **7a** (1.00 g, 4.3 mmol). The resultant mixture was stirred at room temperature for 17 h, diluted with ether (10 mL), and washed with two 10-mL portions of water. The organic layer was dried and evaporated, and the crude product was chromatographed (Activity II silica gel, elution with 10–50% ether–petroleum ether) to give **8a** (0.90 g, 87%): NMR ($CDCl_3$) δ 3.2 (2 H, d), 3.7 (3 H, s), 4.1 (2 H, d), 7.25 (5 H, s); mass spectrum, m/z 240 (M^+). This unstable material was converted promptly to **10a**.

3-Benzyl-4-hydroxyfuran-2(5*H*)-one (10a). A solution of triethylamine (440 μL) and **8a** (240 mg, 1.0 mmol) in dry benzene (3.5 mL) was refluxed for 20 h. The benzene and excess triethylamine were removed at reduced pressure, and 50% aqueous methanol (5 mL) was added. This solution was stirred for 12 h at room temperature, and most of the methanol was removed under reduced pressure. The aqueous solution was acidified with 4 N sulfuric acid (2 mL) and extracted with ethyl acetate (5 mL). The organic extract was dried (Na_2SO_4) and evaporated to give 170 mg of crude **10a**. This was triturated with ether to give 90 mg (43%) of virtually pure **10a** as an amorphous solid: IR (Nujol) 3300–2000, 1740, 1650 (br) cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 3.5 (2 H, s), 4.55 (2 H, s), 7.25 (5 H, s); mass spectrum, m/z 190.063 (M^+, calcd for $C_{11}H_{10}O_3$ 190.063). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.19; H, 5.24.

(24) Kato, T.; Ishii, K.; Ichinose, I.; Nakai, Y.; Kumagai, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1106.

(25) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance in Organic Chemistry"; Pergamon Press: Oxford, United Kingdon 1969; p 239.

(26) Reference 25, pp 281–282.

(27) Hoye, T. R.; Caruso, A. J.; Dellaria, J. F.; Kurth, M. J. *J. Am. Chem. Soc.*, in press.

Table I. Cyclization Studies of 10c and 24

compd	reagent	no. of equiv	solvent	reaction time, h	reaction temp, °C	product(s) (yield, %)
10c	$Hg(OCOCF_3)_2$[a]	1.2	CH_3NO_2	2.0	25	**15** (13), **21** (28)
10c	$PhSeCl/AgPF_6$	1.0/1.0	CH_2Cl_2	0.33	−78	**17** (10), **18** (15)
10c	$PhSeCl/Et_3N$	1.0/1.0	CH_2Cl_2	1.0	0	**19** (20), **20** (37)[b]
24	$HgNO_3$[c]	1.05	CH_3NO_2	1.0	0	**26** (18)
24	$Hg(OCOCF_3)_2$[c]	1.1	CH_3NO_2	2.0	0	**26** (23)[d]

[a] Followed by $NaBH_4$ (4 equiv) in MeOH–NaOH. [b] This substance was a mixture of two stereoisomers. [c] Followed by aqueous KBr (excess), LiBr (2 equiv), and Br_2 (1.5 equiv) in pyridine saturated with O_2. [d] In addition, 6% of **27** was isolated.

Methyl 2-(Chloroacetyl)-5,9-dimethyldeca-4,8-dienoate (8b). To dry tetrahydrofuran (30 mL) containing *n*-butyllithium (22.2 mL of a 1.6 M solution in hexane, 35.5 mmol) cooled in an ice bath under nitrogen was added dry diisopropylamine (4.97 mL, 35.5 mmol), and the mixture was stirred at 0 °C for 10 min. The solution was then cooled in Dry Ice–acetone and methyl 5,9-dimethyldeca-4,8-dienoate (**5b**; 6.86 g, 32.2 mmol) was added dropwise with stirring. After the mixture had been stirred for 0.5 h, trimethylchlorosilane (8.0 mL, 63 mmol) was added and the mixture was stirred briefly at −78 °C and then at room temperature for 0.5 h. The solution was diluted with an equal volume of pentane and filtered, and the filtrate was evaporated at reduced pressure. This cycle was repeated once more, the residue was taken up into dry tetrahydrofuran (30 mL), and the solution (under nitrogen) was cooled in an ice–salt bath. Triethylamine (4.5 mL, 32.2 mmol) followed by chloroacetyl chloride (2.45 mL, 32.2 mmol) was added to the mixture, and the resulting brown suspension was stirred for 20 h. The mixture was diluted with ether (40 mL) and washed twice with 40-mL portions of water. The organic layer was separated, dried, and evaporated, and the residue was chromatographed on 150 g of silica gel (Activity II). Elution with ether–hexane (1:9) gave 4.30 g (45%) of **8b** as a colorless oil: IR (film) 1740 (br) cm^{-1}; NMR (CCl_4) δ 1.60 (3 H, s), 1.65 (3 H, s), 1.69 (3 H, s), 2.01 (4 H, m), 2.57 (2 H, t, J = 7 Hz), 3.73 (3 H, s), 4.13 (2 H, s), 4.64 (1 H, m), 5.05 (2 H, broadened t, J = 7 Hz). This unstable compound was promptly converted to **10b**.

3-(3,7-Dimethylocta-2,6-dienyl)-4-hydroxyfuran-2(5*H*)-one (10b). To a solution of **8b** (4.26 g, 14.8 mmol) in dry benzene (60 mL) under nitrogen was added 1,5-diazabicyclo[5.4.0]undec-5-ene (2.37 mL, 15.8 mmol), and the mixture was stirred at room temperature for 20 h. During this time the solution turned brown and colorless crystals separated. The mixture was filtered, the filtrate was evaporated under reduced pressure, and the residue was taken up into methanol (60 mL). The solution was acidified with 1 N hydrochloric acid (4 mL), stirred for 4 h, and then concentrated to a small volume. Water (5 mL) and ether (60 mL) were added to the residue, the ether layer was separated and dried, and the solvent was evaporated. The residue was recrystallized several times from nitromethane to give 0.73 g (21%) of **10b**: mp 63–64 °C; IR (Nujol) 3050 (br), 1720, 1650 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.62 (3 H, s), 1.68 (3 H, s), 1.72 (3 H, s), 2.10 (4 H, m), 2.96 (2 H, d, J = 8 Hz), 4.67 (2 H, s), 5.10 (1 H, broadened t, J = 7 Hz), 5.31 (1 H, broadened t, J = 7 Hz), 10.43 (1 H, br); mass spectrum m/z 236.314 (M^+, calcd for $C_{14}H_{20}O_3$ 236.314).

5,9-Dimethyldeca-4,8-dienoic Acid (Geranylacetic Acid, 11). To a stirred solution of diethyl geranylmalonate[16] (40.0 g, 0.13 mol) in anhydrous ethanol (200 mL) was added sodium hydroxide (10.8 g, 0.27 mol). The mixture was refluxed for 2 h, the ethanol was evaporated under reduced pressure, and the residue was dissolved in the minimum amount of water. The aqueous solution was washed twice with equal volumes of ether and acidified with concentrated hydrochloric acid. The organic layer was washed with water, dried, and evaporated, and the residue was heated at 150–160 °C for 0.5 h. Distillation at 125–135 °C (0.8 torr) gave 20.5 g (77%) of **11**: NMR ($CDCl_3$) δ 1.60 (6 H, s), 1.65 (3 H, s), 1.98 (4 H, br s), 2.35 (4 H, br s), 4.6–5.3 (2 H, m), 10.9 (1 H, br s); mass spectrum, m/z 196 (M^+).

Methyl 6,10-Dimethylundeca-5,9-dienoate (5c). To a solution of **11** (10.00 g, 0.05 mol) in 50 mL of dry benzene was added oxalyl chloride (10 mL, 14.50 g, 0.11 mol). The mixture was stirred for 20 min, at which point gas evolution had ceased. The benzene was evaporated at reduced pressure, and the crude product was shown by IR spectroscopy to be free of carboxylic acid. This material was used without purification.

To a gently stirred, ice-cold ether solution of diazomethane (0.15 mol), prepared from 25 g of nitrosomethylurea, was added the crude geranylacetyl chloride in 125 mL of dry ether during 0.5 h. After addition was complete, the ice bath was removed and the solution was stirred at room temperature for 4 h. The ether was evaporated at reduced pressure, and the residue was dissolved in anhydrous methanol (130 mL). This solution was irradiated with a Hanovia 450-W mercury lamp through Pyrex glass for 3 h. After the methanol was removed, the crude product was chromatographed on 100 g of silica gel (Activity II). Elution with 5% ether in petroleum ether gave 8.90 g (80%) of **5c**: IR (film) 1740 cm^{-1}; NMR (CCl_4) δ 1.58 (6 H, s), 1.66 (3 H, s), 1.3–2.4 (10 H, br m), 3.59 (3 H, s), 4.6–5.3 (2 H, m); mass spectrum, m/z 224.178 (M^+, calcd for $C_{14}H_{24}O_2$ 224.178).

(*E*)-1-Methoxy-1-(trimethylsiloxy)-6,10-dimethylundeca-1,5,9-triene (7c). To a flame-dried, 50-mL three-neck flask equipped with a magnetic stirrer and addition funnel and swept with nitrogen was added dry tetrahydrofuran (25 mL), followed by butyllithium (13 mL of a 2.4 M solution in hexane, 31 mmol). The solution was cooled in an ice bath, and dry diisopropylamine (4.4 mL, 3.20 g, 32 mmol) was added dropwise with stirring. After addition was complete (ca. 10 min), the solution was stirred in a Dry Ice–acetone bath for 0.5 h and **5c** (6.32 g, 28.2 mmol) was added dropwise. The mixture was stirred at −78 °C for 0.5 h, and trimethylchlorosilane (7 mL, 55 mmol) was added dropwise. The solution was stirred briefly at Dry Ice temperature and then at room temperature for 0.5 h, after which it was diluted with an equal volume of dry pentane and filtered. The solution was evaporated at reduced pressure, and the residue again was taken up in pentane, filtered, and evaporated to give 8.86 g of crude unstable **7c**. This material was used without further purification.

Methyl 2-(Chloroacetyl)-6,10-dimethylundeca-5,9-dienoate (8c). Crude **7c** (8.86 g) from the previous reaction was dissolved in dry tetrahydrofuran (25 mL), and the cooled solution was stirred in an ice–salt bath and swept with nitrogen. Triethylamine (6.0 mL, 4.40 g, 43 mmol) was added, followed by chloroacetyl chloride (3.4 mL, 4.8 g, 42 mmol), and the brown suspension was stirred for 18 h. The mixture was diluted with ether (50 mL) and washed twice with 50-mL portions of water. The organic layer was separated, dried, and evaporated, leaving 10 g of a crude residue which was submitted to rapid chromatography on silica gel (40–63 μm, 200 g). Elution with hexane–ethyl acetate (10:1) gave 4.43 g (52%) of **8c**: NMR (CCl_4) δ 1.49 (6 H, s), 1.55 (3 H, s), 1.95 (8 H, br s), 3.6 (3 H, s), 4.15 (2 H, s), 4.5–5.4 (2 H, m). This material was converted promptly to **10c**.

3-(4,8-Dimethylnona-3,7-dienyl)-4-hydroxyfuran-2(5*H*)-one (10c). To a solution of **8c** (5.60 g, 18.7 mmol) in dry benzene (100 mL) under nitrogen was added 1,5-diazabicyclo[5.4.0]undec-5-ene (3.9 mL, 3.10 g, 20 mmol), and the brown mixture was stirred for 12 h. The colorless crystals which separated were filtered off, and the filtrate was evaporated under reduced pressure to give a dark brown oil. This was taken up into methanol (100 mL), and the solution was acidified with 1 N hydrochloric acid (5 mL) and stirred for 4 h. The mixture was concentrated to a small volume, and water (5 mL) and ether (60 mL) were added. The ethereal layer was separated, dried, and concentrated to give a brown oil which was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1) yielded a semisolid which crystallized slowly from nitromethane to give 2.86 (61%) of **10c**: mp 95–96 °C; IR (Nujol) 2700 (br), 1720, 1660, 1600 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.61 (6 H, s), 1.71 (3 H, s), 2.04 (4 H, s), 2.30 (4 H, br s), 4.70 (2 H, s), 5.17 (2 H, m); mass spectrum, m/z 250.158 (M^+, calcd for $C_{15}H_{22}O_3$ 250.158). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.96; H, 8.86. Found: C, 71.35, H, 9.00.

$\Delta^{8(12)}$-Aplysistene (15). Method A. Reductive Cyclization of 10c with Mercuric Trifluoroacetate. Mercuric trifluoroacetate (300 mg, 0.70 mmol) and **10c** (140 mg, 0.56 mmol) were mixed in nitromethane (1.5 mL) under nitrogen. The solution became warm and was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was taken up into methanol (1.5 mL). To this solution was added a 1 M solution of sodium borohydride in 10% aqueous sodium hydroxide (0.55 mL), and the mixture was left for 1 h at room temperature before dilution with ether (10 mL). The ethereal solution was separated, and the aqueous layer was acidified with hydrochloric acid and extracted with ether. The combined ether extract was dried, the solvent was evaporated, and the residue was chromatographed on silica gel. Elution with hexane–ether (1:1) gave a mixture of two compounds which was subjected to a second chromatography on silica gel. Elution with hexane–ether (2:1) gave a solid which, upon crystallization from hexane–acetone, afforded 18 mg (13%) of **15**: mp 89–90 °C; IR (Nujol)

1760, 1675 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s), 1.00 (3 H, s), 1.35 (3 H, s), 1.2–2.4 (9 H), 2.5 (1 H, m), 2.67 (1 H, m), 4.33 (2 H, s); mass spectrum, m/z 250 (M^+). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.54 H, 8.65.

Further elution of the chromatogram gave 39 mg (28%) of **21** which was recrystallized from hexane–acetone: double mp 125–127 °C and then 171–172° C; IR (Nujol) 3530, 1765 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (6 H, s), 0.95 (3 H, d, J = 6 Hz), 1.10–1.85 (9 H), 1.90–2.50 (5 H), 4.13 (2 H, ABq, J = 9 Hz); mass spectrum, m/z 252.175 (M^+, calcd for $C_{15}H_{24}O_3$ 252.174).

Method B. Cyclization of 10c with Bromine and Silver Hexafluorophosphate. To a suspension of silver hexafluorophosphate (50.6 mg, 0.2 mmol) in dichloromethane (0.5 mL) stirred at room temperature under argon was added bromine (32 mg, 10.3 μL, 0.2 mmol). The color of the mixture turned from red to light yellow during 0.5 h, and, after 1 h, the mixture was cooled in a Dry Ice–acetone bath and a solution of **10c** (50.1 mg, 0.2 mmol) in dichloromethane (1 mL) was added dropwise. The solution was left at −78 °C for 3 h, at 0 °C for 15 h, and then at room temperature for 5 h. Dichloromethane (10 mL), followed by water (5 mL), was added to the solution, the organic layer was separated and dried, and the solvent was evaporated. The residue was subjected to preparative TLC, eluting with hexane–ether (1:1), to give 3.5 mg (7%) of **15**, identical with material prepared by method A. In addition, there was isolated from the chromatogram 4.4 mg (9%) of **16** as an oil: IR (film) 1785, 1745 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (6 H, s), 0.94 (3 H, s), 1.0–2.1 (11 H), 4.40 (2 H, s); mass spectrum, m/z 250 (M^+).

3-(Phenylseleno)-$\Delta^{8(12)}$-aplysistene (17). Phenylselenyl chloride (38.3 mg, 0.2 mmol) and silver hexafluorophosphate (50.6 mg, 0.20 mmol) were mixed in dichloromethane under an argon atmosphere in the dark. After 20 min the mixture was cooled in a Dry Ice–acetone bath and a solution of **10c** (50.1 mg, 0.2 mmol) in dichloromethane (1 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h and at 0 °C for 1 h and was then diluted with dichloromethane (10 mL). The suspension was filtered and the filtrate was washed with saturated aqueous sodium bicarbonate, dried, and evaporated under reduced pressure. The residue was subjected to preparative TLC; elution with hexane–ether (1:1), followed by crystallization (twice) from hexane–acetone, gave 8.1 mg (10%) of **17**: mp 137–138 °C; IR (Nujol) 1760, 1678 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (3 H, s), 1.35 (6 H, s), 1.1–2.1 (9 H), 3.00 (1 H, m), 4.33 (2 H, s), 7.15–7.65 (5 H, m); mass spectrum, m/z 405 (M^+). Anal. Calcd for $C_{21}H_{26}O_3Se$: C, 62.22; H, 6.47. Found: C, 61.72; H, 6.31.

A second band from the chromatogram, after recrystallization from hexane–acetone, gave 11.8 mg (15%) of **18**: mp 119–121 °C; IR (Nujol) 1800, 1755 cm^{-1}; NMR ($CDCl_3$) δ 0.92, 1.10 (3 H, two s corresponding to two epimers, ca. 1:1), 0.98 (3 H, s), 1.25 (3 H, s), 1.3–2.5 (9 H), 2.78 (1 H, m), 4.35 (2 H, s), 7.1–7.6 (5 H, m); mass spectrum, m/z 405 (M^+). Anal. Calcd for $C_{21}H_{26}O_3Se$: C, 62.22; H, 6.47. Found: C, 61.71; H, 6.26.

Bromide 22. To a solution of **10c** (100 mg, 0.40 mmol) in nitromethane (5 mL) at 0 °C under nitorgen was added a solution of mercuric trifluoroacetate (179.1 mg, 0.42 mmol) in nitromethane (1.5 mL). After 1 h at 0 °C the solution was diluted with a saturated aqueous solution of potassium bromide (10 mL) and the mixture was stirred at room temperature for 20 h. The mixture was extracted with dichloromethane (20 mL), and the extract was evaporated under reduced pressure to leave a residue which, after being washed with a hexane–dichloromethane (1:1) mixture, gave 112 mg of a colorless solid. This material was taken up into pyridine (1 mL), to which was added lithium bromide (20.1 mg, 0.23 mmol) followed by bromine (36.8 mg, 11.9 μL, 0.23 mmol). The solution was stirred for 18 h under an oxygen atmosphere in the dark at room temperature and then was diluted with ether (15 mL). The ethereal layer was washed with 2 N hydrochloric acid, followed by saturated aqueous sodium bicarbonate and water, and dried. Evaporation of the solvent gave a dark residue which was subjected to preparative TLC. Elution with hexane–ethyl acetate (8:5) and crystallization from ether gave 5 mg (4%) of 22: mp 188–191 °C; IR (Nujol) 1790, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (3 H, s), 1.10 (3 H, s), 1.15 (3 H, s), 1.50 (2 H, m), 1.7–2.6 (7 H, m), 3.75 (1 H, dd, J = 10, 8 Hz), 4.40 (2 H, s); mass spectrum, m/z 328, 330 (1:1, M^+). Anal. Calcd for $C_{15}H_{21}BrO_3$: C, 54.72; H, 6.43. Found: C, 54.41; H, 6.23.

3-(Phenylthio)-3-(4,8-dimethylnona-3,7-dienyl)furan-2,4(5*H*)-dione (23). To a stirred solution of **10c** (0.63 g, 2.6 mmol) and *N*-(phenylthio)succinimide (0.60 g, 3.13 mmol) in 15 mL of dichloromethane at 0 °C was added dropwise triethylamine (0.32 g, 0.44 mL, 3.13 mmol). The solution was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was chromatographed on 10 g of silica gel (Activity II) and eluted with ethyl acetate–hexane (1:4) to give 0.77 g (83%) of **23** as a pale yellow oil: IR (film) 1800, 1760, 745, 680 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (3 H, s), 1.57 (3 H, s), 1.67 (3 H, s), 1.94 (4 H, m), 2.15 (4 H, m), 3.82, 4.21 (2 H, ABq, J = 17 Hz), 5.00 (2 H, m), 7.50 (5 H, m); mass spectrum, m/e 358.160 (M^+, calcd for $C_{21}H_{26}O_3S$ 358.159).

3-Hydroxy-2-(phenylthio)-2-(4,8-dimethylnona-3,7-dienyl)-γ-butyrolactone (24). To a stirred suspension of sodium borohydride (0.11 g, 2.94 mmol) in 2-propanol (40 mL) at 0 °C was added a solution of **23** (2.80 g, 7.8 mmol) in 2-propanol (30 mL). The mixture was stirred at 0 °C for 5 h, diluted with benzene–hexane (50 mL, 1:1), and washed with an aqueous solution of sodium chloride. The organic layer was dried and concentrated to a residue which was chromatographed on 70 g of silica gel (Activity II). Elution with hexane–ethyl acetate (3:1) gave 2.20 g (79%) of **24** as on oil: IR (film) 3450, 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (3 H, s), 1.61 (3 H, s), 1.64 (3 H, s), 1.95 (4 H, m), 2.21 (2 H, t, J = 8 Hz), 2.96 (OH, d, J = 6 Hz), 3.88 (1 H, dd, J = 10, 8 Hz), 4.28 (2 H, AB of ABX, J = 17, 10, 8 Hz), 5.02 (2 H, m), 7.15–7.55 (5 H, m); mass spectrum, m/e 360.178 (M^+, calcd for $C_{21}H_{28}O_3S$ 360.176).

3-Bromo-8-(phenylthio)aplysistane (26). To a solution of **24** (122 mg, 0.34 mmol) in dry nitromethane (2.5 mL) at 0 °C was added a solution of mercuric trifluoroacetate (159 mg, 0.37 mmol) in nitromethane (2 mL). The mixture was stirred for 2 h at 0 °C and concentrated to a volume of ca. 1 mL under reduced pressure at room temperature. The mixture was added to a saturated aqueous solution (10 mL) of potassium bromide and stirred for 15 h at room temperature in the dark. The resulting heterogeneous mixture was diluted with dichloromethane (15 mL), and the organic layer was separated, dried, and evaporated. The residue was taken up into dry pyridine (2 mL), and the solution under oxygen and in the dark was treated at room temperature with a solution of lithium bromide (59 mg, 0.68 mmol) and bromine (82 mg, 27 μL, 0.51 mmol) in pyridine (4 mL). After being left standing for 5 h, the solution was concentrated by removal of the pyridine under reduced pressure and the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (3:1) gave a mixture of **26** and **27** which were separated by fractional crystallization from ethanol, yielding 32.6 mg (22%) of **26**: mp 139–141 °C; IR (Nujol) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (3 H, s), 1.19 (3 H, s), 1.44 (3 H, s), 1.45–2.5 (9 H, m), 3.86 (1 H, dd, J = 12, 7 Hz), 4.05–4.55 (3 H, ABX, J = 10, 8.5, 7.5 Hz), 7.4 (5 H, m); mass spectrum, m/z 438, 440 (1:1, M^+). Anal. Calcd for $C_{21}H_{27}BrO_3S$: C, 57.40; H, 6.19; S 7.29. Found: C, 57.19; H, 5.90; S, 6.99.

In addition, 9.1 mg (7%) of **27** was obtained: mp 177.5–179 °C; IR (Nujol) 1775 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.24 (3 H, s), 1.32 (3 H, s), 1.6–2.7 (9 H, m), 4.06 (1 H, m), 4.1–4.65 (3 H, ABX m), 7.36 (5 H, m); mass spectrum, m/z 438, 440 (1:1, M^+).

(±)-Aplysistatin (1). To a solution of **26** (18.0 mg, 0.041 mmol) in dichloromethane (1 mL) cooled in an ice–salt bath was added dropwise a solution of *m*-chloroperbenzoic acid (7.2 mg, 0.042 mmol) in dichloromethane (1 mL) during 5 min. The cold solution was stirred for 2 h and poured into a mixture of ether (20 mL) and 10% aqueous sodium sulfite solution (5 mL). The organic layer was separated, washed twice with saturated aqueous sodium bicarbonate, dried, and evaporated to give 18 mg of virtually pure **28**. This material was taken up into benzene (3 mL) and was heated at reflux for 3 h. After removal of the solvent under reduced pressure, the residue was subjected to rapid chromatography on silica gel. Elution with hexane–ethyl acetate (3:1) gave 9.1 mg (68%) of a solid which, upon crystallization from ethanol, was identified as (±)-aplysistatin (**1**): mp 173.5–176 °C. Comparison of (±)-**1** with a sample provided by Professor Hoye by means of mixture mp showed no depression and TLC behavior of the two samples was identical in two solvent systems. In addition, IR and NMR spectra of the two mateirals corresponded in every detail. Comparison of IR and NMR spectra of (±)-**1** with those of naturally derived aplysistatin provided by Professor Pettit established the correspondence of racemic and optically active materials.

Acknowledgment. We are indebted to Professor Thomas R. Hoye, University of Minnesota, for a sample and spectra of (±)-aplysistatin and for a preprint of his publication. We are also grateful to Professor George R. Pettit, Arizona State University, for a sample of natural (−)-aplysistatin. Funds for support of this work were provided by the National Science Foundation (Grant CHE77-04379).

Registry No. (±)-**1**, 71883-79-9; **5a**, 101-41-7; **5b**, 19894-82-7; **5c**, 25644-70-6; **7a**, 57956-49-7; **7c**, 81790-40-1; (±)-**8a**, 81790-41-2; (±)-**8b**, 81790-42-3; (±)-**8c**, 81802-26-8; **10a**, 3734-22-3; **10b**, 81790-43-4; **10c**, 81790-44-5; **11**, 5579-63-5; **12**, 81790-45-6; (±)-**15**, 81802-27-9; **16**, 81790-46-7; (±)-**17**, 81790-47-8; (±)-**18**, isomer 1, 81790-48-9; (±)-**18**, isomer 2, 81844-68-0; (±)-**19**, 81790-49-0; (±)-**20**, isomer 1, 81790-50-3; (±)-**20**, isomer 2, 81844-69-1; **21**, 81790-51-4; **22**, 81790-52-5; (±)-**23**, 81790-53-6; (±)-**24**, 81790-54-7; (±)-**26**, 81844-70-4; (±)-**27**, 81844-71-5; (±)-**28**, 81790-55-8; chloroacetyl chloride, 79-04-9; diethyl geranylmalonate, 19894-79-2.