Two Syntheses of *dl*-Aplysistatin

Thomas R. Hoye,* Andrew J. Caruso, Joseph F. Dellaria, Jr.,[1a] and Mark J. Kurth[1b]

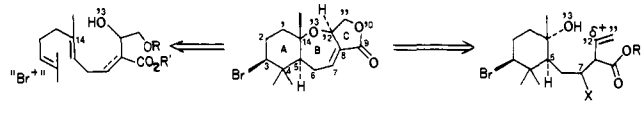
Contribution from the Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. *Received September 28, 1981*

Abstract: *dl*-Aplysistatin (**1**) was synthesized by two independent routes. The first (Scheme II) proceeded in seven steps and 4% yield from homogeraniol, utilized the mercuric ion mediated brominative cyclization of diene **2** as the key transformation, but lacked stereocontrol over the relationship between C_{12} and the A-ring stereocenters. The second synthesis (Scheme III) was achieved in eight steps and 31% yield from lactone **10**, involved the aldol reaction of *tert*-butyl crotonate enolate anion with a single face of the aldehyde derived from hemiacetal **11**, and allowed high 1,3-diastereoselectivity in the Hg(II)-induced cyclization of alcohols **20**. Difference NOE spectroscopy played an important role in the deduction of stereochemistry in lactones **24**.

In 1977 the isolation, structure determination, and antileukemic activity of the brominated sesquiterpene aplysistatin (**1**) were reported.[2] Three total syntheses have since been described.[3] We were intrigued by several of the molecule's structural features, including the A-ring neopentyl bromide, the unique heterocyclic skeleton, and the pair of 1,3-stereochemical relationships between C_3–C_5 and C_{14}–C_{12}, and describe here two syntheses of *dl*-aplysistatin (**1**) that represent various solutions to the problems posed by those molecular components. Each of these fundamentally different approaches has at its core the construction of the seven-membered oxepane ring (Scheme I). Our first synthesis,[3a] as well as those of the White[3b] and Prestwich[3c] groups, involves the closure of O_{13} onto C_{14} (see I) by way of a biomimetic mercuric (bromonium) ion initiated cyclization. This ensures the proper 1,3-stereorelationship between the centers at C_3 and C_5 when the substrate I is of *E*-olefin geometry but suffers from rather low yields in the actual cyclization reaction. Our second synthesis uses to advantage the ability to control transient stereochemistry at C_7 relative to C_5 (see II) and then to relay that information to C_{12} by imparting face selectivity in the attachment of O_{13} to the Δ^{11} olefin.

The first synthesis was begun with the construction of the diene alcohols **2** (Scheme II). The lithium enolate of methyl 1-(phenylthio)acetate was alkylated with the *p*-toluenesulfonate ester of homogeraniol (**3**) in dimethyl sulfoxide at room temperature (64%). The ester **4** was deprotonated with LDA, the enolate was added to a THF solution of zinc chloride at 0 °C, and 2-(benzyloxy)acetaldehyde[4] was added. The reaction was quenched after 10 min at 0 °C, and a separable 65:35 mixture of erythro and threo[5] diastereomeric β-hydroxy esters **2e** and **2t**[6] was obtained in 75% yield. Each of these isomers was subjected to a mercuric trifluoroacetate mediated brominative cyclization reaction.[7] Upon exposure to $Hg(TFA)_2$ in nitromethane followed by ligand exchange with aqueous KBr and bromination of the carbon–mercury bond with a $Br_2/LiBr/py/O_2$ concoction,[7] each diene alcohol isomer gave a nearly 1:1 mixture of diastereomeric, bicyclic ethers **5** in acceptable yield (**2e** → **5a**, 15%; **2e** → **5b**, 15%; **2t** → **5c**, 14%; **2t** → **5d**, 11%).[8] That the four isomers **5a–d** were all of homogeneous stereochemistry at the A-ring C_3, C_5, and C_{14} centers was suggested by the similar width at half-height for the C_{14}-methyl group[9] and further supported by the oxidation (MCPBA) and elimination (110 °C) of the phenyl sulfide from each isomer, which gave olefin **6** (from **5a** and **5c**) or **7** (from **5b** and **5d**). The stereorelationship between C_{12} and C_{14} in each of these olefins was not known until after conversion of **6** to aplysistatin (**1**). To achieve this end it was necessary to invoke an unorthodox removal of the benzyl ether protecting group since the usual reductive methods (H_2, Pd/C; H_2, Pd/C, BF_3·OEt_2, MeOH[10]) failed when applied to sulfides **5** (no reaction) or olefin **6** (double-bond saturation observed). Thus, **5a** was treated with 1 equiv of triphenylcarbenium fluoroborate[11] in deuteriochloroform, which presumably resulted in abstraction of a benzylic hydride ion and trapping by the adjacent carbomethoxy group to afford lactone **8**. Conversion of this sulfide to *dl*-aplysistatin (**1**) (MCPBA; 60 °C) provided the first synthetic sample of the natural product and the basis for assignment of stereochemistry to **5a–d**. The independent oxidative debenzylation of olefins **6** and **7** also provided *dl*-aplysistatin (**1**, 52%) and *dl*-12-epiaplysistatin (**9**, 75%), respectively.

Scheme I



The crucial cyclization of the diene alcohols **2** had served well in the role of establishing the entire A-ring functionality and stereochemistry. However, it had failed to provide any degree of selectivity in favor of the natural over the epi-C_{12} configuration. Therefore, we embarked on a second synthesis, summarized in

(1) (a) University of Minnesota Graduate School Dissertation Fellow 1980–1981. (b) Eastman Kodak Fellow 1979–1980.

(2) Pettit, G. R.; Herald, C. L.; Allen, M. S.; Von Dreele, R. B.; Vanell, L. D.; Kao, J. P. Y.; Blake, W. *J. Am. Chem. Soc.* **1977**, *99*, 262.

(3) (a) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065. (b) White, J. D.; Nishiguchi, T.; Skeean, R. W. *Ibid.* **1982**, *104*, 3923. (c) Shieh, H.-M.; Prestwich, G. *Tetrahedron Lett.*, in press.

(4) Rigby, W. *J. Chem. Soc.* **1950**, 1907.

(5) (a) Throughout this paper the terms erythro and threo are used to describe the stereorelationships between two sets of substituents, each of which has been ranked by their relative Cahn–Ingold–Prelog priorities, on vicinal chiral carbons. (b) **Note Added in Proof**: Under the Carey–Kuehne proposal erythro and threo would correspond to pref (priority reflective) and parf (priority antireflective), respectively. Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.

(6) The stereochemistry of **2e** and **2t** was determined by the trans elimination of the elements of PhSOH to form the *E* and *Z* olefins, respectively: Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1980**, *45*, 3549.

(7) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461.

(8) For the purpose of clarity the structures **5b** and **5d** are derived from the enantiomers of **2e** and **2t**, respectively. All compounds possessing chiral carbons were synthesized as their racemates in this work.

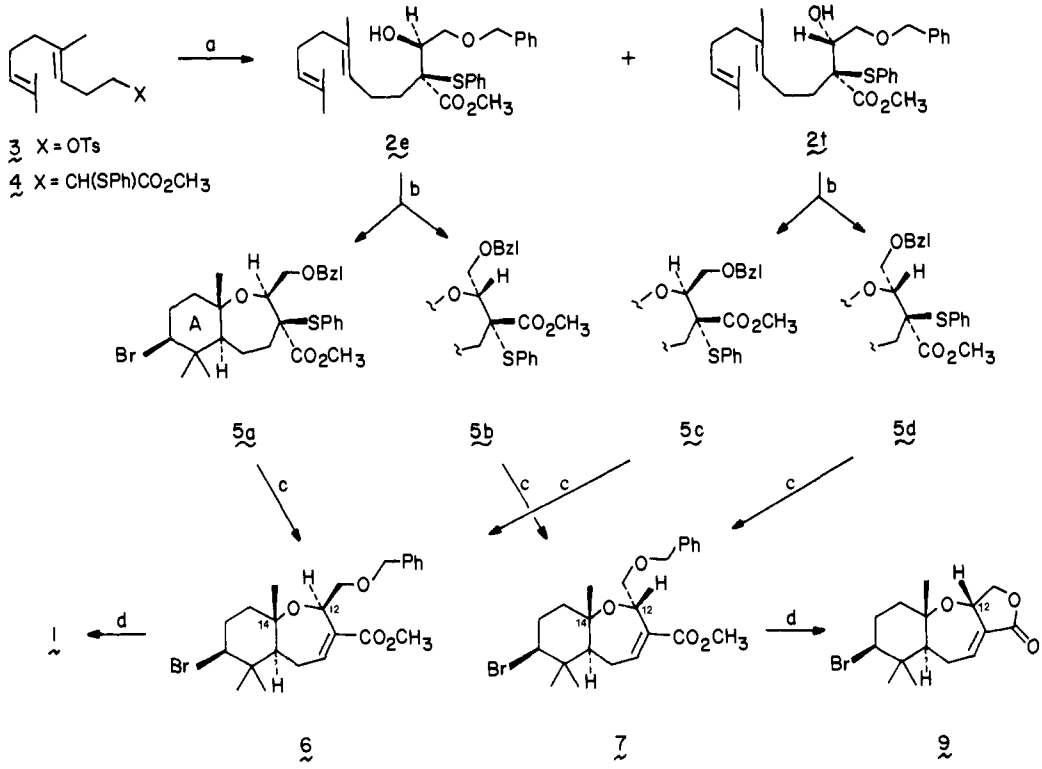
(9) We had observed (ref 7) a sharper methyl absorption for the cis-fused case in a bicyclic ether where both fusion isomers were available. Cf.: Williamson, K. C.; Howell, T.; Spencer, T. A. *J. Am. Chem. Soc.* **1966**, *88*, 325.

(10) Yajima, H.; Kawasake, K.; Kinomura, Y.; Oshima, T.; Kimoto, S.; Okamoto, M. *Chem. Pharm. Bull.* **1968**, *16*, 1342.

(11) (a) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542. (b) Hoye, T. R.; Kurth, M. J.; Lo, V. *Tetrahedron Lett.* **1981**, 815.

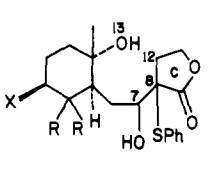
0002-7863/82/1504-6704$01.25/0

Scheme II

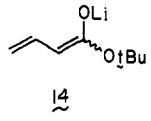


(a) LDA, THF, $ZnCl_2$; $PhCH_2OCH_2CHO$. (b) $Hg(TFA)_2$, CH_3NO_2; KBr; Br_2, O_2, LiBr, py. (c) MCPBA, $CHCl_3$; 110 °C, $PhCH_3$. (d) $Ph_3C^+BF_4^-$, $CHCl_3$.

Scheme III. Reduction of lactone **10**, which is available from homogeranic acid in 33% yield,[7] with DIBALH to the crystalline hemiacetals **11** was best effected in methylene chloride rather than toluene since ease of solvent removal minimized the sometimes extraordinarily efficient dimerization to **12**. An aldol reaction between **11** and the lithium enolate anion derived from α-(phenylthio)-γ-butyrolactone in the presence of $ZnCl_2$ afforded two (of four possible) β-hydroxylactones **13a** of undetermined stere-



	R	X
13g	Me	Br
13b	H	H
13c	Me	H

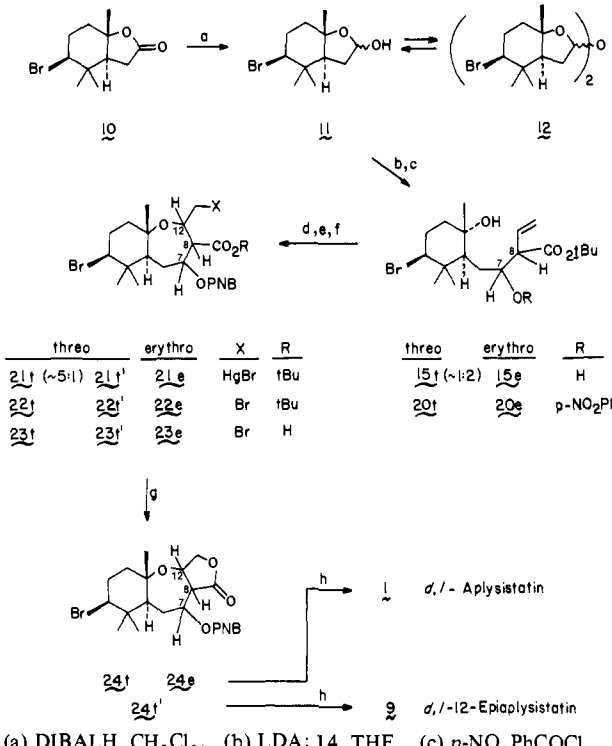


14

ochemistry in a 3.2:1 ratio and 59% yield. It was noted that these two isomers were epimeric at C_8 and not C_7 since oxidation of the sulfide to sulfoxide and elimination led to the same butenolide from each diastereomer.[12] However, all attempts to close O_{13} to C_{12} in this butenolide or its derivatives failed.

Attention was turned to the incorporation of a 3-butenoate unit, a seco C-ring butyrolactone equivalent, into hemiacetal **11**. Although the enolate derived from methyl crotonate (LDA–HMPA complex; −78 °C)[14] or methyl γ-bromocrotonate (Et_2AlCl, Zn, CuBr, THF, −20 °C)[15] could be added smoothly to benz-

Scheme III



threo	erythro	X	R
21t (~5:1)	21t'	21e	HgBr	tBu
22t	22t'	22e	Br	tBu
23t	23t'	23e	Br	H

threo	erythro	R
15t (~1:2)	15e	H
20t	20e	p-NO_2PhCO

(a) DIBALH, CH_2Cl_2. (b) LDA; 14, THF. (c) p-$NO_2PhCOCl$, DMAP, py, CH_2Cl_2. (d) $Hg(TFA)_2$, $EtNO_2$; KBr. (e) $pyHBr_3$, CH_2Cl_2. (f) TFA, CH_2Cl_2. (g) Et_3N (1.1 equiv), CH_3CN. (h) Et_3N (excess), CH_3CN.

aldehyde, each failed to react efficiently with **11**. In the former case small amounts of the desired aldols were observed, but self-consumption of the crotonate unit seemed to predominate.[14b] To thwart this problem, we deprotonated the *tert*-butyl ester of either 2- or 3-butenoic acid with lithium diisopropylamide to give

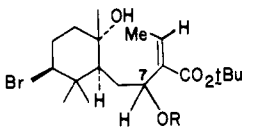
(12) Likewise, the aldol products **13b** and **13c** were formed as mixtures of only two diastereomers. The secondary alcohols in each of these mixtures were oxidized to the corresponding ketones, which again were diastereomeric pairs. On the other hand, removal of the center at C_8 by oxidative elimination of the sulfide provided a single isomer of the alcoholic butenolide. Other examples of reactions that displayed a significant degree of 1,3-diastereoselectivity by virtue of an addition to an sp^2-hybridized C_7 include catalytic hydrogenation of a C_7–C_8 olefin and Michael addition of PhSH to a C_7–C_8 enoate.[13]

(13) Caruso, A. J. Ph.D. Dissertation, University of Minnesota, Minneapolis, MN, 1980.

(14) (a) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433. (b) Rathke, M. W.; Sullivan, D. *Ibid.*, **1972**, 4249.

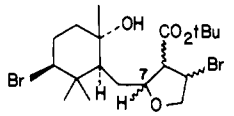
(15) Marouka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705.

14.[16] Little reaction of **14** with **11** (actually the lithium salt formed by titration with 1 equiv of LDA) was observed at −78 °C; substantial oligomerization of the *tert*-butyl ester dienolate competed with productive processes at room temperature; but at −23 °C the desired aldol adducts **15** were formed in 2 h and 83% yield based on 12% recovered **11**. Again only two of the four possible diastereomers were isolated. Their ratio after separation was ~1:1.5. In light of earlier observations[12] we operated under the assumption that the same face of the free aldehyde from **11** was being attacked by **14** and that, therefore, the two isomers were related in a threo/erythro[5] sense and were epimeric at C_8, not C_7 (**14** reacted with PhCHO at −78 °C to produce a nearly 1:1 ratio of the threo and erythro diasteromeric aldols). In support of this conclusion were the facts that (i) the chromatographically less polar (threo) and more polar (erythro) isomers of **15** exhibited coupling constants between H_7 and H_8 of 8 and 6 Hz, respectively,[17] and identical ^{13}C NMR spectra except for the signals assigned to C_7 and C_8, which are slightly deshielded in the faster (threo) isomer[18] (C_7: δ 73.8 vs. 73.0; C_8: δ 59.2 vs. 58.2) and (ii) in the presence of excess **14** and HMPA a significant byproduct, the conjugated enoate **16**, was formed as a *single ste-*

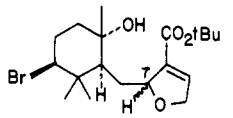


16 R=H

17 R= $SiPh_2Me$



18

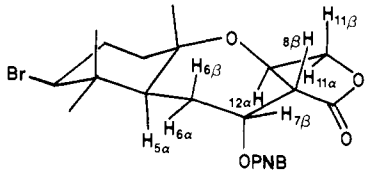


19

reoisomer and isolated as **17** after diphenylmethylsilation in 23% yield from **11**.

With presumed threo and erythro isomers **15t** and **15e** in hand, we investigated the latter's cyclization with mercuric ion. The free diol **15e** upon sequential treatment with $Hg(TFA)_2$ and pyridinium bromide perbromide ($pyHBr_3$) in nitromethane gave rise to the tetrahydrofuran **18** in which the secondary alcohol had preferentially trapped the mercuronium ion. Support for this structure came in the DBU-promoted elimination of HBr to give a single isomer of the dihydrofuran **19**. Thus it was necessary to protect the less hindered hydroxyl group in **15**. For various reasons the diphenylmethylsilyl ether (the silyl ether was unstable to $Hg(TFA)_2$), methanesulfonyl ester (the mesylate was unstable and suffered displacement by the tertiary hydroxyl even upon standing at room temperature), and trifluoroacetate ester (this substrate was inert to $Hg(TFA)_2$ under the usual conditions) were unsuitable protecting groups for **15e**. The *p*-nitrobenzoate esters (**20t** and **20e**) of both threo and erythro **15t** and **15e** were readily formed (66 and 92% yields), stable, crystalline compounds, each of which gratifyingly cyclized with $Hg(TFA)_2$ to oxepane-containing products **21** (Scheme III). Furthermore, the erythro isomer **20e** gave a *single diastereomer* of the organomercury bromide **21e** while the threo *p*-nitrobenzoate **20t** produced a ~5:1 ratio of C_{12}-epimeric mercury bromides **21t** and **21t'**. Eager to learn whether the natural or C_{12}-epi stereochemistry had arisen, we converted **21e** and the mixture of **21t**/**21t'** to the primary bromides **22e** (74% from **20e**) and **22t**/**22t'** (69 and 15% from **20t**, after separation) by reaction with $pyHBr_3$, removed the *tert*-butyl ester from each isomer of **22** (TFA, CH_2Cl_2, room temperature) to give the free acids **23**, lactonized each acid through intramolecular displacement of the bromide by the proximate carboxylate anion (Et_3N (1.1 equiv), CH_3CN, room temperature) to give the lactones **24**, and eliminated the *p*-nitrobenzoate group β to the lactone carbonyl (Et_3N, CH_3CN, room temperature) in each. We were pleased to learn that both the erythro lactone **24e** and the major threo lactone **24t** gave *dl*-aplysistatin (**1**) (75 and 81% from **22e** and **22t**, respectively) while the minor threo isomer **24t'** led to the unnatural, C_{12} epimer, **9**.

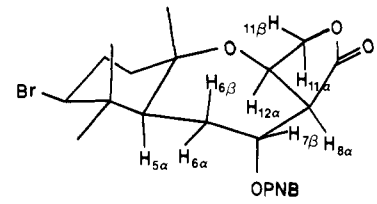
As a result of the transformations just described, the C_{12} stereochemistry in intermediates **21**–**24** had been defined. However, several questions remained. What was the relative stereochemistry between C_7/C_8 and the A-ring centers in compounds **15**–**24**? Which face of the aldehyde in **11** had been specifically attacked in the aldol reaction with **14**? What was the origin of the remarkable stereoselectivities seen in the closure of **20e** and **20t** to the seven-membered cyclic ethers **21**? Answers were discovered through a detailed ^1H NMR analysis of lactones **24e** and **24t**. At 300 MHz coupling constants could be assigned to nearly all protons in each lactone. However, because of the considerable amount of flexibility available in the tricyclic 6–7–5 skeleton, conformations could be found for Dreiding models of several of the four possible (recall that the C_{12} proton was known to be α in both **24e** and **24t**) configurations of **24** that were consistent with the observed coupling constants in each of **24e** and **24t**. We turned to the use of nuclear Overhauser enhancement difference (NOED) spectroscopy.[19] The results were rewarding.



24e

$J_{5\alpha,6\alpha}$ = <1	$J_{7\beta,8\beta}$ = 3.4
$J_{5\alpha,6\beta}$ = 8.7	$J_{8\beta,12\alpha}$ = 10.3
$J_{6\alpha,6\beta}$ = 15.9	$J_{11\alpha,11\beta}$ = 8.5
$J_{6\alpha,7\beta}$ = 4.9	$J_{11\alpha,12\alpha}$ = 7.4
$J_{6\beta,7\beta}$ = 1.6	$J_{11\beta,12\alpha}$ = 9.5

Figure 1. Conformational representation of erythro lactone **24e**.

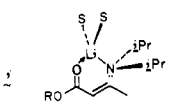


24t

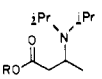
$J_{5\alpha,6\alpha}$ = 3.2	$J_{11\alpha,11\beta}$ = 9.9
$J_{5\alpha,6\beta}$ = 9.3	$J_{11\alpha,12\alpha}$ = 5.1
$J_{7\beta,8\alpha}$ = 5.3	$J_{11\beta,12\alpha}$ = 1.8
$J_{8\alpha,12\alpha}$ = 5.2	

Figure 2. Conformational representation of threo lactone **24t**.

(16) It is noteworthy that to achieve this proton removal the HMPA complex of LDA is *not* required as it is in the case of methyl or ethyl crotonate.[14a] It is conceivable that the more hindered *tert*-butyl ester inhibits the formation of a complex such as i, a perhaps obligatory intermediate for the formation of Michael adducts ii.



i

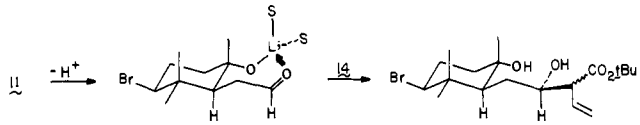


ii

(17) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. For a caveat regarding the use of J_{vic} for threo/erythro assignments in aldols bearing bulky substituents, see: Heng, K. K.; Simpson, J.; Smith, R. A. J.; Robinson, W. T. *J. Org. Chem.* **1981**, *46*, 2932.

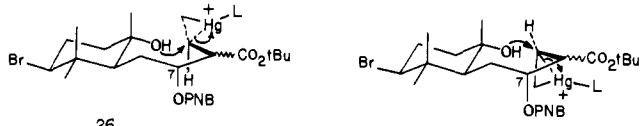
(18) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4295.

In the erythro lactone **24e** a positive NOE between $H_{5\alpha}$ and $H_{12\alpha}$ (see Figure 1) confirmed their cis relationship, between $H_{12\alpha}$ and $H_{11\alpha}$ allowed definitive assignment of the latter proton, which in turn defined the conformation of the C-ring butyrolactone ($J_{11\alpha,12\alpha}$ = 7.4 Hz; $J_{11\beta,12\alpha}$ = 9.5 Hz), and between $H_{8\beta}$ and $H_{7\beta}$ supported their gauche relationship ($J_{7\beta,8\beta}$ = 3.4 Hz). The lack of enhancement between $H_{12\alpha}$ and $H_{8\beta}$ proved the trans fusion between the B and C rings. The configuration as well as predominant conformation of **24e** is therefore as shown in Figure 1. The complimentary experiment on the major threo lactone **24t** revealed a positive NOE between $H_{12\alpha}$ and $H_{5\alpha}$ (see Figure 2), between $H_{12\alpha}$ and $H_{11\alpha}$, which again allowed the conformation of the C-ring to be deduced ($J_{11\alpha,12\alpha}$ = 5.1 Hz; $J_{11\beta,12\alpha}$ = 1.8 Hz), between $H_{8\alpha}$ and $H_{7\beta}$, which supported their gauche nature ($J_{7\beta,8\alpha}$ = 5.3 Hz), and between $H_{8\alpha}$ and $H_{12\alpha}$, which proved the cis fusion of the B and C rings. Therefore the configuration and major solution conformation of **24t** are as shown in Figure 2. It follows that the stereochemistry in intermediates **15–23** can be defined as follows: **15t** and **20t** ($H_{7\beta}$, $H_{8\alpha}$); **15e** and **20e** ($H_{7\beta}$, $H_{8\beta}$); **16–19** ($H_{7\beta}$); **21t**, **22t**, and **23t** ($H_{7\beta}$, $H_{8\alpha}$, $H_{12\beta}$); **21t'**, **22t'**, and **23t'** ($H_{7\beta}$, $H_{8\alpha}$, $H_{12\alpha}$); and **21e**, **22e**, and **23e** ($H_{7\beta}$, $H_{8\beta}$, $H_{12\beta}$). The erythro and threo series do indeed differ from each other by being epimeric at C_8 and not at C_7.[20] That is, the free aldehyde of hemiacetal **11** was attacked by dienolate **14** only from the *si* face (of the



25 15e + 15t

enantiomer shown), perhaps via a lithium chelated structure similar to **25**. Finally, in view of the high degree of similarity between the arrangements of atoms in the B rings of both **24e** and **24t** (cf. Figure 1 vs. Figure 2), we were in a position to explain the stereoselectivities in the Hg(II)-initiated closures of **20t** to **21t**/**21t'** and **20e** to **21e**. If this conformational preference is strongly manifested in the transition-state geometries for closure, then the mercuronium ions **26** would preferentially cyclize over



26 27

the diastereomeric ions **27** since the former would avoid a severe 1,3 interaction between the (*p*-nitrobenzoyl)oxy group and the methylene unit of the mercuronium ion which is present in the latter. We suggest therefore that the mercuric ion adds rapidly and reversibly to the vinyl group and that the diastereomer leading to the natural stereochemistry at C_{12}, **26**, closes faster than its epimer **27** because of the spatial orientation of the C_7 alcohol protecting group. Thus, the stereoselectivity in this second aplysistatin synthesis arises from two sequential 1,3-diastereoselective reactions: addition of the *tert*-butyl butenoate enolate ion to one face of aldehyde **25** to generate a single, transient stereocenter at C_7 and the subsequent transfer of that chirality in a 1,3 sense to C_{12} as just described.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot stage and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. Proton and carbon magnetic resonance spectra were obtained in deuteriochloroform on a Varian HFT-80/CFT-20 instrument unless otherwise indicated. Mass spectra were determined on AE1 MS-30 (electron impact, EI) or Finnigan 4000 (chemical ionization, CI) instruments. Compounds **1**, **5a**, **5b**, **5c**, **6**, **7**, **8**, **9**, **15t**, **15e**, **20e**, **21e**, **22e**, **24e**, **24t**, and **24t'** each gave an appropriate peak for the molecular ion plus NH_4^+ in the positive ion CI mass spectrum when ammonia was used as reagent gas. MPLC refers to chromatography done at 10–50 psi through EM Lobar columns packed with LiChropep Si60 (40–63 μm) and monitored by refractive index and/or ultraviolet (254/280) detection. Short-column chromatography was done by a modification of the reported procedure.[21] HPLC on EM Hibar columns of 10 μm Si60 was frequently used for the separation/purification of small quantities of sample for spectral and combustion analysis.

(2α,3α,5aβ,7α,9aα)-(±)-, (2α,3α,5aα,7β,9aβ)-(±)-, (2α,3β,5aβ,7α,9aα)-(±)-, and (2α,3β,5aα,7β,9aβ)-(±)-Methyl 7-Bromodecahydro-6,6,9a-trimethyl-2-[(phenylmethoxy)methyl]-3-(phenylthio)-1-benzoxepin-3-carboxylate (5a, 5b, 5c, and 5d).[22] A 2:1 mixture of esters **2e** and **2t**[7] (521 mg, 1.08 mmol) in dry nitromethane (3.2 mL) at room temperature under nitrogen was treated with a nitromethane (9.7 mL) solution of mercuric trifluoroacetate (645 mg, 1.51 mmol). After 1 h, saturated aqueous potassium bromide (75 mL) was added and the mixture was stirred at room temperature for 17 h. Extraction (methylene chloride, 3x), drying ($MgSO_4$), and concentration gave a brown oil (856 mg), which was dissolved in dry pyridine (4 mL) and saturated with oxygen. An oxygen-saturated pyridine (12 mL) solution of bromine (90 μL, 1.73 mmol) and lithium bromide (190 mg, 2.16 mmol) was added, and the resulting mixture was stirred in the dark at room temperature for 3 h. Diethyl ether was added, and the mixture was washed (3 × 2 N HCl, saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated to give a yellow oil (368 mg). Purification by short-column chromatography (30 g of SiO_2, 9:1 hexanes–EtOAc) gave, in order of elution, bromobenzoxepins **5a** (15%), **5c** (14%), **5b** (15%), and **5d** (11%). **5a**: IR (neat) 1730 cm^{-1}; ^1H NMR δ 0.92, 1.05, and 1.31 (3 s, 3 CH_3), 1.35–2.3 (m, 9 H), 3.57 (s, CO_2CH_3), 3.65–4.0 (m, CH_2OCH_2Ph and CHBr), 4.4 (dd; J = 4, 7 Hz; OCHRR), 4.55 (s, CH_2Ph), 7.35 (m, Ar H). **5b**: IR (neat) 1725 cm^{-1}; ^1H NMR δ 0.77, 0.98, and 1.30 (3 s, 3 CH_3), 1.4–2.45 (m, 9 H), 3.62 (s, CO_2CH_3), 3.6–4.1 (m, CH_2OCH_2Ph and CHBr), 4.53 (m, $CH(O)CH_2OCH_2Ph$), 7.35 (m, Ar H). **5c**: IR (neat) 1735 cm^{-1}; ^1H NMR δ 0.84, 1.07, and 1.12 (3 s, 3 CH_3), 1.2–2.35 (m, 9 H), 3.69 (s, CO_2CH_3), 3.7–4.5 (m, $CH(O)CH_2OCH_2Ph$ and CHBr), 4.57 (s, CH_2Ph), 7.33 (br s, Ar H). **5d**: IR (neat) 1735 cm^{-1}; ^1H NMR δ 0.79, 1.05, and 1.31 (3 s, 3 CH_3), 1.3–2.4 (m, 9 H), 3.66 (s, CO_2CH_3), 3.45–4.3 (m, $CH(O)CH_2OCH_2Ph$ and CHBr), 4.52 (s, CH_2Ph), 7.31 (m, Ar H).

(3aα,4aβ,7β,8aα,10aβ)-(±)-7-Bromodecahydro-4a,8,8-trimethyl-10a-(phenylthio)furo[3,4-*b*][1]benzoxepin-1(3*H*)-one (8). To a solution of **5a** (20 mg, 0.035 mmol) in deuteriochloroform (600 μL) was added triphenylcarbenium tetrafluoroborate (47 mg, 0.143 mmol). After 16 h at room temperature, the reaction mixture was subjected directly to preparative layer chromatography (5:1 hexanes–EtOAc) to afford **8** (4.9 mg, 0.011 mmol, 31%): IR ($CHCl_3$) 1778 cm^{-1}; ^1H NMR δ 1.00, 1.20, and 1.45 (3 s, 3 CH_3), 1.4–2.5 (m, 9 H), 3.87 (m, ABX, CHBr), 4.2–4.7 (m, $CH(O)CH_2O$), 7.40 (m, Ar H).

***dl*-Aplysistatin (1) from Sulfide 8.** Lactone sulfide **8** (4.9 mg, 0.011 mmol) in deuteriochloroform (250 μL) was treated at room temperature with *m*-chloroperoxybenzoic acid (2.0 mg in 75 μL of $CDCl_3$, 0.011 mmol), warmed to 60 °C for 15 min, and purified by preparative layer chromatography (5:1 hexanes–EtOAc) to give *dl*-aplysistatin (**1**) (1.2 mg, 0.0037 mmol 31%) as white crystals, which were recrystallized from hexanes/acetone to give NMR and MS spectra which were identical and an IR spectrum which was nearly identical with those of natural aplysistatin:[23] mp 179–181 °C (lit.[1] mp 173–175 °C); IR (KBr) 3020, 2970, 2943, 2856, 1754, 1673, 1450, 1385, 1346, 1222, 1202, 1157, 1105, 1043, 1019, 997, 874, 739, 609 cm^{-1}; ^1H NMR (270 MHz, numbering as in Figures 1 and 2) δ 0.96, 1.18, 1.30 (3 s, 3 CH_3), 1.61 (ddd; J = 3.5, 3.5, 13 Hz; $H_{1\beta}$), 1.79 (ddd; J = 3.5, 13, 14 Hz; $H_{1\alpha}$), 2.05 (dd; J = 3.5, 7.5 Hz; $H_{5\alpha}$), 2.12 (dddd; J = 3.5, 14, 14, 14 Hz; $H_{2\beta}$), 2.29 (dddd; J = 3.5, 3.5, 3.5, 14 Hz; $H_{2\alpha}$), 2.56 (m, $H_{6\alpha}$ and $H_{6\beta}$), 3.87 (dd; J = 7.5, 8.5 Hz; $H_{11\alpha}$ or $H_{11\beta}$), 3.93 (dd; J = 3.5, 14 Hz; $H_{3\alpha}$), 4.50 (dd; J = 8.5, 8.5 Hz; $H_{11\alpha}$ or $H_{11\beta}$), 5.14 (m, $H_{12\alpha}$), 6.96 (br t, H_7); MS (EI) *m/e* (relative intensity) 328/330 (1/1), 313/315 (2:1), 249 (9), 231 (9), 139 (50), 123 (24), 121 (27), 91 (19), 83 (32), 69 (25), 43 (100). Natural aplysistatin:[23] IR (KBr) 3010, 2974, 2905, 2868, 1759, 1673, 1462, 1385, 1336,

(19) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.
(20) Additional experimental support for this conclusion was found in a competitive rate study of the elimination of *p*-NO_2PhCOOH from the isomers of **24**. The erythro and major threo isomers **24e** and **24t** generate *dl*-aplysistatin at identical rates (Et_3N, CH_2Cl_2, room temperature), which is consistent with an E1cb mechanism wherein the rate-determining step is expulsion of the carboxylate leaving group from the same lactone enolate ion. Both **24e** and **24t** undergo the elimination at least 10^2 faster than **24t'**.
(21) Hunt, B. J.; Rigby, W. *Chem. Ind. (London)* **1967**, 1868.
(22) The numbering scheme used in the nomenclature follows *Chemical Abstracts* usage and not aplysistatin numbering.
(23) A sample of natural aplysistatin was kindly provided by Professor G. R. Pettit.

1199, 1154, 1110, 1038, 1014, 995, 876, 741, 698 cm^{-1}.

(2α,5aβ,7α,9aα)-(±)-Methyl 7-Bromo-2,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-2-[(phenylmethoxy)methyl]-1-benzoxepin-3-carboxylate (6). By the procedure just described a mixture of **5a** and **5c** (180 mg, 0.32 mmol) afforded crystalline **6** (94 mg, 0.21 mmol, 65%). Recrystallization from hexanes gave the analytical sample: mp 98–99 °C; IR ($CHCl_3$) 1712, 1639 cm^{-1}; ^1H NMR δ 0.91, 1.09, and 1.30 (3 s, 3 CH_3), 1.4–2.55 (m, 7 H), 3.62 (s, CO_2CH_3), 3.50–4.02 (m, CH_2OCH_2Ph and CHBr), 4.50 (s, CH_2Ph), 4.68 (m, OCHC=C), 6.79 (m, C=CH), 7.30 (br s, Ar H). Anal. C, H, Br.

(2α,5aα,7β,9aβ)-(±)-Methyl 7-Bromo-2,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-2-[(phenylmethoxy)methyl]-1-benzoxepin-3-carboxylate (7). By analogy to the procedure for the preparation of **6**, **5b** gave **7** as a colorless oil (68%): IR (neat) 1720, 1640 cm^{-1}; ^1H NMR δ 0.93, 1.09 and 1.31 (3 s, 3 CH_3), 1.5–2.3 (m, 5 H), 2.49 (m, CH_2C=C), 3.62 (s, CO_2CH_3), 3.68–4.07 (m, CH_2OCH_2Ph and CHBr), 4.52 (s, CH_2Ph), 4.74 (m, OCHC=C), 6.90 (m, C=CH), 7.31 (m, Ar H).

***dl*-12-Epiaplysistatin (9) from 7.** As for the preparation of **8**, olefin **7** (92 mg, 0.204 mmol) afforded **9** (50.2 mg, 0.152 mmol, 75%) as a white solid that was recrystallized (2×) from hexanes–EtOAc to give the analytical sample: mp 138–140 °C; IR (KBr) 3086, 3064, 3030, 2980, 2927, 2855, 1768, 1690, 1492, 1453, 1386, 1219, 1200, 1045, 1025, 754, 693 cm^{-1}; ^{H} NMR (270 MHz, numbering as in Figures 1 and 2) δ 1.20, 1.25, and 1.42 (3 s, 3 CH_3), 1.5–1.8 (m, $H_{1\alpha}$ and $H_{1\beta}$), 1.72 (br d, J = 10 Hz, $H_{5\alpha}$), 2.09 (dddd; J = 3.5, 13, 14, 14 Hz; $H_{2\beta}$), 2.22 (dddd; J = 3.5, 3.5, 3.5, 13 Hz; $H_{2\alpha}$), 2.46 (br dd; J = 10, 16 Hz; H_{6t}b), 2.61 (dd; J = 8, 16 Hz; $H_{6\alpha}$), 3.92 (dd; J = 7, 9 Hz; $H_{11\alpha}$ or $H_{11\beta}$), 4.01 (dd; J = 4, 12 Hz; $H_{3\alpha}$), 4.50 (dd; J = 8.5, 8.5 Hz; $H_{11\alpha}$ or $H_{11\beta}$), 5.08 (br m, $H_{12\beta}$), 7.15 (br d, J = 8 Hz, H_7); MS (EI) m/e (relative intensity) 328/330 (1/1), 249 (8), 231 (9), 203 (24), 201 (23), 139 (99), 123 (61), 212 (48), 110 (23), 95 (26), 83 (36), 81 (30), 39 (37), 43 (100), 40 (23). Anal. C, H, Br.

***dl*-Aplysistatin (1) from 6.** By analogy to the procedure for the preparation of **9**, **6** gave **1** in 52% yield. A mixture of **6** and **7** was also converted to **1** and **9**, which were separable by multiple (4×) elution preparative layer SiO_2 chromatography (4:1 hexanes–EtOAc).

(2α,3aα,5β,7aβ)-(±)- and (2α,3aβ,5α,7aα)-(±)-5-Bromooctahydro-2-hydroxy-4,4,7a-trimethylbenzo[*b*]furan (11). To a stirred solution of lactone **10** (2.55 g, 9.77 mmol) in CH_2Cl_2 (40 mL) at −78 °C under N_2 was added diisobutylaluminum hydride (1.22 M in hexanes, 8.4 mL, 1.03 mmol) dropwise down the reaction flask side over 10 min. After 30 min the reaction was quenched (excess absolute MeOH) at −78 °C, warmed to 0 °C, diluted with ether, and shaken with brine. The gelatinous emulsion was dissolved with 10% HCl, the layers were immediately separated, and the aqueous layer was extracted with ether. The combined organic layers were washed (2× saturated $NaHCO_3$, 2× brine), dried ($MgSO_4$), and concentrated to give crude hemiacetal **11** (2.5 g, 9.5 mmol, 97%), which was used directly without further purification. Recrystallization (hexanes–EtOAc) provided an analytical sample: mp 112–115 °C; IR ($CDCl_3$) 3645, 3430, 1735 (w), 1150, 1065 cm^{-1}; ^1H NMR (two epimers of **11** and the free aldehyde were detectable in a ratio of ~ 4:1:trace) δ 0.94, 1.08, 1.14 (3 s, 3 minor CH_3), 0.96, 1.06, 1.33 (3 s, 3 major CH_3), 1.2–2.6 (m, 7 H), 3.73–3.98 (2 m, CHBr), 5.39–5.59 (2m, CHOH), 9.20 (t, J = 2 Hz, CHO). Anal. C, H, Br.

[1R-[1α(αS*,βS*),2β,5α]]-(±)- and [1R-[1α(αR*,βS*),2β,5α]]-(±)-*tert*-Butyl 5-Bromo-α-ethenyl-β,2-dihydroxy-2,6,6-trimethylcyclohexanebutanoate (15t and 15e). To a solution of lithium diisopropylamide (LDA, 9.3 mL, 0.95 M, 8.89 mmol) in THF under N_2 at −78 °C was added a THF solution of (*E*)-*tert*-butyl but-2-enoate[24] (1.28 g, 9.07 mmol). This was added by cannula to a solution of the preformed lithium anion of hemiacetal **11**, prepared by titrating **11** (0.7693 g, 2.93 mmol) in THF (6 mL) at −10 °C with LDA (0.95 M) to an end point indicated by 1,10-phenanthroline. The resulting solution was stirred at −23 °C for 2 h and quenched (saturated NH_4Cl) at −23 °C. The isolated oil after MPLC (4:1 hexanes–EtOAc) yielded the threo isomer **15t** (0.24 g, 0.59 mmol, 20%), the erythro isomer **15e** (0.49 g, 1.2 mmol, 41%), and hemiacetal **11** (0.13 g, 0.49 mmol, 24%). The yields of **15** varied from 87% to 65% and the **15e**/**15t** ratio from 3.0 to 1.64. **15t**: Recrystallization (hexanes–EtOAc) gave the analytical sample: mp 104–105 °C; IR ($CDCl_3$) 3420, 1720, 1640 cm^{-1}; ^1H NMR δ 0.93, 1.06, 1.18 (3 s, 3 CH_3), 1.4–2.2 (m, 7 H), 1.47 (s, $C(CH_3)_3$), 2.95 (dd; J = 8, 8 Hz; $CHCO_2$), 3.2–4.2 (m, CHOH and CHBr), 5.21 (dd; J = 19.5, 2 Hz; CH=C*H*H), 5.24 (dd; J = 10, 2 Hz; CH=CH*H*), 5.80 (ddd; J = 19.5, 10, 8 Hz; C*H*=CH_2); ^{13}C NMR δ 17.4 (q), 23.6 (q), 28.0 (q), 30.1 (q), 31.7 (t), 32.4 (t), 41.3 (s), 43.2 (t), 54.5 (d), 58.9 (d), 66.4 (d), 71.7 (s), 73.8 (d), 81.3 (s), 119.4 (t), 133.2 (d), 172.0 (s). Anal. C, H. **15e**: Recrystallization (hexanes–EtOAc) gave the analytical sample: mp 87.5–89 °C; IR ($CDCl_3$) 3430, 1730 cm^{-1}; ^1H NMR δ 0.94, 1.10, and 1.19 (3 s, 3 CH_3), 1.4–2.2 (m, 7 H), 1.47 (s, $C(CH_3)_3$), 2.92 (dd; J = 6, 8 Hz; $CHCO_2$), 3.5–4.25 (m, C*H*OH and CHBr), 5.20 (dd; J = 2, 19 Hz; CH=CH*H*), 5.25 (dd; J = 2, 9 Hz; CH=C*H*H), 5.93 (ddd; J = 8, 9, 19 Hz; C*H*=CH_2); ^{13}C NMR δ 17.4 (q), 23.6 (q), 28.0 (q), 30.1 (q), 32.4 (2 t), 41.3 (s), 43.2 (t), 54.4 (d), 58.2 (d), 66.5 (d), 71.6 (s), 73.0 (d), 81.4 (s), 119.5 (t), 133.0 (d), 172.0 (s). Anal. C, H.

[1R-[1α(αR*,βS*),2β,5α]]-(±)- and -[1R-[1α(αS*,βS*),2β,5α]]-(±)-*tert*-Butyl 5-Bromo-α-ethenyl-2-hydroxy-2,6,6-trimethyl-β-(4-nitrobenzoyloxy)cyclohexanebutanoate (20e and 20t). To a solution of **15e** (0.23 g, 0.579 mmol), 4-(dimethylamino)pyridine (78 mg, 0.637 mmol), and pyridine (94 μL, 1.16 mmol) in CH_2Cl_2 (2 mL) was added *p*-nitrobenzoyl chloride (0.113 g, 0.608 mmol). After 30 min ether was added and the solution was washed (2× 10% HCl, saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated to leave crystalline **20e** (0.295 g, 92%). Recrystallization (hexanes–EtOAc) gave an analytical sample: mp 153–154 °C; IR (KBr) 3500, 1710, 1610, 1530, 1280, 845 cm^{-1}; ^1H NMR δ 0.96, 1.19, and 1.26 (3 s, 3 CH_3), 1.42 (s, $C(CH_3)_3$), 1.2–2.5 (m, 7 H), 3.32 (dd; J = 7, 11 Hz; $CHCO_2$), 3.95 (AB*X*, CHBr), 5.21 (dd; J = 2, 17 Hz; CH=C*H*H), 5.25 (dd; J = 2, 10 Hz; CH=CH*H*), 5.57–6.18 (m, C*H*=CH_2 and C*H*OCOAr), 8.20 (A_2B_2, ArH). Anal. C, H, N. By the same procedure **15t** gave **20t** in 66% yield: mp 107.5–108 °C; IR (KBr) 3580, 1725, 1715, 1635, 1605, 1515, 1300, 1280, 870 cm^{-1}; ^1H NMR δ 0.95, 1.19, and 1.21 (3 s, 3 CH_3), 1.37 (s, $C(CH_3)_3$), 1.3–2.4 (m, 7 H), 3.38 (dd; J = 7.5, 8.5 Hz; $HCCO_2$), 3.95 (m, HCBr), 5.15–6.15 (m, *H*C=CH_2 and HCOCOAr), 8.2 (s; Ar H). Anal. C, H, N.

(2α,3β,4β,5aβ,7α,9aα)-(±)- and (2α,3α,4β,5aβ,7α,9aα)-(±)-*tert*-Butyl 7-Bromo-2-(bromomethyl)decahydro-6,6,9a-trimethyl-4-(4-nitrobenzoyloxy)-1-benzoxepin-3-carboxylate (22e and 22t). To a suspension of benzoate **20e** (152 mg, 0.275 mmol) in dry $MeNO_2$ (1.1 mL) under N_2 at −23 °C was added $Hg(TFA)_2$ (129 mg, 0.302 mmol). After 25 min a solution of saturated KBr (~ 10 equiv) was added at −23 °C. This mixture was stirred vigorously, warmed to room temperature for 1 h, diluted with ether, washed (brine, 2× saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated to leave a viscous oil (1.3 g, 96%), which was subjected to MPLC (5:1 hexanes–EtOAc) to give the primary organomercury bromide **21e** (155 mg, 0.186 mmol, 67%) [IR ($CDCl_3$) 1730, 1610, 1530, 1350, 1270, 845 cm^{-1}; ^1H NMR δ 0.91, 0.93, and 1.25 (3 s, 3 CH_3), 1.35 (s, $C(CH_3)_3$), 1.4–2.5 (m, 9 H), 2.60 (dd; J = 5, 8 Hz; $CHCO_2$), 3.84 (dd; J = 6, 10 Hz; CHBr), 4.53 (br dd; J = 6, 8 Hz; C*H*CH_2Hg), 5.63 (br m, CHOCOAr), 8.22 (A_2B_2, ArH)] and starting **20e** (12 mg, 0.022 mmol, 8%). To crude **21e** (0.75 g, 0.90 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (0.3 mL, omission of py led to substantial loss of the *tert*-butyl ester) was added $pyHBr_3$ (382 mg, 0.96 mmol). After 14 h this mixture was poured into 10% HCl/saturated Na_2SO_3, extracted into ether, washed (10% HCl, 2× brine, saturated $NaHCO_3$, 2× brine), dried ($MgSO_4$), and concentrated to leave **22e** (0.53 g, 0.84, 93%) of sufficient purity for further work. HPLC (9:1 hexanes–EtOAc) gave an analytical sample of **22e**: IR ($CHCl_3$) 1725, 1610, 1530, 1270 cm^{-1}; ^1H NMR δ 0.95, 0.99, and 1.28 (3 s, 3 CH_3), 1.36 (s, $C(CH_3)_3$), 1.35–2.50 (m, 7 H), 2.95 (dd; J = 5, 8 Hz; $CHCO_2$), 3.45 (2 d, J = 5, 6 Hz; C*H*HBr and CH*H*Br), 3.88 (m, CHBr), 4.32 (ddd; J = 5, 6, 9 Hz; C*H*CH_2Br), 5.68 (m, CHOCOAr), 8.23 (A_2B_2, J = 10 Hz, Ar H). Anal. C, H, N.

Likewise, the threo benzoate **20t** was cyclized to **21t** and **21t'** (92% crude). A portion of **21t** was obtained pure via HPLC (9:1 hexanes–EtOAc): IR ($CHCl_3$) 1730, 1610, 1560, 1270, 840 cm^{-1}; ^1HNMR δ 0.92, 0.96, and 1.25 (3 s, 3 CH_3), 1.53 (s, $C(CH_3)_3$), 1.4–2.8 (m, 9 H), 2.78 (br s; $W_{1/2}$ = 6; $CHCO_2$), 3.85 (dd; J = 6.5, 11 Hz; CHBr), 4.78 (br dd; J = 6, 6 Hz; C*H*CH_2Hg), 5.54 (br s; $W_{1/2}$ = 9; CHOCOAr), 8.21 (A_2B_2, J = 10 Hz, Ar H); MS (CI, NH_3, negative) 830/831/832/833/834/836/837 ($M + e^-$). The mixture of **21t** and **21t'** was brominated as for **21e** and purified by MPLC (12:1 hexanes–EtOAc) to give **22t** (69%) and **22t'** (15%). Recrystallization (hexanes–benzene) of each gave the analytical samples. **22t**: mp 168–169 °C; IR ($CHCl_3$) 1725, 1610, 1525, 1270, 840 cm^{-1}; ^1H NMR δ 0.91, 0.95, 1.22 (3 s, 3 CH_3), 1.50 (s, $C(CH_3)_3$), 1.4–2.8 (m, 7 H), 3.14 (br d, J = 3 Hz, $CHCO_2$), 3.49 (dd; J = 7, 11 Hz; C*H*HBr), 3.70 (dd; J = 7, 11 Hz; CH*H*Br), 3.84 (dd; J = 6, 11 Hz; CHBr), 4.36 (dd; J = 7, 7 Hz; C*H*CH_2Br), 5.55 (ddd; J = 3, 3, 3 Hz; CHOCOAr), 8.23 (A_2B_2, J = 9 Hz, ArH); MS (CI, NH_3, positive) 593/595/597 ($M + NH_4^+ - C_4H_8$). Anal. C, H, N. **22t'**: mp 149–150 °C; IR ($CDCl_3$) 1730, 1610, 1530, 1270, 840 cm^{-1}; ^1H NMR δ 0.86, 0.95, and 1.37 (3 s, 3 CH_3), 1.45 (s, $C(CH_3)_3$), 1.4–2.7 (m, 7 H), 2.68 (dd; J = 5, 9 Hz; $CHCO_2$), 3.35 (d, J = 8 Hz, C*H*HBr), 3.38 (d, J = 4 Hz, CH*H*Br), 3.75–4.25 (m, C*H*CH_2Br and CHBr), 5.62 (m, C*H*COCAr), 8.22 (A_2B_2, J = 10, Ar H); MS (CI, NH_3, negative) 631/633/635 ($M + e^-$). Anal. C, H, N.

(2α,3β,4β,5aβ,7α,9aα)-(±)- and (2α,3α,4β,5aβ,7α,9aα)-(±)-7-Bromo-2-(bromomethyl)decahydro-6,6,9a-trimethyl-4-(4-nitrobenzoyloxy)-1-benzoxepin-3-carboxylic Acid (23e and 23t). The *tert*-butyl ester **22e** (172 mg, 0.272 mmol) was dissolved in CH_2Cl_2 (1 mL) and TFA

(24) Ozeki, T.; Kusaka, M. *Bull. Chem. Soc. Jap.* **1966**, *39*, 1995.

(1 mL), stirred at room temperature for 2 h, poured into brine, extracted into ether, washed [saturated $NaHCO_3$ (the acid **23e** did not enter the aqueous phase), brine], dried ($MgSO_4$), and concentrated to leave **23e** (146 mg, 0.253 mmol, 93%). Multiple trituration with 6:1 CH_3CN–$CHCl_3$ gave the analytical sample of **23e**: mp 185–195 °C dec; IR (KBr) 3300–2800, 1720, 1695, 1520, 1275, 840 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 0.97, 1.02, and 1.34 (3 s, 3 CH_3), 1.3–2.76 (m, 7 H), 3.07 (dd; J = 5, 8.5 Hz; $CHCO_2$), 3.51 (dd; J = 7, 11 Hz; C*H*HBr), 3.69 (dd; J = 4, 11 Hz; CH*H*Br), 4.13 (ABX,CHBr), 4.44 (ddd; J = 4, 7, 8.5 Hz; C*H*CH_2Br), 5.75 (br dd; J = 5, 5 Hz; CHOCOAr), 8.30 (s, Ar H); MS (CI, NH_3, positive), 346/348 (M + NH_4^+ – HBr – $NO_2PhCOOH$), (NH_3, negative) 654/656/660 (M + Br^-). Anal. C, H. Likewise, the threo *tert*-butyl ester **22t** gave **23t** (104% crude). Recrystallization (CH_3CN) gave **23t**: mp 224–234 °C dec; IR (KBr) 3300–2800, 1725, 1605, 1530, 1270, 840 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 0.94, 1.13, and 1.24 (3 s, 3 CH_3), 1.5–2.4 (m, 7 H), 3.22 (br d, J = 3.5 Hz, $CHCO_2$), 3.62 (dd; J = 8, 12 Hz; C*H*HBr), 3.80 (dd; J = 6, 12 Hz; CH*H*Br), 4.15 (br dd; J = 6, 8 Hz; C*H*CH_2Br), 5.59 (m, C*H*OCOAr), 8.31 (s, Ar H); MS (CI, NH_3, negative) 495/497 (M + e^- – HBr).

(3aα,4aβ,7β,8aα,10α,10aβ)-(±)-, (3aα,4aβ,7β,8aα,10aα,10aα)-(±)-, and (3aα,4aα,7α,8aβ,10β,10aβ)-(±)-7-Bromodecahydro-4a,8,8-trimethyl-10-(4-nitrobenzoyloxy)furo[3,4-*b*]-1-benzoxepin-1(3*H*)-one (24e, 24t, and 24t′). The crude acid **23e** (190 mg, 0.33 mmol) was suspended in dry CH_3CN (1.3 mL) and Et_3N (60 μL, 0.43 mmol) was added. After 1 h the mixture was poured into brine, extracted with ether, washed (2× 10% HCl, brine, $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated to leave a yellow foam which was subjected to MPLC (2:1 hexanes–EtOAc) to give *dl*-aplysistatin (**1**) (23 mg, 0.070 mmol, 21%) and the lactone **24e** (75 mg, 0.15 mmol, 46%), which was recrystallized (hexanes–benzene) to give the analytical sample: mp ~185 °C dec; IR (KBr) 1800, 1730, 1530, 1275 cm^{-1}; ^1H NMR (300 MHz) (see Figure 1 for numbering) δ 0.85, 0.90, and 1.28 (3 s, 3 CH_3), 1.66 (ddd; J = 4.2, 13.6, 13.7 Hz; $H_{1\alpha}$), 1.74 (ddd; J = 4.0, 4.1, 13.6 Hz; $H_{1\beta}$), 1.90 (ddd; J = 1.6, 8.7, 15.9 Hz; $H_{6\beta}$), 2.06 (dddd; J = 4.1, 13.3, 13.7, 13.9 Hz; $H_{2\beta}$), 2.10 (br d, J = 8.7 Hz, $H_{5\alpha}$), 2.23 (dddd; J = 4.0, 4.2, 4.3, 13.9 Hz; $H_{2\alpha}$), 2.50 (dd; J = 4.9, 15.9 Hz; $H_{6\alpha}$), 2.70 (dd; J = 3.4, 10.3 Hz; $H_{2\beta}$), 3.81 (dd; J = 4.3, 13.3 Hz; $H_{3\alpha}$), 3.90 (dd; J = 8.5, 9.5 Hz; $H_{11\beta}$), 4.41 (br dd; J = 8.5, 7.4 Hz; $H_{11\alpha}$), 4.84 (ddd; J = 7.4, 9.5, 10.3 Hz; $H_{12\alpha}$), 5.72 (m; $H_{7\beta}$), 8.18 (A_2B_2, J = 8.7 Hz, ArH). Anal. C, H.

By the procedure just described, the threo acid **23t** was converted to *dl*-aplysistatin (**1**) (17%) and the threo lactone **24t** (56%). Chromatographed **24t** was washed with hot CH_3CN (4×): mp 200–212 °C dec; IR (KBr) 1780, 1720, 1575, 1280 cm^{-1}; ^1H NMR (300 MHz, numbering as in Figure 2) δ 0.94, 1.03, and 1.26 (3 s, 3 CH_3), 1.56 (ddd; J = 3.2, 4.0, 13.0 Hz; $H_{1\beta}$), 1.68 (ddd; J = 4.0, 13.0, 13.2 Hz; $H_{1\alpha}$), 1.78 (dd; J = 3.2, 9.3 Hz; $H_{5\alpha}$), 2.01–2.37 (3 m, $H_{2\beta}$, $H_{6\alpha}$, $H_{6\beta}$), 2.28 (dddd; J = 4.0, 4.0, 4.2, 14.3 Hz; $H_{2\alpha}$), 2.86 (dd; J = 5.2, 5.3 Hz; $H_{8\alpha}$), 3.89 (dd; J = 4.2, 12.5 Hz; $H_{3\alpha}$), 4.24 (dd; J = 1.8, 9.9 Hz; $H_{11\beta}$), 4.39 (dd; J = 5.1, 9.9 Hz; $H_{11\alpha}$), 4.73 (ddd; 1.8, 5.1, 5.2; $H_{12\alpha}$), 5.86 (m, $H_{7\beta}$), 8.19 (A_2B_2, J = 10 Hz, Ar H). Anal. C, H, N.

The minor threo lactone **24t′** was prepared from the *tert*-butyl ester **22t′** by the TFA and Et_3N reactions described above to give lactone **24t′** in 25% yield (6 mg): IR ($CDCl_3$) 1785, 1725, 1525, 1270 cm^{-1}; ^1H NMR (300 MHz, numbering as in Figures 1 and 2) δ 0.86, 0.89, and 1.34 (3 s, 3 CH_3), 1.63 (ddd; J = 4.0, 14.0, 14.0 Hz; $H_{1\alpha}$), 1.84 (d, J = 8.5 Hz, $H_{5\alpha}$), 1.86 (ddd; J = 3.5, 3.5, 13.5 Hz; $H_{1\beta}$), 2.06 (dddd; J = 3.6, 14.0, 14.0, 14.0 Hz; $H_{2\beta}$), 2.09 (ddd; J = 3.9, 8.4, 16.6 Hz; $H_{6\beta}$), 2.20 (dddd; J = 4, 4, 4, 14.0 Hz; $H_{2\alpha}$), 2.33 (dd; J = 2.0, 16.8 Hz; $H_{6\alpha}$), 3.11 (dd; J = 8.8, 8.8 Hz; $H_{8\alpha}$), 3.85–3.93 (m, $H_{11\alpha}$ or $H_{11\beta}$), 3.93 (dd; J = 4.8, 12.8 Hz; $H_{3\alpha}$), 4.33–4.43 (2m, $H_{12\beta}$ and $H_{11\alpha}$ or $H_{11\beta}$), 5.65 (ddd; J = 2, 4, 9 Hz; $H_{7\alpha}$), 8.25 (A_2B_2, J = 9.0 Hz, ArH).

***dl*-Aplysistatin(1) from *p*-Nitrobenzoate Lactones 24e and 24t or Acids 23e and 23t.** Lactones **24e** and **24t** were reexposed to Et_3N (1 equiv) in CH_3CN at room temperature to provide **1** in 87% (from **24e**) and 91% (from **24t**) yield after chromatography. Careful monitoring of reaction progress by HPLC (254 nm, 1:1 hexanes–EtOAc) indicated that **24e** and **24t** disappeared from a 1:1 mixture at identical rates. The most efficient preparation of **1** involved treatment of crude acids **23e** or **23t** with 3 equiv of Et_3N in CH_3CN at room temperature (89% and 78% of pure **1** from **23e** and **23t**, respectively; 62% of **1** from **20e** without purification of intermediates).

***dl*-12-Epiaplysistatin (9) from *p*-Nitrobenzoate Lactone 24t′.** Lactone **24t′** (5 mg) in $CDCl_3$ (300 μL) was treated with excess diazabicyclooctane. After several days MPLC (4:1 hexanes–EtOAc) gave pure **9** (3.4 mg, 80%).

Acknowledgment. This investigation was supported by Grant 24056, awarded by the National Cancer Institute, DHEW. The assistance of Drs. Stephen B. Philson (Department of Chemistry, University of Minnesota) and Robert L. Thrift (Gray Freshwater Biological Institute, University of Minnesota) and Mr. David Vander Velde (Midwest Regional NMR Facility, University of Illinois, Grant NSF CHE 79-16100) with high-field NMR experiments is greatly appreciated. Purchase of the Nicolet NT-300 WB NMR instrument (Department of Chemistry, University of Minnesota) was made possible through Grant NSF CHE 79-26027. We thank Professors J. D. White and G. D. Prestwich for communicating their work to us prior to publication.

Registry No. (±)-**1**, 71883-79-9; (±)-**2e**, 71841-10-6; (±)-**2t**, 71841-11-7; **3**, 71841-08-2; (±)-**4**, 71841-09-3; (±)-**5a**, 71841-12-8; (±)-**5b**, 71883-80-2; (±)-**5c**, 71885-18-2; (±)-**5d**, 71883-81-3; (±)-**6**, 71841-15-1; (±)-**7**, 71883-82-4; (±)-**8**, 81844-70-4; (±)-**9**, 71883-83-5; (±)-**10**, 71041-54-8; (±)-**11** (isomer 1), 83220-42-2; (±)-**11** (isomer 2), 83220-48-8; (±)-**15t**, 83220-43-3; (±)-**15e**, 83289-28-5; (±)-**20t**, 83220-44-4; (±)-**20e**, 83289-72-9; (±)-**22e**, 83220-45-5; (±)-**22t**, 83289-29-6; (±)-**22t′**, 83289-30-9; (±)-**23e**, 83220-46-6; (±)-**23t**, 83289-31-0; (±)-**24e**, 83220-47-7; (±)-**24t**, 83289-32-1; (±)-**24t′**, 83289-33-2; methyl 2-(phenylthio)acetate, 17277-58-6; 2-(benzyloxy)acetaldehyde, 60656-87-3.