select ^1H NMR signals at 300 MHz. The integrals were normalized to that of the starting material before heating was initiated. Generally, five data points run in duplicate were obtained for each substrate at each temperature.

Acknowledgment. We are grateful to the National Institutes of Health for the financial support of this work (Grant CA-12115), to Dr. Charles Cottrell for the 2D-COSY and NOE measurements at 500 MHz, and to Professor Horst Prinzbach for his generous hospitality during the time in which this manuscript was written.

Registry No. **9**, 97253-52-6; **10**, 123623-06-3; **11**, 97253-53-7; **12**, 123623-07-4; **13**, 123623-08-5; **14**, 123623-09-6; **15**, 123623-10-9; **16**, 123623-11-0; **17**, 123673-17-6; **18**, 123623-12-1; **19**, 123623-13-2; **20**, 123623-14-3; **21**, 123623-15-4; **22**, 123623-16-5; **23**, 123673-18-7.

Supplementary Material Available: X-ray experimental data and tables of crystal data, bond distances and angles, least-squares planes, final fractional coordinates, and thermal parameters for **10**, **13**, **15**, **16/17**, and **20** (43 pages). Ordering information is given on any current masthead page.

(±)-Benzoabikoviromycin, a Potential Antiviral Agent Synthesized by the Palladium-Catalyzed Ring Expansion of 2-Alkynyl-2-hydroxybenzocyclobutenones

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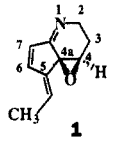
Received April 21, 1989

Abstract: Abikoviromycin [(4*R*,4a*S*)-5-(1′*E*)-ethylidene-2,3-dihydro-1,5-pyridine 4,4a-oxide] is an antiviral and antifungal antibiotic isolated from culture broths of *Streptomyces abikoensis* and *Streptomyces rubescens* and more recently from *Streptomyces* sp. NA-337. It was shown to be identical with latumcidin, isolated in 1958 from the culture broth of *Streptomyces reticular liatumcidicus*. Given its interesting biological acitivity and novel structure, abikoviromycin should have attracted the attention of both synthesis and medicinal chemists interested in probing further the chemical and biological properties of this highly functionalized molecule, as well as its analogues. However, abikoviromycin is highly unstable and polymerizes rapidly upon isolation even at −50 °C. It is readily decomposed by heat, by acid, or on standing in the dry state. This extreme reactivity has probably precluded in-depth studies of the molecule, and therefore, it is not surprising that there have been no synthetic efforts in the area published to date. Starting from the premise that the chemical reactivity of abikoviromycin is associated with polymerization of the diene–imine portion of the molecule, masking of the 6,7-double bond as part of a benzene ring might lead to increased stability of the resulting molecule while still retaining aspects of the biological activity. A brief and concise synthesis of racemic benzoabikoviromycin is described on the basis of the previously developed facile and stereoselective palladium(2+)-catalyzed ring expansion of 2-alkynyl-2-hydroxybenzocyclobutenone monoketals to alkylideneindandione monoketals.

Abikoviromycin is an antiviral and antifungal antibiotic isolated from culture broths of *Streptomyces abikoensis* and *Streptomyces rubescens* and more recently from *Streptomyces* sp. NA-337.[2] It was shown to be identical with latumcidin, isolated in 1958 from the culture broth of *Streptomyces reticular liatumcidicus*.[3] Abikoviromycin was studied by Gurevich and co-workers using chemical and spectroscopic methods, and they assigned the structure (4*S*,4a*R*)-5-(1′*E*)-ethylidene-2,3-dihydro-1,5-pyrindine 4,4a-oxide to the antibiotic.[4] In a later X-ray crystallographic study of the selenate salt, the molecule was assigned the opposite configuration at C-3 and C-4.[5] Therefore, abikoviromycin has the structure shown in **1** [(4*R*,4a*S*)-5-(1′*E*)-ethylidene-2,3-dihydro-1,5-pyrindine 4,4a-oxide or 7-ethylidene-1a,2,3,7-tetrahydrocyclopent[*b*]oxireno[*c*]pyridine].



1

Abikoviromycin is highly unstable and polymerizes rapidly upon isolation even at −50 °C. It is readily decomposed by heat, by acid, or on standing in the dry state; however, it can be handled in dilute solutions and in the form of its salts (sulfate, picrate, selenate). It is effective against eastern and western but not Venezuelan equine encephalomyelitis viruses at dilutions of 1:8 000 000 when mixed with virus suspensions and injected intracerebrally into mice. It was shown to inhibit infection of cell cultures by influenza A and B viruses, Newcastle disease virus, and Chikungunya virus.[6] It is weakly antibacterial and antifungal, and it does not appear to have been tested in antitumor assays. Reduction of abikoviromycin with $NaBH_4$ was shown to produce dihydroabikoviromycin, the product of imine reduction. Dihydroabikoviromycin was subsequently isolated directly from a culture broth that also produced an enzyme capable of oxidizing dihydroabikoviromycin to abikoviromycin.[7] Most recently a related antibiotic, *N*-hydroxydihydroabikoviromycin, with antimicrobial activity against *Klebsiella pneumoniae* was isolated from a *Streptomyces* species.[8]

Given its interesting biological activity and novel structure, abikoviromycin should have attracted the attention of both synthesis and medicinal chemists interested in probing further the chemical and biological properties of this highly functionalized

(1) Camille and Henry Dreyfus Teacher Scholar, 1985–1990.
(2) (a) Umezawa, H.; Tazaki, T.; Fukuyama, S. *Jpn. Med. J.* **1951**, *4*, 331; *Chem. Abstr.* **1952**, *46*, 7167c. (b) Onda, M.; Konda, Y.; Narimatsu, Y.; Tanaka, H.; Awaya, J.; Omura, S. *Chem. Pharm. Bull.* **1974**, *22*, 2916.
(3) (a) Sakagami, Y.; Yamaguchi, I.; Yonehara, H.; Okimoto, Y.; Yamanouchi, S.; Takiguchi, K.; Sakai, H. *J. Antibiot.* **1958**, *11A*, 231. (b) Sakagami, Y.; Utahara, R.; Yagishita, K.; Umezawa, H. *J. Antibiot.* **1958**, *11A*, 231.
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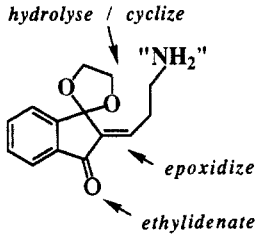
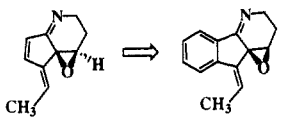


Figure 1.

molecule, as well as its analogues. However, the extreme reactivity of abikoviromycin, noted above, probably has precluded in-depth studies of the molecule, and therefore, it is not surprising that there have been no synthetic efforts in the area published to date. Starting from the premise that the chemical reactivity of abikoviromycin is associated with polymerization of the diene–imine portion of the molecule, we anticipated that masking the 6,7-double bond as part of a benzene ring might lead to increased stability of the resulting molecule while still retaining aspects of the biological activity (**1** ⇒ **2**). We have named compound **2** benzo-

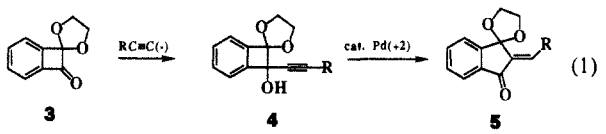


1 **2**

abikoviromycin and describe herein a brief and concise synthesis of racemic **2** based on the facile and stereoselective palladium-(2+)-catalyzed ring expansion of 2-alkynyl-2-hydroxybenzocyclobutenone monoketals to alkylideneindandione monoketals previously developed in our laboratory.[9]

Results and Discussion

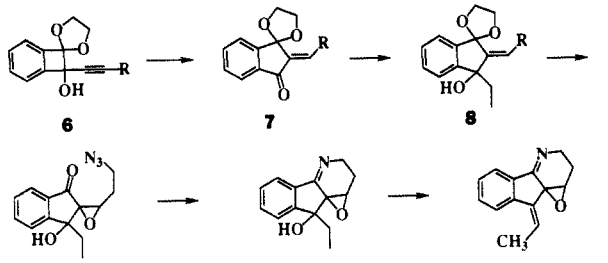
Benzocyclobutenedione monoketal (**3**) reacts with alkynyl anions to give good yields of adducts **4** which on treatment with a catalytic amount of $Pd(OCOCF_3)_2$ at room temperature (rt) in CH_2Cl_2 undergo a highly stereoselective ring expansion to give (*Z*)-2-alkylideneindandione monoketals **5** in good isolated yields (eq 1).[9] In this chemistry the ketal group selectively migrates to the alkyne and provides an exocyclic double bond such that the newly introduced vinyl hydrogen atom is situated trans to the migrating ketal carbon. If the R group of **5** were an appropriately protected aminoethyl unit or equivalent functional group, the palladium-catalyzed ring expansion would produce a species properly functionalized and of correct stereochemistry for conversion into benzoabikoviromycin by the correct sequencing of (1) introduction of the ethylidene group by reaction of the free carbonyl group with a C-2 unit, (2) formation of the imine by cyclization of the amine equivalent functional group with the ketone established by hydrolysis of the ketal, and (3) epoxidation of the exocyclic double bond (Figure 1).



3 **4** **5** (1)

The general strategy chosen to establish the epoxydihydropyridine ring of benzoabikoviromycin is shown in Scheme I. After the initial palladium-catalyzed ring expansion of **6** to enone **7**, the two-carbon unit required for the ethylidene formation would be introduced as an ethyl group by standard nucleophilic 1,2-addition to the ketone of **7**. This would create an allylic alcohol, **8**, that should transform to epoxy keto alcohol **9** on treatment with standard epoxidizing reagents such as *t*-BuOOH/catalytic $VO(acac)_2$ followed by ketal hydrolysis. Cyclic imine **10** would then be created via the intramolecular Staudinger reaction described

Scheme I[a]



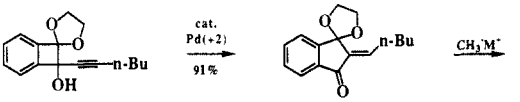
6 **7** **8**

9 **10** **2**

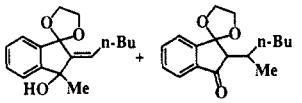
[a] R = $CH_2CH_2N_3$.

by Lambert, Vaultier, and Carrie[10] where an iminophosphorane generated under very mild conditions from an alkyl azide and PPh_3 reacts with an intramolecularly situated carbonyl group. The synthesis of benzoabikoviromycin would then be completed by the nonstereoselective dehydration of the tertiary allylic–benzylic alcohol to the ethylidene group (**10** → **2**).

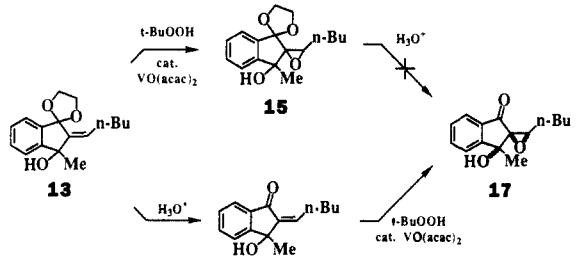
The feasibility of the early stages of the sequence shown in Scheme I was probed with substrate **11** (eq 2 and 3). Treatment



11 **12**



13 **14** (2)



15 **13** **17** **16** (3)

of **11** with 2.5% $Pd(OCOCF_3)_2$ in CH_2Cl_2 at rt for 12 h produced enone **12** in 91% yield with greater than 20:1 selectivity for formation of the *Z* isomer.[9a] Surprisingly, reaction of **12** with MeLi gave a mixture of both 1,2-adduct **13** and 1,4-adduct **14** in 84% combined yield (1:1 ratio). Use of MeMgBr favored the 1,4-adduct to an even greater extent (71% yield, 1:2 ratio). In 1984 Imamoto reported that organocerium(III) reagents react with α,β-unsaturated carbonyl compounds to yield only the 1,2-addition products.[11] To overcome the tendency of substrate **12** to react via the conjugate addition mode, we resorted to the use of organocerium reagents. Enone **12** was treated with methylcerium diiodide prepared according to the Imamoto procedure, and only 1,2-adduct **13** was obtained in high yield (98%). Epoxidation of **13** with *t*-BuOOH/5% $VO(acac)_2$[12] gave an excellent yield of epoxy alcohol **15** (only one diastereomer was obtained); however, attempts to hydrolyze the ketal of this compound failed. The desired epoxy keto alcohol was obtained by reversing the order of the epoxidation–hydrolysis sequence. Ketal **13** was hydrolyzed with 10% *p*-toluenesulfonic acid in 1:1 THF/H_2O at room tem-

(9) (a) Liebeskind, L. S.; Mitchell, D.; Foster, B. *J. Am. Chem. Soc.* **1987**, *109*, 7908. (b) Liebeskind, L. S.; Chidambaram, R.; Mitchell, D.; Foster, B. *Pure Appl. Chem.* **1988**, *60*, 2734.

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(12) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

perature giving ketone **16** in 90% yield. More vigorous hydrolysis conditions must be avoided because of facile equilibration of the double bond stereochemistry. Treatment of **16** with *t*-BuOOH/5% $VO(acac)_2$ in benzene at room temperature led to a very rapid epoxidation providing **17**, as one diastereomer, in very good yield (79%). On the basis of the known stereochemical directing effect of the alcohol in vanadium-catalyzed epoxidations, a syn relationship is assigned to the alcohol and epoxide in **17**.[12]

Having established a sequence of reactions for the initial steps of the synthetic approach shown in Scheme I, the synthesis of benzoabikoviromycin was initiated (Scheme II). Deprotonation of the *tert*-butyldimethylsilyl ether of 3-butyn-1-ol with lithium diisopropylamide and treatment of the resulting anion with benzocyclobutenedione monoketal (**3**) provided addition product **18** in multigram quantities in isolated yields averaging 85%. Application of the palladium-catalyzed ring expansion to **18** gave expected ring expansion product **19** as a yellow-orange solid in isolated yields averaging 75%. As anticipated, the stereoselectivity in the reaction was greater than 20:1, *Z*:*E*. Following the lead established in the brief model study described above, addition of ethylcerium diiodide to enone **19** proceeded in a 1,2-fashion to give allylic alcohol **20** in 83% yield after crystallization (white needles).

With compound **20** in hand, introduction of the epoxydihydropyridine ring was undertaken. The plan called for treatment of a keto azide with triphenylphosphine to induce the intramolecular Staudinger reaction (**9** → **10**, Scheme I) and thus required conversion of the *tert*-butyldimethylsilyl ether protected primary alcohol on the alkylidene side chain of **20** into a primary azide. This was easily accomplished by selective deprotection of the silyl ether with tetra-*n*-butylammonium fluoride in THF at low temperature (−78 °C → 0 °C) providing diol **21** (96% yield). This was followed by conversion of the primary alcohol to a methanesulfonate ester leaving group, which without purification was treated with sodium azide in DMF to provide azido alcohol **22** in 96% yield as a colorless oil. Preparation of imine precursor **23** was then completed by ketal hydrolysis using 3% *p*-toluenesulfonic acid monohydrate in 1:1 THF/H_2O at rt (83% yield, yellow gum).

Several attempts to cyclize keto azide **23** by utilizing the intramolecular Staudinger reaction failed. Reasoning that removal of the alkylidene unsaturation prior to imine formation might improve the chances for a successful reaction (more reactive carbonyl group, less ring strain), the required epoxidation of the alkylidene group was carried out next. Treatment of **23** with *t*-BuOOH and catalytic vanadyl acetylacetonate in benzene gave epoxy keto alcohol **24** in 98% yield as a very polar yellow gum. Then, by utilization of Lambert's conditions for imine formation (PPh_3, diethyl ether) desired cyclic imine **25** could be obtained, but only in poor yields. However, simply switching the reaction solvent from diethyl ether to benzene produced imine **25** in 97% yield as a white solid.

The final step in the synthesis of benzoabikoviromycin involved formation of the (*E*)-ethylidene group by dehydration of the tertiary benzylic alcohol under conditions compatible with the presence of the epoxy imine. A priori, the preferred stereochemical course of the dehydration was not obvious. Although molecular modeling[13] showed the (*E*)-ethylidene stereoisomer to be less stable than the *Z* isomer by 1.32 kcal/mol, an assessment by MM2 calculations of conformers A and B (Figure 2), where the H–C–C–OH bond angle was constrained near 180° to model an E2 elimination pathway, predicts them to be of almost equal energy (ΔE = 0.39 kcal/mol). Therefore, dehydration of **25** by an E2 mechanism might be expected to lead to a 1:1 mixture of stereoisomers. This, in fact, is what occurs. Dehydration of alcohol **25** with Burgess' reagent[14] in benzene at room temperature gave a 1:1 mixture of benzoabikoviromycin and its *Z* stereoisomer **26** in 60% yield. Performing the reaction above room temperature led to decomposition of starting material, while reaction below room temperature proceeded too slowly. The best yield of dehydration products was obtained with methanesulfonyl chloride and triethylamine at 0 °C in CH_2Cl_2 (69%, 1:1 *Z*:*E*). Reactions performed at lower temperature were unsuccessful. Separation of the double bond isomers was achieved by radial chromatography. Unlike abikoviromycin, benzoabikoviromycin is stable and can be stored for at least 3 months or longer when kept below 0 °C. The only sign of decomposition was a slight yellow-brown discoloration.

The 1:1 mixture of benzoabikoviromycin and its (*Z*)-ethylidene stereoisomer **26** was screened for in vitro antiviral, antitumor, and antifungal activity.[15] Significant in vitro activity against five tumor cell lines was observed in the cytotoxicity tests, and the results are shown in Table I with comparison to the clinically useful drugs cisplatin and mitomycin C. Subsequent in vivo assays did not demonstrate useful levels of activity; however, the exceptional levels of in vitro activity suggest that further studies of abikoviromycin or modified analogues is warranted.

Conclusions

The palladium(2+)-catalyzed ring expansion of 2-alkynyl-2-hydroxybenzocyclobutenone monoketals provides a simple method for the stereospecific synthesis of alkylideneindandione monoketals. By utilization of this procedure, a concise and efficient synthesis of racemic benzoabikoviromycin, a potential antiviral antibiotic, has been developed.

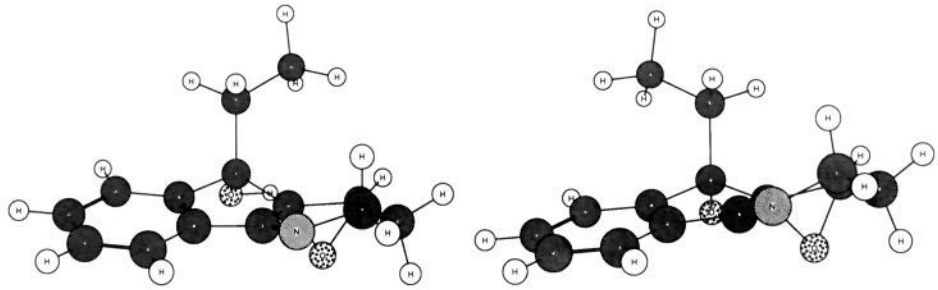
Experimental Section

Benzocyclobutenedione was prepared according to the published procedure.[16] Benzocyclobutenedione mono(ethylene acetal) was prepared according to the method of Cava.[17]

2-(1-Hexynyl)-2-hydroxybenzocyclobutenone Ethylene Acetal (11). Lithium diisopropylamide (LDA) in tetrahydrofuran (THF) was generated as follows: to a dry 250-mL round-bottomed flask under an argon atmosphere was added diisopropylamine (5.29 mL, 37.5 mmol) and tetrahydrofuran (15 mL). The solution was cooled to −78 °C and *n*-butyllithium (2.5 M in hexanes, 15.0 mL, 37.5 mmol) was added slowly dropwise by syringe. The resulting reaction mixture was allowed to warm to room temperature for 20 min and then recooled to −78 °C. To the solution of LDA at −78 °C was added 1-hexyne (2.78 g, 37.5 mmol) by syringe, and the resulting solution was allowed to warm to 0 °C and then stirred for 1 h. The reaction mixture was again cooled to −78 °C, and benzocyclobutenedione mono(ethylene acetal) (6.0 g, 34.1 mmol) in a small amount of THF was added dropwise. The reaction of 1-lithio-1-hexyne proceeded slowly at −78 °C, so the reaction mixture was allowed to warm toward 0 °C and monitored by TLC (SiO_2, 1:1 light petroleum ether/ethyl ether) for disappearance of starting material. Then, the reaction mixture was recooled to −78 °C and was quenched by addition of aqueous NH_4Cl. The reaction mixture was partitioned between ether and H_2O, and the combined ether extracts were dried over $MgSO_4$, filtered, and concentrated to an amorphous brown solid that was purified by flash chromatography (SiO_2, 1:1 light petroleum ether/ethyl ether) yielding 7.80 g (89%) of a yellow-brown solid: mp 68 °C; IR (CH_2Cl_2) 3520 (br m), 3540–3180 (br m), 3065, 2925, 2220, 1600, 1460, 1345, 1035; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45–7.33 (m, 4 H), 4.28–4.08 (m, 4 H), 2.24 (t, *J* = 7.14 Hz, 2 H), 0.86 (t, *J* = 7.33 Hz, 3 H); mass spectrum (EI), *m*/*e* (relative intensity) 258 (M^+, <1), 299 (2), 213 (5), 197 (5), 188 (8), 159 (10), 149 (15), 144 (8), 133 (7), 128 (6), 115 (16), 109 (10), 77 (6), 69 (100), 66 (3), 53 (2). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02; O, 18.58. Found: C, 74.45; H, 7.02.

Palladium-Catalyzed Rearrangement of 11 to >20:1 *Z*:*E* 2-Pentylidene-1,3-indandione Mono(ethylene acetal) (12). To a dry 25-mL round-bottomed flask under an argon atmosphere was added 2-(1-hexynyl)-2-hydroxybenzocyclobutenone ethylene acetal (300 mg, 1.16 mmol), 5 mL of dry methylene chloride, and palladium trifluoroacetate (9.6 mg, 2.5 molar %). The reaction mixture was allowed to stir under argon at room temperature while being monitored for the disappearance of starting material by TLC (SiO_2, 1:1 light petroleum ether/ethyl ether). As the reaction proceeded, there was a gradual color change from light brown to black. After 12 h at room temperature, TLC indicated that all of the starting material was transformed into a less polar compound.

(13) MM2 calculations were performed on a Vax 8550 using Model 2.94. We thank Professor Kosta Steliou for a prerelease version of this program.
(14) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 1968; Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(15) Bioassays were conducted at Bristol-Myers Pharmaceutical Research and Development. We are grateful to A. Crosswell and K. Johnston of Bristol-Myers for arranging the tests.
(16) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815.
(17) Cava, M. P.; Stein, R. P. *J. Am. Chem. Soc.* **1966**, *31*, 1866.



MM2 Energy: 40.17 kcal/mol conformer A

MM2 Energy: 40.56 kcal/mol conformer B

Figure 2.

Scheme II

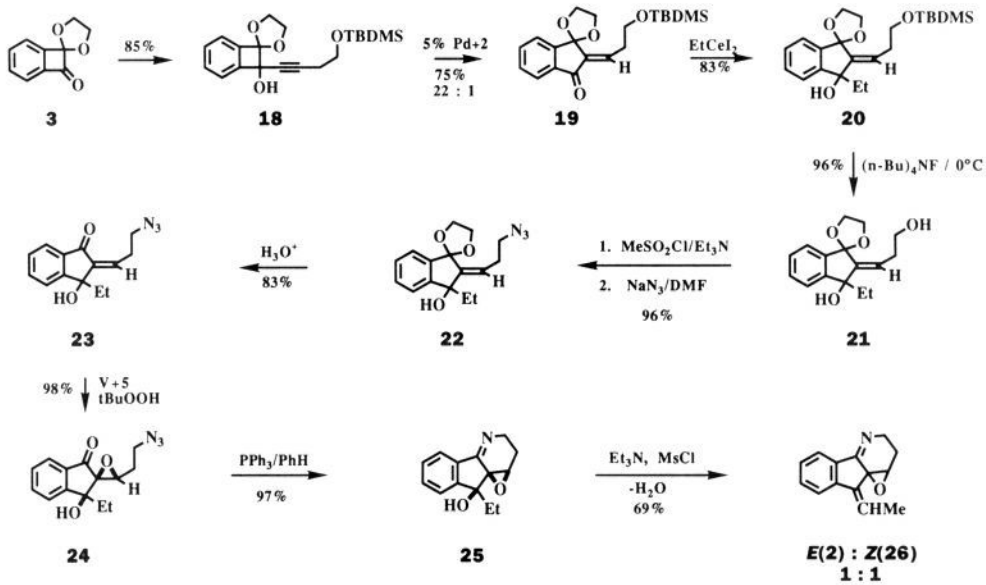


Table I. In Vitro Cyctotoxicity Bioassays

compound	IC-50 (mg/mL)/active dilution				
	A549	A549/VP	B16-PRIM	HCT-116	HCT/VP35
benzoabikoviromycin + **26** (1:1)	5.48	4.18	0.16	1.41	1.16
	5.01	4.76	0.16	1.47	1.26
cisplatin	2.48	2.42	0.23	3.59	0.98
	1.55	2.30	0.22	2.17	1.63
	2.88	2.46	0.66	4.45	2.06
	1.94	3.02	0.23	5.45	2.10
mitomycin C	0.03	0.03	0.04	0.07	<0.004
	0.01	0.03	0.04	0.06	<0.004
	0.04	0.01	0.04	0.02	0.01
	0.01	0.05	0.03	0.11	0.01

The reaction was terminated by concentration of the solution and flash chromatography of the residue (SiO_2, 20% ethyl ether in light petroleum ether) to yield 273 mg (95%) of a yellow-brown solid: mp 45 °C; IR (CH_2Cl_2) 3050, 2960, 1705 (s), 1655 (s), 1600, 1465, 1325, 1290, 995 (s); ^1H NMR (360 MHz, $CDCl_3$) δ 7.82 (d, J = 7.64 Hz, 1 H), 7.65 (dt, J = 4.58 Hz, J = 1.18 Hz, 1 H), 7.60 (d, J = 7.73 Hz, 1 H), 7.51 (dt, J = 7.32 Hz, J = 1.04 Hz, 1 H), 7.02 (t, J = 7.79 Hz, 1 H of Z isomer), 6.58 (t, J = 7.63 Hz, vinyl H of E isomer), 4.41 (m, 4 H), 2.91 (q, J = 7.50 Hz, allylic H of E isomer), 2.45 (q, J = 7.67 Hz, 2 H of Z isomer), 1.33 (quintet, J = 7.35 Hz, 2 H), 1.38 (sextet, J = 7.18 Hz, 2 H), 0.93 (t, J = 7.27 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 190.1, 151.5, 144.6, 137.2, 135.9, 130.3, 124.1, 123.8, 109.3, 66.4, 31.8, 28.1, 23.2, 14.6; mass spectrum (EI), m/e (relative intensity) 258 (M^+, 8), 229 (16), 216 (100), 201 (26), 185 (9), 172 (5), 159 (15), 144 (20), 128 (9), 115 (12), 104 (8), 77 (6), 73 (2), 55 (2). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.38; H, 7.03. Found: C, 74.46; H, 7.04.

2(Z)-Pentylidene-3-methyl-3-hydroxy-1-indanone (13). Following the procedure of Imamoto[11] cerium diiodide was generated by the addition of iodine (180 mg, 1.42 mmol) to cerium metal (135 mg, 0.96 mmol) under an argon atmosphere. Dry THF (5 mL) was added at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h and then at room temperature for 11 h. The resulting suspension of CeI_3 was cooled to −78 °C, MeLi (0.70 mL of a 1.4 M solution in ethyl ether, 0.97 mmol) was added slowly by syringe, and the reaction mixture was allowed to stir at −78 °C for 30 min. Allylic alcohol **13** (100 mg, 0.39 mmol) in a small amount of THF was added via syringe, and the reaction was held at −78 °C and monitored by TLC (SiO_2, 1:1 ethyl ether/light petroleum ether). The reaction was completed after 15 min, and aqueous NH_4Cl was added to quench the mixture. The reaction was partitioned between ether and H_2O, and the combined ether extracts were dried over $MgSO_4$, filtered, and concentrated to a residue. Flash chromatography of the residue (SiO_2, 1:1 ethyl ether/light petroleum ether) provided 94 mg (88%) of 2(Z)-pentylidene-3-methyl-3-hydroxy-1-indanone ethylene acetal: IR (CH_2Cl_2) 3580, 3045, 2960, 2935, 2870, 1635, 1465, 1290, 1065, 940; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50–7.30 (m, 4 H), 6.09 (t, J = 7.57 Hz, 1 H), 4.30 (m, 4 H), 2.34 (m, 2 H), 1.96 (br s, 1 H), 1.61 (s, 3 H),

0.93 (t, J = 7.20 Hx, 3 H). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.26; H, 8.14.

2(*Z*)-Pentylidene-3-methyl-3-hydroxy-1-indanone (16). Acetal **13** (165 mg, 0.60 mmol) was stirred at room temperature in a mixture of 1:1 THF/H_2O (10 mL) containing *p*-toluenesulfonic acid monohydrate (11.4 mg, 0.06 mmol) for 8.5 h with monitoring for loss of starting material by TLC (SiO_2, 1:1 ethyl ether/light petroleum ether). Workup involved dilution of the reaction mixture with saturated aqueous $NaHCO_3$ and extraction of the product into ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated to provide 125 mg (90%) of product as a yellow oil: IR (CH_2Cl_2) 3580 (br m), 3050, 2960, 2920, 2860, 1688 (s), 1645, 1605, 1462, 1090, 968, 700; ^1H NMR (360 MHz, $CDCl_3$) δ 7.74 (d, J = 7.7 Hz, 1 H), 7.65 (m, 2 H), 7.46 (dt, J = 7.3 Hz, J = 0.92 Hz, 1 H), 6.58 (t, J = 7.74 Hz, 1 H), 2.91 (q, J = 7.40 Hz, 2 H), 1.68 (s, 3 H), 1.51 (m, 2 H), 1.39 (m, 2 H), 0.92 (t, J = 7.26 Hz, 3 H); mass spectrum (EI), m/e (relative intensity) 230 (M^+, 100), 212 (19), 201 (46), 197 (9), 183 (59), 179 (6), 173 (42), 170 (18), 165 (11), 159 (80), 155 (14), 147 (15), 141 (10), 128 (15), 115 (22), 105 (11), 77 (11), 69 (68). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.34; H, 7.90.

3′-*n*-Butyl-3-hydroxy-3-methylspiro[indan-2,2′-oxiran]-1-one (17). *tert*-Butyl hydroperoxide (0.05 mL of a 90% solution, 0.60 mmol) was added slowly dropwise to a solution of **16** (101 mg, 0.44 mmol) in dry benzene (5 mL) containing a suspension of vanadyl acetylacetonate (5 mg, 5 molar %). Monitoring by TLC (SiO_2, 1:1 ethyl ether/light petroleum ether) indicated that the reaction was complete in 1 h. After addition of saturated aqueous $NaHCO_3$, the product was extracted into CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. Filtration and evaporation gave a residue that was flash chromatographed (SiO_2, 1:1 ethyl ether/light petroleum ether) and gave 86 mg (79%) of a colorless oil: IR (CH_2Cl_2) 3885, 3050, 2960, 2930, 2860, 1697 (s), 1646 (s), 1608, 1465, 1380, 1365, 1330, 1090, 970, 700; ^1H NMR (360 MHz, $CDCl_3$) δ 7.79 (m, 3 H), 7.75 (m, 1 H), 3.56 (t, J = 6.06 Hz, 1 H), 2.63 (s, 1 H), 2.11 (m, 1 H), 1.95 (m, 1 H), 1.56 (s, 3 H), 1.36 (m, 4 H), 0.09 (t, J = 7.18 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 198.6, 155.2, 136.1, 135.1, 129.7, 124.3, 123.2, 71.5, 69.1, 66.5, 28.5, 26.2, 25.1, 22.3, 13.9; ^{13}C NMR APT (75.4 MHz, $CDCl_3$) of carbons with even H attached δ 198.6 155.2, 135.1, 71.5, 69.1, 28.5, 26.2, 22.3; ^{13}C NMR APT (75.4 MHz, $CDCl_3$) of carbons with odd H attached δ 136.1, 129.7, 124.3, 123.2, 66.5, 25.1, 13.9; mass spectrum (EI), m/e (relative intensity) 246 (M^+, 52), 228 (20), 160 (48), 148 (100), 131 (27), 115 (17), 105 (68), 97 (11), 91 (13), 77 (28), 55 (15). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H. 7.37. Found: C, 73.08; H, 7.41.

1-(*tert*-Butyldimethylsiloxy)-3-butyne. 3-Butyn-1-ol (9.0 g, 0.129 mol), triethylamine (18 mL), and *tert*-butyldimethylsilyl chloride (19.4 g, 0.129 mol) were stirred at 0 °C in 20 mL of dry DMF in a 250-mL round-bottomed flask under an argon atmosphere. The resulting thick, white paste was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was cooled in an ice bath and was quenched with an equal volume of water. The product was extracted into pentane, and the combined pentane layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give 22.3 g (94%) of a colorless oil that was used without further purification: IR (CH_2Cl_2) 3295, 2950, 2920, 2880, 2830, 1100, 835, 775, 650; ^1H NMR (360 MHz, $CDCl_3$) δ 3.73 (t, J = 7.04 Hz, 2 H), 2.39 (dt, J = 2.65 Hz, J = 7.22 Hz, 2 H), 1.95 (t, J = 2.62 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

2-Hydroxy-2-[4-(*tert*-butyldimethylsiloxy)-1-butynyl]benzocyclobutenone Ethylene Acetal (18). A dry 250-mL round-bottomed flask under an argon atmosphere and containing 20 mL of THF and 7.0 mL of diisopropylamine (50 mmol) was cooled to −78 °C. After addition of *n*-BuLi (20 mL of a 2.5 M solution in hexanes, 50.0 mmol) by syringe, the reaction mixture was allowed to warm to room temperature and was stirred for 20 min before being recooled to −78 °C. At that temperature, 1-(*tert*-butyldimethylsiloxy)-3-butyne (8.36 g, 45.4 mmol) was added, and the reaction mixture was allowed to warm to 0 °C and was stirred for 1 h to effect formation of the acetylide anion. The reaction mixture was recooled to −78 °C, and benzocyclobutenedione mono(ethylene acetal) (8.0 g, 45.4 mmol) dissolved in a small amount of THF was added slowly dropwise. Stirring was continued for 10 min at −78 °C and then for an additional 20 min after warming to 0 °C. By this time analysis by TLC showed no starting material present, and the reaction was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined ether extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, concentrated to a brown solid on a rotary evaporator, and flash chromatographed (SiO_2, 1:1 ethyl ether/light petroleum ether) to yield 13.2 g (81%) of product as a light yellow solid: mp 52–54 °C; IR (CH_2Cl_2) 3600–3480 (br), 2980, 2900, 1600, 1100, 8.40; ^1H NMR (360 MHz), $CDCl_3$) δ 7.47–7.35 (m, 4 H), 4.33–4.14 (m, 4 H), 3.72 (t, J = 7.37 Hz, 2 H), 3.27 (br s, 1 H), 2.48 (t, J = 7.35 Hz, 2 H), 0.88 (s, 9 H), 0.02 (s, 6 H); mass spectrum (low-resolution FAB, 3-NBA/Li = matrix), m/e (relative intensity) 367 [$(M + Li)^+$, 100], 343 (28), 323 (11), 303 (10), 227 (14), 185 (69), 160 (12), 115 (26). Anal. Calcd for $C_{20}H_{28}O_4Si$: C, 66.58; H, 7.83. Found: C, 66.64; H, 7.82.

2(*Z*)-[3-(*tert*-Butyldimethylsiloxy)propylidene]-1,3-indandione Mono(ethylene acetal) (19). 2-Hydroxy[4-(*tert*-butyldimethylsiloxy)-1-butynyl]benzocyclobutenone ethylene acetal (12.5 g, 38.5 mmol), 70 mL of dry CH_2Cl_2, and palladium trifluoroacetate (640 mg, 1.93 mmol, 5 molar %) were added to a 250-mL round-bottomed flask under an argon atmosphere. After being stirred at room temperature for 10 h, the black reaction mixture was concentrated on a rotary evaporator to a black gum that was purified by flash chromatography (SiO_2, 1:4 ethyl ether/light petroleum ether) providing 9.08 g (73%) of an orange-yellow solid after recrystallization from ethyl ether/light petroleum ether: mp 112–114 °C; IR (CH_2Cl_2) 2950, 2930, 2900, 2800, 1710 (s), 1660, 1095, 840; ^1H NMR (360 MHz, $CDCl_3$) δ 7.82 (d, J = 7.22 Hz, 1 H), 7.63 (dt, J = 7.03 Hz, J = 0.90 Hz, 1 H), 7.59 (d, J = 7.20 Hz, 1 H), 7.51 (dt, J = 7.28 Hz, J = 0.93 Hz, 1 H), 7.04 (t, J = 7.57 (Hz, 1 H), 4.38–4.51 (m, 4 H), 3.80 (t, J = 6.80 Hz, 2 H), 2.68 (q, J = 7.28 Hz, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 189.8, 150.6, 140.0, 137.9, 136.7, 135.3, 130.2, 123.6, 123.1, 108.5, 65.6, 61.6, 31.7, 25.8, 18.2, −5.5; mass spectrum (low-resolution FAB, 3-NBA = matrix), m/e (relative intensity) 367 [$(M + Li)^+$, 81], 229 (28), 72 (100). Anal. Calcd for $C_{20}H_{28}O_4Si$: C, 66.58; H, 7.83. Found: C, 66.69; H, 7.85.

2(*Z*)-[3-(*tert*-Butyldimethylsiloxy)propylidene]-3-ethyl-3-hydroxy-1-indanone Ethylene Acetal (20). To a suspension of cerium turnings (6.7 g, 47.9 mmol) in dry THF (80 mL) was added resublimed iodine (9.03 g, 71.0 mmol) at 0 °C under an argon atmosphere. After being stirred for 1 h at 0 °C, the suspension was cooled to −65 °C, and ethyllithium (50.21 mL of a 1.0 M solution in benzene, 50.21 mmol) was added dropwise via syringe. After the temperature had been lowered to −78 °C, compound **19** dissolved in a small amount of THF was added slowly dropwise with stirring, and the mixture was stirred at −78 °C for 1 h. The reaction was quenched at that temperature with saturated aqueous NH_4Cl, and after being warmed to ambient temperature, the product was extracted into ethyl ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator to an orange gum that was flash chromatographed (SiO_2, 1:1 ethyl ether/light petroleum ether). Recrystallization of the product from light petroleum ether gave 6.0 g (83%) of white needles: mp 86–87 °C; IR (CH_2Cl_2) 3580, 2960, 2920, 2880, 1460, 980, 835; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44–7.30 (m, 4 H), 6.07 (t, J = 7.48 Hz, 1 H), 4.19–4.42 (m, 4 H), 3.75 (t, J = 7.16 Hz, 3 H), 2.59 (m, 2 H), 2.03 (br s, 1 H), 1.94 (q, J = 7.44 Hz, 2 H), 0.09 (s, 9 H), 0.76 (t, J = 7.41 Hz, 3 H), 0.01 (s, 6 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 147.0, 145.6, 142.3, 130.0, 128.8, 128.0, 123.4, 122.7, 111.7, 80.1, 65.3, 64.8, 62.6, 34.7, 31.1, 25.8, 18.2, 8.7, −5.4; mass spectrum (EI), m/e (relative intensity) 390 (M^+, <1), 373 (8), 334 (18), 289 (14), 259 (41), 229 (40), 197 (24), 155 (12), 75 (base). Anal. Calcd for $C_{22}H_{24}OSi$: C, 67.65; H, 8.78. Found: C, 67.80; H, 8.83.

2(*Z*)-(3-Hydroxypropylidene)-3-ethyl-3-hydroxy-1-indanone Ethylene Acetal (21). To a flame-dried round-bottomed flask was added compound **20** (4.0 g, 10.26 mmol) and dry THF (15 mL), and the resulting solution was brought under an argon atmosphere and cooled to −78 °C. At that temperature, tetra-*n*-butylammonium fluoride (30.76 mL of a 1.0 M solution in THF, 30.76 mmol) was added slowly by syringe, and the resulting mixture was allowed to warm to 0 °C and stirred at that temperature for 3 h. Saturated aqueous NH_4Cl was added to quench the reaction, and the product was extracted into ethyl ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated, and the resulting residue was chromatographed (SiO_2, ethyl ether) giving 2.7 g (96%) of product as a colorless gum: IR (CH_2Cl_2) 3580, 3540–3120 (br), 2990, 2890, 1450, 980; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48 (m, 4 H), 6.03 (dd, J = 7.82 Hz, J = 1.05 Hz, 1 H), 4.22–4.43 (m, 4 H), 3.55–3.80 (m, 2 H), 3.00 (br s, 1 H), 2.42–2.75 (m, 2 H), 1.91 (q, J = 7.44 Hz, 2 H), 0.75 (t, J = 7.40 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 147.9, 145.8, 141.7, 130.0, 128.5, 128.0, 123.6, 122.6, 111.6, 79.8, 64.9, 64.5, 61.0, 30.3, 8.6; mass spectrum (EI), m/e (relative intensity) 276 (M^+, <1), 247 (100), 229 (50), 185 (78), 157 (26), 115 (35), 91 (10), 77 (28). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.95; H, 7.30. Found: C, 69.67; H, 7.33.

2(*Z*)-(3-Azidopropylidene)-3-ethyl-3-hydroxy-1-indanone Ethylene Acetal (22). A flame-dried 50-mL round-bottomed flask was charged with 20 mL of dry CH_2Cl_2, diol **21** (2.50 g, 9.10 mmol), and triethylamine (2.54 mL, 18.24 mmol) and was brought under an argon atmosphere and then cooled to 0 °C. Methanesulfonyl chloride (1.04 g, 9.10 mmol) was added slowly dropwise. After TLC indicated disappearance of starting material, the reaction mixture was quenched at 0 °C with a saturated aqueous solution of NaCl. The crude product was extracted into CH_2Cl_2, and the organic layers were combined, dried over $MgSO_4$, filtered, and then concentrated on a rotary evaporator to yield a light

yellow gum. The crude mesylate was dissolved in a minimum amount of DMF (5.0 mL) under an argon atmosphere, and NaN_3 (1.77 g, 27.2 mmol) was added. The resulting creamy white suspension was stirred for 10 h at room temperature, quenched with a saturated aqueous NaCl solution, and extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator at room temperature to yield the crude azide. Flash chromatography (SiO_2, 1:1 ethyl ether/light petroleum ether) gave 2.6 g (96%) of a colorless oil: IR (CH_2Cl_2) 3580, 3530–3200 (br), 2960, 2930, 2890, 2100, 1680, 1455, 980; ^1H NMR (360 MHz, $CDCl_3$) δ 7.24 (A of AA'BB', 2 H), 7.35 (B of AA'BB', 2 H), 5.93 (t, J = 7.62 Hz, 1 H), 4.61–4.42 (m, 4 H), 3.35 (t, J = 6.97 Hz, 2 H), 2.41–2.71 (m, 3 H), 1.90 (q, J = 7.39 Hz, 2 H), 0.74 (t, J = 7.38 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 148.6, 145.3, 142.0, 130.2, 128.9, 126.7, 123.5, 122.7, 111.6, 80.0, 65.2, 64.7, 50.8, 34.8, 27.1, 8.6; mass spectrum (low-resolution FAB, 3-NBA/Li = matrix), m/e (relative intensity) 308 [(M + Li)$^+$, 100], 284 (12), 256 (7), 200 (12), 115 (23). Anal. Calcd for $C_{16}H_{19}O_3N_3$: C, 63.76; H, 6.36; N, 13.95. Found: C, 63.61; H, 6.41; N, 13.95.

2(*Z*)-(3-Azidopropylidene)-3-ethyl-3-hydroxy-1-indanone (23). A 50-mL round-bottomed flask was charged with 2(*Z*)-(3-azidopropylidene)-3-ethyl-3-hydroxyindanone ethylene acetal (1.77 g, 5.88 mmol), 15 mL of a 1:1 THF/H_2O solution, and *p*-toluenesulfonic acid monohydrate (55 mg, 0.18 mmol). The resulting reaction mixture was allowed to stir at room temperature for 12 h, then it was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with ether, and the combined ether extracts were dried over $MgSO_4$, filtered, and concentrated to a yellow oil. The oil was flash chromatographed (SiO_2, ether) providing 1.25 g (83%) of **23** as a yellow gum that darkened to golden brown on storage: IR (CH_2Cl_2) 3590, 3540–3100 (br), 3050, 2980, 2930, 2880, 2100, 1695, 1645, 1600, 1460, 1350, 1225, 1030, 960; ^1H NMR (360 MHz, $CDCl_3$) δ 7.77 (d, J = 6.9 Hz, 1 H), 7.64 (t, J = 7.01 Hz, 1 H), 7.62 (d, J = 6.89 Hz, 1 H), 7.53 (t, J = 7.0 Hz, 1 H), 6.45 (t, J = 7.23 Hz, 1 H), 3.44 (t, J = 7.44 Hz, 2 H), 3.20 (m, 2 H), 2.51 (br s, 1 H), 2.10 (m, 2 H), 0.50 (t, J = 7.48 Hz, 3 H); mass spectrum (EI), m/e (relative intensity) 228 (M$^+$ – CH_2CH_3, 4), 200 (30), 173 (100), 155 (21), 115 (74), 101 (13), 91 (14), 77 (44), 63 (12). Anal. Calcd for $C_{14}H_{15}O_2N_3$: C, 65.34; H, 5.88; O, 12.44; N, 16.34. Found: C, 65.34; H, 5.90; N, 16.28.

3'-(Azidoethyl)-3-ethyl-3-hydroxyspiro[indan-2,2'-oxiran]-1-one (24). A flame-dried 25-mL round-bottomed flask was brought under an argon atmosphere and was charged with 2(*Z*)-(3-azidopropylidene)-3-ethyl-3-hydroxyindanone (1.23 g, 4.78 mmol), 5 mL of dry benzene, and vanadyl acetylacetonate (63.4 mg, 0.12 mmol). The resulting mixture was allowed to stir at room temperature while 1.5 equiv of 90% *tert*-butyl hydroperoxide (0.79 mL, 7.71 mmol) was being added dropwise, slowly, by syringe. Stirring was continued at room temperature for an additional 2 h, then the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated at room temperature on a rotary evaporator. The resulting colorless gum was flash chromatographed (SiO_2, ethyl ether) to give 1.22 g (98%) of **24** as a colorless oil: IR (CH_2Cl_2) 3540 (br), 3060, 2980, 2940, 2890, 2100, 1720, 1605, 1460, 1090, 930; ^1H NMR (360 MHz, $CDCl_3$) δ 7.76 (d, J = 7.01 Hz, 1 H), 7.74 (d, J = 7.12 Hz, 1 H), 7.68 (t, J = 7.45 Hz, 1 H), 7.48 (t, J = 7.32 Hz, 1 H), 3.58 (dd, J = 6.29 Hz, J = 5.57 Hz, 1 H), 3.54 (t, J = 6.15 Hz, 2 H), 2.80 (br s, 1 H), 2.60–2.45 (m 1 H), 2.36–2.14 (m, 2 H), 1.85–1.70 (m, 1 H), 0.65 (t, J = 7.46 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 198.34, 154.25, 136.25, 135.87, 129.52, 124.66, 123.09, 74.30, 66.29, 62.88, 48.53, 30.98, 26.30, 8.27; mass spectrum (EI), m/e (relative intensity) 244 (M$^+$ – CH_2CH_3, 4) 228 (7), 217 (16), 199 (58), 162 (59), 147 (80), 133 (37), 105 (86), 77 (100). Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.51; H, 5.54; N, 15.38; O, 17.57. Found: C, 61.59; H, 5.57; N, 15.31.

4,4a-Epoxy-5-ethyl-3,4,4a,5-tetrahydro-5-hydroxy-2*H*-indeno[1,2-*b*]-pyridine (25). To a 25-mL round-bottomed flask under an argon atmosphere was added dry benzene (7 mL), keto azide **24** (1.19 g, 4.36 mmol), and triphenylphosphine (1.37 g, 3.22 mmol). The resulting dark brown solution was stirred at room temperature for 8 h followed by removal of solvent on a rotary evaporator. The resulting residue was flash chromatographed (SiO_2, ethyl ether) to yield 968 mg (97%) of imine **25** as a flaky, white solid: mp 131–132 °C; IR (CH_2Cl_2) 3550 (br), 2985, 2940, 1660, 1610, 1460, 1430, 1350, 1330, 1095, 915; ^1H NMR (360 MHz, $CDCl_3$) δ 7.78 (d, J = 6.91 Hz, 1 H), 7.58 (m, 2 H), 7.45 (dt, J = 7.01 Hz, J = 0.93 Hz, 1 H), 3.98 (br s, 1 H), 3.97–3.90 (m, 1 H), 3.74–3.62 (m, 1 H), 2.70 (m, 1 H), 2.40–2.29 (m, 1 H), 2.16–2.03 (m, 1 H), 1.84–1.65 (m, 2 H), 0.57 (t, J = 7.52 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.81, 150.10, 136.60, 133.53, 129.29, 124.00, 121.03, 75.67, 60.51, 58.93, 44.49, 32.15, 22.86, 8.21; mass spectrum (EI), m/e (relative intensity) 229 (M$^+$, 1), 212 (3), 200 (100), 182 (21), 170 (8), 158 (16), 146 (10), 127 (10), 115 (12), 77 (6). Anal. Calcd for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; O, 13.96; N, 6.11. Found: C, 73.41; H, 6.64; N, 6.04.

Benzoabikoviromycin (2) and the *Z* Isomer (26). A flame-dried 10-mL round-bottomed flask was brought under an argon atmosphere and was charged with compound **25** (150 mg, 0.65 mmol), methylene chloride (4 mL), and triethylamine (66 mg, 0.65 mmol), and the resulting solution was cooled to 0 °C. At that temperature, methanesulfonyl chloride (75 mg, 0.65 mmol) was added dropwise as a solution in CH_2Cl_2 followed by addition of another equivalent of triethylamine. The reaction mixture was allowed to stir at room temperature for 1 h, then saturated aqueous NH_4Cl was added to quench the reaction, and the organics were partitioned between CH_2Cl_2 and H_2O. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated at room temperature on a rotary evaporator, and the residue was flash chromatographed (SiO_2, ethyl ether) to give 95 mg (69%) of a 1:1 mixture of benzobikoviromycin (**2**) and the *Z* stereoisomer (**26**). The mixture was separated by radial chromatography (SiO_2, 3% ethyl ether in light petroleum ether): IR (*E*/*Z* mixture, CH_2Cl_2) 3040, 2940, 2865, 1655, 1605, 1465, 1345, 1320, 920, 825; ^1H NMR [*E* isomer (**2**), 360 MHz, $CDCl_3$] δ 7.78 (d, J = 8.10 Hz, 1 H), 7.56 (d, J = 7.91 Hz, 1 H), 7.45 (t, J = 8.1 Hz, 1 H), 4.37 (br s, 1 H), 3.86 (m, 2 H), 2.25 (m, 1 H), 1.89 (d, J = 7.53 Hz, 3 H), 1.70 (m, 1 H); ^1H NMR [*Z* isomer (**26**), 360 MHz, $CDCl_3$] δ 7.84 (d, J = 7.69 Hz, 1 H), 7.76 (d, J = 7.67 Hz, 1 H), 7.50 (t, J = 7.87 Hz, 1 H), 7.32 (t, J = 7.72 Hz, 1 H), 5.75 (q, J = 7.49 Hz, 1 H), 3.94 (br s, 1 H), 3.86 (m, 2 H), 2.26 (m, 1 H), 2.13 (d, J = 7.48 Hz, 3 H), 1.70 (m, 1 H); ^{13}C NMR [*E* isomer (**2**), 75.4 MHz, $CDCl_3$] δ 168.18, 143.15, 135.49, 132.00, 131.79, 124.66, 121.41, 120.83, 119.46, 59.48, 57.48, 44.58, 44.58, 22.14, 14.31; ^{13}C NMR [*Z* isomer (**26**), 75.4 MHz, $CDCl_3$] δ 168.07, 144.42, 137.43, 131.74, 131.39, 124.61, 121.82, 121.41, 121.30, 60.30, 56.47, 43.94, 22.10, 12.21; mass spectrum of *E* isomer (**2**) (EI), m/e (relative intensity) 211 (M$^+$, 100), 193 (50), 182 (48), 168 (46), 154 (32), 142 (35), 128 (31), 115 (31), 101 (9), 77 (19), 69 (35), 59 (18); mass spectrum of *Z* isomer (**26**) (EI), m/e (relative intensity) 211 (M$^+$, 100), 182 (52), 168 (49), 156 (36), 142 (43), 128 (35), 115 (35), 102 (10), 89 (14), 77 (20), 63 (19). Anal. Calcd for *E*/*Z* mixture of $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63; O, 7.57. Found: C, 79.88; H, 6.32; N, 6.47.

Acknowledgment. This investigation was supported by Grant CA44404 awarded by the National Cancer Institute, DHHS. We are grateful to Professor Steven Weinreb of The Pennsylvania State University for first bringing to our attention the interesting structure of abikoviromycin. We acknowledge the use of a VG 70-S mass spectrometer and a Micro-Vax work station purchased through funding from the National Institutes of Health, S10-RR-02478 and S10-RR-04177, respectively, and a 300-MHz NMR and a 360-MHz NMR purchased through funding from the National Science Foundation, NSF CHE-8516614 and NSF CHE-8206103, respectively.