Construction of the Bicyclic Core Structure of the Enediyne Antibiotic Esperamicin-A_1 in Either Enantiomeric Form from (−)-Quinic Acid

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Employed as a common chiral starting material, (−)-quinic acid (**7**) was converted in a concise manner to both enantiomers of the β,γ-unsaturated ketone **12**. On the one hand, (+)-**12** was obtained by stereospecific borohydride reduction of the conjugated ketone intermediate **9**, transketalization, and oxidation of the derived homoallylic alcohol using the Dess–Martin periodinane reagent. Alternatively, dehydration of the tertiary alcohol **13** and oxidation of the free hydroxyl group in **14** furnished (−)-**12** in good overall yield. Reaction of (+)-**12** with dichlorocerium TMS acetylide was followed by Pd(0)-assisted construction of the acyclic enediyne **21**. Cyclization of this intermediate on treatment with KHMDS proved efficient, providing the esperamicin intermediate (−)-**22** in 60% isolated yield. In an identical fashion −)-**12** was converted to the enantiomeric bicyclic enediyne (+)-**22**. Subsequent liberation of the diol system, and selective oxidation of the allylic alcohol in **25** gave ketone **26**. Reaction of this intermediate with $Ph_2S{=}NH$ monohydrate gave aziridine **27** which was readily converted to its carbamate derivative **28** in preparation for aziridine ring opening.

Calicheamicin-γ_1^I (**1**) and esperamicin-A_1 (**2**) are amongst the most potent antitumoral agents known, displaying *in vitro* and *in vivo* activities at ng/mL levels (IC_{50}'s) against a number of tumor systems (B16 melanoma, Moser human carcinoma, HCT-116 carcinoma, and normal and vincristine resistant leukemia).[1-3] This activity derives from the capacity of the aglycone component of these two structurally unique "enediyne" antibiotics to cleave duplex DNA by a totally unprecedented multistep mechanism initiated by nucleophilic attack on (reduction of) the allylic trisulfide moiety (Scheme 1). Reaction of the resultant thiolate anion with the bridgehead enone system then occurs giving the Michael addition product **3**. This opens the way to Bergman-type cycloaromatization of **3** to a highly reactive 1,4-benzenoid diradical **4**, which abstracts hydrogen from the ribosyl backbone of duplex DNA causing single and/or double strand breaks.[1c,4] The observed cycloaromatization of **3** at physiological temperature is truly remarkable and reflects the very highly strained nature of the bicyclic enediyne system.

To explore the many new possibilities that the enediyne antibiotics offer for the development of therapeutic agents against cancer, intense efforts have been made to achieve the total synthesis of compounds **1** and **2** and to conceive mechanism based analogues.[5-12] Considering different bond disconnections to identify potential routes to calicheamicin/esperamicin one immediately perceives

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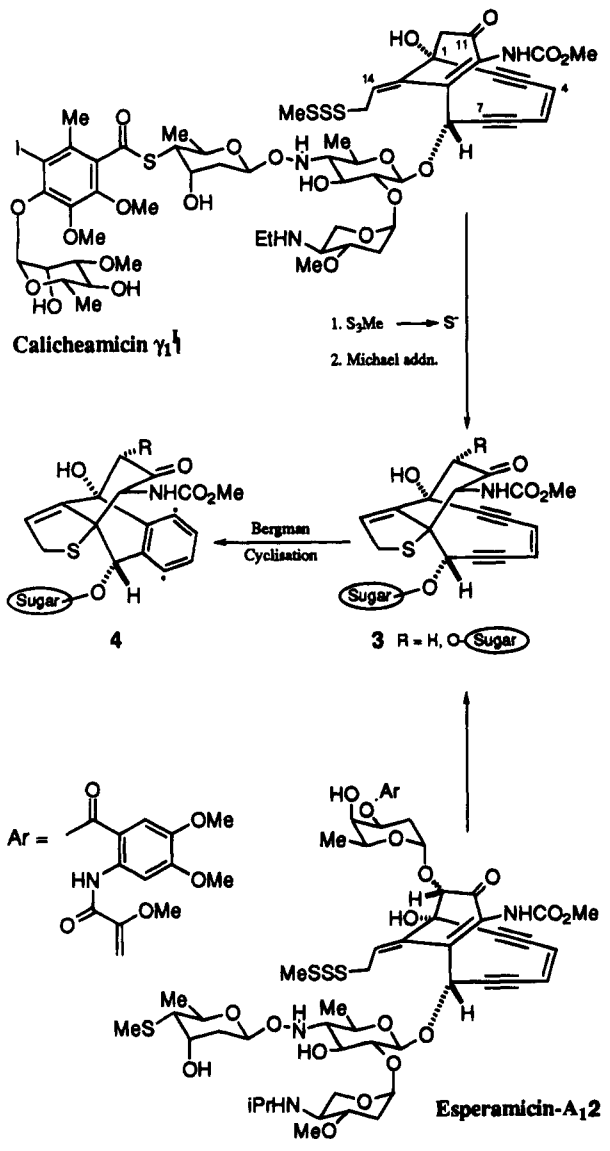
Scheme 1



that the central core structure (aglycon) can be constructed by building the enediyne bridge across the keto-aldehyde component of a highly functionalized six-membered ring "platform" structure represented by **5** (Scheme 2). This approach, central to the synthesis of calicheamicinone **6** (R = H) by the Danishefsky and Nicolaou teams,[9,10] is rendered highly attractive by the fact that very efficient Pd(0) coupling technology can be used to assemble the enediyne component from two acetylene units and *cis*-dichloroethylene.[13] On the other hand, it also presents a number of challenges, necessitating that the platform synthon be judiciously designed such that, in its preferred conformation, the atoms involved in the final step of enediyne bridge formation are within effective bond forming distance of each other, and that, once formed, the possibility exists for the different functionalities present in the target molecule to be revealed, or elaborated, with the correct sense of timing. A further condition is that this synthon be readily prepared in monochiral form from accessible starting materials.

Inspired by this strategy we initiated, several years back, a program to develop an enantioselective synthesis of the esperamicin-A_1 aglycon **6** (R = OH) and to access analogs of similar complexity for evaluation of different strategies for tumor targeting.[14] From a number of potential candidates for the platform structure in this work the β,γ-unsaturated ketone **12** was chosen, since (i) with respect to "esperamicinone" the $\Delta^{1,2}$ double bond and the two oxygens of the diol system in this molecule are correctly positioned,[15] (ii) the two carbonyl functions are also correctly placed, and their order of reactivity is such that enediyne bridge formation can be initiated at the ketone center,[16] and (iii) its diol system is a convenient vehicle for the eventual connection of a simple triggering device, as well as a DNA recognition element and/or tumor vectoring device (monoclonal antibody,[17] etc.) in esperamicin analogs derived from it.

Despite one report that a β,γ-unsaturated ketone closely related to **12** is highly unstable under acid and base conditions,[18] results from our previous work[11] on the condensation of β,γ-unsaturated ketones with dichlorocerium acetylides gave us confidence that, once prepared, compound **12** could be successfully manipulated. In this paper we describe a short and simple sequence of reactions for the preparation of *both* enantiomers of ketone **12** on a large scale (>20 g) using readily available and inexpensive (−)-quinic acid **7** as a common starting material (Scheme 3). The elaboration of (+)-**12** to the pivotal intermediate (−)-(1*S*,8*R*)-**22** possessing the natural esperamicin configuration,[19] and its enantiomer (+)-**22** from (−)-**12** is then described (Scheme 4). Finally, the steps involved in introducing the keto group at C-11 and the urethane nitrogen at C-10 of esperamicinone are subsequently detailed.

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(15) Note, however, that the stereochemistry of the C-12 OH group in **12** is opposite to that observed in esperamicin. This orientation is necessary to ensure proper stereocontrol in the acetylene addition step (**12** → **15**). Epimerization of this center is programmed at a latter stage in the synthesis of esperamicinone, see ref 8c.

(16) Employing a keto aldehyde platform synthon to construct calicheamicinone, Danishefsky et al. (ref 9) showed the importance of both initiating enediyne bridge construction at the ketone center and effecting ring closure through 1,2-addition to the more reactive aldehyde carbonyl.

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(19) Golik, J.; Krishnan, B.; Doyle, T. W.; Van Duyne, G.; Clardy, J. *Tetrahedron Lett.* **1992**, *33*, 6049.

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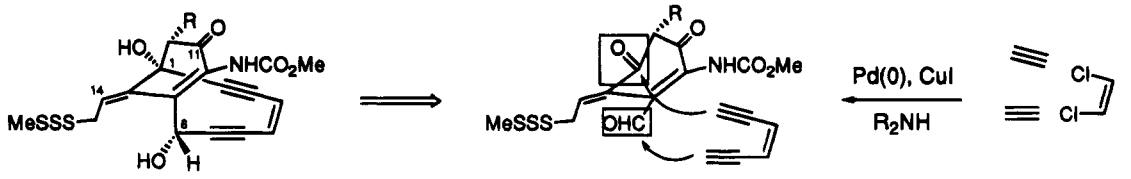
Scheme 2

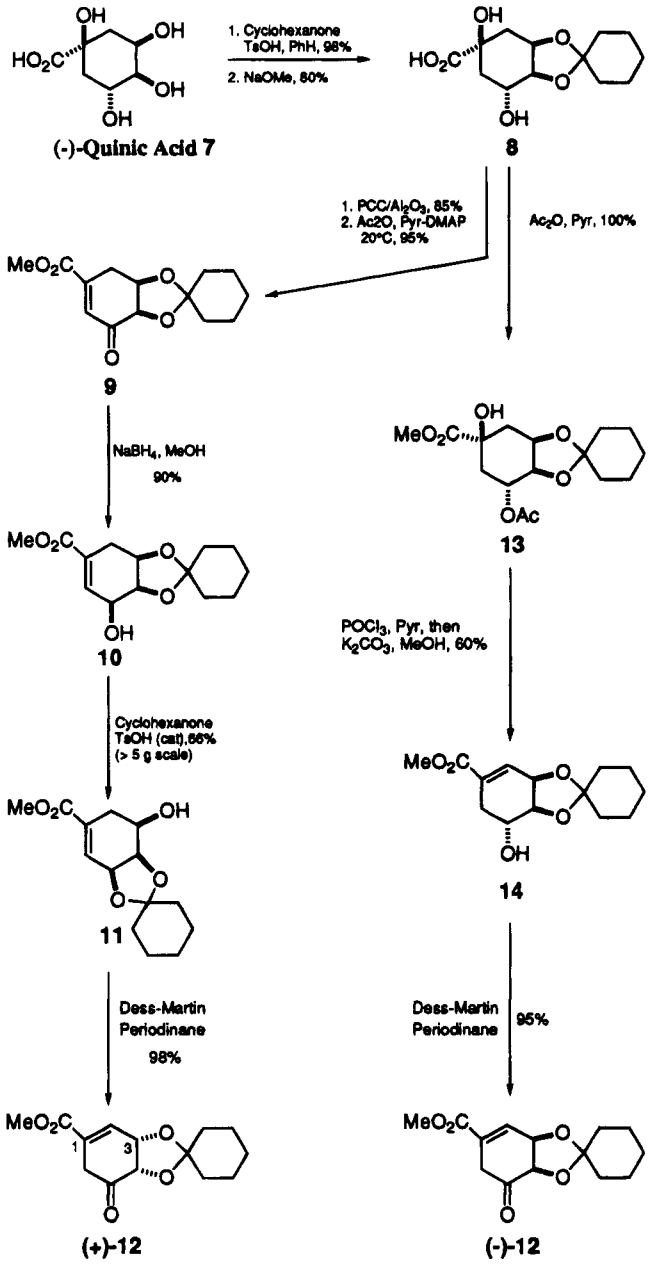


6

Calicheamicinone R = H
Esperamicinone R = OH

5

Scheme 3



Results and Discussion

By minor modification of a known procedure,[20] (−)-quinic acid (**7**) was converted to ester **8** by reaction with cyclohexanone and TsOH (cat.) in benzene, followed by ring opening of the derived diol protected 1,5-lactone intermediate under mild base conditions (NaOMe, MeOH).[21] Several methods have been described for the oxidation of the secondary alcohol function in **8** and introduction of the $\Delta^{1,2}$ double bond to give **9**. However, in our hands, the "one pot" protocol developed by Shing *et al.*[22] (PCC, 3 Å molecular sieves) proved inefficient on a large scale (>25 g). Somewhat better yields were obtained (approximately 60%) using PCC on Al_2O_3[23] in combination with 3 Å molecular sieves. However, purification still remained a problem. The best results were obtained by first oxidizing **8** (PCC/Al_2O_3; 85%) and then treating the chromatographically pure ketone product with Ac_2O/Pyr−DMAP (cat.) at 20 °C (95%). As expected,[24] borohydride reduction of **9** was stereospecific producing alcohol **10** (90%) in which the three contiguous oxygen substituents are *cis*. Reaction of this α-hydroxy ketal with TsOH (cat.) in benzene containing cyclohexanone (0.1 equiv) resulted in formation of the more thermodynamically stable transketalized product **11** in which the ketal function is adjacent to the $\Delta^{1,2}$ double bond.[25] Although the conversion of **10** to crystalline **11** was quantitative in small scale experiments, scaleup required that the mother liquors be recycled (2−3 cycles) in order to eliminate small quantities of unreacted starting material (66% overall yield; mp 78−79 °C; $[\alpha]_D$ −7.58; *c* 1.20, $CHCl_3$). For the subsequent step it was crucial to find conditions under which quantitative oxidation of the C-5 OH function in **11** could be achieved without concomitant double bond isomerization. The Dess−Martin periodinane reagent[26] performed remarkably in this regard providing the sensitive ketone (+)-**12** as a colorless oil in greater than 98% purity.

To access the enantiomeric β,γ-unsaturated ketone (−)-**12**,[27] the secondary hydroxyl group in ester **8** was selectively converted to its acetate derivative **13**, and the remaining tertiary hydroxyl was activated toward dehydration by reaction with $POCl_3$. As planned, elimination occurred solely in the direction of the protected diol to give the more stable flattened half chair ring system. Subsequent deacetylation on simple treatment with K_2CO_3 in MeOH gave alcohol **14** in 60% overall yield from **8** ($[\alpha]_D$ −74.57; *c* 3.46, $CHCl_3$). Oxidation of this intermediate once again proceeded smoothly to give the desired ketone in high purity. Characteristic in the ^1H NMR spectra of ketone **12** are the signals at δ 3.20 (dt) and δ 3.42 (ddd) for the two nonequivalent C-6 methylene protons, and the signal at δ 6.96 (ddd with $J_{2,3}$ = 1.8 Hz)

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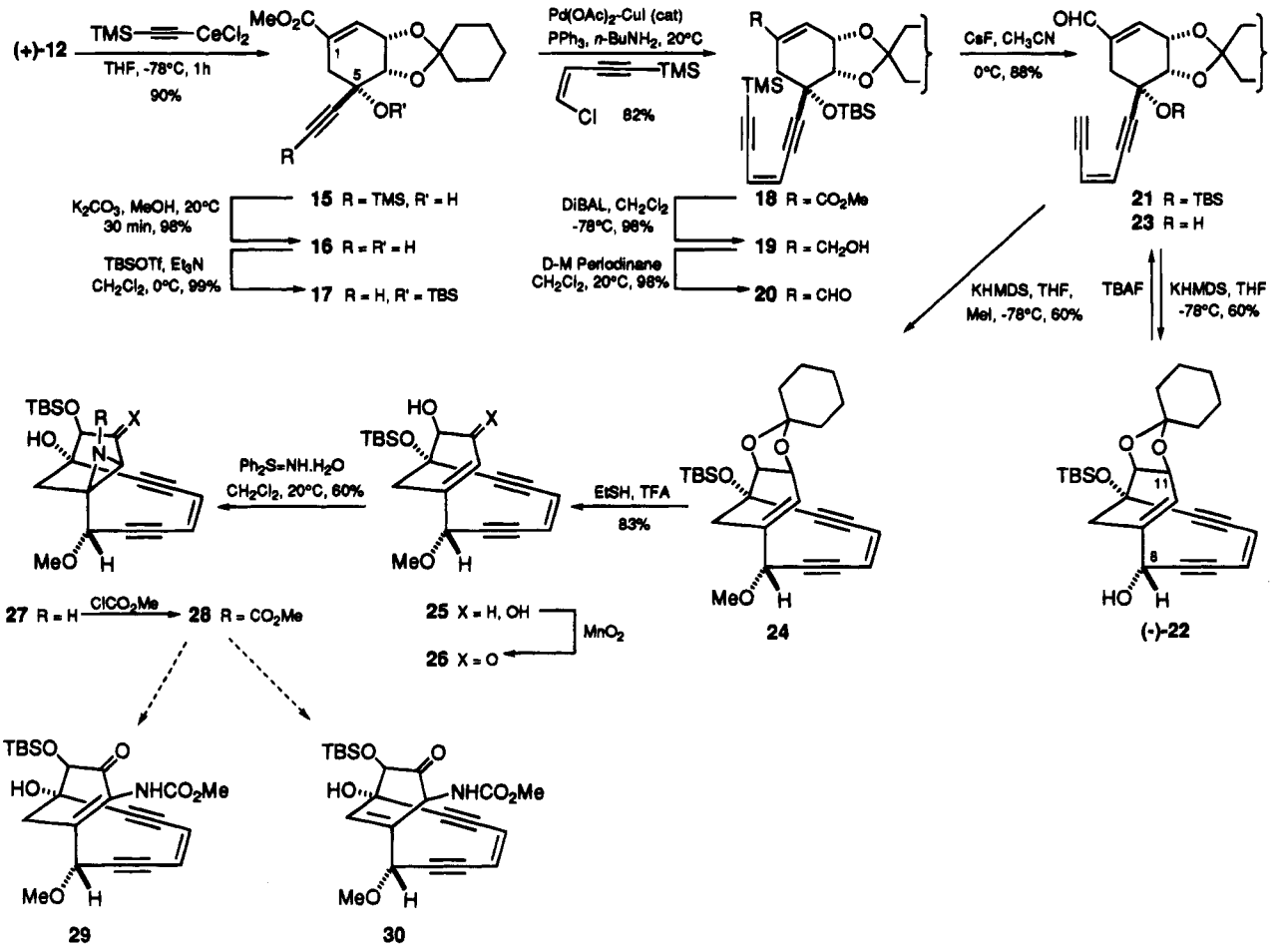
(27) Although a prohibitively expensive route, ketone (−)-12 can also be prepared in three steps (approx. 90% overall yield) from natural (−)-shikimic acid: (i) esterification (CH_2N_2), (ii) transketalization (cyclohexanone dimethyl ketal/*p*-TsOH), (iii) oxidation (Dess−Martin periodinane).

Scheme 4



for the vinylic H-2 proton. In compound **9** the corresponding vinylic proton absorption appears as a simple doublet at δ 6.84 (J = 2.7 Hz).

Construction of the enediyne bridge to give the natural-configuration esperamicin analog (−)-**22** started with reaction of (+)-keto ester **12** with the cerium reagent derived from lithium (trimethylsilyl)acetylene in THF at −78 °C.[11,28] Under these very weakly basic conditions competitive enolate formation through deprotonation at C-6 was totally avoided, and regiospecific addition to the least hindered top face of the keto group was observed giving compound **15** in 90% yield. Subsequent C-desilylation and O-silylation of the derived tertiary alcohol **16** gave the C-5 *O*-TBS acetylene derivative **17** (98% overall yield) whose optical ($[\alpha]_D$ + 7.95; *c* 1.41, $CHCl_3$) and chemical purity was carefully checked by chiral column HPLC (Chiracel column; heptane/EtOH 90/10). It is noteworthy that the main purpose in derivatizing alcohol **16** was to lock compound **17** in the desired conformation in which the less bulky acetylene function is axial. Reaction of this intermediate with *cis*-(1-chloro-4-(trimethylsilyl)-1-buten-3-yne under Sonogashira's conditions[13c] ($Pd(OAc)_2$, CuI, *n*-$BuNH_2$, Ph_3P) completed formation of the acyclic enediyne unit in **18**. Subsequent ester to aldehyde interconversion giving **20** was achieved by a classical reduction (DIBAL-H, 98%)−oxidation (Dess−Martin periodinane, 98%) sequence. With this *C*-TMS aldehyde in hand its reaction with CsF was studied in an attempt to effect direct ring closure to **22** via a hypervalent silicon species.[29] However, the desilylated aldehyde **21** was the only product detected (89%). The distance between the terminal acetylene carbon of the enediyne unit and the aldehyde carbonyl was not a factor behind the failure of this transformation. Indeed, inspection of molecular models reveals that the two reacting centers can approach to within bond forming distance of each other without major distortion of the platform structure. This design feature in our synthetic planning is a consequence of the overall shape of the six-membered platform structure imposed by the presence of the cyclohexylidene system, and strongly suggested at the outset that, barring other factors, ring closure should be particularly facile. This prediction was born out in subsequent experiments in which aldehyde **21** was treated with KHMDS in THF at −78 °C. Under these conditions rapid and highly stereoselective cyclization occurred, providing (−)-**22** as a colorless crystalline solid in 60% yield (mp 153−154 °C; $[\alpha]_D$ −91.36; *c* 1.03, $CHCl_3$). In the ^1H NMR spectrum of this bicyclic enediyne product the H-10 absorption occurs at higher field (δ 5.66) relative to the corresponding absorption (δ 6.52) in aldehyde **21**, consistent with the loss of conjugation of the double bond to the aldehyde carbonyl. Assignment of the *R* absolute stereochemistry at C-8 was initially based on a NOE experiment in which an 11% enhancement of the vinylic (H-10) signal was observed upon irradiation of H-8 (δ 5.22) and later confirmed by the X-ray diffraction struc-

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ture of aziridine **27** (*vide infra*). Obtention of the correct stereochemistry at the newly formed C-8 alcohol center most probably results from the absence of any important steric, or other, interactions which would obstruct the enal from adopting the more stable *s-trans* conformation.[30]

To correlate the optical activity of certain key intermediates and the bicyclic enediyne product with their opposite antipodes, the synthesis of (+)-**22** ($[\alpha]_D$ +89.20; *c* 0.50, $CHCl_3$) from (−)-ketone **12** was undertaken. Identical NMR data, closely matching yields, and opposite rotation values were obtained for each compound on the way to the target molecule.

To further approach esperamicinone from (−)-**22**, cleavage of the C-13 *O*-TBS group was initially examined under TBAF conditions (THF, 0 °C). This led to rapid and very clean reconversion to the acyclic aldehyde **23** (single product by TLC). The facility of this retrocyclization, which is probably promoted by the presence of water (hydroxide ion) in the TBAF employed, provides a clear indication of the ring strain contained in the tetracyclic structure of **22.** It was thus apparent that in order to proceed with *O*-TBS deprotection and/or liberation of the diol system in **22** it would first be necessary to protect its C-8 hydroxy group. To avoid all problems at this stage in our investigation, enediyne **22** was converted to its corresponding O-8 methyl ether derivative **24**. As might be expected attempts to achieve this by quenching the alkoxide formed on reaction of **22** with NaH using MeI resulted in ring opening to **21**. However, by adding MeI to the reaction medium shortly after treatment of aldehyde **21** with KHMDS at low temperature the desired ether **24** was formed and isolated in 60% yield after flash column chromatography.

Attempts to hydrolyze the cyclohexylidene system in **24** under aqueous acid conditions were unsuccessful, leading either to recovery of starting material or to decomposition. However, on treatment with EtSH in neat trifluoroacetic acid, the diol **25** was obtained in 83% yield, *via* a transketalization process. Subsequent conversion of **25** to the conjugated enone **26** was readily achieved using MnO_2 (79%). The decision was then taken to elaborate the urethane at C-10 prior to attacking the problem of activating the C-13 methylene center toward construction of the allylic trisulfide unit. To achieve this enone **26** was reacted with S,S-diphenylsulfilimine monohydrate in CH_2Cl_2 at rt for 16 h.[31] Under these conditions efficient formation of the aziridine intermediate **27** was observed (60%). This transformation is quite remarkable as in the first step it involves a Michael type addition to the enone system in **26** which temporarily eliminates the bridgehead double bond. Fortunately, ring closure of the intermediate enolate which is generated to the observed aziridine product is more rapid than Bergman cycloaromatization. The X-ray crystal structure of aziridine **27** (Figure 1) provided interesting structural information concerning the distance between the terminal carbons of the enediyne system ($dist_{2,7}$ = 3.439 Å) and the deformation of the acetylene bonds in this bridged bicyclic system [bond $angle_{1,2,3}$ = 167.8°, $BA_{2,3,4}$ = 168.9°, $BA_{3,4,5}$ = 118.3°, $BA_{4,5,6}$ = 119.9°, $BA_{5,6,7}$ = 167.4°, $BA_{6,7,8}$ = 167.4°].

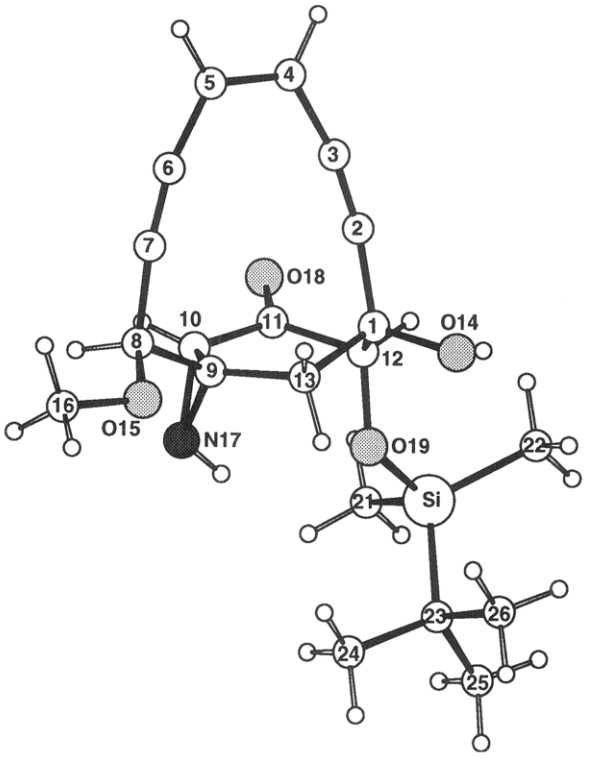

Figure 1. ORTEP diagram of the crystal structure of aziridine **27**.

Importantly, it also revealed that during either the MnO_2 oxidation, or aziridine forming steps, migration of the TBS group from the tertiary hydroxyl group at C-1 to the axial C-12 alcohol center occurred. As a substantial downfield shift was observed for the H-12 proton signal in the ^1H NMR spectrum of the acetate derivative of **26** we concluded that silyl group migration took place during the treatment of this enone with the S−N ylide reagent. This fortuitous TBS shift proved to be a blessing in disguise as it enabled us to prepare the corresponding carbamate derivative of **27** without the complications that might arise from cyclic carbamate formation involving the C-12 hydroxyl group.

The problem now is to devise conditions which will permit selective ring opening of aziridine **28** such that either vinyl urethane **29** or the $\Delta^{9,13}$ double bond product **30** is obtained. In the case where base promoted elimination involving the C-10 proton occurs to give **29**,[7a] it will be necessary to develop conditions for allylic oxidation of the C_{13}-methylene center.[32] However, the alternative elimination to give **30** is particularly interesting as it opens up a number of options for introduction of the allylic trisulfide unit.[33] The study of the ring opening of aziridine **27** is currently undergoing active investigation, as are studies to incorporate novel triggering devices into novel esperamicin analogues derived from both enantiomers of **22**. This latter study has been undertaken in order to make comparative measurements of the ability

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(31) (a) Yoshimura, T.; Omata, T.; Furukawa, N.; Oae, S. *J. Org. Chem.* **1976**, *41*, 1728. (b) Furukawa, N.; Yoshimura, T.; Ohtsu, M.; Akasaka, T.; Oae, S. *Tetrahedron*, **1980**, *36*, 73.

(32) This has been achieved in a less elaborated system related to **29** under SeO_2 allylic oxidation conditions, see ref 12.

(33) Although on the basis of calculations, ring closure to a bicyclic dynemicin intermediate possessing a $\Delta^{9,13}$ double bond (calicheamicin numbering) is considered to be an unfavorable process (see Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106), it has been shown that generation of a double bond at this position is possible in ring closed bicyclic enediyne systems, see ref 7c and Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898.

of the two resulting antipodal enediyne systems to cleave duplex DNA.[34]

Experimental Section

Methyl 3,4-*O*-cyclohexylidenequinate (8). A suspension of (−)-quinic acid (**7**) (20.00 g, 104 mmol), cyclohexanone (54 mL, 521 mmol), and *p*-toluenesulfonic acid (≈200 mg) in benzene (150 mL) was refluxed (Dean−Stark) until all the solids had dissolved (≈5 h). The reaction was cooled to room temperature and then poured into cold aqueous $NaHCO_3$ (saturated) (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×), and the organic extracts were combined, washed successively with water (2×), and brine (1×), dried (Na_2SO_4), filtered, and concentrated. The solid residue was recrystallized (ether/heptane) to give 3,4-*O*-cyclohexylidenequinic acid 1,5-lactone as pale yellow needles (26.05 g, 98%): mp 142−143 °C; $[\alpha]^{25}_D$ −30.9 (*c* 4.22, CH_3OH); IR (KBr) ν_{max} 3431, 1775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (dd, J = 6.0, 2.5 Hz, 1 H), 4.46 (ddd, J = 7.0, 7.0, 3.0 Hz, 1 H), 4.28 (ddd, J = 6.0, 2.0, 1.2 Hz, 1 H), 3.15 (s, 1 H), 2.63 (d, J = 11.8 Hz, 1 H), 2.35 (ddd, J = 14.6, 7.0, 2.0 Hz, 1 H), 2.28 (ddd, 11.8, 7.0, 1.2 Hz, 1 H), 2.16 (dd, J = 14.6, 3.0 Hz, 1 H), 1.72−1.20 (complex, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 178.60, 110.18, 75.56, 71.32, 71.17, 70.65, 37.94, 36.47, 33.95, 33.25, 24.58, 23.53, 23.08; HRMS (EI) calcd for $C_{13}H_{18}O_5$ 254.1149, found 254.1139. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.39; H, 7.14. Found: C, 61.50; H, 7.26.

Sodium methoxide (2.56 g, 47.40 mmol) was added in one portion to a dry MeOH (50 mL) solution of the lactone intermediate (10.00 g, 39.40 mmol). The reaction was stirred at room temperature for 5 h, and then it was neutralized by the slow addition of glacial acetic acid (47.40 mmol, 2.70 mL). Evaporation of the solvent *in vacuo* at room temperature gave a paste which was dissolved in CH_2Cl_2 (50 mL), and then preadsorbed on silica gel (230−400 mesh). Flash chromatography (0−50% EtOAc/heptane) gave recovered starting lactone (1.50 g) and dihydroxy ester **2** as white crystals (7.60 g, 80%): mp 79−80 °C; $[\alpha]^{25}_D$ −45.50 (*c* 2.62, CH_3OH); IR (KBr) ν_{max} 3345, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (ddd, J = 6.0, 3.9, 3.7 Hz, 1 H), 4.09 (ddd, J = 10.9, 6.4, 4.3 Hz, 1 H), 3.95 (dd, J = 6.4, 6.0 Hz, 1 H), 3.68 (s, 1 H), 3.48 (s, 1 H), 2.80 (bs, 1 H), 2.30−2.20 (complex, 2 H), 2.06 (ddd, J = 13.6, 4.3, 1.6 Hz, 1 H), 1.83 (dd, J = 13.6, 10.9 Hz, 1 H), 1.75−1.30 (complex, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 176.08, 110.66, 80.14, 74.70, 73.76, 69.22, 53.72, 39.65, 38.65, 35.52, 35.36, 25.64, 24.67, 24.30; HRMS (EI) calcd for $C_{14}H_{22}O_6$ 286.1410, found 286.1396.

Methyl 4,5-*O*-cyclohexylidene-3-didehydro-4-*epi*-shikimate (9). PCC/Al_2O_3 (31.50 mmol) was added at room temperature to a solution of dihydroxy ester **8** (6.00 g, 21.00 mmol) in CH_2Cl_2 (100 mL). The reaction was vigorously stirred at room temperature for 24 h. The slurry was then filtered and thoroughly washed with CH_2Cl_2 (200 mL) and EtOAc (200 mL). Concentration of the filtrate gave an oily residue (5.81 g, 17.85 mmol, 85%). This residue (>95% ketone by NMR) was immediately dissolved in a CH_2Cl_2 (100 mL)-pyridine (5 mL) solution and treated with DMAP (0.1 equiv) and freshly distilled acetic anhydride (3.77 mL, 40.00 mmol) at room temperature for 36 h. Methanol (5 mL) was then added followed by Et_2O (100 mL) and water (100 mL). The aqueous layer was extracted (3×) with Et_2O, and the organic extracts were combined, and washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Recrystallization from ether−heptane gave keto ester **9** (4.52 g, 95%, 80% overall) as white crystals: mp 91−92 °C; $[\alpha]^{25}_D$ −44.8 (*c* 2.21, CH_3OH); IR (KBr) ν_{max} 1719, 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.84 (d, J = 2.7 Hz, 1 H), 4.70 (ddd, J = 5.0, 4.8, 1.2 Hz, 1 H), 4.29 (d, J = 4.8 Hz, 1 H), 3.85 (s, 3 H), 3.24 (bd, J = 20.3 Hz, 1 H), 2.85 (ddd, J = 20.3, 5.0, 2.7 Hz, 1 H), 2.0−1.0 (complex, 10 H); HRMS (EI) calcd for $C_{14}H_{18}O_5$ 266.1149, found 266.1167. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.12; H, 6.82. Found: C, 63.06; H, 6.63.

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Methyl (3*S*,4*S*,5*R*)-4,5-*O*-cyclohexylidene-3,4-*epi*-shikimate (10). Ketone **9** (1.65 g, 6.21 mmol) was dissolved in dry methanol, and the mixture was cooled to 0 °C. Sodium borohydride (1.17 g, 30.93 mmol) was slowly added, and the reaction was stirred for 1 h before being quenched by the addition of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×), and the organic extracts were combined, successively washed with H_2O (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residual oil (0−20% EtOAc/heptane) gave hydroxy ester **10** as white crystals (1.50 g, 90%): mp 70−71 °C; $[\alpha]^{25}_D$ +48.12 (*c* 0.64, $CHCl_3$); IR (KBr) ν_{max} 3237, 1714, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (bs, 1 H), 4.65 (ddd, J = 6.2, 3.8, 2.2 Hz, 1 H), 4.55 (ddd, J = 6.3, 4.8, 1.3 Hz, 1 H), 4.07 (complex, 1 H,), 3.78 (s, 3 H), 3.05 (dd, J = 16.6, 2.1 Hz, 1 H), 2.76 (d, J = 10.1 Hz, 1 H), 1.95 (dddd, J = 16.6, 6.4, 3.8, 2.8 Hz, 1 H), 1.70−1.20 (complex, 10 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 165.8, 142.5, 127.9, 109.2, 75.7, 71.8, 67.9, 51.6, 35.2, 33.6, 26.4, 24.9, 23.6, 23.3; HRMS (EI) calcd for $C_{14}H_{20}O_5$ 268.1305, found 268.1300. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.83; H, 7.56.

Methyl (3*S*,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-3,4-*epi*-shikimate (11). Cyclohexanone (200 μL, cat.) and *p*-toluenesulphonic acid (100 mg, cat.) were added to a solution of hydroxy ester **10** (535 mg, 2.00 mmol) in dry benzene (25 mL), and the reaction was stirred at room temperature for 24 h. Diethyl ether (50 mL) was added followed by aqueous $NaHCO_3$ (saturated), and the aqueous layer was extracted with Et_2O (3×). The organic extracts were combined, washed with H_2O (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−25% EtOAc/heptane) gave a quantitative yield of hydroxy ester **11** as white crystals: mp 78−79 °C; $[\alpha]^{25}_D$ −7.58 (c 1.20, $CHCl_3$) [in larger scale experiments (>5 g) small quantities of unreacted **10** were detected in the crude product mixture. By recrystallization of the crude product mixture and recycling the mother liquors, compound **11** was obtained in 66% overall yield]; IR (KBr) ν_{max} 3390, 1708, 1650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.77 (m, 1 H), 4.70 (ddd, J = 5.7, 3.5, 2.2 Hz, 1 H), 4.38 (dd, J = 5.7, 2.2 Hz, 1 H), 3.90 (m, 1 H), 3.72 (s, 3 H), 2.62 (dd, J = 16.7, 5.2 Hz, 1 H), 2.50 (ddd, J = 16.7, 8.7, 2.2, 2.2 Hz, 1 H), 2.29 (d, J = 7.7 Hz, 1 H), 1.70−1.20 (complex, 10 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 166.7, 135.0, 129.0, 110.4, 75.1, 72.6, 66.9, 51.8, 37.0, 35.5, 27.6, 24.9, 23.9, 23.6; HRMS (EI) calcd for $C_{14}H_{20}O_5$ 268.1305, found 268.1308. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.65; H, 7.52. Found: C, 62.97; H, 7.42.

(+)-Methyl 3,4-*O*-Cyclohexylidene-5-didehydroshikimate (12). Dess−Martin periodinane (300 mg, 0.71 mmol) was added to a solution of hydroxy ester **11** (122 mg, 0.45 mmol) in dry CH_2Cl_2 (20 mL), and the solution was stirred at room temperature for 30 min. Diethyl ether (50 mL) was added followed by an aqueous solution of $Na_2S_2O_3$ in $NaHCO_3$ (20 mL). Once the mixture lost its turbidity (15−30 min) it was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with water (2 × 10 mL) and brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. Ketone **12** was obtained as a clear oily residue (120 mg, 99%), which did not require further purification.: $[\alpha]^{25}_D$ +26.6 (*c* 2.17, $CHCl_3$); IR (neat) ν_{max} 1746, 1723, 1650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.96 (ddd, J = 5.5, 1.8, 1.8 Hz, 1 H), 5.02 (dddd, 6.0, 5.5, 1.2, 1.2 Hz, 1 H), 4.44 (d, J = 6.0 Hz, 1 H), 3.80 (s, 3 H), 3.42 (ddd, J = 19.7, 1.8, 1.2 Hz, 1 H), 3.20 (dt, J = 19.7, 1.8, 1.2 Hz, 1 H), 1.70−1.20 (complex, 10 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 203.2, 165.6, 134.1, 129.2, 112.2, 77.2, 75.7, 52.3, 37.2, 36.7, 35.6, 24.9, 24.0, 23.8; HRMS (EI) calcd for $C_{14}H_{18}O_5$ 266.1149, found 266.1152.

Methyl 5-*O*-Acetyl-3,4-*O*-cyclohexylidenequinate (13). Dihydroxy ester **8** (5.00 g, 17.50 mmol) was dissolved in CH_2Cl_2 (100 mL), and the solution was cooled to 0 °C. Dry pyridine (7.00 mL, 87.5 mmol) and freshly distilled acetic anhydride (1.74 mL, 18.40 mmol) were added, and the reaction was kept at 0 °C for 12 h. Methanol (20 mL) was then slowly added, and after 3 h water (100 mL) was added and the aqueous layer was extracted with Et_2O (2×). The organic extracts were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. Crystallization from ether gave hydroxy acetate

13 (5.70 g, 100%) as white crystals: mp 140 °C; $[\alpha]^{25}_D$ −71.98 (*c* 2.67, $CHCl_3$); IR (KBr) ν_{max} 3345, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.28 (ddd, *J* = 11.5, 7.2, 4.5 Hz, 1 H), 4.48 (ddd, *J* = 5.0, 4.3, 2.5 Hz, 1 H), 4.09 (dd, *J* = 7.2, 5.0 Hz, 1 H), 3.75 (s, 3 H), 2.34 (dt, *J* = 15.6, 2.5 Hz, 1 H), 2.23 (dd, *J* = 15.6, 4.3 Hz, 1 H), 2.15 (ddd, *J* = 13.3, 4.5, 2.5 Hz, 1 H), 2.06 (s, 3 H), 1.90−1.20 (complex, 12 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 174.55, 170.09, 110.38, 76.32, 74.00, 73.44, 71.01, 52.97, 37.81, 36.84, 35.05, 34.44, 24.99, 23.96, 23.73, 21.24; HRMS (EI) calcd for $C_{16}H_{24}O_7$ 328.1522, found 328.1541. Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.51; H, 7.37. Found: C, 58.45; H, 7.48.

Methyl 3,4-*O*-Cyclohexylideneshikimate (14). Hydroxy acetate **13** (2.30 g, 7.00 mmol) was dissolved in dry pyridine (15 mL), $POCl_3$ (0.72 mL, 7.70 mmol) was added, and the reaction was stirred for 3 h at rt. Diethyl ether (25 mL) and aqueous NH_4Cl (saturated) were added successively, the aqueous layer was extracted with Et_2O (3×), and the extracts were combined, washed with water (2×), dilute HCl (≈10%) aqueous solution (2×), and brine, dried (Na_2SO_4), filtered, and concentrated. The crude oily residue was dissolved in MeOH (20 mL), and solid K_2CO_3 (1.00 g, 7.25 mmol) was added. The mixture was stirred overnight at room temperature and then quenched with water (20 mL). The aqueous layer was extracted with ether (3×). The organic extracts were combined, washed with brine (2×), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−25% EtOAc/heptane) gave hydroxy ester **14** (1.12 g, 60% overall) as a colorless oil: $[\alpha]^{25}_D$ −74.57 (*c* 3.46, $CHCl_3$); IR (KBr) ν_{max} 3455, 1721, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (bs, 1 H), 4.73 (dd *J* = 6.0, 4.8 Hz, 1 H), 4.06 (dd, *J* = 8.0, 6.0 Hz, 1 H), 3.87 (ddd, *J* = 8.2, 8.0, 4.6 Hz, 1 H), 3.75 (s, 3 H), 2.75 (dd, *J* = 17.4, 4.6 Hz, 1 H), 2.21 (ddt, *J* = 17.4, 8.2, 1.6 Hz, 1 H), 2.10 (bs, 1 H), 1.70−1.20 (complex, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.5, 134.1, 130.4, 110.3, 77.4, 71.7, 68.9, 52.0, 37.7, 35.1, 29.2, 24.9, 23.9, 23.6; HRMS (EI) calcd for $C_{14}H_{20}O_5$ 268.1305, found 268.1298. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.66; H, 7.52. Found: C, 62.79; H, 7.74.

(−)-Methyl 3,4-*O*-Cyclohexylidene-5-didehydroshikimate (12). Dess−Martin periodinane (1.27 g, 3.00 mmol) was added to a solution of hydroxy ester **14** (530 mg, 2.00 mmol) in dry CH_2Cl_2 (40 mL), and the solution was stirred at room temperature for 30 min. Diethyl ether (50 mL) was added followed by an aqueous solution of $Na_2S_2O_3$ in $NaHCO_3$ (saturated) (10 mL). The reaction was stopped after all solids dissolved (15−30 min), and then the aqueous layer was extracted with Et_2O (3×). The organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. (−)-Ketone **12** was obtained as a clear oil (532 mg, 100%), which did not require further purification.: $[\alpha]^{25}_D$ −26.9 (*c* 2.79, $CHCl_3$); IR, ^1H and ^{13}C NMR data identical to that obtained for (+)-**12**; HRMS (EI) calcd for $C_{14}H_{18}O_5$ 266.1149, found 266.1163.

(+)-(3*S*,4*S*,5*S*)-3,4-*O*-Cyclohexylidene-1-carbomethoxy-5-[2-(trimethylsilyl)-1-ethynyl]-1-cyclohexene-3,4,5-triol (15). $CeCl_3 \cdot 7H_2O$ (6.30 g, 16.90 mmol) was dried at 140 °C under vacuo for 2 h and then cooled to room temperature under an argon atmosphere. THF (55 mL) was added, and the suspension was stirred for 2 h before being cooled to −78 °C. Lithium (trimethylsilyl)acetylide in THF (0.1 M, 5.75 mmol) was transferred through a cannula, and the resulting mixture was stirred (30 min) until a yellow solution was obtained. Crude ketone (+)-**12** (1.46 g, 5.50 mmol) in THF was added dropwise, to the cerium acetylide, and the reaction was stirred at −78 °C for 1 h. A saturated solution of NH_4Cl (20 mL) was added, the mixture was allowed to warm up to room temperature,and then the aqueous layer was extracted with Et_2O (3×). The organic extracts were combined, washed with water (2×), brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−20% ether/heptane) gave hydroxy ester **15** (1.80 g, 90%) as white flakes: mp 125−126 °C; $[\alpha]^{25}_D$ +16.80 (*c* 1.22, $CHCl_3$); IR (KBr) ν_{max} 3382, 2174, 1725, 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 3.5, 1.0 Hz, 1 H), 4.77 (ddd, *J* = 5.5, 3.5, 2.0 Hz, 1 H), 4.39 (d, *J* = 5.5 Hz, 1 H), 3.80 (s, 3 H), 2.75 (bs, 2 H), 2.53 (s, 1 H), 1.70−1.20 (complex, 10 H), 0.15 (s, 9 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.4, 134.7, 128.4, 111.3, 105.0, 89.8, 77.9, 73.2, 67.9, 51.9, 37.0, 35.3, 33.7, 24.8, 23.8, 23.6, −0.4; HRMS (EI) calcd for $C_{19}H_{28}O_5Si$ 364.1706, found 364.1708. Anal. Calcd for $C_{19}H_{28}O_5Si$: C, 62.61; H, 7.75. Found: C, 62.33; H, 7.70.

(+)-(3*S*,4*S*,5*S*)-3,4-*O*-Cyclohexylidene-1-carbomethoxy-5-ethynyl-1-cyclohexene-3,4,5-triol (16). Hydroxy ester **15** (1.70 g, 4.67 mmol) was dissolved in MeOH (50 mL), and K_2CO_3 (1.76 g, 5.60 mmol) was added in one portion. The reaction was stirred for 30 min at room temperature and then quenched by adding Et_2O (100 mL) followed by water (100 mL). The aqueous layer was extracted with Et_2O (3×), and the organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−50% ether/heptane) gave hydroxy ester **16** (1.33 g, 98%) as white crystals: mp 132−134 °C; $[\alpha]^{25}_D$ +25.80 (*c* 0.50, $CHCl_3$); IR (KBr) ν_{max} 3415, 3268, 2114, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (t, *J* = 1.5 Hz, 1 H), 4.80 (ddd, *J* = 5.6, 3.7, 1.5 Hz, 1 H), 4.40 (d, *J* = 5.6 Hz, 1 H), 3.80 (s, 3 H), 2.85 (dt, *J* = 16.8, 1.5 Hz, 1 H), 2.76 (bd, *J* = 16.8 Hz, 1 H), 2.60 (s, 1 H), 2.46 (s, 1 H), 1.70−1.20 (complex, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.1, 134.5, 128.1, 111.1, 83.5, 77.5, 72.7, 72.6, 67.2, 51.8, 36.6, 34.9, 33.3, 24.5, 23.6, 23.3; HRMS (EI) calcd for $C_{16}H_{20}O_5$ 292.1325, found 292.1320. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.72; H, 6.90. Found: C, 65.89; H, 7.01.

(+)-(3*S*,4*S*,5*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-cyclohexylidene-1-carbomethoxy-5-ethynyl-1-cyclohexene-3,4,5-triol (17). Hydroxy ester **16** (1.25 g, 4.30 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled down to 0 °C. Dry Et_3N (1.2 mL, 8.60 mmol) was added followed by t-$BuMe_2SiOTf$ (1.50 mL, 6.50 mmol). The reaction was stirred at 0 °C for 10 h and then quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×), and then the organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−10% ether/heptane) gave ester **17** (1.73 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +7.95 (*c* 1.41, $CHCl_3$); IR (neat) ν_{max} 3306, 3263, 2121, 1720, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (t, *J* = 2.6 Hz, 1 H), 4.73 (ddd, *J* = 5.0, 2.6, 2.6 Hz, 1 H), 4.28 (d, *J* = 5.0 Hz, 1 H), 3.78 (s, 3 H), 2.77 (d, *J* = 16.4 Hz, 1 H), 2.65 (dt, *J* = 16.4, 2.6 Hz, 1 H), 2.38 (s, 1 H), 1.70−1.20 (complex, 10 H), 0.90 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.9, 135.5, 128.6, 111.3, 84.9, 78.5, 74.2, 73.5, 70.2, 52.0, 37.9, 36.1, 34.3, 25.7, 25.2, 24.4, 24.0, 18.3, −2.8; HRMS (EI) calcd for $C_{22}H_{34}O_5Si$ 406.2166, found 406.2177. Anal. Calcd for $C_{22}H_{34}O_5Si$: C, 64.90; H, 8.43. Found: C, 64.61; H, 8.17.

(+)-(3*S*,4*S*,5*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-cyclohexylidene-1-carbomethoxy-5-[6-(trimethylsilyl)-3-hexene-1,5-diynyl]-1-cyclohexene-3,4,5-triol (18). Palladium acetate (16 mg, 0.07 mmol) and PPh_3 (80 mg, 0.30 mmol) were added to a solution of *cis*-1-chloro-4-(trimethylsilyl)-1-buten-3-yne (590 mg, 3.70 mmol) in dry-degassed benzene (2 mL), and the mixture was stirred at room temperature for 30 min. Then, ester **17** (500 mg, 1.23 mmol), also in dry-degassed benzene (3 mL), was added followed by *n*-$BuNH_2$ (250 mL, 2.50 mmol) and CuI (25 mg, 0.13 mmol). The reaction was stirred at room temperature for 12 h and then quenched with aqueous NH_4Cl saturated (2 mL). The aqueous layer was extracted with Et_2O (3×), and the organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−10% ether/heptane) gave ester **18** (535 mg, 82%) as a colorless oil: $[\alpha]^{25}_D$ +10.89 (*c* 1.01, $CHCl_3$); IR (neat) ν_{max} 2369, 2151, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (t, *J* = 2.6 Hz, 1 H), 5.83 (d, *J* = 11 Hz, 1 H), 5.73 (d, *J* = 11 Hz, 1 H), 4.83 (ddd, *J* = 4.8, 2.6, 2.6 Hz, 1 H), 4.32 (d, *J* = 4.8 Hz, 1 H), 3.76 (s, 3 H), 2.78 (d, *J* = 16.5 Hz, 1 H), 2.67 (dt, *J* = 16.5, 2.6 Hz, 1 H), 1.70−1.20 (complex, 10 H), 0.90 (s, 9 H), 0.22 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.9 135.8, 128.3, 120.8, 119.1, 111.3, 103.3, 101.8, 97.6, 82.7, 78.5, 78.3, 74.3, 70.6, 52.1, 37.9, 36.1, 34.2, 25.8, 25.2, 24.2, 18.2, −0.1, −2.6; HRMS (EI) calcd for $C_{29}H_{44}O_5Si_2$ 528.2727, found 528.2701. Anal. Calcd for $C_{29}H_{44}O_5Si_2$: C, 65.87; H, 8.39. Found: C, 65.71; H, 8.47.

(+)-(3*S*,4*S*,5*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-cyclohexylidene-1-(hydroxymethyl)-5-[6-(trimethylsilyl)-3-

hexene-1,5-diynyl]-1-cyclohexene-3,4,5-triol (19). Ester **18** (400 mg, 0.75 mmol) was dissolved in CH_2Cl_2 (30 mL) and then cooled down to −78 °C. DIBAL-H (1.5 M solution in toluene, 1.70 mL, 2.55 mmol) was slowly added, and the reaction was stirred for 5 h. After this time NH_4Cl saturated solution (6 mL) was added, and the mixture was warmed to room temperature and then extracted with CH_2Cl_2 (3×). The organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−50% ether/heptane) gave alcohol **19** (370 mg, 98%) as a colorless oil: $[\alpha]^{25}_D$ +48.12 (*c* 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (dd, *J* = 11.3, 1.2 Hz, 1 H), 5.73 (dd, *J* = 11.3, 1.2 Hz, 1 H), 5.58 (bs, 1 H), 4.75 (bs, 1 H), 4.33 (d, *J* = 5.1 Hz, 1 H), 4.02 (bd, *J* = 5.1 Hz, 1 H), 2.60 (bd, *J* = 15.7 Hz, 2 H), 2.30 (d, *J* = 51.7 Hz, 1 H), 1.70−1.20 (complex, 10 H), 0.90 (s, 9 H), 0.22 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 136.9, 120.9, 120.5, 119.2, 110.7, 103.1, 101.8, 98.5, 52.0, 78.7, 74.7, 71.7, 66.2, 38.0, 36.3, 35.8, 25.8, 25.2, 24.2, 24.2, 18.3, 0.0, −2.6; HRMS (EI) calcd for $C_{28}H_{44}O_4Si_2$ 500.2767, found 500.2778. Anal. Calcd for $C_{28}H_{44}O_4Si_2$: C, 67.16; H, 8.86. Found: C, 67.35; H, 8.82.

(−)-(3*S*,4*S*,5*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-cyclohexylidene-1-formyl-5-[6-(trimethylsilyl)-3-hexene-1,5-diynyl]-1-cyclohexene-3,4,5-triol (20). Dess−Martin periodinane (170 mg, 0.40 mmol) was added in one portion to a solution of alcohol **19** (130 mg, 0.26 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 2 h,and then Et_2O (10 mL) was added followed by $Na_2S_2O_3$ in aqueous $NaHCO_3$ (saturated) (10 mL). The solution was stirred until it became clear, and then it was extracted with Et_2O (3×). The organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Aldehyde **20** (126 mg, 98%) was obtained as a colorless oil which did not require further purification: $[\alpha]^{25}_D$ −11.31 (*c* 0.88, $CHCl_3$); IR (neat) ν_{max} 2720, 2151, 1694, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1 H), 6.51 (t, *J* = 2.6 Hz, 1 H), 5.84 (d, *J* = 11 Hz, 1 H), 5.72 (d, *J* = 11 Hz, 1 H), 4.93 (ddd, *J* = 4.8, 2.6, 2.4 Hz, 1 H), 4.39 (d, *J* = 4.8 Hz, 1 H), 2.79 (bd,16.3, 1 H), 2.56 (dt, *J* = 61.3, 2.4 Hz, 1 H), 1.70−1.20 (complex, 10 H), 0.90 (s, 9 H), 0.22 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 193.4, 145.2, 138.5, 121.0, 118.8, 111.7, 103.4, 101.7, 97.2, 82.8, 79.4, 74.2, 70.5, 37.9, 36.0, 31.5, 25.7, 25.1, 24.1, 23.9, 18.2, 0.0, −2.7; HRMS (EI) calcd for $C_{28}H_{42}O_4Si_2$ 498.2621, found 498.2641.

(3*S*,4*S*,5*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-cyclohexylidene-1-formyl-5-(3-hexene-1,5-diynyl)-1-cyclohexene-3,4,5-triol (21). Aldehyde **20** (36 mg, 0.072 mmol) was dissolved in CH_3CN (2 mL) and cooled to 0 °C. Cesium fluoride (12 mg, 0.078 mmol) was added in one portion, and the reaction was stirred for 4 h and then quenched with aqueous NH_4Cl saturated (1 mL). The aqueous layer was extracted with Et_2O (3×), and the organic extracts were combined, washed with water (2×), and brine, dried (Na_2SO_4), filtered, and concentrated. Aldehyde **21** was obtained (27 mg, 88%) as a colorless oil, which did not require further purification: IR (neat) ν_{max} 2857, 2050, 1695, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1 H), 6.52 (t, *J* = 2.7 Hz, 1 H), 5.80 (s, 2 H), 4.93 (ddd, *J* = 5.0, 2.7, 2.3 Hz, 1 H), 4.39 (d, *J* = 5.0 Hz, 1 H), 3.28 (s, 1 H), 2.82 (d, *J* = 16.3 Hz, 1 H), 2.56 (dt, 16.3, *J* = 2.3 Hz, 1 H), 1.70−1.20 (complex, 10 H), 0.90 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 193.4, 145.2, 138.6, 120.4, 119.9, 111.7, 97.4, 85.1, 82.4, 80.6, 79.3, 74.2, 70.6, 37.9, 36.0, 31.6, 25.7, 25.1, 24.1, 24.0, 18.2, −2.7; HRMS (EI) calcd for $C_{25}H_{34}O_4Si$ 426.2217, found 426.2233.

(−)-(1*S*,8*R*,11*S*,12*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-11,12-*O*-cyclohexylidenebicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-8-ol (22). Aldehyde **21** (27 mg, 0.063 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. KHMDS in THF (0.49 M, 0.12 mmol) was added, and the reaction was quenched after 10 min with aqueous NH_4Cl saturated (1 mL). The aqueous layer was extracted with Et_2O (3×), and the organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Recrystallization from hexane gave alcohol **22** (16 mg, 60%) as white needles: mp 153−154 °C; $[\alpha]^{25}_D$ −91.36 (*c* 1.03, $CHCl_3$); IR (KBr) ν_{max} 3422, 1096, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (d, *J* = 9.4 Hz 1 H), 5.78 (dd, *J* = 9.4, 1.5 Hz, 1 H), 5.66 (dddd, *J* = 4.3, 2.7, 1.6, 1.4 Hz, 1 H), 5.22 (bs, 1 H), 4.57 (ddd, *J* = 5.4, 4.3, 1.6 Hz, 1 H), 4.27 (dd, *J* = 5.4, 1.6 Hz, 1 H), 2.84 (dd, *J* = 14.0, 1.4 Hz, 1 H), 2.78 (ddd, *J* = 14.0, 2.7, 1.6 Hz, 1 H), 1.95 (bs, 1 H), 0.89 (9 H), 0.20 (s, 6 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 141.9, 124.7, 123.5, 120.7, 110.2, 85.0, 77.0, 74.8, 74.4, 68.5, 37.7, 37.4, 35.7, 25.8, 25.2, 24.3, 24.0, 18.4, −2.7; HRMS (EI) calcd for $C_{25}H_{34}O_4Si$ 426.2217, found 426.2228. Anal. Calcd for $C_{25}H_{34}O_4Si$: C, 70.39; H, 8.04. Found: C, 70.25; H, 7.98.

(−)-(1*S*,8*R*,11*S*,12*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-8-*O*-methyl-11,12-*O*-cyclohexylidenebicyclo[7.3.1]trideca-4,9-diene-2,6-diyne (24). Aldehyde **21** (330 mg, 0.77 mmol) was dissolved in dry THF (15 mL), and cooled down to −78 °C. Freshly made KHMDS in THF (0.35 M, 4.4 mL, 1.5 mmol) was added, and the reaction was quenched after 10 min with CH_3I (0.5 mL). The aqueous layer was extracted with ether (3×), and the organic extracts were combined, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (0−10% ether/heptane) gave enediyne **24** (205 mg, 60%) as a clear oil: $[\alpha]^{20}_D$ −105.2° ($CHCl_3$); IR (neat) 2937, 2857, 2400, 1730, 1675, 1463, 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82 (AB, *J* = 9.6 Hz, 2H), 5.70 (dd, *J* = 4.0, 2.0 Hz, 1H), 4.76 (s, 1H), 4.58 (dt, *J* = 5.5, 2.0 Hz, 1H), 4.26 (d, *J* = 5.5 Hz, 1H), 3.34 (s, 3H), 2.88 (d, *J* = 14.5 Hz, 1H), 2.74 (dt, *J* = 14.5, 2.1 Hz, 1H), 1.30−1.75 (m, 10H), 0.91 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 140.8, 124.5, 123.6, 121.8, 110.2, 101.9, 100.1, 87.2, 85.0, 74.7, 74.6, 56.9, 37.7, 37.6, 35.9, 29.8, 25.8, 25.3, 24.3, 24.0, 18.3, −2.8; MS (CI) 440; Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.86; H, 8.23. Found: C, 70.46; H, 8.21.

(−)-(1*S*,8*R*,11*S*,12*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-8-*O*-methyl-11,12-dihydroxybicyclo[7.3.1]trideca-4,9-diene-2,6-diyne (25). Enediyne **24** (0.10 g, 0.277 mmol) was treated with ethanethiol (0.34 mL, 4.55 mmol) and triflouroacetic acid (0.87 mL, 11.4 mmol) and stirred at rt for 8 h. The solution was then diluted with 20 mL of CH_2Cl_2, washed with saturated $NaHCO_3$, water, and brine, dried ($NaSO_4$), filtered, and concentrated. The resulting oil was subjected to flash chromatography (50% ether/heptane) to give diol **25** as a clear oil (68 mg, 83%): $[\alpha]^{20}_D$ −225° ($CHCl_3$); IR (neat) 3425, 2955, 2929, 2896, 2857, 2200, 1472 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.84 (s, 2H), 5.65 (t, *J* = 3.0 Hz, 1H), 4.79 (s, 1H), 4.20−4.30 (m, 1H), 3.96 (d, *J* = 5.0 Hz, 1H), 3.35 (s, 3H), 2.86 (d, *J* = 15.0 Hz, 1H), 2.73 (s, 1H), 2.68 (s, 1H), 2.65 (dt, *J* = 15.0, 3.0 Hz, 2H), 0.91 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.9, 124.4, 123.9, 123.7, 99.7, 88.2, 86.9, 77.7, 74.6, 73.0, 69.4, 56.9, 38.0, 25.9, 18.1, −2.7, −3.0; HRMS (EI) calcd for *m/z* 360.1749, found 360.1740. Anal. Calcd for $C_{20}H_{28}O_4Si$: C, 66.63; H, 7.83; found: C, 66.62; H, 7.59.

(−)-(1*S*,8*R*,11*S*,12*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-8-*O*-methyl-9,10-imino-12-hydroxybicyclo[7.3.1]tridec-4-ene-2,6-diyn-11-one (26). To a solution of diol **25** (16 mg, 0.04 mmol) in dry CH_2Cl_2 was added activated MnO_2 (19 mg, 0.22 mmol), and the suspension was stirred at rt for 16 h. The resulting black suspension was filtered through a pad of Celite and concentrated. The resulting yellow oil was subjected to flash chromatography (25−50% ether/heptane) to give **26** as a clear oil (11 mg, 79%): $[\alpha]^{20}_D$ −263° ($CHCl_3$); IR (neat) 3435, 2955, 2930, 2898, 2857, 1677 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.06 (d, *J* = 2.5 Hz, 1H), 5.87 (s, 2H), 4.29 (s, 1H), 3.92 (s, 1H), 3.41 (s, 1H), 3.18 (dd, *J* = 15.3, 1.1 Hz, 1H), 2.98 (dd, *J* = 15.3, 2.5 Hz, 1H), 2.87 (s, 1H), 0.93 (s, 9H), 0.28 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.4, 159.8, 124.2, 123.9, 97.5, 88.9, 76.4, 76.1, 76.0, 74.4, 57.3, 38.7, 29.8, 25.8, 18.2, −2.7, −3.0; MS (FAB) (L. SIMS+) Na/381, H+/359.

(+)-(1*S*,8*R*,11*S*,12*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-8-*O*-methyl-9,10-imino-12-hydroxybicyclo[7.3.1]tridec-4-ene-2,6-diyn-11-one (27). To a solution of ketol **26** (59 mg, 0.16 mmol) in 5 mL of dry CH_2Cl_2 was added *S,S*-diphenylsulfilimine monohydrate (359 mg, 1.64 mmol) and the resulting suspension stirred at rt for 16 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organics were washed with water (2×) and brine (1×), dried ($NaSO_4$), filtered, and concentrated. The resulting crude material was subjected to flash chromatography (50%

ether/heptane) to give aziridine **27** as a white needles (36 mg, 60%): mp 197 °C dec; $[\alpha]^{20}_D$ +126° ($CHCl_3$); IR (CH_2Cl_2) 3581, 3289, 3054, 2959, 2939, 2857, 1708, 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.93 (s, 2H), 3.98 (s, 1H), 3.57 (s, 1H), 3.47 (s, 3H), 3.17 (d, J = 14.4 Hz, 1H), 2.48 (s, 1H), 2.45 (d, J = 14.4 Hz, 1H), 2.39 (s, 2H), 0.90 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.2, 124.8, 124.0, 98.8, 97.6, 88.6, 86.3, 81.0, 79.1, 73.7, 57.6, 49.2, 42.2, 38.5, 25.8, 18.2, −4.9; MS (CI) 373. Anal. Calcd for $C_{20}H_{27}NO_4Si$: C, 64.31; H, 7.29; N, 3.75. Found: C, 64.48; H, 7.04; N, 3.64.

(+)-(1*S*,8*R*,11*S*,12*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-8-*O*-methyl-9,10-[*N*-methoxycarbonyl)imino]-12-hydroxybicyclo[7.3.1]tridec-4-ene-2,6-diyn-11-one (28). To a solution of aziridine **27** (25 mg, 0.067 mmol), K_2CO_3 (18 mg, 0.133 mmol), and 18-crown-6 (3.5 mg, 0.013 mmol) was added freshly distilled methyl chloroformate (0.008 mL , 0.10 mmol) and stirred at rt for 36 h. The resulting solution was poured into a 1:1 ether/water mixture. The aqueous phase was seperated and extracted with ether (3×). The combined organic phases were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The resulting oil was subjected to flash chromatography (10−50% ether/heptane) to give carbamate **28** as a clear oil (19 mg, 65%): $[\alpha]^{20}_D$ +52.4° ($CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 5.95 (s, 2H), 4.00 (s, 1H), 3.80 (s, 3H), 3.60 (s, 1H), 3.46 (s, 3H), 3.15 (d, J = 14.2 Hz, 1H), 2.95 (s, 1H), 2.60 (d, J =14.2 Hz, 1H), 2.59 (s, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.7, 158.3, 124.7, 124.3, 98.1, 96.3, 88.7, 87.3, 79.9, 76.0, 73.1, 57.6, 54.2, 51.8, 43.6, 37.0, 25.7, 18.3, −4.6, −5.1; MS (CI) 432.

X-ray Structure Analysis for Aziridine 27: Crystal data. $C_{20}H_{27}NO_4Si$, M_w = 373.52, orthorhombic, space group $P2_12_12_1$, Z = 4 , a = 7.118 (2), b = 15.547 (4), c = 19.083 (6) Å, V = 2111.8 Å^3, d_c = 1.17 g cm^{-3}, $F(000)$ = 800, λ (Cu Kα) = 1.5418 Å, μ = 1.15 mm^{-1}; 1803 unique Nonius diffractometric intensities measured of which 1196 with $I > 3.0\,\sigma(I)$ considered as observed.

The structure was solved by direct methods using *SHELXS86*[35] and refined by full matrix least-squares with *SHELX76*[36] minimizing the function $\Sigma w(F_o - |F_c|)^2$. The hydrogen atoms located in difference Fourier maps were replaced at theoretical positions (d C−H = 1.00 Å), except those attached to N17, C10, and O14 which were refined. All were assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.047 and R_w = 0.060 (with $R_w = \{\Sigma w(F_o - |F_c|)^2/\Sigma w F_o^2\}^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.0011F_o^2]$. No residue was higher than 0.29 e Å^{-3} in the final difference map. An intramolecular hydrogen bond is observed between the hydrogen atom of the aziridine and the ether oxygen atom O19 (N17···O19: 2.989(7) Å). In the crystal, the neighboring molecules are linked in chains by a hydrogen bond established between the hydroxyl groups HO14 and the aziridine nitrogen atoms (O14···N17: 2.903(7) Å). Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.

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