Tandem [3,3]-Sigmatropic Rearrangements in an Ansamycin: Stereospecific Conversion of an (*S*)-Allylic Alcohol to an (*S*)-Allylic Amine Derivative

Rodney C. Schnur* and Michael L. Corman

Pfizer Inc., Central Research, Groton, Connecticut 06340

Received December 14, 1993®

Ansamycin ring modifications in the geldanamycin oncogene inhibitor series were investigated. A carbamate to urea interchange was accomplished with net retention at the 7(*S*)-center of a geldanamycin analog. This chirally specific transformation was efficiently accomplished by employing tandem [3,3]-sigmatropic rearrangements involving first, the conversion of the allylic 7(*S*)-alcohol **2b** to an allylic 9(*S*)-thiol, **4b**, and then the rearrangement to the allylic 7(*S*)-isothiocyanate **6**, which was carried on to allylic 7(*S*)-amine derivatives **1a** and **1b**. This tandem rearrangement strategy may have wide applicability for the preparation of chiral allylic amines from the large array of readily available chiral allylic alcohols.

The *erbB-2* oncogene encodes a 185-kD protein that has been observed in a high percentage of breast cancer patients and appears to be inversely correlated with survival.[1] Natural product inhibitors of p185^{erbB-2}, for example herbimycin A[2] and 4,5-dihydrogeldanamycin,[3] have been reported to cause depletion of the oncoprotein from human breast tumor cells (SKBr-3). In addition, geldanamycin, 17-amino-17-demethoxygeldanamycin and other analogs were also found to inhibit cell growth of SV40 virus infected cells[4] as well as cells transformed by Rauscher Leukemia virus.[5]

As part of a program aimed at discovering novel, potent, and selective inhibitors of the p185^{erbB-2}, we investigated structural modification of the ansamycin ring functionality. The 7(*S*)-carbamate moiety of geldanamycin analog **2a**[6] was observed to be readily cleaved with base. Thus, rapid pharmacological deactivation and/or elimination may potentially occur through its sensitivity to circulating esterases *in vivo*. We identified the 7(*S*)-urea **1a** as an attractive target for synthesis. The unique opportunity presented itself to selectively modify, with stereochemical control, this hindered secondary functionality amid the many chemically labile centers in the geldanamycin (GDM) nucleus due to its juxtaposition with the 8,9-trisubstituted double bond.

Precedent for the rearrangement of allylic thiocyanates to isothiocyanates has been known since 1875[7] and was shown to proceed via a suprafacial mechanism.[8] More recently, Nicolaou has reported that allylic alcohols react with thiocarbonyldiimidazole (TCDI) to yield allylic thiocarbonyl imidazole esters which rearrange thermally to afford allylic carbonyl imidazole thioesters via a [3,3]-sigmatropic process.[9] These two processes suggested a strategy of tandem [3,3]-sigmatropic rearrangement for accomplishing the desired production of 7(*S*)-urea **1a**.

The 17-methoxy group of GDM was readily replaced by amines, for example, such as azetidine to afford 17-azetidine analog **2a** (97% yield[10]) which was resistant to attack by other nucleophiles used in Scheme 1. After decarbamylation with 2 equiv of K*O-t*-Bu/DMSO (93%), the allylic alcohol **2b** was treated with TCDI. Although the saccharide intermediate thiocarbonyl ester obtained by Nicolaou required heating at 100 °C to effect rearrangement, in our case, the corresponding ester **3** could not be observed[11] but spontaneously rearranged to **4a** (90% from **2b**) at room temperature. Hydrolysis to thiol **4b** with ammonia was quantitative. Then **4b** was treated with K-O-*t*-Bu and 1 equiv of BrCN to give **6** (83%), after the second spontaneous [3,3]-sigmatropic rearrangement.[12] The thiocyanate **5** was not observed as expected based upon our experience with the facility of the previous rearrangement as well as the literature precedents for allylic thiocyanate to isothiocyanate rearrangements. Urea analog **1a** was obtained from **6** by conventional means: first, treatment with ammonia to give **1b** (100%) and then S → O interchange with basic H_2O_2 (56%[10]).

The absolute configurations of geldanamycin[13] and **2a**[14] (Figure 1) have been determined by X-ray crystallography; however, we were not able to obtain diffraction-quality

• Abstract published in *Advance ACS Abstracts,* April 1, 1994.

(1) Slamon, D. A.; Clark, G. M.; Wong, S. G.; Levin, W. J.; Ullrich, A.; McGuire, W. L. *Science* **1989**, *244*, 707.

(2) Miller, P.; DiOrio, C.; Cullen, W.; Moyer, J. D. *Am. Assoc. Cancer Res. Proc.* **1993**, *34*, 344.

(3) Cullen, W.; Jefferson, M.; Moyer, J.; Moyer, M.; Sciavolino, F. Canadian Society of Microbiology/International Society of Microbiology (CSM/SIM) Meeting, Toronto, 1993, Abstr. no. P55.

(4) Sasaki, K.; Yasuda, H.; Onodera, K.-J. *Antibiotics* **1993**, *32*, 849.

(5) Li, L. H.; Clark, T. D.; Cowie, C. H.; Rinehart, K. L. *Cancer Treat. Rep.* **1977**, *61*, 815.

(6) Compound **2a** differs from geldanamycin at the 17-position; geldanamycin bears a 17-methoxy group while **2a** has the azetidine moiety.

(7) (a) Gerich, G. *Ann.* **1875**, *178*, 80. (b) Billeter, O. *Chem. Ber.* **1875**, *8*, 462.

(8) (a) Smith, P. A. S.; Emerson, D. W. *J. Am. Chem. Soc.* **1960**, *82*, 3076. (b) Giles, D. E. In *The Chemistry of Cyanates and their Thio Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1977; p 399.

(9) Nicolaou, K. C.; Groneberg, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4085.

(10) Reaction conditions and yields are unoptimized. In the final step in Scheme 1 although **1a** was produced quantitatively from **1b**, the low yield recorded (56%) was due to complications in crystallizing small quantities.

(11) By TLC. We have prepared for NMR comparison a sample of an analog of **3** where the thiocarbonyl group is replaced by a carbonyl group. Spectral data on **4** were consistent with other authentically prepared 9-substituted ansamycins with the 7–8 double bond; unpublished results.

(12) Compound **6** could also be produced by treatment of **2b** with mesyl chloride and triethylamine followed by reaction of the mesylate with ammonium thiocyanate. Presumably the sulfur of the thiocyanate attacked in an S_N2' manner at the 9-position followed by rearrangement of the thiocyanate to the 7-isothiocyanate **6** (~20%). However, the mesylate of **2b** decomposed during 16 h at room temperature. Its displacement was accompanied by competitive reactions yielding alternative isothiocyanates among an array of products.

(13) Rinehart, K. L.; Shield, L. S. The Chemistry of Ansamycin Antibiotics. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1976; p 244.

0022-3263/94/1959-2581$04.50/0

Scheme 1

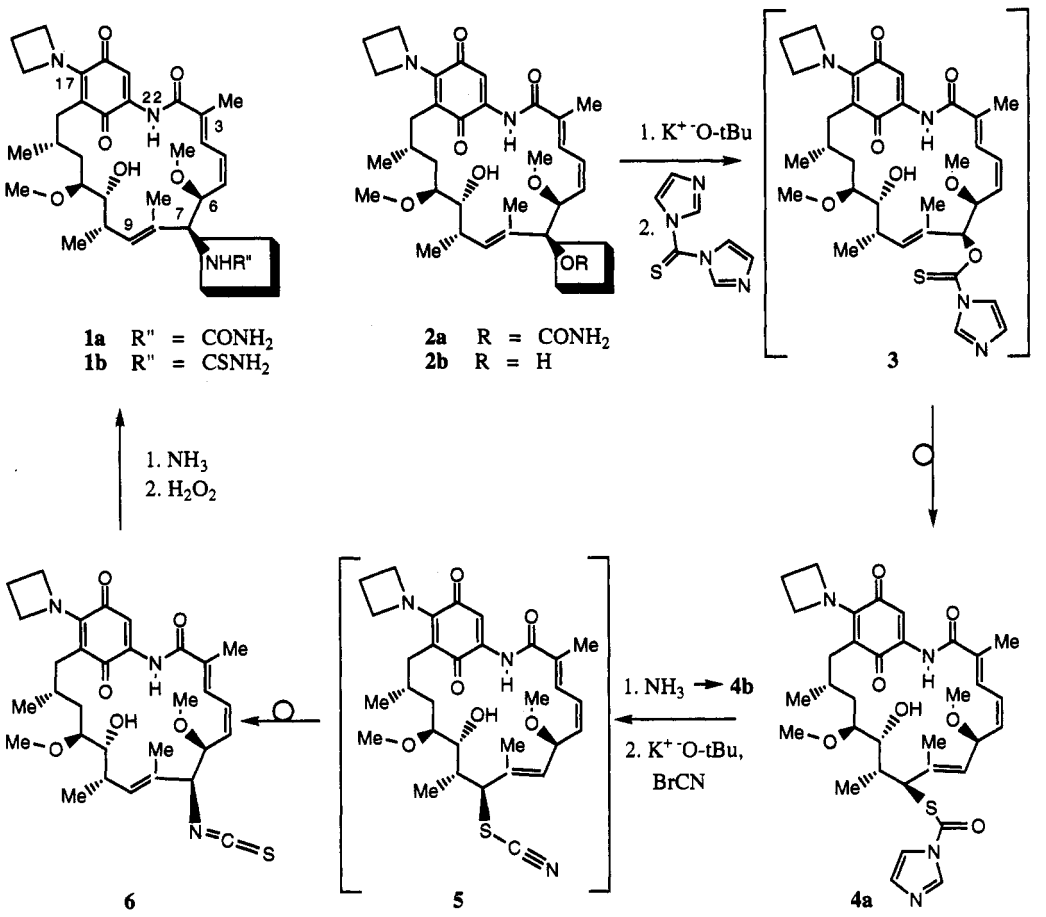


Table 1. Partial Nuclear Overhauser Effect (NOE) for Compounds 6 and 2a[a]

proton irradiated	proton enhanced	effect (%) 6	2a
H-3	H-6	35	19
	H-22	25	16
H-6	H-3	26	12
	H-7	11	11
H-7	H-6	10	8
	H-9	26	19
H-9	H-7	31	20
H-22	H-3	34	20

[a] Other significant and reciprocal NOEs were seen for H-4 with H-5 and 2-Me in **6** and **2a**.

crystals from urea **1a**. NMR chemical shift, coupling constants, and COSY indicated that **1a** and **2a** adopt similar conformations in $CDCl_3$ solution. Nuclear Overhauser effect (NOE) NMR spectra of compounds in the sequence provide convincing evidence that the nitrogen atom of **6** was introduced with the 7(*S*)-configuration found in the starting material **2a** (Table 1). In the X-ray structure of **2a**, protons H-3, H-6, H-7, H-9, and H-22 are oriented on the inside of the ansa ring in good agreement with the observed NOE data. This is depicted in Figure 1 showing with the double arrows the identity of the key NOE interactions that were observed. Table 1 shows the comparison between the NOE enhancements (in %) of **6** with those of **2a** where NOE signals for key protons are shown as a function of irradiation of the specified

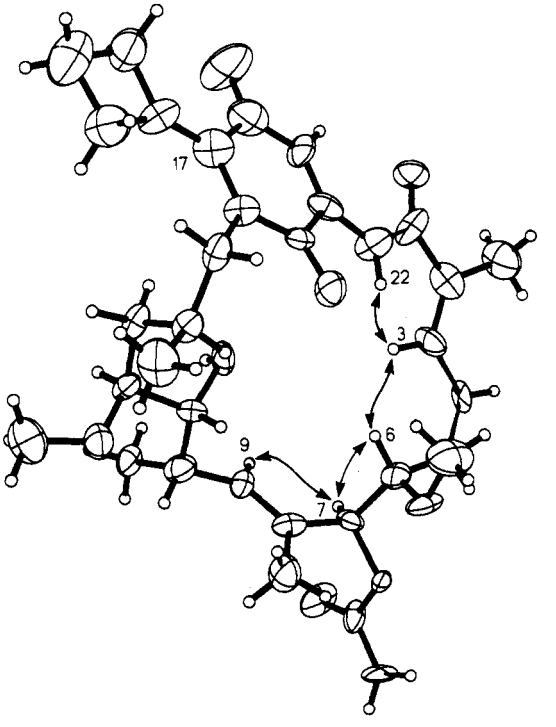


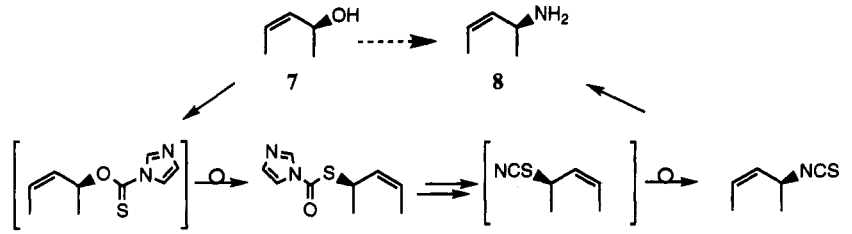
Figure 1. X-ray structure of **2a** indicating the key nuclear Overhauser effect (NOE) enhancements.

hydrogens. Model studies with **6** and **2a** suggest that the epimer of **6**, a 7-(*R*)-isothiocyanate, would lack the 6,7-NOE and 9,7-NOE that are observed and predicted for the compounds with the 7(*S*)-configuration.

The ease of the rearrangement from **3** to **4a** was not

(14) Figure 1 depicts the X-ray structure of **2a** generated from the PDB file, obtained from crystallographic analysis, using the "Nemesis" program (Oxford Molecular Limited, Inc.).

Scheme 2



predicted from the literature; however, examination of the X-ray conformation of **2a** indicated that the ester moiety was perfectly aligned orthogonal to the plane of the 8,9-double bond.[15ab] Thus, in the relatively rigid ansa ring, no bond rotations were required and activation energy was minimal prior to electronic reorganization.

In spite of the special aspects of this case our tandem rearrangement strategy may be uniquely suited for the general overall conversion of chiral allylic alcohols **7** to the analogous chiral allylic amines **8** with stereocontrol.[16] This is depicted in Scheme 2 for the special case of secondary carbons at C-1 and C-3 of the allylic system. Experiments are in progress aimed at defining the generality and scope of this approach with regard to its application in a broader range of substituted, acyclic, and electronically diverse allylic alcohols. The final step in this scheme, conversion of the isothiocyanate to the amine, has been accomplished efficiently by a number of procedures with the most attractive and mildest, perhaps, being that of Posner.[17]

Since the allylic alcohol functionality is encountered in numerous natural products with important biological activity, usually in optically pure form, and is readily prepared optically pure by a variety of synthetic means, this transformation provides a unique opportunity for its stereocontrolled amplification to chiral allylic amine derivatives of potentially significant biological or medicinal use.

Experimental Section[18]

17-Azetidinyl-17-demethoxygeldanamycin (2a). Geldanamycin (14.0 g, 25.0 mmol) was added to a flame-dried flask under N_2 and slurried in 350 mL of CH_2Cl_2. Azetidine (Aldrich, 2.85 g, 49.9 mmol, 3.36 mL) in 10 mL of CH_2Cl_2 was added dropwise. The yellow suspension turned purple during the addition. After 1 h the reaction mixture was evaporated to dryness and the residue dissolved in 50 mL of $CHCl_3$ and precipitated with 600 mL of hexane. Filtration and vacuum drying at 70 °C afforded pure product: 14.2 g (97%); mp 225 °C; NMR ($CDCl_3$) δ 0.94 (brd t, 6H), 1.2 (m, 1H), 1.65 (m, 1H), 1.73 (m, 1H), 1.76 (s, 3H), 2.0 (s, 3H), 2.17 (dd, J = 12 Hz, 16 Hz, 1H), 2.40 (p, J = 8 Hz, 2H), 2.56 (d, J = 16 Hz, 1H), 2.67 (m, 1H), 3.20 (s, 3H), 3.30 (s, 3H), 3.40 (m, 1H), 3.50 (m, 1H), 4.25 (d, J = 10.5, 1H), 4.5–4.9 (m, 6H), 5.13 (s, 1H), 5.79 (t, J = 9 Hz, 1H), 5.87 (d, J = 9 Hz, 1H), 6.53 (t, J = 9 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 7.06 (s, 1H), 9.13 (s, 1H); m/z 608 (M^+ + Na); IR (KBr, cm^{-1}) 1730, 1680, 1645. Anal. Calcd for $C_{31}H_{43}N_3O_8$: C, 63.54; H, 7.40; N, 7.17. Found: C, 63.09; H, 7.33; N, 6.85.

17-Azetidinyl-7-decarbamoyl-17-demethoxygeldanamycin (2b). Compound **2a** (5.00 g, 8.54 mmol) was dissolved in 125 mL of DMSO and treated with K-O-t-Bu (2.42 g, 21.6 mmol). After 3 h at rt the mixture was partitioned between 300 mL of water and 150 mL of ethyl acetate and neutralized to pH 4 with 1 N HCl. The aqueous layer was extracted with 2 × 100 mL of ethyl acetate. The pooled organic layers were washed with water, saturated $NaHCO_3$, and brine, dried with $MgSO_4$, filtered, and evaporated in vacuo to a purple solid: 4.32 g (93%); mp 98–102 °C; NMR ($CDCl_3$) δ 0.94 (brd t, 6H), 1.75 (s, 3H), 1.97 (s, 3H), 2.20 (dd, J = 12 Hz, 16 Hz, 1H), 2.40 (p, J = 8 Hz, 2H), 2.54 (d, J = 16 Hz, 1H), 2.77 (d and m, 2H), 3.20 (s, 3H), 3.31 (s, 3H), 3.41 (m, 1H), 3.50 (m, 1H), 3.95 (d, J = 10 Hz, 1H), 4.12 (d, J = 10.5, 1H), 4.5–4.75 (m, 6H), 5.65 (d, J = 9 Hz, 1H), 5.94 (t, J = 9 Hz, 1H), 6.5 (t, J = 9 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 7.06 (s, 1H), 9.24 (s, 1H).

Synthesis of 4a. Compound **2b** (0.320 g, 0.590 mmol) was dissolved in 25 mL of benzene and vacuum evaporated. This procedure was repeated. The anhydrous residue was dissolved in 3 mL of dry acetonitrile and treated with 1,1′-thiocarbonyldiimidazole (0.155 g, 0.866 mmol) at rt for 48 h. The mixture was diluted with 100 mL of ethyl acetate and extracted as above. The residue obtained was dissolved in 3 mL of $CHCl_3$ and 50 mL of hexane and evaporated in vacuo to a purple powder: 0.344 g (90%); NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 3H), 1.04 (d, J = 7 Hz, 3H), 1.4 (m, 1H), 1.58 (m, 1H), 1.77 (s, 3H), 1.8 (m, 1H), 1.93 (s, 3H), 2.0–2.2 (m, 2H), 2.40 (p, J = 8 Hz, 2H), 2.54 (d, J = 16 Hz, 2H), 2.70 (d, J = 16 Hz, 1H), 3.20 (s, 3H), 3.31 (s, 3H), 3.65–3.85 (m, 2H), 4.5–4.73 (m, 6H), 4.77 (bd t, 1H, H-6), 4.90 (bd d, 1H), 5.64 (d, J = 9 Hz, 1H), 5.82 (dd, J = 7 and 9, 1H), 6.25 (t, J = 9 Hz, 1H), 6.56 (d, J = 9 Hz, 1H), 7.0 (s, 2H), 7.37 (s, 1H), 8.10 (s, 1H), 9.26 (s, 1H) (Proton assignments were made by analysis of the COSY NMR.); m/z 653. (M^+ + H).

Synthesis of 4b. Compound **4a** (56.8 mg, 87.0 μmol) was dissolved in 2 mL of ethanol and treated with 650 μL of ethanolic ammonia (41.6 mg/mL, 1.59 mmol). After 2 h at rt the mixture was diluted with 50 mL of ethyl acetate and 50 mL of water, adjusted to pH 3 with 3 N HCl, washed with 50 mL of water and 50 mL of brine, dried with $MgSO_4$, filtered, and evaporated in vacuo to a purple film which was used without further purification in the next step: 46.8 mg (96%); NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 1.2 (m, 1H), 1.45 (d, J = 7 Hz, 1H), 1.6 (m, 1H), 1.74 (s, 3H), 1.87–2.13 (m, 3H), 1.97 (s, 3H,), 2.45 (p, J = 8 Hz, 2H), 2.80 (d, J = 16 Hz, 1H), 3.26 (s, 3H), 3.40 (s, 3H), 3.76 (m, 1H), 3.95 (m, 1H), 4.29 (bd t, 1H), 4.5–4.73 (m, 6H), 4.75–4.83 (bd dd, 1H), 5.70 (d, J = 9 Hz, 1H), 5.96 (dd, J = 7 and 9, 1H), 6.30 (t, J = 9 Hz, 1H), 6.56 (d, J = 9 Hz, 1H), 7.04 (s, 1H), 9.00 (s, 1H) (Proton assignments were made by analysis of the COSY NMR.); m/z 558. (M^+); IR (KBr, cm^{-1}) 1725, 1690, 1650.

17-Azetidinyl-7-isothiocyanato-7-decarbamoyl-17-demethoxygeldanamycin (6). The compound of the above procedure, **4b** (46.8 mg, 83.8 μmol), was dissolved in 5 mL of CH_2Cl_2 and treated with K-O-t-Bu (13.1 mg, 117 μmol) at rt for 15 min and then cyanogen bromide (28 μL of a 3 M solution in CH_2Cl_2, 84.0 μmol). After 17 h at rt the reaction mixture was diluted with 50

(15) (a) This is not readily visualized in the X-ray view shown in Figure 1 but can be easily seen in models or other views of **2a**. The particular view of Figure 1 was chosen in order to assist in depicting the NOE interactions. (b) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(16) For a review on the synthesis of allylic amines see: Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685. Stereochemical allylic amine synthesis from chiral allylic alcohols has been reported by Overman (Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901). However, C-1 alcohols, after treatment with trichloroacetonitrile, yielded C-3 amino compounds via a [3,3]-sigmatropic rearrangement.

(17) Among a number of examples cyclohexenyl isothiocyanate was converted to cyclohexenylamine in 70% yield by treatment with 4-methyl-1,2-benzenedithiol; Cho, C.-G.; Posner, G. H. *Tetrahedron Lett.* **1992**, *33*, 3599.

(18) For general experimental procedures see: Schnur, R. C. *et al. J. Med. Chem.* **1991**, *34*, 1975. Compounds **1a,b**, **2b**, **4a,b**, and **6** were characterized for purity by analysis of their ^1H NMR spectra on either a 250- or 300-MHz spectrometer.

mL of ethyl acetate and washed with 50 mL of water, brine, dried with $MgSO_4$, filtered, and evaporated in vacuo. The purple residue was dissolved in a minimal amount of $CHCl_3$ and precipitated with hexane: 40.4 mg (83%); NMR ($CDCl_3$) δ 0.97 (d, 3H), 1.00 (d, J = 7 Hz, 3H), 1.2 (m, 1H), 1.65 (m, 1H), 1.78 (m, 1H), 1.87 (s, 3H), 2.05 (s, 3H), 2.27 (dd, J = 12 Hz, 16 Hz, 1H), 2.45 (p, J = 8 Hz, 2H), 2.56 (d, J = 16 Hz, 1H), 2.75 (m, 1H), 3.25 (s, 3H), 3.36 (s, 3H), 3.45 (m, 1H), 3.55 (m, 1H), 4.04 (s, 1H), 4.23 (d, J = 10.5 Hz, 1H), 4.5–4.8 (m, 6H), 4.90 (d, J = 7 Hz, 1H), 5.77 (d, J = 9 Hz, 1H), 5.91 (t, J = 9 Hz, 1H), 6.61 (t, J = 9 Hz, 1H), 6.85 (d, J = 9 Hz, 1H), 7.11 (s, 1H), 9.13 (s, 1H) (Proton asignments were made by analysis of the NOSY and COSY NMR.); m/z 584 (M^+ + H); IR (KBr, cm^{-1}) 2060, 1720, 1680, 1640.

17-Azetidinyl-7-thioureido-7-decarbamoyl-17-demethoxygeldanamycin (1b). Isothiocyanate **6** (97.0 mg, 0.166 mmol) was dissolved in 10 mL of ethanol at rt and perfused during four sessions with ammonia while the reaction was monitored by TLC (4:1 ethyl acetate:hexane). After 40 min the TLC indicated complete conversion to a single polar product. Evaporation in vacuo afforded pure thiourea: 97 mg (97%); NMR ($CDCl_3$) δ 0.95 (d, 6H), 1.55–1.80 (m, 3H), 1.70 (s, 3H), 2.05 (s, 3H), 2.25 (dd, J = 12 Hz, 16 Hz, 1H), 2.46 (p, J = 8 Hz, 2H), 2.55 (d, J = 16 Hz, 1H), 2.77 (m, 1H), 3.23 (s, 3H), 3.36 (s, 3H), 3.40 (m, 1H), 3.56 (m, 1H), 3.70 (d, J = 7 Hz, 1H), 4.29 (d, J = 10.5, 1H), 4.55–4.85 (m, 6H), 5.8–6.1 (m, 3H), 6.57 (t, J = 9 Hz, 1H), 6.85 (d, J = 9 Hz, 1H), 7.02 (d, J = 7 Hz, 1H), 7.10 (s, 1H), 9.12 (s, 1H); m/z 601 (M^+ + H); IR (KBr, cm^{-1}) 1730, 1685, 1650, 1480, 1100.

17-Azetidinyl-7-ureido-7-decarbamoyl-17-demethoxygeldanamycin (1a). Thiourea **1b** (18.6 mg, 31.0 μmol) was dissolved in 600 μL of methanol and 400 μL of water containing $NaHCO_3$ (10.4 mg, 120 μmol) and treated with 30% H_2O_2 (35 μL, 344 μmol). After 30 min the mixture was diluted with 50 mL of ethyl acetate and washed with 50 mL each of water and brine, dried with $MgSO_4$, filtered, and evaporated in vacuo to a purple residue. This material was dissolved in a minimal amount of $CHCl_3$ and precipitated with 25 mL of hexane, isolated by centrifugation, and dried in vacuo: 10.2 mg (56%); mp 157–161 °C; NMR ($CDCl_3$) δ 0.95–1.05 (m, 6H), 1.65 (brd s, 2H), 1.75 (s, 3H), 1.80 (brd s, 1H), 2.05 (s, 3H), 2.26 (dd, J = 12 Hz, 16 Hz, 1H), 2.46 (p, J = 8 Hz, 2H), 2.60 (d, J = 16 Hz, 1H), 2.77 (m, 1H), 3.21 (s, 3H), 3.38 (s, 3H), 3.45 (m, 1H), 3.57 (m, 1H), 4.27 (d, J = 10.5 Hz, 1H), 4.47 (brd s, 1H), 4.55–4.85 (m, 7H), 5.40 (brd d, 1H), 5.8–5.95 (m, 2H), 6.57 (t, J = 9 Hz, 1H), 6.93 (d, J = 9 Hz, 1H), 7.12 (d, J = 7 Hz, 1H), 7.10 (s, 1H), 9.27 (s, 1H); m/z 585 (M^+ + H); IR (KBr, cm^{-1}) 1730, 1685, 1650, 1480, 1100.

X-ray Crystallographic Analysis of 2a. Purple swords of **2a** were obtained from a solution of 1,2-dimethoxyethane and hexane by slow evaporation: $C_{31}H_{43}N_3O_8C_4H_{10}O_2$; crystal size, 0.06 × 0.12 × 0.27 mm; space group $P2_1$; cell dimensions, a = 15.334(3) Å, b = 7.999(2) Å, c = 15.919(3) Å, α = 90.0°, β = 104.58(3)°, γ = 90.0°, V = 1889.7(7) Å^3; two molecules/unit cell. A total of 2102 unique reflections were observed. Lattice constants and intensity data were measured by using graphite monochromatic Cu K_α on a Nicolet R3m/u diffractometer. The structure was solved by the SHEXTL system and refined to a final R value of 0.0698.

Acknowledgment. We thank J. D. Moyer and M. P. Moyer for helpful discussions, E. R. Whipple for NMR consultations, J. Bordner and D. DeCosta for X-ray analysis, and R. J. Gallaschun for technical assistance.

Supplementary Material Available: Copies of ^1H NMR spectra of **1a,b**, **2b**, **4a,b**, and **6** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.