JOC Article

Progress toward a Peptidomimetic of Laminin-Derived Pentapeptide YIGSR: Synthesis of the Unique Tricyclic Core Structure

Félix Busqué, Stephanie A. Hopkins, and Joseph P. Konopelski*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

joek@chemistry.ucsc.edu

Received April 23, 2002

The peptide sequence YIGSR, a segment of the basement membrane matrix glycoprotein laminin, has been identified as a key component in tumor cell invasion. Guided by extensive NMR work and de novo design algorithms, a nonpeptide mimetic of this pentapeptide was identified as a lead candidate for synthesis. The target displays the key amino acid side chains from a novel tricyclic scaffold. The first synthesis of this unique scaffold is completed in 11 steps and 7% overall yield.

Introduction

Interactions of metastatic cells with basement membrane components are considered to be critical for the spread of cancer to sites distant from the origin. Binding of tumor cells to the protein laminin, one of the main components of the extracellular matrix,[1] is key to this metastasis process.[2] The laminin binding protein (LBP) is a cell surface molecule whose expression has been recognized to be an excellent prognostic indicator in human breast cancer.[3,4] A nine amino acid peptide from laminin (CDPGYIGSR, **1**) has been identified as the primary binding site for LBP on tumor cells.[5] Antibodies to **1** were found to block the laminin binding domain from adhering to cancer cells. The smaller fragment YIGSR[6] (**2**) has been shown to be the minimal active sequence of this nonapeptide necessary to block invasion of basement membranes by tumor cells.[7]

Due to the potential antimetastatic activities of peptides **1** and **2**, several groups have studied derivatives of these peptides in an effort to find a bioavailable and potent therapeutic agent.[8,9] However, peptides themselves are, in general, poor drugs. They cannot be delivered orally owing to hydrolysis in the gut and tend to have a short residence time in the blood stream. Thus, early studies provided additional knowledge of YIGSR chemistry[10] but did not lead to substantial increases in activity. Attempts to improve the biological activity of **2** by producing larger molecules less susceptible to proteolysis have been more successful. Short polymers (e.g., $(YIGSR)_4$) were shown to be more active,[11] as were several polymers branched with YIGSR segments.[12−14] Even though these larger molecules have the best activity so far, they still fall well short of what is needed for useful therapeutic lead compounds. Unconstrained peptides have large negative entropies of binding because very few conformations of the flexible chain are able to bind.[15] By designing relatively rigid mimics of the peptide lead structure, it is possible to obtain compounds that have a reduced entropy requirement for binding and thus exhibit much more avid binding.[16]

In this paper, we present an approach toward the synthesis of a class of novel potential antimetastatic nonpeptide agents, structural rigid mimetics to laminin peptide **2**, based on the knowledge of the active conformation of this peptide.

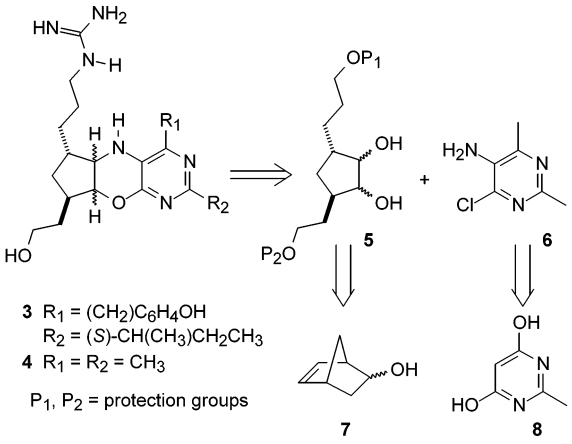
Results and Discussion

Structure-based drug design efforts usually utilize X-ray crystal structures of biological macromolecules as

(1) Fields, G. B. *Pept. Res.* **1993**, *6*, 115−120.
(2) Terranova, V. P.; Williams, J. E.; Liotta, L. A.; Martin, G. R. *Science* **1984**, *226*, 982−4.
(3) Gasparini, G.; Barbareschi, M.; Boracchi, P.; Bevilacqua, P.; Verderio, P.; Dalla-Palma, P.; Ménard, S. *Int. J. Cancer* **1995**, *60*, 604−610.
(4) Martignone, S.; Ménard, S.; Bufalino, R.; Cascinelli, N.; Pellegrini, R.; Tagliabue, E.; Andreola, S.; Rilke, F.; Colnaghi, M. I. *J. Natl. Cancer Inst.* **1993**, *85*, 398−402.
(5) Graf, J.; Iwamoto, Y.; Sasaki, M.; Martin, G. R.; Kleinman, H. K.; Robey, F. A.; Yamada, Y. *Cell* **1987**, *48*, 989−996.
(6) Y = tyrosine, I = isoleucine, G = glycine, S = serine, R = arginine.
(7) Iwamoto, Y.; Robey, F. A.; Graf, J.; Sasaki, M.; Kleinman, H. K.; Yamada, Y. Martin, G. R. *Science* **1987**, *238*, 1132−1134.
(8) Kawasaki, K.; Murakami, T.; Koshino, K.; Namikawa, M.; Maeda, M.; Hama, T.; Mayumi, T. *Chem. Pharm. Bull.* **1994**, *42*, 792−795.
(9) Zhao, M.; Kleinman, H. K.; Mokotoff, M. *J. Med. Chem.* **1994**, *37*, 3383−3388.
(10) Kawasaki, K.; Namikawa, M.; Murakami, T.; Mizuta, T.; Iwai, Y.; Hama, T.; Mayumi, T. *Biochem. Biophys. Res. Commun.* **1991**, *174*, 1159−1162.
(11) Murata, J.; Saiki, I.; Azuma, I.; Nishi, N. *Int. J. Biol. Macromol.* **1989**, *11*, 97−99.
(12) Kaneda, Y.; Yamamoto, S.; Kihira, T.; Tsutsumi, Y.; Nakagawa, S.; Miyake, M.; Kawasaki, K.; Mayumi, T. *Invasion Metastasis* **1995**, *15*, 156−162.
(13) Maeda, T.; Titani, K.; Sekiguchi, K. *J. Biochem.* **1994**, *115*, 182−189.
(14) Mu, M.; Kamada, H.; Kodaira, H.; Sato, K.; Tsutsumi, Y.; Maeda, M.; Kawasaki, K.; Nomizu, M.; Yamada, Y.; Mayumi, T. *Biochem. Biophys. Res. Commun.* **1999**, 264, 763−767.
(15) Weber, P. C.; Pantoliano, M. W.; Thompson, L. D. *Biochemistry* **1992**, *31*, 9350−9354.
(16) For example, see Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217−8.

10.1021/jo025847n CCC: $22.00 © 2002 American Chemical Society
Published on Web 07/25/2002

SCHEME 1

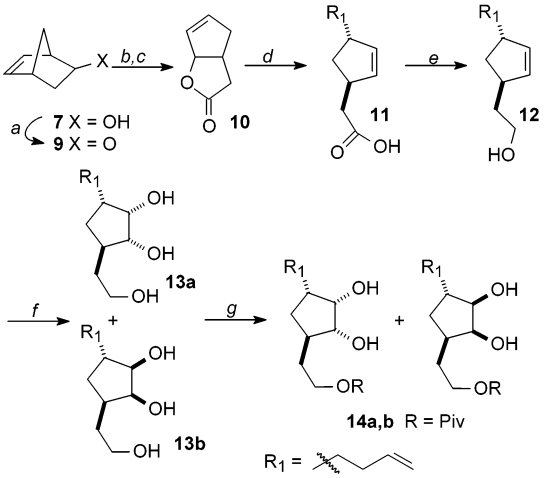


negative templates in the design process. Unfortunately, no X-ray structure is available for the LBP, and information on the conformations of peptides **1** and **2** has been derived from NMR experiments and computational methods. By incorporating NOESY constraints into molecular dynamics[17] and mechanics calculations,[18] conformational information about peptide **1** has been obtained. More recently, a likely structure for the biologically active conformation of pentapeptide **2** bound to LBP has been deduced using transferred NOESY NMR correlation data.[19]

This structural information was used to guide the design of a nonpeptide rigid mimetic via computational efforts.[20] The full peptide sequence **1** was used for structure determination to facilitate deriving the best possible conformation for the minimal active domain **2**. However, only the structure coordinates for the minimal sequence were used in the drug design process. This provided a reasonably sized template for the design of nonpeptide mimics. From the nearly 2000 candidate structures generated by this method, we considered compound **3** (Scheme 1) as our top candidate and lead molecule, owing to its excellent balance between seemingly synthetic accessibility and high ranking as defined by its overlap with the conformation of peptide **1** bound to LBP. Candidate **3** is composed of a rigid core that presents the four key side chains (YISR). Variations on the vectorial arrangement (by means of a trans or cis fused system) and functionality of these side chains, while maintaining the tricyclic rigid core, lead to several related derivatives. Compound **4** was chosen as a focus of the initial synthetic investigation into production of the core tricyclic structure.[21]

The retrosynthetic analysis of **4** is outlined in Scheme 1. Strategic disconnections suggested assembly of the target from the fragments **5** and **6** through a convergent strategy. In this way, analogues of the pyrimidine moiety

SCHEME 2[a]



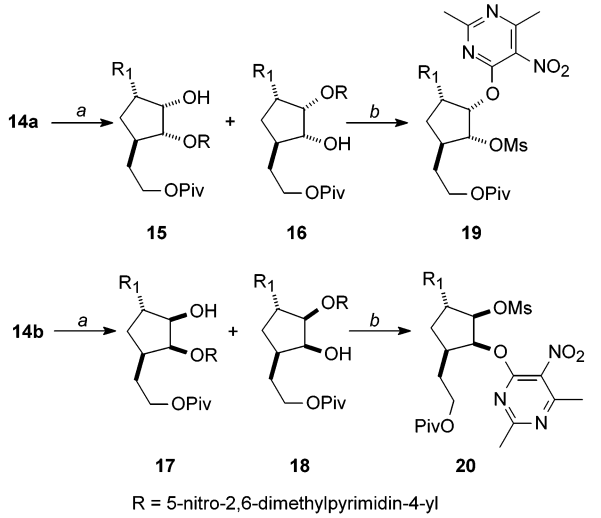
[a] (a) $(COCl)_2$, DMSO, NEt_3; (b) *m*-CPBA; (c) H_3O^+, 72% from **7**; (d) CuBr·DMS, 3-butenyl MgBr, 72%; (e) $LiAlH_4$, 82%; (f) AD-mix, 87%; (g) PivCl, 67%.

6 could be readily generated through primary synthesis of the heterocycle using differently substituted starting materials. It was expected that the differentially protected primary alcohols on carbocycle **5** could be easily converted into the appropriate arginine and serine side chains. Further retrosynthetic analysis of the individual subunits led us to consider the production of carbocycle **5** in a diastereoselective manner from bicyclic alcohol **7**, whereas heterocycle **6** could be obtained from commercial pyrimidine **8**.

The synthesis of fragment **5** followed the work of Curran (Scheme 2),[22] starting with a Swern oxidation[23] of alcohol **7** to give ketone **9**, followed by a Baeyer–Villiger oxidation[24] and rearrangement in acid media to provide lactone **10** in 72% overall yield from alcohol **7**. Unsaturated lactone **10** is regio- and stereoselectively opened by 3-butenylmagnesium bromide and copper(I) bromide, affording cyclopentene acid **11** in 72% yield. By contrast, no useful product is obtain from the mixture of copper salt and allylmagnesium bromide. The S_N2'-anti selectivity is only achieved when a stoichiometric amount of CuBr–Me_2S is employed. Reduction of the acid functionality with lithium aluminum hydride provided known alcohol **12** in 82% yield.[22] Unexpectedly,[25] a selective dihydroxylation of the internal olefin using the Sharpless AD-mix reagent[26] was achieved, with no external dihydroxylation or tetrahydroxylation products observed, obtaining a mixture of the corresponding diastereoisomeric triols **13a** and **13b** in a 1:1 ratio and a 87% yield. Separation of these isomers was accomplished by chromatography, and the relative stereochemistry of the isomers was assigned by a combination of ^{13}C chemical

(17) Ostheimer, G. J.; Starkey, J. R.; Lambert, C. G.; Helgerson, S. L.; Dratz, E. A. *J. Biol. Chem.* **1992**, 267, 25120–25128.
(18) Starkey, J. R.; Dai, S.; Dratz, E. A. *Biochim. Biophys. Acta Protein Struct. Mol. Enzymol.* **1998**, 1429, 187–207.
(19) Starkey, J. R., personal communication.
(20) (a) Pitman, M. *Automating molecular invention-fragment assembly in the molecular invention system: INVENTON*, Ph. D. Dissertation, 1995, University of California, Santa Cruz.
(21) Our research suggests that the tricyclic core structure of **3** and **4** is unique. We have found no evidence of the 5,5a,6,7,8,8a-hexahydrocyclopenta[*b*]pyrimido[5,4-*e*][1,4]oxazine system in the literature.
(22) (a) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943–3958. (b) Curran, D. P.; Chen, M.-H.; Leszczweski, D.; Elliott, R. L.; Rakiewicz, D. M. *J. Org. Chem.* **1986**, *51*, 1612–1614.
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
(24) Krow, G. R. *Tetrahedron* **1981**, *37*, 2697–2724.
(25) (a) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106–11112. (b) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159–12169.
(26) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

SCHEME 3[a]

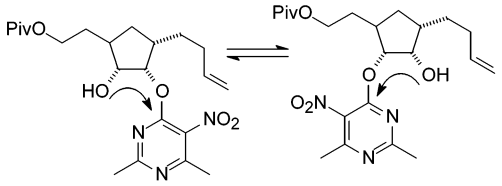


[a] (a) (i) Bu_2SnO, (ii) 4-chloro-5-nitro-2,6-dimethylpyrimidine (**21**), 78%; (b) MsCl, pyridine, 80%.

shifts and NOE experiments on a later intermediate. The primary hydroxyl group of **13a** and **13b** was selectively converted to the corresponding pivaloyl esters **14a/14b**.

Several methodologies were explored for the coupling of these carbocycle fragments with a pyrimidine unit (Scheme 3). Originally, a nucleophilic amino pyrimidine system was envisioned to react in a regiospecific manner with an electrophilic center developed from one of the alcohol functionalities on **14**. However, this approach proved unworkable. After much experimentation, diols **14a** and **14b**, as the corresponding cyclic stannylene derivatives,[27] were coupled to pyrimidine **21**, affording the mixtures of regioisomers **15**/**16** and **17**/**18**, respectively. Pyrimidine **21** is readily available in five steps and 25% overall yield from commercially available **8** following literature procedures.[28] Combined yields were in the range of 70−80%. The regiochemistry of each isomer was tentatively assigned considering ^{1}H NMR data and was confirmed on more advanced derivatives by performing NOE NMR experiments (vide infra).

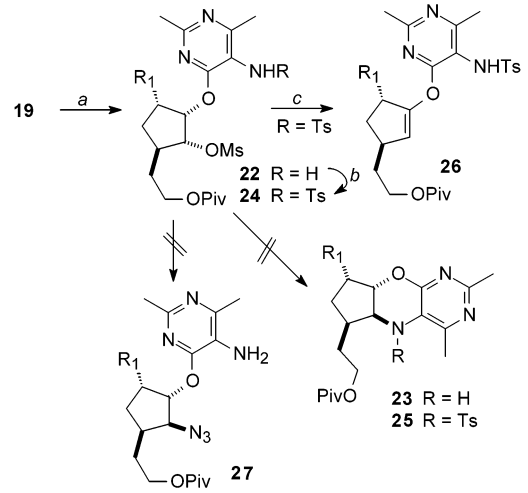
Although each regioisomer could be isolated by chromatography, they reverted very easily to the original mixture. We believe that the regioisomers are in equilibrium as a result of the secondary alcohol acting as an intramolecular nucleophile on the electron-deficient nitropyrimidine ring in an extremely facile S_NAr reaction (Smiles rearrangement, eq 1).[29] Fortunately, when these mixtures were subjected to standard mesylation conditions (MsCl, pyridine), both isomers converged to a single compound in good yield. Only one regioisomer, **19** or **20**, in each case was obtained (Scheme 3).



(1)

With the ability to obtain pure samples of coupled material **19** and **20** in good yield, attention was focused

SCHEME 4[a]



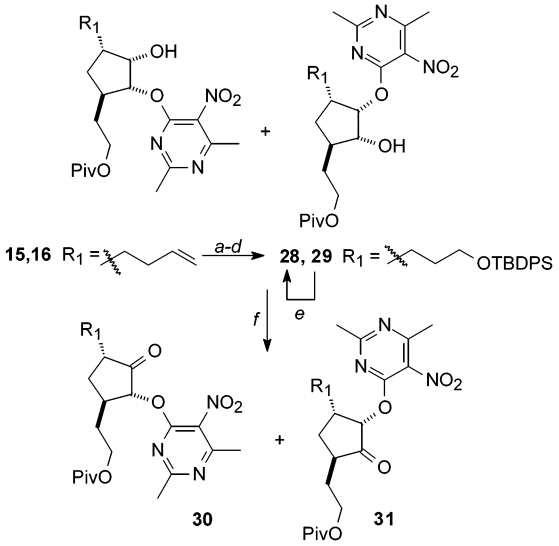
[a] (a) $SnCl_2$, 72%; (b) TosCl, 92%; (c) KOBu^t, 15%.

on generating the morpholine ring system. It was expected that the ring could be closed by an intramolecular S_N2 reaction between the corresponding 5-aminopyrimidine and the mesylate functionality. However, this ring-closure turned out to be much more difficult than originally envisioned. Clean reduction of the nitro group of compound **19** was achieved using $SnCl_2$[30] in ethanol, affording amine **22** in a 72% yield (Scheme 4). All attempts to achieve the direct ring-closure of **22** to **23** failed, despite testing different bases (pyridine, K_2CO_3), solvents (acetonitrile, DMF, dioxane−water) and temperatures (from room temperature to reflux). Therefore, compound **22** was treated with TosCl and pyridine to generate sulfonamide **24** (92% yield), which was in turn deprotonated with various bases in hope that the corresponding anion would undergo the desired S_N2 reaction to give tricycle **25**. When sulfonamide **24** was treated with 2 equiv of KOBu^t in THF under reflux, the elimination product **26** was isolated in poor yield (Scheme 4). Although other conditions were explored, no useful product was obtained. It is possible that the intramolecular reaction did not proceed due to a poor trajectory; i.e., the geometry of nucleophilic amine approach toward the mesylate center in this proposed 6-*Exo*-*Tet*[31] ring closure was not optimal. However, compound **22** proved to be equally unreactive with sodium azide (to produce **27**) making it clear that this sp^3 center was too unreactive for our synthetic goals.

Since the secondary mesylate **22** was unreactive with nucleophiles, attention was turned to a ring closure strategy via reductive amination (Scheme 5). First, the side chain olefin of the regioisomeric mixture of **15** and **16** was elaborated to the desired protected alcohol in order to reduce the number of transformations that would

(27) (a) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24−30. (b) Danishefsky, S.; Hungate, R. *J. Am. Chem. Soc.* **1986**, *108*, 2486-2487.
(28) (a) Rose, F. L. *J. Chem. Soc.* **1954**, 4116−4126. (b) Albert, A.; Brown, D. J.; Wood, H. C. S. *J. Chem. Soc.* **1954**, 3832−3839.
(29) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273−412.
(30) (a) Agrofoglio, L. A.; Demaison, C.; Toupet, L. *Tetrahedron* **1999**, *55*, 8075−8082. (b) Gourdel-Martin, M.-E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166−2172.
(31) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley-Interscience: New York, 2001; pp 282−4.

SCHEME 5[a]



[a] (a) AD-mix; (b) $NAlO_4$; (c) $NaBH_4$, 67% overall; (d) TBDPS-Cl, 77%; (e)CH_2Cl_2 or toluene, heat; (f) TEMPO, bleach, 86%.

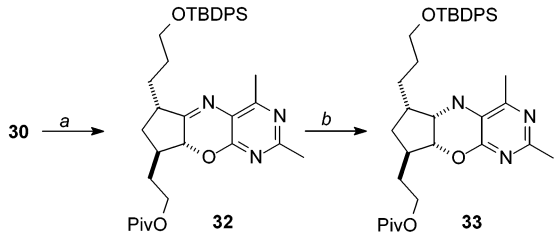
be needed for side chain development after formation of the tricyclic core. This elaboration involved dihydroxylation of the double bond, oxidative cleavage of the resulting diols with sodium periodate[25] and reduction of the corresponding aldehydes with sodium borohydride to obtain the mixture of primary alcohols with a overall yield of the three steps of 67%. The primary hydroxyl groups are selectively converted to the corresponding *tert*-butyldiphenylsilyl ether, yielding the mixture of alcohols **28** and **29** in a 1:2 ratio and a 77% yield. Interestingly, these alcohols underwent the Smiles rearrangement at a slow enough rate to allow separation of the regioisomers by chromatography. It should be noted that the major product **29** (from **16**) is the undesired regioisomer for our synthetic purposes. However, it was found that **29** could be isomerized back to the original **28/29** mixture by heating in refluxing methylene chloride (4 d) or toluene (80 °C, 12 h).

The alcohols **28** and **29** were rapidly and cleanly oxidized to the corresponding ketones **30** and **31** using the TEMPO−bleach system[32] (86% yield). Other methods, such as Swern oxidation and TPAP/NMO, induced isomerization of the regioisomers. By means of NOE and TOCSY NMR experiments, the regiochemistry and relative stereochemistry for these ketones were confirmed, corroborating our assignments based upon coupling constants and chemical shifts made in previous compounds. Several attempts were performed to reduce the nitro group of these ketones to the corresponding amine, using reagents such as $SnCl_2$ as well as both commercial basic and neutral Raney nickel, but results were not reproducible. Finally, this reduction and subsequent cyclization was achieved using either iron or zinc powder in hot acetic acid and ethanol. Thus, imine **32** was obtained in a 90% yield from nitroketone **30** using these conditions (Scheme 6).

This tricyclic compound **32** is the immediate precursor of our target molecule **4**. In fact, we were pleased to find

(32) De Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153−1174.

SCHEME 6[a]



[a] (a) Iron powder, 90%; (b) $NaBH_4$, 80%.

that imine **32** could be reduced to the corresponding target amine (cis fusion, **33**) using $NaBH_4$ or $NaBH_3CN$ as reducing agent (70−80% yield).

In summary, the preparation of a novel heterocyclic core structure designed to mimic the biologically active conformation of a key pentapeptide fragment has been accomplished in 11 steps and 7% yield. Two of the four desired side chains are in place and awaiting functional group manipulation; two other side chains must still be incorporated into the pyrimidine unit for completion of target compound **3**. These synthetic studies are ongoing and will be reported in due course.

Experimental Section

General Methods. Infrared spectra were recorded as thin films on salt plates with ν_{max} in inverse centimeters. Proton (^{1}H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were obtained in $CDCl_3$ at 500 MHz and 62 MHz or 125 MHz, respectively (as noted).

All air and moisture sensitive reactions were carried out under an atmosphere of dry argon or nitrogen using oven-dried or flame-dried glassware and standard syringe techniques. Flash chromatography was performed on 40−75 mesh silica gel using EtOAc−hexane mixtures as solvent unless otherwise indicated. Thin-layer chromatography TLC was carried out on silica gel plates with UV detection.

(±)-[1α,2α,3*β*,5α]-5-(3-Butenyl)-3-(2-hydroxyethyl)-1,2-cyclopentanediol 13a and (±)-[1*β*,2*β*,3*β*,5α]-5-(3-Butenyl)-3-(2-hydroxyethyl)-1,2-cyclopentanediol 13b. A solution of diene **12** (6.60 g, 39.8 mmol) and methanesulfonamide (3.78 g, 39.8 mmol) in 300 mL of *t*-BuOH−H_2O 1/1 was treated with 59.64 g of AD-mix-*β* (1.5 g/mmol olefin) over 15 min. The mixture was allowed to react for 5 h at room temperature and was filtered. The solids were washed with *t*-BuOH/EtOAc 1/3 (3 × 50 mL) and discarded. The whole liquid parts were combined, and the aqueous phase was separated and extracted with more ethyl acetate (2 × 50 mL). All organic phases were combined and evaporated. The residue was redissolved in 200 mL of ethyl acetate, and the aqueous phase was separated and extracted with ethyl acetate (1 × 50 mL). The organic phases were combined, dried over magnesium sulfate, and concentrated under reduced pressure to afford 5.30 g of a mixture of diastereoisomeric triols **13a** and **13b** (approximately 1/1) and a small amount of methanesulfonamide. The isomers were separated by chromatography (hexanes/EtOAc, 1:10) to afford 1.925 g of triol **13a** (9.6 mmol, 24%), 0.620 g of mixed isomers, and 1.050 g of triol **13b**.

13a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.64 (m, 4H), 1.86 (m, 1H), 2.05 (m, 3H), 3.41 (br s, 1H), 3.59 (m, 2H), 3.74 (m, 1H), 3.90 (s, 1H), 4.16 (br s, 1H), 4.75 (br s, 1H), 4.93 (d, J = 10.5 Hz, 1H), 4.96 (dd, J = 1.5 Hz, J = 17 Hz, 1H), 5.78 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 29.3, 32.3, 34.6, 37.7, 40.0, 40.6, 62.1, 75.4, 80.8, 114.6, 139.0; IR (film) cm^{-1}: 3374, 2931, 1640. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 64.94; H, 9.27.

13b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (m, 2H), 1.70, (m, 3H), 1.83 (m, 1H), 2.0−2.76 (m, 4H), 2.76 (br s, 1H), 2.82 (br s, 1H), 3.50 (br s, 1H), 3.63 (m, 2H), 3.76 (m, 1H), 3.99 (m, 1H), 4.93 (d, J = 10 Hz, 1H), 4.99 (d, J = 21 Hz, 1H), 5.82 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 32.6, 32.9, 33.8, 38.2, 42.3, 61.7, 75.1, 80.5, 114.5, 139.0; IR (film) cm^{-1}: 3360, 2929, 1639. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.79; H, 10.18.

(±)-[1α,2α,3*β*,5α]-5-(3-Butenyl)-3-(2-pivaloyloxyethyl)-1,2-cyclopentanediol 14a. A cooled (0 °C) solution of triol **13a** (4.49 g, 0.022 mol), pyridine (2.9 mL, 0.023 mol), and DMAP (0.134 g, 0.0011 mmol) in dry CH_2Cl_2 (11 mL) was treated with a solution of pivaloyl chloride in CH_2Cl_2 (11 mL) via addition funnel. The reaction was allowed to come to room temperature, and after 3 h the reaction mixture was washed with 10% HCl. The aqueous layer was back extracted with CH_2Cl_2. The combined organics are washed with brine, dried ($MgSO_4$), and evaporated to an oil. The crude oil was column purified (10:1) to remove traces of bis-pivaloylated material and starting material, affording 4.24 g (67%) of the desired material. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.40 (m, 2H), 1.65 (m, 3H), 1.88 (m, 2H), 1.95 (m, 1H), 2.02 (dd, J = 7.5 Hz, J = 14.5 Hz, 2H), 2.71 (br s, 1H), 3.04 (br s, 1H), 3.6 (m, 1H), 3.8 (m, 1H), 4.1 (m, 1H), 4.15 (m, 1H), 4.90 (dd, J = 1 Hz, J = 10.5 Hz, 1H), 4.96 (dd, J = 1.5 Hz, J = 15 Hz, 1H), 5.77 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 27.3, 29.1, 32.3, 34.0, 34.2, 38.9, 39.6, 40.2, 63.8, 75.1, 80.6, 114.6, 138.9, 179.0; IR (neat oil) cm^{-1}: 3429, 1727, 1640. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.70; H, 10.07.

(±)-[1*β*,2*β*,3*β*,5α]-5-(3-Butenyl)-3-(2-pivaloyloxyethyl)-1,2-cyclopentanediol 14b. Following the procedure outlined above, isomer **14b** was prepared from **13b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.36 (m, 2H), 1.68 (m, 3H), 1.92 (m, 3H), 2.10 (m, 2H), 2.86 (br s, 1H), 3.62 (dd, J = 4 Hz, J = 8.5 Hz, 1H), 3.90 (t, J = 3.5 Hz, 1H), 4.91 (d, J = 10.5 Hz, 1H), 4.97 (s, J = 17 Hz, 1H), 5.79 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 27.3, 29.1, 32.5, 33.8, 34.2, 37.2, 38.9, 42.6 63.7, 75.2, 80.6, 114.6, 138.9, 178.9; IR (neat oil) cm^{-1}: 3429, 1727, 1640. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.35; H, 10.03.

(±)-[1α,2α,3*β*,5α]-5-(3-Butenyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-3-(2-pivaloyloxyethyl)cyclopentanol 15 and (±)-[1α,2α,3α,5*β*]-3-(3-Butenyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-5-(2-pivaloyloxyethyl)cyclopentanol 16. A suspension of cyclopentane diol **14a** (1.51 g, 3.45 mmol) and Bu_2SnO (0.91 g, 3.62 mmol) in 25 mL of methanol was heated to reflux for 6 h or until the solid white Bu_2SnO disappeared. The mixture was concentrated under reduced pressure, redissolved in dry THF, concentrated again, and dried under vacuum. The resulting oil was dissolved in 40 mL of dry THF, and 1.16 g of tetrabutylammonium bromide was added, followed by a solution of 0.760 g (4.03 mmol) of 4-chloro-5-nitro-2,6-dimethylpyrimidine **(21)** in THF (1 mL). The mixture was allowed to react for ∼24 h at reflux temperature. After this time, the mixture was concentrated under reduced pressure, and the crude material was purified by chromatography (hexanes/EtOAc, 3:1) to afford a 1:1 mixture of regioisomeric products as an oil (1.61 g, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of regioisomers) δ 0.9 (t, J = 7.5 Hz, 2H), 1.15 (s, 9H), 1.19 (s, 1H), 1.23 (m, 2H), 1.34−2.18 (m, 15H), 2.46, (m, 2H), 2.49 (s, 6H), 2.59 (s, 3H), 2.60 (s, 3H), 3.85 (m, 1H), 4.08 (m, 2H), 4.13 (m, 2H), 4.25 (t, J = 3.5 Hz, 1H), 4.98 (m, 4H), 5.21 (dd, J = 8.5 Hz, J = 4 Hz 1H), 5.71 (m, 1H), 5.71 (m, 1H), 5.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 20.5, 26.1, 26.2, 26.9, 27.22, 27.28, 28.5, 29.1, 32.0, 32.1, 32.8, 33.1, 33.3, 33.4, 37.0, 38.2, 38.8, 39.4, 40.3, 62.9, 63.3, 72.8, 80.2, 82.9, 85.3, 114.7, 115.0, 138.2, 138.7, 160.1, 160.62, 160.65, 161.3, 168.3, 168.5, 178.6, 178.7; IR (film) cm^{-1}: 3430, 1726, 1640. HRMS Calcd for [M + 1]$^+$ $C_{22}H_{33}N_3O_6$: calcd 436.2447; found 436.2449.

(±)-[1*β*,2*β*,3*β*,5α]-5-(3-Butenyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-3-(2-pivaloyloxyethyl)cyclopentanol 17 and (±)-[1*β*,2*β*,3α,5*β*]-3-(3-Butenyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-5-(2-pivaloyloxyethyl)cyclopentanol 18. Following the procedure outlined above, the inseparable isomer mixture **17/18** was prepared from **14b**. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of regioisomers) δ 0.88 (m, 1H), 1.18 (s, 9H), 1.20 (s, 9H), 1.20 (m, 3H), 1.42−2.14 (m, 16H), 2.46 (m, 1H), 2.39 (m, 1H), 2.51 (s, 3H), 2.52 (s, 1H), 2.615 (s, 3H), 2.619 (s, 3H), 3.87 (dd, J = 3.5 Hz, J = 8.5 Hz, 1H), 4.06 (m, 2H), 4.12 (m, 2H), 4.28 (t, J = 3.5 Hz, 1H), 4.98 (m, 4H), 5.19 (dd, J = 3.5 Hz, J = 8.5 Hz, 1H), 5.69 (t, J = 3.5 Hz), 5.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 20.6, 26.1, 27.2, 28.5, 29.0, 29.1, 32.0, 32.3, 32.5, 32.9, 33.5, 33.6, 33.8, 33.9, 34.1, 36.0, 37.1, 37.2, 39.4, 42.8, 62.9, 63.4, 63.6, 73.0, 75.1, 80.4, 80.6, 83.3, 85.4, 114.7, 114.8, 138.3, 138.6, 138.8, 160.2, 160.5, 160.8, 161.3, 168.4, 168.5, 178.6, 178.7; IR (film) cm^{-1}: 3489, 1726, 1640. HRMS Calcd for [M + 1]$^+$ $C_{22}H_{33}N_3O_6$: calcd 436.2447; found 436.2449.

(±)-[1α,2α,3α,5*β*]-3-(3-Butenyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-5-(2-pivaloyloxyethyl)-1-cyclopentanol Methanesulfonate 19. A solution of alcohols **15/16** (1.0 g, 2.28 mmol) in CH_2Cl_2 (5 mL) was added to a solution of MsCl (0.353 mL, 4.56 mmol) and pyridine (0.402 mL, 5.01 mmol) in 5 mL of CH_2Cl_2. The reaction was allowed to stir 20 h. The solvent was removed, and the pyridinium salts were removed by trituration with 1:1 EtOAc/Hex. Any remaining MsCl was removed by heating to 60 °C under high vacuum. The crude product (939 mg, 80.2%) was utilized without purification in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.41 (m, 1H), 1.56 (m, 1H), 1.63 (m, 2H), 1.77 (m, 2H), 2.02 (m, 2H), 2.21 (m, 1H), 2.43 (m, 1H), 2.50 (s, 3H), 2.60 (s, 3H), 2.93 (s, 3H), 4.10 (m, 2H), 4.67 (dd, J = 3.5 Hz, J = 9 Hz, 1H), 4.94 (m, 2H), 5.69 (m, 1H), 6.00 (t, J = 3.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 20.1, 25.7, 27.0, 28.7, 31.6, 31.8, 31.9, 37.2, 37.9, 38.2, 38.6, 38.7, 62.4, 78.6, 84.0, 115.1, 132.1, 137.6, 160.14, 160.19, 167.9, 178.2; IR (film) cm^{-1}: 2960, 2937, 2873, 1724, 1640. HRMS Calcd for [M + 1]$^+$ $C_{23}H_{35}N_3O_8S$: calcd 514.2223; found 514.2225.

(±)-[1*β*,2*β*,3*β*,5α]-5-(3-Butenyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-3-(2-pivaloyloxyethyl)-1-cyclopentanol Methanesulfonate 20. Following the procedure outlined above, the inseparable isomer mixture **17/18** resulted in the preparation of **20**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.20, (m, 3H), 1.38−2.40 (m, 7H), 2.52 (s, 3H), 2.62 (s, 3H), 2.93 (s, 3H), 4.05 (t, J = 6.5 Hz, 2H), 4.69 (dd, J = 3.5 Hz, J = 9 Hz, 1H), 5.00 (m, 2H), 5.79 (m, 1H), 5.98 (t, J = 4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 25.8, 27.1, 28.8, 31.7, 31.9, 32.6, 35.8, 38.3, 39.7, 62.4, 78.8, 84.2, 115.1, 126.9, 137.6, 160.0, 160.2, 168.2, 178.3; IR (film) cm^{-1}: 1725. HRMS Calcd for [M + 1]$^+$ $C_{23}H_{35}N_3O_8S$: calcd 514.2223; found 514.2225.

(±)-[1α,2α,3α,5*β*]-3-(3-Butenyl)-2-(5-amino-2,6-dimethyl-4-pyrimidyloxy)-5-(2-pivaloyloxyethyl)-1-cyclopentanol Methanesulfonate 22. Nitromesylate **19** (200 mg, 0.387 mmol) was heated with $SnCl_2$ (294 mg, 1.55 mmol) in 2 mL of EtOH at 70 °C for 1.5 h. The warm reaction mixture was poured into 40 mL of crushed ice and neutralized with saturated aqueous $NaHCO_3$ solution. The solids were isolated by filtration and stirred with EtOAc. The water layer was extracted several times with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated to yield the desired material (140 mg, 72%). This compound was used without further purification in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.37 (m, 1H), 1.55 (m, 1H), 1.67 (m, 2H), 1.85 (m, 1H), 2.04 (m, 3H), 2.23 (m, 1H), 2.32 (s, 3H), 2.44 (s, 3H), 2.44 (m, 1H), 2.88 (s, 3H), 3.49 (br s, 2H), 4.12 (m, 2H), 4.74 (dd, J = 4 Hz, J = 9 Hz, 1H), 4.92 (m, 2H), 5.68 (m, 1H), 5.91 (t, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 24.9, 27.3, 29.1, 31.8, 32.3, 32.5, 38.2, 38.4, 38.8, 38.9, 63.0, 75.6, 85.6, 115.2, 123.5, 138.1, 148.9, 155.3, 156.9, 178.7; IR (film) cm^{-1}: 3374, 1725. HRMS Calcd for [M + 1]$^+$ $C_{23}H_{37}N_3O_6S$: calcd 484.2481; found 484.2481.

(±)-[1α,2α,3α,5*β*]-3-(3-Butenyl)-2-(5-tosylamino-2,6-dimethyl-4-pyrimidyloxy)-5-(2-pivaloyloxyethyl)-1-cyclopentanol Methanesulfonate 24. Aminomesylate **22** (288 mg, 0.592 mmol) was dissolved in 3 mL of dry CH_3CN. Solid TosCl (0.124 mL, 0.651 mmol) was added, followed by pyridine (0.062 mL, 0.769 mmol). The reaction did not go to completion despite addition of more pyridine and TosCl (0.3 equiv each). After 24 h, the mixture was evaporated and triturated with 1:1 EtOAc/hexanes to remove the pyridinium salts. The *crude* material, 347 mg (91.6%), was used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (m, 1H), 1.22 (s, 9H), 1.30 (m, 1H), 1.50 (m, 1H), 1.58 (m, 1H), 1.65 (m, 1H), 1.95 (m, 3H), 2.10 (m, 1H), 2.37 (m, 1H), 2.39 (s, 3H), 2.41 (s, 3H), 2.54 (s, 3H), 2.91 (s, 3H), 4.10 (m, 2H), 4.59 (dd, J = 4.5 Hz, J = 9 Hz, 1H), 4.95 (m, 2H), 5.68 (m, 2H), 6.22 (br s, *NH*), 7.26 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.0, 21.5, 25.4, 27.1, 28.2, 31.6, 31.8, 32.3, 37.9, 38.4, 38.7, 62.6, 84.7, 99.1, 114.0, 115.0, 127.2, 129.8, 137.5, 137.8, 143.9, 164.5, 164.9, 166.4, 178.4; IR (film) cm^{-1}: 3256, 1723, 1640. HRMS Calcd for [M + 1]$^+$ $C_{30}H_{43}N_3O_8S_2$: calcd 638.2569; found 638.2570.

(±)-*trans*-5-(3-Butenyl)-1-(5-tosylamino-2,6-dimethyl-4-pyrimidyloxy)-3-(2-pivaloyloxyethyl)cyclopentene 26. Compound **24** (340 mg, 0.531 mmol) was treated with ^{t}BuOK (59.6 mg, 1.062 mmol) in dry THF at reflux temperature. After 19 h, a product was observed (TLC), but the reaction did not go to completion even after 3 days. The mixture was quenched with 10% HCl and extracted with EtOAc. Column purification (EtOAc/Hex) produced 45 mg of the title compound and 27 mg of starting material. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.14 (m, 1H), 1.31 (m, 1H), 1.61−1.72 (m, 3H), 1,86 (m, 1H), 2.00 (m, 1H), 2.39 (s, 3H), 2.52 (s, 3H), 2.59 (s, 3H), 2.68 (m, 1H), 4.06 (t, J = 6.5 Hz, 2H), 4.93 (m, 2H), 4.99 (s, 1H), 5.69 (m, 1H), 6.17 (s, 1H *NH*), 7.23 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.3, 21.4, 25.5, 27.1, 31.1, 31.7, 34.2, 35.0, 36.7, 38.6, 41.6, 62.8, 113.8, 114.6, 127.3, 129.5, 136.7, 138.2, 143.8, 154.1, 163.0, 165.5, 167.8, 178.4; IR (film) cm^{-1}: 1726, 1640. HRMS Calcd for [M + 1]$^+$ $C_{29}H_{39}N_3O_5S$: calcd 542.2688; found 542.2688.

(±)-[1α,2α,3*β*,5α]-5-(3-*tert*-Butyldiphenylsilyloxypropyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-3-(2-pivaloyloxyethyl)cyclopentanol 28 and (±)-[1α,2α,3α,5*β*]-3-(3-*tert*-Butyldiphenylsilyloxypropyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-5-(2-pivaloyloxyethyl)cyclopentanol 29. A solution of olefins **15/16** (4.3 g, 9.81 mmol) in water/*n*-BuOH (40 mL each) was treated with $MeSO_2NH_2$ (0.933 g, 9.81 mmol) and AD-mix-*β* (14.7 g, 1.5 g/mmol substrate). The mixture was stirred rapidly for 1 h or until complete by TLC ($KMnO_4$), filtered, and rinsed with *n*-BuOH (2×) and EtOAc (2×). The water was separated, and the organics were concentrated. The mixture was redissolved in EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The material was passed through a SiO_2 plug (EtOAc/Hex) to remove $MeSO_2NH_2$ contaminants. A yield of 3.4 g (75%) of the desired material was obtained. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of regioisomers) δ 1.14 (s, 9H), 1.18 (s, 9H), 1.3−2.2 (m, 20H), 2.48 (s, 6H), 2.58 (s, 3H), 2.60 (s, 3H), 3.35 (m, 2H), 3.58−3.66 (m, 4H), 3.86 (br m, 1H), 4.03−4.13 (br m, 4H), 4.28 (br m, 1H) 5.18 (br m, 1H), 5.69 (br q, J = 4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 26.1, 27.3, 31.6, 33.2, 33.5, 33.7, 37.1, 37.2, 38.8, 39.2, 40.3, 63.0, 63.3, 66.8, 66.9, 72.1, 72.2, 72.6, 72.8, 80.3, 82.8, 82.9, 85.2, 132.6, 160.2, 160.6, 160.7, 161.4, 168.4, 168.6, 178.7, 178.8; IR (film) cm^{-1}: 3384, 1724. HRMS Calcd for [M + 1]$^+$ $C_{22}H_{35}N_3O_8$: calcd 470.2502; found 470.2504.

The mixture (3.5 g, 7.38 mmol) was dissolved in water/*n*-BuOH (40 mL each), and $NaIO_4$ (4.7 g, 22.1 mmol) was added. The reaction was judged complete in 30 min by TLC. To the mixture was added 150 mL of H_2O and 250 mL of EtOAc, and the layers were separated. The aqueous layer was back extracted with EtOAc (3×). The combined organics were dried ($MgSO_4$) and concentrated. The crude aldehyde mixture of regioisomers (2.99 g, 92.0%) were dissolved in MeOH and cooled to 0 °C. Solid $NaBH_4$ (0.20 g, 5.44 mmol) was added. After 15 min, a few drops of 10% HCl was added. The mixture was concentrated in vacuo, redissolved in EtOAc, and washed with 10% HCl. Sodium hydroxide (6 N) was added to the aqueous layer until pH 8 and was then extracted with EtOAc to remove additional product. The crude yield was 1.94 g, 96.6%. HRMS Calcd for [M + 1]$^+$ $C_{21}H_{33}N_3O_7$: calcd 440.2396; found 440.2397.

The mixture of alcohols (2.89 g, 6.52 mmol) was dissolved in CH_2Cl_2 (13 mL) and TEA (1.09 mL, 7.82 mmol) and then DMAP (0.032 g, 0.26 mmol) was added. The solution was cooled to 0 °C. A solution of TBDPSCl (1.79 mL, 6.84 mmol) in 13 mL of CH_2Cl_2 was added dropwise to the alcohol. The reaction was complete after 3 h was washed with 10% HCl and H_2O and dried ($MgSO_4$). The regioisomers were separated (1:4 EtOAc/hexanes) to obtain a 1:2 ratio of **28** to **29** (total recovery, 2.51 g, 77%).

Compound 28. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.17 (s, 9H), 1.47 (m, 1H), 1.50 (m, 1H), 1.60 (m, 2H), 1.67 (m, 2H), 1.81 (m, 1H), 1.87 (m, 1H), 1.97 (br m, 2H), 2.51 (s, 3H), 2.62 (s, 3H), 3.68 (m, 1H), 4.21 (br s, 1H), 4.97 (m, 2H), 5.18 (dd, J = 3.5 Hz, J = 8.5 Hz, 1H), 7.39 (m, 6H), 7.67 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.3, 20.5, 25.7, 26.1, 27.0, 27.2, 31.0, 33.0, 33.3, 37.1, 38.8, 39.9, 63.0, 64.1, 72.8, 85.5, 127.7, 129.6, 132.6, 134.2, 135.7, 160.2, 160.5, 168.4, 178.5; IR (film) cm^{-1}: 3440, 1726. HRMS Calcd for [M + 1]$^+$ $C_{37}H_{51}N_3O_7Si$: calcd 678.3574; found 678.3576.

Compound 29. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.21 (s, 9H), 1.32 (m, 1H), 1.54 (m, 4H), 1.65 (m, 1H), 1.72 (m, 1H), 1.95 (m, 1H), 2.0 (m, 1H), 2.18 (m, 1H), 2.50 (s, 3H), 2.58 (s, 3H), 3.60 (t, J = 6.5 Hz, 2H), 3.83 (dt, J = 4 Hz, J = 9 Hz, 1H), 4.14 (m, 2H), 5.72 (t, J = 4 Hz, 1H), 7.37 (m, 6H), 7.62 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2, 20.5, 26.0, 26.4, 26.9, 27.3, 30.8, 33.4, 33.6, 38.8, 40.3, 53.5, 63.2, 63.7, 80.2, 82.8, 127.6, 129.6, 132.5, 134.0, 135.6, 160.5, 161.3, 168.2, 178.5; IR (film) cm^{-1}: 3477, 1725. HRMS Calcd for [M + 1]$^+$ $C_{37}H_{51}N_3O_7Si$: calcd 678.3574; found 678.3576.

(±)-[2α,3*β*,5α]-5-(3-*tert*-Butyldiphenylsilyloxypropyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-3-(2-pivaloyloxyethyl)cyclopentanone 30. Alcohol **28** (1.05 g, 1.55 mmol) was dissolved in CH_2Cl_2 (0.4 mL) and mixed with TEMPO (2.4 mg, 0.015 mmol) and aqueous KBr (1 M, 2.58 mL) at −10 °C. A solution of commercial bleach (5.25%) (2.58 mL, 1.70 mmol) containing $NaHCO_3$ (169 mg/10 mL) was added dropwise to the alcohol with rapid stirring. After completion (∼10 min), the reaction mixture was washed with 10% HCl containing NaI (150 mg/10 mL HCl), 10% $Na_2S_2O_3$, and H_2O. The organics were dried ($MgSO_4$) and concentrated to afford the ketone in 86% yield (904 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.18 (s, 9H), 1.47 (m, 1H), 1.63 (m, 2H), 1.85 (m, 3H), 2.03 (m, 2H), 2.44 (m, 2H) 2.51 (s, 3H), 2.56 (s, 3H), 3.67 (m, 1H), 4.15 (m, 2H), 5.52 (d, J = 10 Hz, 1H) 7.40 (m, 6H), 7.66 (dd, J = 1.5 Hz, J = 8 Hz, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.3, 20.5, 25.9, 26.8, 27.2, 28.0, 29.6, 30.2, 32.6, 35.8, 38.8, 43.1, 62.0, 63.4, 83.2, 127.6, 129.7, 132.0, 133.9, 135.6, 159.7, 160.6, 167.9, 178.5, 211.0; IR (film) cm^{-1}: 1757, 1728. HRMS Calcd for [M + 1]$^+$ $C_{37}H_{49}N_3O_7Si$: calcd 676.3418; found 676.3417.

(±)-[2α,3α,5*β*]-3-(3-*tert*-Butyldiphenylsilyloxypropyl)-2-(2,6-dimethyl-5-nitro-4-pyrimidyloxy)-5-(2-pivaloyloxyethyl)cyclopentanone 31. Following the procedure outlined above, isomer **29** was transformed into **31**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.19 (s, 9H), 1.54 (m, 2H), 1.67(*H*6)-1.80 (m, 4H), 2.12 (m, 1H), 2.22 (m, 1H), 2.35 (m, 1H, *H*4), 2.51 (s, 3H), 2.59 (m, 1H, *H*2), 2.59 (s, 3H), 3.65 (m, 2H, *H*8), 4.15 (m, 2H), 5.87 (d, J = 7.5 Hz, 1H, *H*1), 7.39 (m, 6H), 7.63 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2, 20.5, 23.5, 26.0, 26.9, 27.3, 28.7, 30.0, 30.2, 36.6, 38.3, 40.2, 62.1, 63.5, 80.2, 129.7, 129.7, 132.1, 133.8, 135.6, 159.6, 160.7, 168.1, 178.4, 211.6; IR (Film) cm^{-1}: 1757, 1726. HRMS Calcd for [M + 1]$^+$ $C_{37}H_{49}N_3O_7Si$: calcd 676.3418; found 676.3417.

Imine 32. Nitroketone **30** (100 mg, 0.147 mmol) was dissolved in EtOH (1 mL) and HOAc (84 μL, 1.47 mmol) and

was heated to 70 °C. Iron powder (−325 mesh, 41 mg, 0.735 mmol) was added. After 1 h, the hot reaction mixture was passed through Celite and evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with sat. aqueous $NaHCO_3$. The organics were dried ($MgSO_4$) and concentrated to yield 88.3 mg (90%) of the desired imine. The crude material was taken directly on to the next step. Note: this material degrades upon sitting over a period of days.

Tricycle 33. Imine **32** (88.3 mg, 0.140 mmol) was dissolved in MeOH (∼1 mL) and cooled to 0 °C. $NaBH_4$ (6.4 mg, 0.168 mmol) was added as a solid in one portion. The reaction was complete in minutes, and a drop of 10% HCl was added. The MeOH was removed in vacuo. The residue was dissolved in EtOAc, and the solution was washed with saturated aqueous $NaHCO_3$ to liberate 68.5 mg of the free amine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.13 (s, 9H), 1.42 (m, 1H), 1.5−1.7 (m, 5H), 2.02, (m, 1H), 2.06 (m, 1H), 2.16 (m, 1H), 2.26 (s, 3H), 2.49 (s, 3H), 3.29 (br s, *NH*), 3.44 (br q, $J = 4$ Hz, $J = 6$ Hz, 1H), 3.69 (m, 2H), 4.10 (m, 2H), 4.38 (ddd, $J = 1$ Hz, $J = 3.5$ Hz, $J = 7$ Hz, 1H), 7.39 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 19.3, 24.6, 25.9, 27.0, 27.2, 30.9, 32.9, 33.0, 38.6, 39.0, 52.2, 63.1, 63.6, 84.4, 112.2, 127.7, 129.7, 133.9, 135.6, 149.0, 154.9, 156.3, 178.5; IR (film) cm^{-1}: 1801, 1725. HRMS Calcd for $[M + 1]^+$ $C_{37}H_{51}N_3O_4Si$: calcd 630.3727; found 630.3727.

Acknowledgment. We are pleased to thank the University of California Breast Cancer Research Program (3CB-0183) for support of this work. Moreover, partial support from the DOD Breast Cancer Research Program (DAMD 17-97-1-7207) and the Susan G. Komen Breast Cancer Foundation is also acknowledged. Purchase of the 500 MHz NMR used in these studies was supported by funds from the Elsa U. Pardee Foundation and the National Science Foundation (BIR-94-19409). In addition, we thank Dr. Andras Kotschy (Eotvos Lorand University, Budapest, Hungary) and our collaborators Dr. Jean R. Starkey (Montana State University) and Professor W. Todd Wipke (UCSC) for many stimulating discussions.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025847N