Articles

Keto/Enol Epoxy Steroids as HIV-1 Tat Inhibitors: Structure–Activity Relationships and Pharmacophore Localization

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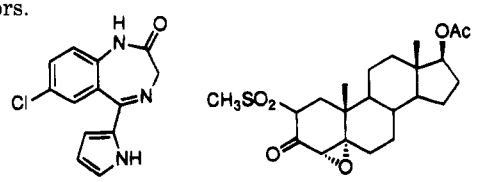
Inhibition of the HIV-1 nuclear regulatory protein tat could potentially yield particularly useful drugs because it functions as an activator of transcription. It has no known cellular counterpart, and deletions in the tat gene destroy the ability of HIV-1 to replicate. We recently reported that a structurally unique class of tat inhibitors, 3-keto/enol 4,5-α-epoxy steroids bearing electron-withdrawing substituents at position 2, specifically inhibit tat-induced gene expression in virus free transfected SW480 cells. In this paper, we report on additional SAR (structure–activity relationships) for the steroid series and the localization of the pharmacophore to the A-ring functionality. There is a weak enantioselective preference for the natural steroid stereochemistry and hints of additional SAR in the electron-withdrawing group. Compound **34a** is of particular interest in that it inhibits HIV replication in H9 cells at a concentration equivalent to its inhibitory level in the primary tat assay.

Introduction

In the search for effective AIDS therapies, a number of virus-specific molecular targets have emerged.[1] Research directed at inhibition of the HIV-1 reverse transcriptase, protease, and receptor has resulted in several potent compounds[2] whose clinical utility is being assessed.[3] Several inhibitors of the nuclear regulatory tat protein have also been reported, including a benzodiazepine derivative (Ro 24-7429, **1**),[4] a transdominant peptide,[5] a transdominant peptidomimetic (ALX40-4C),[6] an antisense oligonucleotide,[7] and a tat-responsive element RNA decoy.[8] Two of these have reached clinical trials. Ro 24-7429 did not show efficacy at nontoxic doses, and development has been discontinued.[9] ALX40-4C has recently entered clinical trials.[6] In a previous communication, we reported on a structurally unique class of small molecule tat inhibitors (keto/enol epoxy steroids, e.g., **2**) which we discovered by screening of our compound library.[10] In our hands, **2** was somewhat more potent than **1** in both a primary assay for tat inhibitory activity and a whole cell assay for inhibition of HIV-1 replication. We also presented NMR data which led to the speculation that the enol form, perhaps stabilized by interaction with a target molecule, is responsible for the tat inhibitory effect. In this paper, we report on the results of additional testing of library compounds and of a synthetic program designed to develop structure–activity relationships and to localize the pharmacophore.

Figure 1. Structures of benzodiazepine and steroid HIV tat inhibitors.



1 **2**

Chemistry

The preparations of compounds **1**,[11] **2**–**5**,[10] **6**,[12] **21** and **22**,[13] and **23** and **24**[14] have been reported. Compounds **10**, **11**, and **14** were prepared as shown in Scheme 1. Testosterone **7** was allowed to react with magnesium methyl carbonate in hot DMF, and the resulting acid was esterified with 1-methyl-3-tolyltriazine to give **8**. Acetylation of the enol and alcohol hydroxy groups followed by *m*-CPBA epoxidation gave **9**. Mild base hydrolysis ($KHCO_3$) gave **10**, whereas more vigorous base hydrolysis (KOH) provided **11**. (Hydroxymethylene)testosterone **12**[12] was allowed to react with phenyl benzenethiosulfate with concomitant decarbonylation; the resulting crude phenylthio ether was immediately oxidized with *m*-CPBA to give **13**. Acetylation of the enol and alcohol hydroxy groups, epoxidation with *m*-CPBA, and strong base hydrolysis gave **14**. Throughout this work, compounds which contained a 2-carboxamide and 4,5-epoxide or 4,5-chlorohydrin (steroid, decalin, and cyclohexane derivatives) were predominantly (>95%) in the enol form as shown by NMR and are so indicated in the schemes. Compounds **15**–**20** were prepared as shown in Scheme 2. Compound **4** was reduced with PtO_2 in EtOH to give **15** and **16**. Alternatively, **4** was reduced with Zn to give **17** which hydrolyzed with LiOH to give **18**. In addition, **4** was treated with HCl/H_2O/acetone to give **19**. Compound **5** was reduced with PtO_2 in EtOH to give **20**. In this case, no attempt was made to isolate the minor *cis*-β-isomer.

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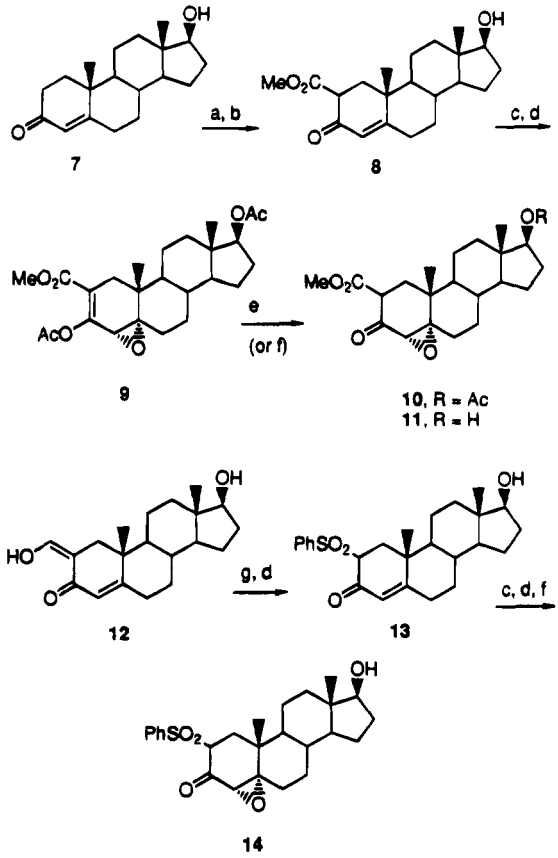
Scheme 1[a]



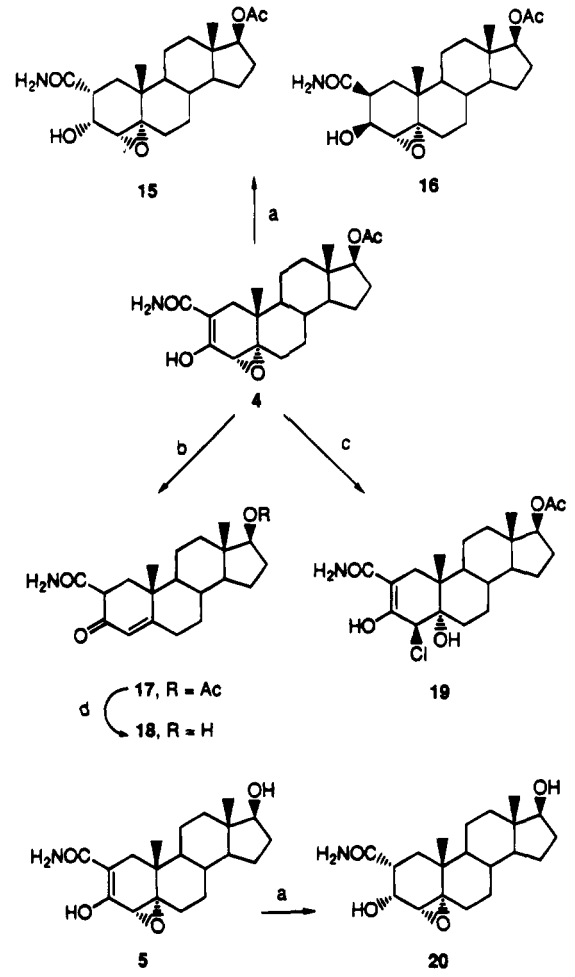
[a] Reagents: (a) MMC, DMF; (b) 1-methyl-3-tolyltriazine; (c) Ac_2O, pyridine; (d) *m*-CPBA, CH_2Cl_2; (e) $KHCO_3$, MeOH; (f) KOH, MeOH; (g) $PhSO_2SPh$, KOAc, EtOH.

The suffix **a** in the following numbering scheme refers to the *S* configuration (natural steroid stereochemistry) of carbon 8a of the decalin system. All stereochemistry is shown relative to this center. The suffix **b** designates the corresponding enantiomer. Compounds **28a**, **30a**, and **31a** were prepared as shown in Scheme 3. Beginning with enantiomerically pure **25a**, treatment with HCO_2Me followed by H_2NOH gave **26a**. Epoxidation with *m*-CPBA gave **27a** which, in the presence of NaOMe, underwent isoxazole ring opening to give nitrile **28a**. Reaction with H_2NOH gave the reversed isoxazole **29a**. The latter compound was reduced and hydrolyzed to give **30a** which could be further hydrolyzed with HCl/H_2O/acetone to afford the chlorohydrin **31a**. Repeating these reactions starting with the enantiomeric **25b** (not shown) led to the corresponding **28b**, **30b**, and **31b**.

The synthesis of additional bicyclic analogs is shown in Scheme 4. Compound **25a** was converted to the silyl enol ether **32a**. Reaction with PhNCO gave the anilide **33a**. Diacetylation (enol and amide) followed by epoxidation with *m*-CPBA and subsequent hydrolysis gave **34a**. Treatment with HCl/H_2O/acetone opened the epoxide to give the chlorohydrin **35a**. Compounds **37a** and **38a** were prepared via reaction of the Li enolate of **25a** with (*o*-MeO)PhNCO to give **36a**. As above, acetylation followed by epoxidation and hydrolysis gave **37a** which in turn was converted to the chlorohydrin **38a** using HCl/H_2O/acetone.

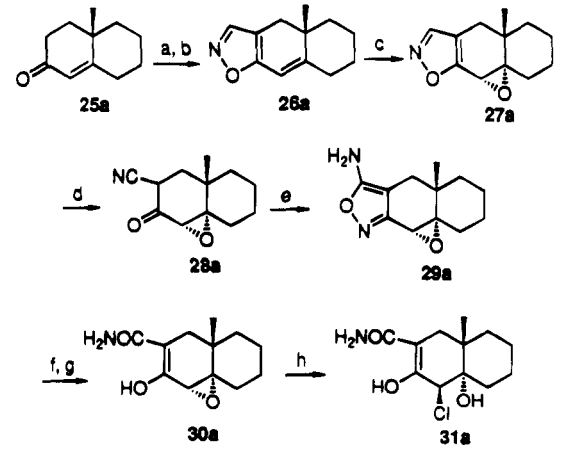
The preparation of the monocyclic analogs **40**–**45** is shown in Scheme 5. The Li enolate of **39** reacted with ArNCO to provide either **40** or **41**. Each of these compounds was in turn epoxidized with H_2O_2 to give **43** and **44**, respectively. The preparation of **42** required

Scheme 2[a]



[a] Reagents: (a) PtO_2, H_2, EtOH; (b) Zn, HOAc, NaOAc, KI; (c) HCl, acetone, H_2O; (d) LiOH, THF, H_2O.

Scheme 3[a]



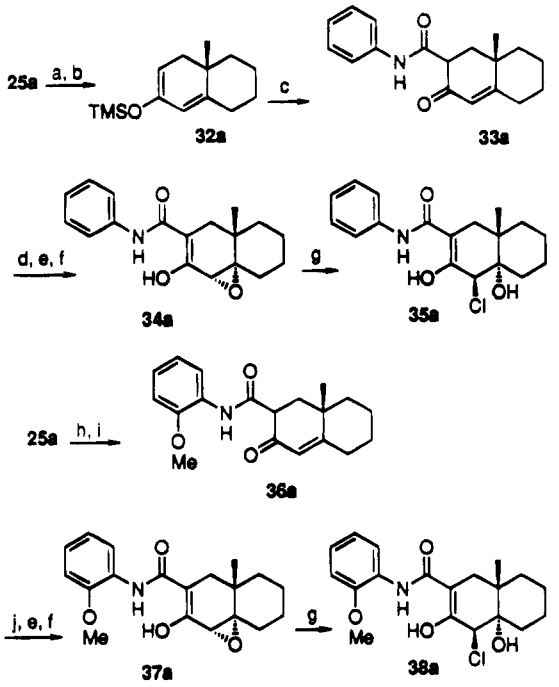
[a] Reagents: (a) HCO_2Me, NaOMe, THF; (b) H_2NOH·HCl, EtOH; (c) *m*-CPBA, CH_2Cl_2; (d) NaOMe, THF; (e) H_2NOH·HCl, EtOH, H_2O; (f) 10% Pd/C, H_2, THF; (g) HOAc, H_2O; (h) HCl, acetone, H_2O.

the intermediacy of the silyl enol ether of **39** which is hydrolyzed back to the ketone **42** after reaction with the isocyanate. Finally, epoxidation with alkaline peroxide gave **45**.

Structure–Activity Relationships

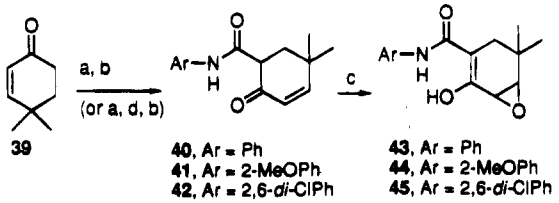
Table 1 shows the activities in the primary tat and HIV whole cell assays of steroid analogs with changes at positions 2 and 17 (see the Experimental Section for

Scheme 4[a]



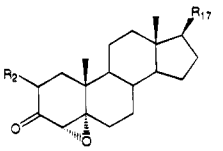
[a] Reagents: (a) LDA, THF; (b) TMSCl; (c) PhNCO, pyridine; (d) Ac_2O, pyridine; (e) *m*-CPBA, CH_2Cl_2; (f) $NaHCO_3$, MeOH, H_2O; (g) HCl, acetone, H_2O; (h) $LiN(TMS)_2$, THF; (i) 2-MeOPhNCO; (j) $LiN(TMS)_2$, AcCl.

Scheme 5[a]



[a] Reagents: (a) LDA, THF; (b) ArNCO; (c) H_2O_2, NaOH, MeOH; (d) TMSCl.

Table 1. Activities of Keto/Enol Epoxy Steroids in the HIV Tat and Whole Cell Assays

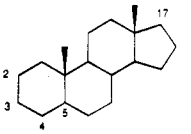


			tat assay	whole cell assay	
no.	R_2	R_{17}	IC_{50}[a]	IC_{50}[d]	index[c]
1			4.0 (2.0–7.4)	0.6 (3)	5.9
2	SO_2CH_3	OAc	2.6 (2.0–7.4)	0.3 (4)	4.3
3	SO_2CH_3	OH	8.4 (5.8–12)	1.4 (4)	3.9
4	$CONH_2$	OAc	2.6 (2.0–3.1)	2.4 (4)[d]	1.6
5	$CONH_2$	OH	14.3 (10.3–22.1)	1.2 (3)	6.5
6	CN	OAc	24.5 (10.2–?)		
10	CO_2CH_3	OAc	2.7 (0–6.4)	1.4 (4)	3.1
11	CO_2CH_3	OH	3.6 (1.9–5.2)	2.4 (4)	4.5
14	$SO_2C_6H_5$	OH	10.3 (7.2–16.6)	1.6 (4)[d]	2.6

[a] Units of micromolar (95% confidence limits). [b] Mean of *n* determinations with units of micromolar. [c] Whole cell assay. [d] Apparent activity may be due to cytotoxicity; note the low therapeutic index. See the text.

a detailed description of these assays). The data for compounds **1**–**5** were reported[10] and are included for completeness. The presence of an electron-withdrawing group at position 2 is associated with activity in the primary tat assay but may not be necessary (*vide infra*).

Table 2. Activities of Variously Substituted Steroids in the HIV Tat Assay



	substituent at position					tat assay
no.	2	3	4	5	17	IC_{50}[a]
15	$CONH_2$	α-OH	α-epoxide		OAc	NA[b] at 80
16	$CONH_2$	β-OH	α-epoxide		OAc	NA[b] at 80
17	$CONH_2$	α-OH	unsaturated		OAc	NA[b] at 80
18	$CONH_2$	O=	unsaturated		OH	NA[b] at 90
19	$CONH_2$	O=	β-Cl	α-OH	OAc	8.4 (3.3–17)
20	$CONH_2$	O=	α-epoxide		OH	NA[b] at 90
21	$CONH_2$	O=	saturated		OAc	NA[b] at 80
22	$CONH_2$	O=	saturated		OH	NA[b] at 90
23	H	O=	α-epoxide		OH	15.4 (11.1–24.3)
24	H	O=	β-epoxide		OH	NA[b] at 130

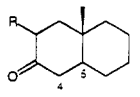
[a] Units of micromolar (95% confidence limits). [b] Not active.

Beyond that, however, the nature of the group at this position does not seem to affect activity greatly. Thus, in the 17-OAc series, the sulfone, amide, and ester groups (**2**, **4**, and **10**) are equivalent, although the nitrile **6** has lost considerable activty. This suggests that substituents at this position might well serve to alter the pharmacokinetics of the compounds so as to achieve a disease relevant biodistribution. Note that, for a compound to be considered positive in the whole cell assay, its therapeutic index must be 3.0 or greater. This level of safety is not meant to imply therapeutic relevance; rather, it was felt to be sufficient to distinguish real activity from apparent activity due to cytotoxicity and to establish the utility of these compounds as chemical starting points for lead optimization. In general, the compounds are somewhat more potent in the whole cell than in the primary tat assay. Further, a comparison of the 17-OH compounds **3** and **11** with their corresponding acetates **2** and **10** shows that esterification may be favorable for whole cell activity. For these and subsequent compounds, differences in rank order potencies between the two assays may be the result of using cell lines with slightly different physicochemical requirements for cell penetration.

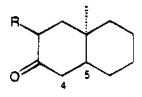
Table 2 shows the results of several changes in the A-ring functionality on activity in the primary tat assay. Attention was focused largely on the 2-$CONH_2$ series because of its synthetic accessibility. The three 3-OH epimers **15**, **16**, and **20** are devoid of activity and establish the importance of the carbonyl group. Compounds **17** and **18** and **21** and **22**, which replace the epoxide with either an unsaturated or saturated carbon–carbon bond, are all inactive and establish the importance of the epoxide. Compound **19** replaces the epoxide with a chlorohydrin. The activity of this compound may actually be due to the corresponding epoxide since mild base treatment results in rapid ring closure. Finally, the stereochemistry of the epoxide must be α as shown by comparing **23** and **24**. The former (α-epoxide) has measurable activity even though it lacks an electron-withdrawing group at position 2, whereas the latter (β-epoxide) is devoid of activity.

The sensitivity of the SAR (structure–activity relationship) to ring-A functionality suggested that the pharmacophore may be localized in this region, and we proceeded to truncate the steroid skeleton to rings A and B. Table 3 shows the activities of these analogs in both assays. Compounds **28a,b**, **30a,b**, and **31a,b** are

Table 3. Activities of A,B-Ring Analogs in the HIV Tat and Whole Cell Assays



a-series

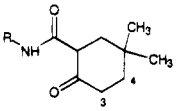


b-series

		substituent at position		tat assay	whole cell assay	
no.	R	4	5	IC_{50}[a]	IC_{50}[b]	therapeutic index[c]
28a	CN	α-epoxide		34 (21–62)	11.0 (3)	3.0
28b	CN	β-epoxide		278 (195–434)	25.9 (3)	3.8
30a	$CONH_2$	α-epoxide		9.9 (5.4–1.6)	6.4 (3)	4.1
30b	$CONH_2$	β-epoxide		72 (58–86)	10.3 (3)[d]	2.6
31a	$CONH_2$	β-Cl	α-OH	16.5 (8.3–26.4)	9.3 (4)[d]	2.0
31b	$CONH_2$	α-Cl	β-OH	32.1 (22.5–43.8)		
33a	C_6H_5NHCO	unsaturated		NA[e] at 100		
34a	C_6H_5NHCO	α-epoxide		2.8 (1.8–4.0)	2.1 (3)	3.8
35a	C_6H_5NHCO	β-Cl	α-OH	7.0 (5.3–9.1)	3.3 (3)[d]	1.9
36a	(4-MeO)C_6H_4NHCO	unsaturated		NA[e] at 100		
37a	(4-MeO)C_6H_4NHCO	α-epoxide		25.7 (17.7–40.3)	8.5 (2)[d]	1.3
38a	(4-MeO)C_6H_4NHCO	β-Cl	α-OH	33.5 (23.8–51.8)	3.3 (2)	4.2

[a] Units of micromolar (95% of confidence limits). [b] Mean of *n* determinations. [c] Whole cell assay. [d] Apparent activity may be due to cytotoxicity; note the low therapeutic index. See the text. [e] Not active.

Table 4. Activities of A-Ring Analogs in the HIV Tat and Whole Cell Assays



		substituent at position		tat assay	whole cell assay	
no.	R	3	4	IC_{50}[a]	IC_{50}[b]	therapeutic index[c]
40	C_6H_5	unsaturated		NA[d] at 123		
41	(4-MeO)C_6H_4	unsaturated		NA[d] at 37		
42	(2,6-Cl_2)C_6H_3	unsaturated		NA[d] at 32		
43	C_6H_5	epoxide		4.5 (3.2–5.9)	4.3 (3)[e]	1.4
44	(4-MeO)C_6H_4	epoxide		21.4 (16.0–27.7)	5.2 (2)[e]	1.2
45	(2,6-Cl_2)C_6H_3	epoxide		31.7 (22.2–46.8)	2.7 (2)[e]	2.3

[a] Units of micromolar (95% confidence limits). [b] Mean of *n* determinations with units of micromolar. [c] Whole cell assay. [d] Not active. [e] Apparent activity may be due to cytotoxicity; note the low therapeutic index. See the text.

enantiomeric pairs. While tat activity is not lost in the **b** series, it is clear that the **a** series is preferred and that therefore interaction with a chiral environment is likely. The elimination of the hydrophobic C and D rigs of **4** to give **30a** resulted in a decrease in potency. The introduction of compensatory hydrophobicity by addition of a phenyl group to the amide nitrogen in **34a** resulted in recovery of potency in the tat assay to that of **4**. This compound (**34a**) is particularly noteworthy in that, unlike **4**, it is clearly positive in the whole cell assay. Indeed, **34a** is the most potent member of the bicyclic series in both assays. Interestingly, the *o*-MeO analog **37a** exhibits about a 10-fold potency loss in the tat assay which suggests that additional SAR may be found in this region. Changes in the substituents on positions 4 and 5 (compounds **33a–38a**) result in potency changes consistent with what was observed in the steroids and supports the likelihood of identical mechanisms for the two series. The system was further simplified by preparing the monocyclic analogs shown in Table 4. Compound **43** is only slightly less potent than steroid **4** in the tat assay. Compounds **44** and **45** again suggest SAR around the phenyl ring. Compounds **40–42** are also consistent with the steroids in losing activity with unsaturation in the corresponding 3,4-position. This series is of less practical importance than the bicyclics because of the low therapeutic indexes observed in the whole cell assay.

The above data support the localization of a pharmacophore for tat inhibitory activity to an epoxycyclohexanone bearing an electron-withdrawing group α to the carbonyl. There is a weak enantioselective preference for the natural steroid stereochemistry, and there are hints of additional SAR in the electron-withdrawing group. This information, particularly in the bicyclic series as represented by **34a**, serves as the basis for expanding the series in the hope of finding candidates for clinical evaluation for the suppression of AIDS.

Experimental Section

All solvents were purchased HPLC grade and were used as received with the exception of THF which was freshly distilled from sodium benzophenone ketyl. Solutions were dried over Na_2SO_4, and solvent was removed on a rotary evaporator unless otherwise noted. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were run as 1% KBr pellets, unless otherwise specified, on a Nicolet 20-SX spectrometer or obtained by Oneida Research Services, Inc., Oneida, NY. Optical rotations were measured using a Rudolph Auto-Pol III spectrometer. Mass spectra were recorded as follows: desorption chemical ionization (CI) spectra were obtained on a Nermag R-10-10C spectrometer; fast atom bombardment (FAB) spectra were obtained on a Kratos Profile HV-2 spectrometer; high-resolution mass spectra (HRMS) were obtained by M-Scan, Inc., West Chester, PA. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, unless otherwise specified, on Varian Unity 300 or General Electric QE-300 spectrometers. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were ±0.4% of the theoretical values. No elemental

analyses were available for historical compounds **8**, **9**, and **13**; they are intermediates for which no biological data are presented.

Primary Tat Assay. SW480 (human colon carcinoma) cells were obtained from the American Type Culture Collection and were cultured in Dulbecco's Modified Eagle Media (DMEM), low glucose, containing 10% by volume heat-inactivated fetal bovine serum (IFCS). Plasmid pBennCAT[15] contains the chloramphenicol acetyltransferase (CAT) gene under the control of the HIV-1 3'-LTR (long terminal repeat) and was obtained from Dr. Howard E. Gendelman of the Walter Reed Army Institute of Research, Washington, DC. Plasmid pSV_2-tat72[16] contains a synthetic gene for tat (residues 1–72) under the control of the simian virus 40 (SV40) early promoter and was provided by Dr. Alan D. Frankel of the Gladstone Institute of Virology and Immunology, San Francisco, CA. Plasmid pSV_2CAT[17] contains the CAT gene under the control of the SV40 early promoter and was obtained from Dr. Richard Ciccarelli. Sterling Winthrop Pharmaceuticals Research Division, Collegeville, PA. Salmon sperm DNA (2 μg/well), pBennCAT alone (0.2 mg/well), or pBennCAT + pSV_2tat (0.2 mg of each/well) was transfected into monolayer SW480 cells grown to 70–80% confluency in six-well tissue culture dishes using the calcium phosphate precipitation procedure.[18] The total amount of DNA transfected per well was adjusted to 4 mg with salmon sperm DNA to control for transfection efficiency. Duplicate salmon sperm-transfected wells served as a control. Duplicate pBennCAT-transfected wells indicated the basal level expression from the HIV-1 LTR. Duplicate pBennCAT + pSV_2tat-transfected wells (without test compound) indicated the level of tat-activated expression from the HIV-1 LTR. After a 5 h transfection period, the calcium phosphate/DNA precipitate was aspirated and DMEM + 10% IFCS containing 1% DMSO was added to control wells. Test compounds were solubilized in 100% DMSO, diluted 100-fold in DMEM + 10% IFCS, and added 5 h after transfection to duplicate pBennCAT + pSV_2tat-transfected wells. Cells were incubated for 48 h at 37 °C in 5% CO_2, collected, pelleted, and frozen at −20 °C until use. CAT activity was measured by incubating cell extracts for 2 h in a reaction which contained 0.25 M Tris-HCl (pH 7.8), 0.5 mCi [^{14}C]chloramphenicol (Amersham Corp., Arlington Heights, IL; 55 mCi/mmol), 62 mM cold chloramphenicol (Sigma Chemical Co., St. Louis, MO), and 500 mM acetyl coenzyme A (Pharmacia Biotech, Piscataway, NJ). The acetylated products were extracted with ethyl acetate, dried, and separated from unreacted substrate by ascending chromatography on plastic-backed Baker-Flex silica gel plates in 95:5 chloroform/methanol. The reaction products were quantitated using a Betagen Betascope 603 Blot Analyzer. Test compounds were considered positive if they reduced the level of activity of pBennCAT + pSV_2tat by ≥50% relative to the controls without test compound. Positive compounds were then tested against a tat-independent promoter, pSV_2CAT (1 mg/well), using the same procedure to determine whether the compound was a selective inhibitor or tat-dependent transcription. Positive test compounds which inhibited pSV_2CAT by ≤20% were considered active and were dose-ranged. Multiple (3–5 experiments) percent inhibition dose response curves were generated for these compounds. Percent inhibition was transformed to a logit, and concentration was transformed to log concentration. When the data from the multiple runs was combined, inverse regression[19] on the logits was used to calculate the IC_{50} (50% inhibitory concentration of pBennCAT + pSV_2tat) for each compound. The 95% confidence intervals were generated using Fieller's theorem.[20] The maximum testable level (MTL) was the highest concentration that showed ≤50% inhibition of pSV_2-CAT.

Whole Cell Assay. H9 cells were obtained from the AIDS Research and Reference Reagent Program, AIDS Program, NIAID, NIH, and were cultured in RPMI 1640 + 10% IFCS. The HIV-1 IIIB strain was obtained from Virotech International, Rockville, MD. To assay for inhibition of HIV-1 replication,[21] H9 cells were infected with three different concentrations of virus (0.5 $\log_{10}$ dilutions) and then seeded in 96-well tissue culture plates at 2 × 10^4 cells/well. The most dilute virus dose was approximately 5–10 infectious units per well. Test compounds were solubilized in 100% DMSO and diluted to a final concentration of 0.5% DMSO in the assay medium. The infected cells were exposed in quadruplicate to 3–5 concentrations of test compound for 5 days at 37 °C in 5% CO_2 with replacement of fresh media and compound on day 3. On day 5, the amount of HIV replication was determined by assaying the tissue culture media for p24 antigen using the Coulter P24 Elisa kit (catalog no. 6603698). The average OD reading (n = 4 per dose) was calculated, and the IC_{50} value for at least two of the viral doses was determined for 3–5 individual assays. An AZT dose response control (1–1000 nM) was routinely included as a positive control for antiviral activity. To measure cytotoxicity of the compounds, uninfected cells were seeded in 96-well tissue culture plates at 2 × 10^4 cells/well and exposed in quadruplicate to 3–5 concentrations of compounds for 5 days at 37 °C in 5% CO_2 with replacement of fresh media and compound on day 3. The number of viable cells was determined using trypan blue exclusion. The ratio of IC_{50} inhibition of HIV replication was compared to the cell cytotoxicity IC_{50}, with a cutoff of 3 considered positive.

(17β)-17-Hydroxy-3-oxoandrost-4-ene-2-carboxylic Acid Methyl Ester (8). Testosterone **7** (20 g, 100 mmol) and magnesium methyl carbonate (400 mmol) were heated to 125–135 °C in DMF (370 mL) overnight while they were stirred. The reaction mixture was concentrated to a dark resin. The resin was taken up in H_2O/HOAc and extracted with CH_2Cl_2. The organic layer was extracted with aqueous base. Acidification of the aqueous solution deposited the acid 6.35 g (19%). The acid (6.35 g, 19 mmol) and 1-methyl-3-*p*-tolyltriazine (4.5 g, 30 mmol) were stirred as a suspension in CH_2Cl_2 containing 1 drop of 2 N HCl. After 1 h, TLC indicated only a trace of starting material. The reaction mixture was washed with dilute HCl, H_2O, and $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed and the residue recrystallized from methanol to yield 3.5 g (53%) of ester **8**: mp 161–163 °C; ^{1}H-NMR (100 MHz) δ 5.76 (s, 1H), 3.80 (s, 3H), 3.40–3.70 (mult, 2H), 0.8–2.8 (mult, 17H), 1.24 (s, 3H), 0.80 (s, 3H); IR 3550, 1725, 1672, 1619 cm^{-1}; MS *m/e* 346 (M^+), 331 (M − CH_3).

(4α,5α,17β)-3,17-Bis(acetyloxy)-4,5-epoxyandrost-2-ene-2-carboxylic Acid Methyl Ester (9). The ester **8** (2.85 g, 7.3 mmol) was refluxed in a mixture of acetic anhydride (10 mL) and pyridine (20 mL) overnight. The solvents were removed, and the residue was recrystallized from CH_3CN to yield 2.4 g (76%) of white solid: mp 178–181 °C; ^{1}H-NMR (100 MHz) δ 5.45 (s, 1H), 4.65 (dd, J = 8 and 8 Hz, 1H), 3.73 (s, 3H), 2.22 (s, 3H), 2.04 (s, 3H), 1.0–2.4 (mult, 17H), 1.06 (s, 3H), 0.86 (s, 3H); IR 1768, 1732, 1690–1720, 1655 cm^{-1}; MS *m/e* 430 (M^+), 388 (M − CH_2CO). The enol acetate (2.0 g, 4.6 mmol) and *m*-CPBA (1.1 g, 5 mmol) in CH_2Cl_2 (50 mL) were kept at 0 °C for 12 h. Additional *m*-CPBA (0.4 g) was added and stirring continued for 3 h. The reaction mixture was washed with Na_2SO_3 and $NaHCO_3$ and dried. The solvent was removed and the residue recrystallized from acetone to yield 1.9 g (92%) of epoxide **9**: mp 201–203 °C; ^{1}H-NMR (100 MHz, $CDCl_3$) δ 4.66 (dd, J = 8 and 8 Hz, 1H), 3.70 (s, 3H), 3.08 (s, 1H), 2.24 (s, 3H), 2.04 (s, 3H), 1.06–2.60 (mult, 17H), 1.04 (s, 3H), 0.86 (s, 3H); IR 1768, 1732, 1700 cm^{-1}; MS *m/e* 466 (M^+), 431 (M − CH_3).

(4α,5α,17β)-3,17-Bis(acetyloxy)-4,5-epoxyandrost-2-ene-2-carboxylic Acid Methyl Ester (10). The diacetate **9** (135 g, 30 mmol) and $KHCO_3$ (4.0 g, 40 mmol) were stirred in a mixture of CH_3OH (300 mL) and H_2O (30 mL) at reflux for 1.5 h. The MeOH was removed on a rotary evaporator. The residue was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, washed with H_2O, and dried over $MgSO_4$. The solvent was removed and the residue recrystallized from EtOAc to yield 9.1 g (75%) of monoacetate **10**: mp 178–188 °C; ^{1}H-NMR (100 MHz) δ 4.68 (dd, J = 8 and 8Hz, 1H), 3.76 (s, 3H), 3.22 (s, 1H), 2.06 (s, 3H), 1.04–2.40 (mult, 17H), 0.98 (s, 3H), 0.86 (s, 3H); IR 3440, 1725, 1665, 1620 cm^{-1}; MS *m/e* 404 (M^+), 389 (M − CH_3). Anal. ($C_{23}H_{32}O_6$) C, H.

(4α,5α,17β)-4,5-Epoxy-17-hydroxyandrost-2-ene-2-carboxylic Acid Methyl Ester (11). The diacetate **9** (4.5 g, 10 mmol) and KOH (1.33 g, 20 mmol) were stirred in a mixture

of CH_3OH (90 mL) and H_2O (10 mL) for 5 h. The CH_3OH was removed on a rotary evaporator. The residue was partitioned between H_2O and Et_2O. The organic layer was separated and dried over $MgSO_4$. The Et_2O was removed and replaced with CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed and the residue recrystallized from EtOH to yield 2.8 g (77%) of **11**: mp 168–169 °C; ^{1}H-NMR (100 MHz) δ 3.76 (s, 3H), 3.68 (dd, J = 8 and 8 Hz, 1H), 3.20 (s, 1H), 1.00–2.40 (mult, 18H), 0.96 (s, 3H), 0.80 (s, 3H); IR 3540, 1658, 1630 cm^{-1}; MS *m/e* 362 (M^+), 347 (M – CH_3). Anal. ($C_{21}H_{30}O_5$) H; C: calcd, 69.58; found, 68.74.

(17β)-17-Hydroxy-2-(phenylsulfonyl)androst-4-en-3-one (13). Hydrogen peroxide (114 g at 30%, 1.02 mol) was added dropwise to a stirred suspension of phenyl disulfide (109 g, 0.5 mol) in glacial acetic acid (400 mL). The mixture was cooled after 24 h to separate an oil which crystallized on standing. This material (79.8 g, 63%) was used without further purification. (Hydroxymethylene)testosterone **12**[12] (63 g, 0.2 mol), phenyl benzenethiosulfonate (55 g, 0.22 mol), and KOAc (79 g, 0.8 mol) were stirred for 2 h in refluxing EtOH (2.6 L). Solvent was removed on a rotary evaporator. The residue was taken up in CH_2Cl_2 (2 L) and filtered to remove insoluble matter. The CH_2Cl_2 was washed with 1 N NaOH and dried over $MgSO_4$. The solvent was removed and the residue recrystallized from acetonitrile to yield 29 g (37%) of a yellow solid: mp 201–203 °C. The sulfide (43 g, 0.11 mol) was dissolved in CH_2Cl_2 (1 L) and cooled in an ice bath. *m*-CPBA (48.5 g, 0.24 mol) was added in batches over 30 min. The reaction mixture was allowed to warm to room temperature as it was continously stirred for 2 h. Solid which had precipitated was removed by filtration, and the filtrate was washed with 5% Na_2SO_3 and saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed to give 67 g (78%) of **13** as a yellow solid: ^{1}H-NMR (100 MHz) δ 7.8–8.1 (mult, 2H), 7.2–7.7 (mult, 3H), 5.64 (s, 1H), 4.10 (dd, J = 6, and 14 Hz, 1H), 3.64 (dd, J = 8 and 8 Hz, 1H), 0.8–2.8 (mult, 17H), 1.24 (s, 3H), 0.80 (s, 3H); MS *m/e* 428 (M^+).

(4α,5α,17β)-4,5-Epoxy-17-hydroxy-2-(phenylsulfonyl)-androstan-3-one (14). The keto sulfone **13** (65 g) was heated to reflux in a mixture of acetic anhydride (760 mL) and pyridine (300 mL). The volatiles were removed on a rotary evaporator. The residue was taken up in CH_2Cl_2, washed with 1 N HCl and saturated $HaHCO_3$, and dried over $MgSO_4$. The solvent was removed and the residue recrystallized from acetonitrile to yield 79 g (95%): mp 210–212 °C. The diacetate (29 g, 54 mmol) was dissolved in CH_2Cl_2 (1 L) and cooled in an ice bath. *m*-CPBA (17.2 g, 82 mmol) was added slowly in batches. Stirring was continued as the system warmed to room temperature. The reaction mixture was washed with 5% Na_2SO_3 and saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed and the residue recrystallized from CH_2Cl_2/EtOAc to yield 23 g (81%) of a white solid: mp 230–233 °C. The epoxide (23 g, 44 mmol) and KOH (9.9 g, 176 mmol) were heated to reflux in a mixture of H_2O (90 mL) and MeOH (1.8 L) for 1.5 h. The reaction mixture was neutralized with HOAc (1 L), filtered, and concentrated on a rotary evaporator. The residue was triturated with H_2O (150 mL) to give 14.6 g (75%) of **14**: mp 211–212 °C; ^{1}H-NMR δ 7.85 (d, J = 7.2 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.1 Hz, 2H), 3.83 (dd, J = 8 and 12 Hz, 1H), 3.68 (dd, J = 8.5 and 8.5 Hz, 1 H), 3.07 (s, 1H), 2.35 (dd, J = 12.5 and 12.5 Hz, 1H), 1.0–2.4 (mult, 17H), 1.03 (s, 3H), 0.77 (s, 3H). Anal. ($C_{25}H_{32}O_5S$) C, H, S.

(2α,3α,4α,5α,17β)-17-(Acetyloxy)-4,5-epoxy-3-hydroxyandrostane-2-carboxamide (15) and (2β,3β,4α,5α,17β)-17-(Acetyloxy)-4,5-epoxy-3-hydroxyandrostane-2-carboxamide (16). The enolamide **4** (7.6 g, 19.6 mmol) was hydrogenated on a Parr apparatus in EtOH (200 mL) with PtO_2 (1 g) at 60 psi for 7 h. The catalyst was removed by filtration, and the solvent volume was reduced to 30 mL. Upon the mixture being chilled, the 2-α-carboxyamide 3-α-hydroxy steroid **15** (2.2 g) precipitated. The mother liquor was further concentrated, and the residue was applied to a silica gel column, eluting with 5% MeOH in $CHCl_3$. Eluting first was unreacted starting material (1 g), followed by the 2-β-carboxamide 3-β-hydroxy steroid **16** (400 mg), and finally additional **15** (900 mg). This represents a chemical yield of 72% based on recovered starting material and a ratio of α:β stereoisomers of 8:1. Major product *cis*-α-**15**: mp 230–232 °C; ^{1}H-NMR δ 6.70 (br s, 1H), 5.25 (br s, 1H), 4.60 (dd, J = 7.8 and 7.8 Hz, 1H), 4.31 (ddd, J = 4.5, 4.8, and 8.6 Hz, 1H), 3.29 (d, J = 4.8 Hz, 1H), 2.79 (d, J = 8.6 Hz, 1H), 2.38 (ddd, J = 4.5, 4.5, and 11.5 Hz, 1H), 2.00–2.25 (mult, 2H), 2.03 (s, 3H), 1.0–1.8 (mult, 5H), 1.12 (s, 3H), 0.82 (s, 3H); ^{13}C-NMR δ 176.0, 171.1, 82.6, 70.1, 63.1, 62.8, 50.3, 50.0, 42.7, 42.6, 36.8, 36.6, 35.1, 30.8, 29.2, 27.8, 27.4, 23.4, 21.1, 20.2, 17.7, 12.1; IR br 3315, 2969, 1735, 1660 cm^{-1}; HRMS (nba, FAB) $C_{22}H_{34}NO_5$ (MH^+) requires 392.2437, found 392.2445, Δ = −2.04 ppm. Anal. ($C_{22}H_{33}NO_5$ + H_2O) C, H, N. Minor product *cis*-β-**16**: mp 230–232 °C; ^{1}H-NMR δ 5.55 (br s, 1H), 5.35 (br s, 1H), 4.61 (dd, J = 7.6 and 9.3 Hz, 1H), 4.46 (d, J = 4.3 Hz, 1H), 4.39 (ddd, J = 3.5, 3.6, and 3.7 Hz, 1H), 3.15 (d, J = 3.1 Hz, 1H), 2.74 (ddd, J = 4.0, 8.3, and 8.3 Hz, 1H), 2.00–2.25 (mult, 2H), 2.04 (s, 3H), 1.0–1.8 (mult, 15H), 1.28 (s, 3H), 0.82 (s, 3H); IR br 3347, 2969, 1731, 1717, 1662 cm^{-1}; HRMS (nba, FAB) $C_{22}H_{34}NO_5$ (MH^+) requires 392.2437, found 392.2431, Δ = −1.53 ppm. Anal. ($C_{22}H_{33}NO_5$ + H_2O) C, H, N.

(17β)-17-(Acetyloxy)-3-oxoandrost-4-ene-2-carboxamide (17). Epoxide **4** (2 g, 5.1 mmol) was dissolved in 9:1 HOAc/H_2O (20 mL), and the solution was cooled to 0 °C. KI (1.7 g, 10.2 mmol), NaOAc (420 mg, 5.1 mmol), and Zn dust (1.3 g, 21 mmol) were added, and the reaction was allowed to reach room temperature over 1 h. Stirring was continued for an additional 2 h. The remaining Zn dust was removed by filtration. The solvent was removed, and the residue was triturated with H_2O. Chromatography on silica gel, eluting with 1:1 Hex/EtOAc, gave 600 mg (31%) of olefin **17**: mp 178–180 °C; ^{1}H-NMR δ 7.69 (br s, 1H), 5.77 (s, 1H), 5.54 (br s, 1H), 4.59 (dd, J = 4.8 and 8.8 Hz, 1H), 3.17 (dd, J = 4.6 and 14.5 Hz, 1H), 2.05–2.10 (mult, 2H), 2.04 (s, 3H), 1.22 (s, 3H), 1.22 (s, 3H), 0.84 (s, 3H), 0.8–1.83 (mult, 14H); ^{13}C-NMR δ 196.2, 172.8, 171.7, 171.0, 123.5, 82.3, 53.1, 50.1, 46.8, 42.3, 39.0, 38.4, 36.4, 35.1, 32.3, 31.2, 27.4, 23.3, 21.0, 20.4, 17.2, 11.9; IR 3405, 2950, 1735, 1681 cm^{-1}; MS *m/e* 373 (M^+). Anal. ($C_{22}H_{31}NO_4$) C, H, N.

(17β)-17-Hydroxy-3-oxoandrost-4-ene-2-carboxamide (18). Acetate **17** (600 mg, 1.6 mmol) was stirred in 3:1 H_2O/THF (25 mL) with LiOH (360 mg, 15 mmol) for 4 h at room temperature. The THF was removed on the rotary evaporator. The aqueous layer was made acidic with HCl and extracted with EtOAc. The combined organics were washed with brine, dried, and concentrated. Chromatography on silica gel, eluting with 5% MeOH in $CHCl_3$, gave 350 mg (66%) of alcohol **18**: ^{1}H-NMR δ 7.67 (br s, 1H), 5.78 (br s, 1H), 5.52 (d, J = 1.5 Hz, 1H), 3.65 (dd, J = 8.5 and 8.5 Hz, 1H), 3.17 (dd, J = 4.7 and 14.4 Hz, 1H), 2.59 (dd, J = 4.6 and 13.6 Hz, 1H), 0.9–2.4 (mult, 16H), 1.22 (s, 3H), 0.80 (s, 3H); ^{13}C-NMR δ 196.2, 173.3, 171.9, 123.5, 81.3, 54.0, 50.41, 46.6, 42.8, 39.1, 38.4, 36.3, 35.5, 32.4, 31.3, 30.1, 23.2, 20.6, 17.3, 11.0; IR 3562, 3200–3400, 2950, 1690, 1653 cm^{-1}; MS *m/e* 332 (MH^+). Anal. ($C_{20}H_{29}NO_3$ + $^1/_4H_2O$) C, H, N.

(4β,5α,17β)-17-(Acetyloxy)-4-chloro-5-hydroxy-3-oxoandrostane-2-carboxamide (19). The epoxide **4** (500 mg, 1.3 mmol) was stirred at room temperature in 5:1 acetone/1 N HCl (6 mL) for 14 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The combined organics were dried and evaporated to give 280 mg of **19** which was crystallized from MeOH: mp 210–215 °C dec; ^{1}H-NMR δ 14.00 (s, 1H), 5.93 (br s, 2H), 4.59 (dd, J = 7.9 and 8.8 Hz, 1H), 0.9–2.4 (mult, 18H), 2.02 (s, 3H), 1.13 (s, 3H), 0.78 (s, 3H); ^{13}C-NMR δ 174.8, 171.4, 163.5, 97.8, 82.7, 75.3, 61.4, 50.4, 46.9, 42.6, 38.9, 36.8, 34.5, 33.4, 31.0, 27.4, 25.8, 23.4, 21.2, 20.1, 16.7, 12.0; IR 3592, 3450, 3358, 2940, 1717, 1654, 1585 cm^{-1}; MS *m/e* 425 (M^+). Anal. ($C_{22}H_{32}ClNO_5$ + $^1/_2H_2O$) C, H, N.

(2α,3α,4α,5α,17β)-3,17-Dihydroxy-4,5-epoxyandrostane-2-carboxamide (20). The enolamide **5** (700 mg, 2 mmol) was hydrogenated on a Parr apparatus in EtOH (50 mL) with PtO_2 (300 mg) at 60 psi for 4 h. The catalyst was removed by filtration, and the solvent volume was reduced to 5 mL. Upon the mixture being triturated with Et_2O and chilled, the 2-α-carboxamide 3-α-hydroxy steroid **20** precipitated. Recrystallization from MeOH gave 225 mg (32%) of a single diastereomer: mp 230–232 °C; ^{1}H-NMR (CD_3OD) δ 4.28 (dd, J = 5.0

and 5.0 Hz, 1H), 3.58 (dd, J = 8.5 and 8.7 Hz, 1H), 3.17 (d, J = 4.7 Hz, 1H), 2.51 (ddd, J = 3.1, 5.6, and 13.71 Hz, 1H), 1.00–2.25 (mult, 18H), 2.04 (s, 3H), 1.10 (s, 3H), 0.70 (s, 3H); IR br 3362, 2969, 1692, 1605 cm^{-1}; HRMS (nba, FAB) $C_{20}H_{32}NO_4$ (MH^+) requires 350.2331, found 350.2309, Δ = −6.28 ppm. Anal. ($C_{20}H_{31}NO_4 + \frac{1}{2}H_2O$) C, H, N.

(4a*S*)-4,4a,5,6,7,8-Hexahydro-4a-methylnaphth[2,3-*d*]isoxazole (26a). A solution of NaOMe in THF (100 mL) was prepared from NaH (2.5 g, 100 mmol) and MeOH (7.5 mL, 175 mmol) at 0 °C. The enone **25a** was added in THF (5 mL), followed by methyl formate (10.5 mL, 175 mmol) in THF (10 mL). The reaction mixture was allowed to warm to room temperature while being stirred overnight. The reaction was quenched with half-saturated brine and the mixture made acidic with HCl (pH 1). The organic layer was separated, and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine and dried. Evaporation of solvent gave a quantitative yield of hydroxymethylene decalone which was used without further purification: ^{1}H-NMR δ 8.05 (s, 1H), 7.35 (s, 1H), 5.80 (s, 1H), 1.25–2.40 (mult, 10H), 1.05 (s, 3H). The hydroxymethylene decalone (7.7 g, 35 mmol) was refluxed in EtOH (50 mL) containing NH_2OH·HCl (2.45 g, 35 mmol) and H_2O (1 mL) for 2 h. The reaction mixture was cooled to room temperature, and the EtOH was removed on the rotary evaporator. The residue was partitioned between CH_2Cl_2 (120 mL) and H_2O (30 mL) and then neutralized with $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were treated with charcoal, dried, and evaporated to give a brown oil. The oil was filtered through silica gel, eluting with 19:1 Hex/EtOAc. The appropriate fractions were taken up in pentane (25 mL) and cooled to −78 °C to crystallize the product. This gave 4.2 g (63%, two steps) of isoxazole **26a**: mp 43–44 °C; ^{1}H-NMR δ 7.97 (s, 1H), 6.15 (s, 1H), 2.52 (d, J = 15.6 Hz, 1H), 2.46 (d, J = 15.6 Hz, 1H), 2.33–2.38 (mult, 2H), 1.44–1.77 (mult, 6H), 1.02 (s, 3H); ^{13}C-NMR δ 165.3, 153.6, 148.4, 108.9, 107.6, 41.6, 37.7, 35.0, 32.0, 25.9, 23.4, 22.2; IR 2935, 1630, 1596, 1466, 835 cm^{-1}; MS *m/e* 190 (MH^+). Anal. ($C_{12}H_{15}NO$) C, H. N. The enantiomer **26b** was prepared identically and gave identical spectra.

(1a*S*,5a*S*,9b*S*)-3,4,5,5a,6,9b-Hexahydro-5a-methyl-2*H*-oxireno[4,4a]naphth[2,3-*d*]isoxazole (27a). Isoxazole **26a** (4 g, 21 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. *m*-CPBA (70%, 5.4 g, 24 mmol) was added in small portions over 5 min. The reaction mixture was allowed to warm to room temperature while it was stirred over 2 h. A precipitate formed which was filtered off and rinsed with CH_2Cl_2. The combined organics were washed with saturated $NaHCO_3$ and H_2O, dried, and evaporated. The white solid was recrystallized from EtOAc/hex. This gave 4 g (93%) of epoxide **27a**: mp 119–121 °C; ^{1}H-NMR δ 8.05 (s, 1H), 3.83 (s, 1H), 2.25 (d, J = 15 Hz, 1H), 2.09 (d, J = 15 Hz, 1H), 2.20–2.35 (mult, 1H), 1.59–1.81 (mult, 6H), 1.27 (d, J = 12.7 Hz, 1H), 0.92 (s, 3H); ^{13}C-NMR δ 164.7, 149.4, 110.8, 68.4, 51.6, 38.0, 34.4, 32.2, 30.2, 23.4, 21.6, 21.0; IR 2936, 1636, 1596, 1484 cm^{-1}; MS *m/e* 206 (MH^+). Anal. ($C_{12}H_{15}NO_2$) C, H, N. The enantiomer **27b** was prepared identically and give identical spectra.

(1a*S*,4a*S*,8a*S*)-3-Cyano-4,4a,5,6,7,8-hexahydro-4a-methyl-1a*H*-naphth[1,8a-*b*]oxiren-2(3*H*)-one (28a). A solution of NaOMe in THF (40 mL) was prepared from NaH (1 g, 42 mmol) and MeOH (1.7 mL, 42 mmol) at 0 °C. The isoxazole **27a** (3.7 g, 20 mmol) was added in THF (20 mL) and the mixture allowed to stir at 0 °C for 5 h, over which time a precipitate formed. The reaction mixture was diluted with cold Et_2O and filtered. The white solid was dissolved in H_2O (50 mL) containing KH_2PO_4 (1 g) and acidified to pH 1 with 3 N HCl. The product, which precipitated, was isolated by filtration. This gave 3.3 g (89%) of cyano ketone **28a** as a mixture of epimers at C-3. The cyano ketone could be recrystallized from 2:1 Hex/EtOAc: mp 118–119 °C; ^{1}H-NMR δ 3.67 (dd, J = 1.1 and 10.9 Hz, 1H, CN_{ax}), 3.26 (s, 1H), 3.37 (dd, J = 6.4 and 12.6 Hz, 1H, CN_{eq}), 3.17 (s, 1H), 2.05–2.35 (mult, 2H), 1.40–1.80 (mult, 7H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C-NMR δ 198.2, 195.0, 117.9, 116.1, 79.4, 70.8, 68.7, 61.6, 61.3, 56.2; IR 3133, 2945, 2211, 1726, 1625, 1215 cm^{-1}; MS *m/e* 206 (MH^+), 188 (M = CN). Anal. ($C_{12}H_{15}NO_2$) C, H, N. The enantiomer **28b** was prepared identically and gave identical spectra: mp 116.5–118 °C. Anal. ($C_{12}H_{15}NO_2$) C, H, N.

(4a*S*,8a*S*,9*R*)-3-Amino-8a,9-epoxy-4a-methyl-4,4a,5,6,7,8,8a,9-octahydronaphth[2,3-*c*]isoxazole (29a). To an EtOH solution (45 mL) of cyano ketone **28a** (3.1 g, 15 mmol) at reflux were added NH_2OH·HCl (1.16 g, 16.5 mmol) and NaOAc (2.26 g, 16.5 mmol) in H_2O (5 mL). The reaction was maintained at reflux for 4 h. The EtOH was removed on a rotary evaporator, and the residue was taken up with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and concentrated to half volume. This yielded 1.6 g of crystalline **29a**. Chromatography of the mother liquor on silica gel, eluting with 5% MeOH/$CHCl_3$, gave an additional 700 mg (66% total): mp 202–205 °C; ^{1}H-NMR δ 4.17 (br s, 2H), 3.67 (s, 1H), 2.22 (ddd, J = 5.1, 14.1, and 14.1 Hz, 1H), 2.13 (d, J = 14 Hz, 1H), 1.80 (d, J = 14.1 Hz, 1H), 1.55–1.80 (mult, 6H), 1.25 (d, J = 14.4 Hz, 1H), 0.94 (s, 3H); ^{13}C-NMR (CD_3OD) δ 167.4, 162.1, 85.9, 68.1, 53.7, 39.3, 35.8, 31.4, 31.2, 24.9, 22.8, 21.4; IR 3435, 3377, 3169, 2933, 1662, 1524 cm^{-1}; MS *m/e* 221 (MH^+). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N. The enantiomer **29b** was prepared identically and gave identical spectra: mp 204–207 °C. Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

(4*R*,4a*S*,8a*S*)-4,4a-Epoxy-3-hydroxy-8a-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxamide (30a). The aminoisoxazole **29a** (2 g, 9.1 mmol) was hydrogenated on a Parr apparatus in THF (50 mL) with 10% Pd/C (300 mg) at 60 psi for 3 h. The catalyst was removed by filtration and the solvent evaporated. The residue was taken up in 9:1 HOAc/H_2O (50 mL) and warmed to 70 °C for 2 h. The HOAc was removed on a rotary evaporator, and the residue was diluted with H_2O. The water was extracted with Et_2O. The organic layer was washed with H_2O and brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with 19:1 $CHCl_3$/MeOH, to give 910 mg (45%) of **30a**: mp 130–131 °C; $[\alpha]^{589}$ +172 (c = 1.08, EtOH); ^{1}H-NMR δ 13.94 (s, 1H) 5.26 (br s, 2H), 3.19 (s, 1H), 2.17 (ddd, J = 4.2, 13.7, and 13.7 Hz, 1H), 2.14 (d, J = 13.7 Hz, 1H), 1.40–1.80 (mult, 6H), 1.25 (d, J = 13.7 Hz, 1H), 1.02 (s, 3H); ^{13}C-NMR (CD_3OD) δ 167.4, 162.1, 85.9, 68.1, 53.7, 39.3, 35.8, 31.4, 31.2, 24.9, 22.8, 21.4; IR 3443, 3194, 2940, 1654, 1585, 1449 cm^{-1}; MS (FAB, tgly matrix) *m/e* 224 (MH^+). Anal. ($C_{12}H_{17}NO_3$) C, H, N. The enantiomer **30b** was prepared identically and gave identical spectra: mp 131–133 °C; $[\alpha]^{589}$ −172 (c = 1.08, EtOH). Anal. ($C_{12}H_{15}NO_2$) C, H, N.

(4*R*,4a*S*,8a*S*)-4-Chloro-3,4a-dihydroxy-8a-methyl-1,4,-4a,5,6,7,8,8a-octahydronaphthalene-2-carboxamide (31a). The epoxide **30a** (800 mg, 3.6 mmol) was stirred at room temperature in 9:2 acetone/2 N HCl (10 mL) for 3 h. The reaction mixture was diluted with Et_2O, washed with brine, and dried. Evaporation of solvent gave 1 g of **31a** which was taken up in acetone and triturated with hexane: mp 186–187 °C dec; ^{1}H-NMR (CD_3COCD_3) δ 14.7 (s, 1H), 6,75 (br s, 2H), 4.13 (s, 1H), 3.83 (s, 1H), 2.35 (d, J = 15.3 Hz, 1H), 2.27 (ddd, J = 4.1, 13.4, and 13.7 Hz, 1H), 1.87 (d, J = 15.3 Hz, 1H), 1.75–1.89 (mult, 2H), 1.44–1.61 (mult, 4H), 1.15–1.20 (mult, 1H), 1.19 (s, 3H); ^{13}C-NMR (CD_3COCD_3/CD_3OD) δ 176, 163.6, 99.3, 74.5, 62.6, 37.3, 36.5, 36.2, 32.0, 22.9, 21.9, 21.7; IR 3476, 3362, 2925, 1644, 1584, 1443 cm^{-1}; MS *m/e* 260 (MH^+). Anal. ($C_{12}H_{18}ClNO_3$) C, H, N. The enantiomer **31b** was prepared identically and gave identical spectra. Anal. ($C_{12}H_{18}ClNO_3$) C, H, N.

(8a*S*)-1,5,6,7,8,8a-Hexahydro-8a-methyl-3(2*H*)-oxonaphthalene-2-*N*-phenylcarboxamide (33a). A solution of LDA was prepared at −78 °C in THF (45 mL) from BuLi (11.5 mL at 2.0 M, 23 mmol) and diisopropylamine (3.4 mL, 24 mmol). Ketone **25a** was added dropwise as a solution in THF (10 mL). After the mixture was stirred 30 min, TMSCl (5.3 mL, 42 mmol) in THF (10 mL) was added dropwise. The reaction mixture was maintained at −78 °C for 20 min and then allowed to warm to room temperature. It was diluted with hexane and washed with H_2O. The aqueous wash was extracted with hexane. The combined organic layers were dried over K_2CO_3. Evaporation of solvent gave 5 g (quantitative) of enol ether **32a**. NMR indicated a single regioisomer. A portion of the enol ether was used directly in the next step.

Enol ether **32a** (3 g, 12.7 mmol) and phenyl isocyanate (1.4 mL, 12.8 mmol) were heated neatly to 140 °C under N_2 in the presence of a catalytic amount of pyridine (150 mL) for 14 h. The mixture was cooled to room temperature, diluted with 1:1 EtOAc/1 N HCl, and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried. Evaporation of the solvent gave 2.35 g of material which was chromatographed on silica gel, eluting with 4:1 Hex/EtOAc. This gave 1.6 g (39% over two steps) of β-keto amide **33a**: ^{1}H-NMR δ 10.04 (br s, 1H), 7.60 (dd, J = 1.2 and 8.7 Hz, 2H), 7.32 (ddd, J = 2.1, 7.9 and 7.9 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 5.28 (d, J = 1.3 Hz, 1H), 3.38 (dd, J = 4.70 and 14.4 Hz, 1H), 2.45 (dd, J = 4.6 and 13.7 Hz, 1H), 2.33–2.39 (mult, 2H), 1.99 (dd, J = 14 and 14 Hz, 1H), 1.91–1.94 (mult, 1H), 1.80 (td, J = 2 and 13.5 Hz, 1H), 1.67–1.78 (mult, 2H), 1.38–1.46 (mult, 2H), 1.30 (s, 3H); IR 3331, 3294, 2930, 1697, 1667, 1554 cm^{-1}; MS *m/e* 283 (M^+). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

(4*S*,4a*S*,8a*S*)-4,4a-Epoxy-3-hydroxy-8a-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-*N*-phenylcarboxamide (34a). The keto amide **33a** (900 mg, 3.2 mmol) was stirred at room temperature in pyridine (10 mL) containing Ac_2O (3 mL) overnight. Most of the pyridine was removed on a rotary evaporator. The residue was diluted with Et_2O (100 mL), washed with 1 N HCl and brine, and dried. Evaporation of the solvent gave 900 mg of material in which the enol oxygen and amide nitrogen had been acetylated. This was taken on without further purification. To a 0 °C solution of the bisacetate (900 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was added 70% (*m*-CPBA (660 mg, 2.7 mmol). Over 40 min, a precipitate formed. This was filtered and washed with cold CH_2Cl_2 (15 mL). The mother liquor was diluted with CH_2Cl_2 to 80 mL, washed with saturated $NaHCO_3$ and brine, and dried. Evaporation of solvent gave 1 g of a white solid. Excess oxidant was removed by filtering through silica gel, eluting with 4:1 Hex/EtOAc. This gave 520 mg of epoxide which was taken on directly. The epoxide (520 mg, 1.4 mmol) was refluxed in 15:1 MeOH/H_2O (16 mL) with $NaHCO_3$ (250 mg, 3 mmol) for 2 h. The reaction mixture was diluted with Et_2O (80 mL), washed with 1 N HCl and brine, and dried. Evaporation gave 420 mg of a white solid. Recrystallization from 9:1 Hex/EtOAc gave 200 mg (21% over three steps) of **34a**: mp 147–149 °C; ^{1}H-NMR δ 13.90 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.32 (dd, J = 7.7 and 7.9 Hz, 2H), 7.12 (t, J = 7.7 Hz, 1H), 7.02 (br s, 1H), 3.22 (s, 1H), 2.20–2.40 (mult, 1H), 1.50–1.90 (mult, 7H), 1.23 (br d, J = 13.9 Hz, 1H), 1.06 (s, 3H); ^{13}C-NMR δ 170.2, 167.0, 136.9, 129.0, 124.8, 120.9, 119.8, 95.9, 67.2, 57.4, 37.8, 34.6, 29.0, 23.4, 21.6, 20.7; IR 3391, 2934, 1638, 1599, 1538 cm^{-1}; MS *m/e* 299 (M^+). Anal. ($C_{18}H_{21}NO_3$) C, H, N.

(4*R*,4a*S*,8a*S*)-4-Chloro-3,4a-dihydroxy-8a-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-*N*-phenylcarboxamide (35a). The epoxide **34a** (200 mg, 0.6 mmol) was stirred at room temperature for 6 h in 10:1 aetone/1 N HCl (6 mL). The reaction mixture was diluted with Et_2O, washed with brine, and dried. Evaporation of solvent gave a foam which was chromatographed on silica gel, eluting with 4:1 Hex/EtOAc. This yielded 80 mg (36%) of **35a**: mp 157–158 °C; ^{1}H-NMR δ 14.06 (s, 1H), 7.49 (d, J = 8.7 Hz, 2H), 7.35 (dd, J = 7.5 and 7.5 Hz, 2H), 7.16 (t, J = 7.7 Hz, 1H) 7.16 (br s, 1H), 4.14 (s, 1H), 2.42 (d, J = 13.8 Hz, 1H), 2.17–2.45 (mult, 1H), 1.87 (d, J = 14.1 Hz, 1H), 1.30–1.73 (mult, 9H), 1.28 (s, 3H); ^{13}C-NMR δ 170.3, 164.0, 129.1, 129.0, 125.0, 121.1, 97.9, 74.7, 61.1, 36.7, 36.2, 35.5, 31.5, 22.8, 20.9, 20.8; IR 3551, 3304, 2931, 1634, 1595, 1534 cm^{-1}; MS *m/e* 335 (M^+). Anal. ($C_{18}H_{22}ClNO_3$) C, H, N.

(8a*S*)-1,5,6,7,8,8a-Hexahydro-8a-methyl-3(2*H*)-oxonaphthalene-2-*N*-(2-methoxyphenyl)carboxamide (36a). A solution of $LiN(TMS)_2$ (10 mL at 1.0 M, 10 mmol) in THF (10 mL) was cooled to −78 °C. Ketone **25a** (1.7 g, 10 mmol) was added dropwise as a solution in THF (5 mL). After the mixture was stirred for 20 min 2-methoxyphenyl isocyanate was added neatly in a dropwise fashion. The reaction mixture was maintained at −78 °C for 2 h and then allowed to warm to room temperature. It was diluted with Et_2O and washed with H_2O. The combined aqueous washes were extracted with Et_2O. The combined organic layers were washed with brine, dried, and evaporated. Purification on silica gel, eluting with 6:1 Hex/EtOAc, gave 620 mg (38%) of recovered starting material and 920 mg (30%) of β-keto amide **36a**: ^{1}H-NMR δ 10.16 (s, 1H), 8.37 (dd, J = 1.6 and 8.7 Hz, 1H), 7.02 (ddd, J = 1.7, 7.8, and 7.9 Hz, 1H), 6.92 (ddd, J = 1.5, 7.7, and 7.8 Hz, 1H), 6.87 (dd, J = 1.5 and 7.9 Hz, 1H), 5.80 (d, J = 1.5 Hz, 1H), 3.92 (s, 3H), 3.41 (dd, J = 4.7 and 14.4 Hz, 1H), 2.38 (dd, J = 4.6 and 13.6 Hz, 1H), 2.32–2.42 (mult, 2H), 2.03 (dd, J = 14.8 and 14.8 Hz, 1H), 1.30–2.0 (mult, 6H), 1.28 (s, 3H); ^{13}C-NMR δ 197.0, 172.8, 166.8, 148.5, 127.9, 124.0, 123.6, 120.8, 120.1, 110.1, 55.9, 47.8, 41.4, 40.5, 36.4, 32.4, 26.9, 22.0, 21.5; IR 3551, 3304, 2931, 1634, 1595, 1534 cm^{-1}; HRMS (FAB, nba) $C_{19}H_{24}NO_3$ (MH^+) requires 314.1756, found 314.1769, Δ = 1.2 ppm. Anal. ($C_{19}H_{23}NO_3 + {}^1/_4H_2O$) C, H. N.

(4*S*,4a*S*,8a*S*)-4,4a-Epoxy-3-hydroxy-8a-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-*N*-(2-methoxyphenyl)carboxamide (37a). The keto amide **36a** (800 mg, 2.5 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. A solution of $LiN(TMS)_2$ (2.7 mL at 1.0 M, 2.7 mmol) was added dropwise, and stirring was continued for 30 min. Acetyl chloride (430 mL, 6.0 mmol) in THF (10 mL) was added. The reaction mixture was maintained at −78 °C for 30 min and then allowed to warm to room temperature. It was diluted with Et_2O, washed, with saturated $NaHCO_3$ and brine, and dried. Evaporation of solvent gave 1 g of monoacetate which was carried on without further purification. To a 0 °C solution of monoacetate (1 g, 2.5 mmol) in CH_2Cl_2 (10 mL) was added 70% *m*-CPBA (615 mg, 2.8 mmol). Over 40 min, a precipitate formed which was filtered off and washed with cold CH_2Cl_2. The mother liquor was diluted with CH_2Cl_2, washed with 1 N NaOH, saturated $NaHCO_3$, and brine, and dried. Solvent evaporation gave 910 mg of white solid which was used without further purification. The epoxide (870 mg, 2.3 mmol) was refluxed in 10:1 MeOH/H_2O (40 mL) with $NaHCO_3$ (640 mg, 4.7 mmol) for 2 h. The MeOH was removed and the aqueous residue partitioned with Et_2O. The aqueous layer was extracted with Et_2O. Combined organics were washed with brine and dried. Evaporation of solvent gave 610 mg which was chromatographed on silica gel, eluting with 6:1 Hex/EtOAc. This gave 454 mg (55% over three steps) of **37a**: mp 147–149 °C; ^{1}H-NMR δ 13.95 (s, 1H), 8.30 (dd, J = 1.7 and 7.9 Hz, 1H), 7.75 (br s, 1H), 6.87–7.06 (mult, 3H), 3.92 (s, 3H), 3.23 (s, 1H), 2.24 (d, J = 14.0 Hz, 1H), 1.50–1.90 (mult, 7H), 1.68 (d, J = 13.8 Hz, 1H), 1.20–1.25 (mult, 1H), 1.06 (s, 3H); IR 3426, 2936, 1696, 1640, 1600, 1532 cm^{-1}; HRMS (FAB, PEG) $C_{19}H_{24}NO_4$ (MH^+) requires 330.1706, found 330.1680, Δ = 7.1 ppm. Anal. ($C_{19}H_{23}NO_4 + {}^1/_4H_2O$) C, H, N.

(4*R*,4a*S*,8a*S*)-4-Chloro-3,4a-dihydroxy-8a-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-*N*-(2-methoxyphenyl)carboxamide (38a). The epoxide **37a** (200 mg, 0.6 mmol) was stirred at room temperature for 24 h in 6:1 acetone/1 N HCl (4 mL). The reaction mixture was diluted with Et_2O, washed with brine, and dried. Evaporation of solvent gave a foam which was chromatographed on silica gel, eluting with 6:1 Hex/EtOAc. This gave 80 mg (36%) of **38a**: ^{1}H-NMR δ 14.14 (s, 1H), 8.31 (dd, J = 1.687 and 8.1 Hz, 1H), 7.91 (br s, 1H), 7.08 (ddd, J = 1.7, 7.6, and 7.9 Hz, 1H), 6.98 (ddd, J = 1.5, 7.8, and 7.8 Hz, 1H), 6.89 (dd, J = 1.4 and 7.9 Hz, 1H), 4.15 (s, 1H), 3.91 (s, 3H), 2.42 (d, J = 14.3 Hz, 1H), 2.32–2.38 (mult, 1H), 1.89 (d, J = 14.7 Hz, 1H), 1.20–1.80 (mult, 8H), 1.28 (s, 3H); IR 3421, 2935, 1641, 1602, 1538 cm^{-1}; MS *m/e* 366 (MH^+). Anal. ($C_{19}H_{24}ClNO_4$) C, H, N, Cl.

5,5-Dimethyl-2-oxocyclohex-3-ene-1-*N*-phenylcarboxamide (40). A solution of LDA (7.6 mL at 2.0 M, 15.2 mmol) in Et_2O (60 mL) was cooled to −78 °C. Ketone **39** (2 mL, 15.2 mmol) was added dropwise in Et_2O (10 mL). The mixture was stirred cold for 30 min. Phenyl isocyanate (1.6 mL, 15.2 mmol) was added neatly and the reaction mixture kept at −78 °C. After 2.5 h, a second equivalent of isocyanate was added and the reaction mixture allowed to warm to room temperature. The mixture was partitioned with 1 N NaOH. The aqueous layer was acidified and extracted with Et_2O. The basic Et_2O extract was washed with brine, dried, and concentrated. Chromatography on silica gel, eluting with 9:1 Hex/EtOAc gave 500 mg (13%) of **40**: mp 108–109 °C; ^{1}H-NMR δ 9.70 (br s, 1H), 7.57 (dd, J = 1.2 and 8.7 Hz, 2H), 7.31 (ddd, J = 2.1,

7.6, and 8.3 Hz, 2H), 7.10 (tt, J = 1.3 and 7.4 Hz, 1H), 6.78 (dd, J = 2.1 and 10.1 Hz, 1H), 5.93 (d, J = 9.9 Hz, 1H), 3.40 (dd, J = 5.0 and 13.3 Hz, 1H), 2.42 (ddd, J = 2.0, 5.0, and 13.8 Hz, 1H), 2.13 (dd, J = 13.4 and 13.4 Hz, 1H), 1.22 (s, 3H), 1.21 (s, 3H); ^{13}C NMR δ 197.6, 166.4, 161.7, 137.9, 128.9, 126.5, 124.2, 120.1, 47.8, 38.0, 33.5, 29.9, 25.2: IR 3315, 2968, 1673, 1660 cm^{-1} MS *m/e* 244 (MH^+). Anal. ($C_{15}H_{17}NO_2$) C, H, N.

5,5-Dimethyl-3,4-epoxy-2-hydroxycyclohex-1-ene-1-*N*-phenylcarboxamide (43). Enone **40** (634 mg, 2.6 mmol) and 30% H_2O_2 (900 mL, 7.8 mmol) were cooled to 0 °C in MeOH (8 mL). A 1.5 N NaOH solution (1.5 mL) was added dropwise. The reaction mixture was kept cold for 3 h. The pH was adjusted to 9 using HCl and the mixture allowed to stir for an additional 2 h. It was partitioned with Et_2O (100 mL). The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried, and concentrated to give 700 mg of material. Chromatography on silica gel, eluting with 4:1 Hex/EtOAc, gave 100 mg (15%) of enol epoxide **43** which crystallized from CH_2Cl_2: mp 93–95 °C; ^{1}H-NMR δ 13.91 (s, 1H), 7.48 (dd, J = 7.5 and 7.5 Hz, 1H), 7.34 (dd, J = 7.5 and 8.4 Hz, 1H), 6.99 (br s, 1H), 3.42 (d, J = 4.1 Hz, 1H), 3.18 (dd, J = 1.7 and 4.1 Hz, 1H), 2.20 (d, J = 13.9 Hz, 1H), 1.74 (dd, J = 1.7 and 14.0 Hz, 1H), 1.28 (s, 3H), 1.01 (s, 3H); ^{13}C-NMR δ 166.3, 164.0, 144.0, 136.0, 129.0, 124.9, 120.9, 62.9, 51.3, 32.1, 27.3, 22.8; IR 3334, 2958, 1635, 1598, 1529 cm^{-1}; MS *m/e* 259 (M^+). Anal. ($C_{15}H_{17}NO_3$) C, H, N.

5,5-Dimethyl-2-oxocyclohex-3-ene-1-*N*-(2-methoxyphenyl)carboxamide (41). A solution of LDA (3.8 mL at 2.0 M, 7.6 mmol) in THF (20 mL) was cooled to −78 °C. Ketone **39** (1 g, 7.6 mmol) was added dropwise in THF (5 mL). The mixture was stirred cold for 20 min. Methoxyphenyl isocyanate (1 mL, 7.6 mmol) was added neatly and the reaction mixture was kept at −78 °C for 20 min and then allowed to warm to room temperature. The reaction mixture was diluted with Et_2O, washed with 1 N HCl, dried, and evaporated. Chromatography on silica gel, eluting with 9:1 Hex/EtOAc, gave 620 mg (30%) of keto amide **41** as an oil: ^{1}H-NMR δ 9.91 (br s, 1H), 8.36 (dd, J = 0.9 and 7.8 Hz, 1H), 7.04 (ddd, J = 1.7, 7.9, and 7.9 Hz, 1H), 6.95 (dd, J = 7.8 and 7.8 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.78 (dd, J = 2.0 and 10.1 Hz, 1H), 5.96 (d, J = 10.1 Hz, 1H), 3.93 (s, 3H), 3.44 (dd, J = 5.0 and 13.2 Hz, 1H), 2.40 (ddd, J = 1.9, 5.1, and 13.8 Hz, 1H), 2.18 (dd, J = 13.6 and 13.6 Hz, 1H), 1.23 (s, 6H); ^{13}C-NMR δ 197.2, 166.4, 161.3, 148.5, 127.9, 126.6, 123.8, 120.9, 120.2, 110.2, 55.9, 48.6, 38.2, 33.5, 29.9, 25.5; IR (thin film) br 3400, 2960, 1682, 1601, 1538 cm^{-1}; HRMS (FAB, nba) $C_{16}H_{20}NO_3$ (MH^+) requires 274.1448, found 274.1440, Δ = 1.9 ppm. Anal. ($C_{16}H_{19}NO_3 + {}^1/_4H_2O$) C, H, N.

5,5-Dimethyl-3,4-epoxy-2-hydroxycyclohex-1-ene-1-*N*-(2-methoxyphenyl)carboxamide (44). Enone **41** (600 mg, 2.2 mmol) and 30% H_2O_2 (3.7 mL, 33 mmol) were cooled to 0 °C in MeOH (40 mL). A 0.2 N NaOH solution (10 mL) was added dropwise over 1 h. The reaction mixture was kept cold for 5 h. It was partitioned with Et_2O (40 mL) and H_2O (30 mL) and made acidic wit 1 N HCl. The aqueous layer was extracted with Et_2O. The combined organics were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel, eluting with 4:1 Hex/EtOAc, to give 150 mg (23%) of enol epoxide **44**: mp 98–100 °C; ^{1}H-NMR δ 13.94 (s, 1H), 8.30 (dd, J = 1.6 and 7.9 Hz, 1H), 7.76 (br s, 1H), 7.05 (ddd, J = 1.6, 7.6, and 7.6 Hz, 1H), 6.97 (ddd, J = 1.3, 7.8, and 7.8 Hz, 1H), 6.89 (dd, J = 1.5 and 8.1 Hz, 1H), 3.91 (s, 3H), 3.43 (d, J = 4.2 Hz, 1H), 3.17 (dd, J = 1.8 and 4.2 Hz, 1H), 2.21 (d, J = 13.6 Hz, 1H), 1.76 (dd, J = 1.8 and 14.1 Hz, 1H), 1.29 (s, 3H), 100 (s, 3H); IR 3416, 2958, 1645, 1580, 1532 cm^{-1}; MS *m/e* 289 (M^+). Anal. ($C_{16}H_{19}NO_4$) C, H, N.

5,5-Dimethyl-2-oxocyclohex-3-ene-1-*N*-(2,6-dichlorophenyl)carboxamide (42). A solution of LDA was prepared at −78 °C in THF (40 mL) from BuLi (11.5 mL at 2.0 N, 23 mmol) and diisopropylamine (3.2 mL, 23 mmol). Ketone **39** (3 mL, 23 mmol) was added dropwise as a solution in THF (10 mL). After the mixture was stirred 30 min, TMSCl (5.4 mL, 43 mmol) in THF (10 mL) was added dropwise. The reaction mixture was maintained at −78 °C for 20 min and then allowed to warm to room temperature. It was diluted with hexane and washed with H_2O. The aqueous wash was extracted with hexane. The combined organic layers were dried over K_2CO_3. Evaporation of solvent gave 5.7 g (quantitative) of TMS enol ether. NMR indicated a single regioisomer. The enol ether was used directly in the next step. Enol ether (5.7 g, 23 mmol) and 2,6-dichlorophenyl isocyanate (4.3 g, 23 mmol) were heated to 170 °C under N_2 in the presence of a catalytic amount of pyridine (150 mL) for 3 h. The mixture was cooled to room temperature diluted with 4:1 MeOH/1 N HCl (50 mL), and stirred for 30 min. The MeOH was evaporated, and the aqueous layer was extracted with Et_2O. The combined organics were washed with brine, dried, and concentrated to give 4 g (56%) of **42**: ^{1}H-NMR δ 9.65 (br s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 6.82 (dd, J = 2.0 and 9.9 Hz, 1H), 5.98 (d, J = 10.1 Hz, 1H), 3.50 (dd, J = 5.0 and 13.3 Hz, 1H), 2.49 (ddd, J = 1.9, 5.0, and 13.8 Hz, 1H), 2.15 (dd, J = 13.6 and 13.6 Hz, 1H), 1.25 (s, 6H); ^{13}C-NMR δ 197.3, 166.7, 161.8, 133.2, 128.3, 128.0, 126.5, 47.2, 38.0, 33.5, 29.9, 25.3; IR br 3242, 2960, 1700, 1653, 1529 cm^{-1}; Ms *m/e* 312 (MH^+). Anal. ($C_{15}H_{15}Cl_2NO_2$) C, H, N, Cl.

5,5-Dimethyl-3,4-epoxy-2-hydroxycyclohex-1-ene-*N*-(2,6-dichlorophenyl)carboxamide (45). Enone **42** (1.55 g, 5 mmol) and 30% H_2O_2 (5.6 mL, 50 mmol) were cooled to 0 °C in MeOH (40 mL). A 2.5 N NaOH solution (1 mL) was added dropwise. The reaction mixture was kept cold for 3 h. Additional 2.5 N NaOH (1 mL) was added and the reaction mixture allowed to stir for 2 h. The reaction mixture was partitioned with Et_2O (100 mL) and 1:1 brine/1 N HCl (40 mL). The aqueous layer was extracted with Et_2O. The combined organics were washed with brine and dried. Chromatography on silica gel, eluting with 4:1 Hex/EtOAc, yielded 600 mg (37%) of enol epoxide **45** as a foam: ^{1}H-NMR δ 13.51 (s, 1H), 7.38 (t, J = 8.3 Hz, 1H), 7.13–7.23 (mult, 2H), 6.84 (br s, 1H), 3.44 (dd, J = 4.0 Hz, 1H), 3.20 (dd, J = 1.8 and 4.0 Hz, 1H), 2.28 (d, J = 14.1 Hz, 1H), 1.86 (dd, J = 1.8 and 14.1 Hz, 1H), 1.29 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR δ 170.2, 166.6, 133.8, 131.4, 128.7, 128.4, 95.8, 62.9, 51.1, 32.0, 27.2, 22.8; IR 3312, 2960, 1639, 1508 cm^{-1}; MS *m/e* 328 (M^+). Anal. ($C_{15}H_{15}Cl_2NO_3$) C, H, N, Cl.

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