Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo-[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) Derivatives. 3

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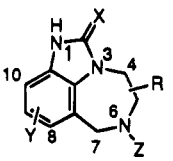
4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-ones (TIBO), **1**, have been shown to significantly inhibit HIV-1 replication in vitro by interfering with the virus's reverse transcriptase enzyme. They have also demonstrated potential clinical efficacy in combating HIV-1, on the basis of a preliminary study. Our prior publications have discussed the discovery of this series of compounds and reported some preliminary chemical and biological studies around N-6 substitutions and 5-membered ring variations of **1**. This manuscript describes our synthetic endeavors around 4, 5, and 7 mono- and disubstitutions of **1** and discusses related HIV-1 inhibitory structure–activity relationships. On the basis of inhibition of HIV-1's cytopathic effects in MT-4 cells, we found that 5-mono-Me-substituted analogues, the original substitution in the early lead compounds, and 7-mono-Me-substituted analogues of **1** were comparable as being consistently the most active compounds. Although generally less active, the 4,5,7-unsubstituted, 4-mono-substituted, *cis*- and *trans*-5,7-di-Me-substituted, and *cis*-4,5-di-Me-substituted analogues of **1** also exhibited some significant desired activity. The remaining *trans*-4,5-di-Me-substituted, *cis*- and *trans*-4,7-di-Me-substituted, and all 4,5-, 5,6-, 6,7-, and 7,8-fused disubstituted analogues of **1** possessed no noticeable desired activity.

Introduction

We have previously reported that a series of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-ones, **1**, have been found to possess significant inhibitory activity against the human immunodeficiency virus type 1 (HIV-1).[1] To those following the progress of potential therapeutic agents to combat the HIV-1 virus, the causative infection of acquired immune deficiency syndrome (AIDS), this series of compounds are readily identifiable by the acronym TIBO.



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Our previous medicinal chemistry publications[2,3] around the TIBO series have discussed, in addition to their discovery, preliminary synthetic endeavors and related structure–activity relationships (SAR). Both the synthesis and SAR reported to date have dealt with varying substitution at the N-6 site, evaluating the pure enantiomers related to the 5-Me substituent, which was a racemic center in the initial leads, and exploring both slight and major alterations of the 5-membered ring of **1**. In summary, from these preliminary studies we found that having a dimethylallyl group at the N-6 site and a thiourea as the 5-membered ring proved most promising for maximizing the blocking of HIV-1 virus's cytopathic effects. Also, the 5-Me *S* enantiomer analogues proved consistently more potent as inhibitors of HIV-1 than either their corresponding *R* enantiomers or racemates. Combining these features led to compound **1bt** which, in vitro, proved more potent than the recently approved DDI and about one-tenth as potent as AZT.

Since this original work, further pharmacological studies have shown that the TIBO series of compounds are hindering HIV-1 replication by inhibiting the HIV-1 reverse transcriptase (RT) enzyme, a crucial enzyme in the virus's life cycle, at an allosteric site.[4] A phase I clinical study of **1bt** on 22 late stage AIDS patients run over a 50 week period has also recently been reported.[5] This study demonstrated that compound **1bt** had no overt toxicities but did indicate its possible efficacy against HIV based on significant lowering of patients p24 antigen levels, a marker for the HIV virus levels.

Our original findings that altering the stereochemistry at the C-5 site of **1** led to variation of anti-HIV activity added credence to the obvious need for further exploration of alterations around the 7-membered ring portion of the TIBO series. This manuscript will describe our systematic variations around this 7-membered ring addressing the topic of related HIV-1 inhibition SAR as well as the various chemistry tied to these modifications.

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Table 1. Inhibition of HIV-1 Replication in MT-4 Cells

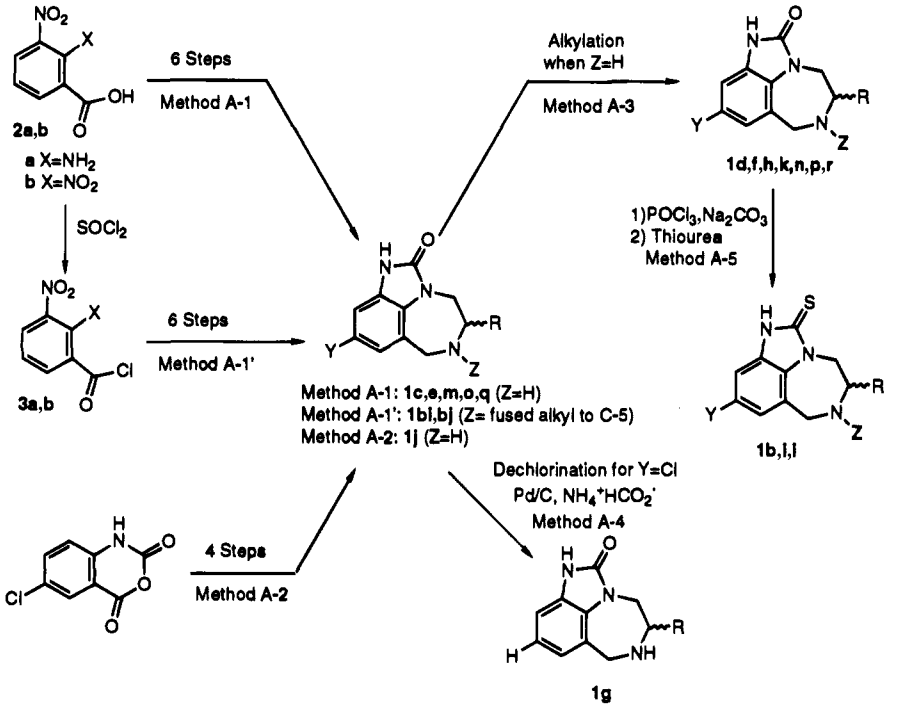
no.	R	X	Y	Z	IC_{50},[a] μM	n[b]
1a	H	S	8-Cl	DMA	0.046	2
1b	H	S	9-Cl	DMA	0.16	3
1c	5-Et	O	–	H	>250	5
1d	5-Et	O	–	2-MA	>50	4
1e	5-*i*-Pr	O	–	H	>250	5
1f	5-*i*-Pr	O	–	2-MA	>10	5
1g	5-*i*-Pr (*S*)	O	–	H	>250	2
1h	5-*i*-Pr (*S*)	O	–	DMA	>10	1
1i	5-*i*-Pr (*S*)	S	–	DMA	>10	1
1j	5-*i*-Pr (*S*)	O	9-Cl	H	>10	1
1k	5-*i*-Pr (*S*)	O	9-Cl	DMA	>10	1
1l	5-*i*-Pr (*S*)	S	9-Cl	DMA	>10	1
1m	5-*n*-Pr	O	–	H	>250	2
1n	5-*n*-Pr	O	–	2-MA	>10	2
1o	5-Ph	O	–	H	>250	1
1p	5-Ph	O	–	2-MA	>10	3
1q	5,5-di-Me	O	–	H	>250	5
1r	5,5-di-Me	O	–	2-MA	23.1[c]	5
1s	5-keto	O	–	n-Pr	>250	2
1t	4-Me	O	–	H	>250	5
1u	4-Me	O	–	2-MA	32.1	5
1v	4-Me (*S*)	S	9-Cl	2-MA	0.67	5
1w	4-Me (*R*)	S	9-Cl	CH_2-c-Pr	2.18	6
1x	4-*i*-Pr	O	–	H	>250	2
1y	4-*i*-Pr	O	–	*n*-Pr	73.3[d]	3
1z	4-*i*-Pr	O	–	2-MA	12.6	2
1aa	4-*n*-Pr	O	–	H	>250	2
1ab	4-*n*-Pr	O	–	*n*-Pr	>180	2
1ac	4-*n*-Pr	O	–	2-MA	48.1	2
1ad	4-Ph	O	–	H	>250	1
1ae	4-Ph	O	–	*n*-Pr	>250	1
1af	4-Ph	O	–	2-MA	>250	1
1ag	7-Me	O	–	H	>250	1
1ah	7-Me	O	–	*n*-Pr	>83	3
1ai	7-Me	O	–	DMA	12.1	2
1aj	7-Me	O	8-Cl	DMA	0.145	2
1ak	7-Me	O	9-Cl	DMA	0.16	5
1al	7-Me	S	–	*n*-Pr	2.43	3
1am	7-Me	S	–	DMA	0.078	5
1an	7-Me	S	8-Cl	DMA	0.012	2
1ao	7-Me	S	9-Cl	DMA	0.023	5
1ap	7-(2-Me-propyl)	O	9-Cl	DMA	>2	1
1aq	7-(2-Me-propyl)	S	9-Cl	DMA	>2	1
1ar	7-Ph	S	–	DMA	>2	1
1as	4,5-di-Me (cis)	O	–	DMA	56.7	3
1at	4,5-di-Me (cis)	S	–	DMA	2.22	2
1au	4,5-di-Me (trans)	S	–	CH_2-c-Pr	13.4	1
1av	4,5-di-Me (trans)	S	–	DMA	14.3[e]	5
1aw	4-keto-5-Me	S	9-Cl	*n*-Pr	>50	1
1ax	7-oxo-4,5-benzo	S	–	H	>250	1
1ay	4,5-benzo	S	–	CH_2-c-Pr	>10	2
1az	5,7-di-Me (trans)	S	–	DMA	0.042	8
1ba	5,7-di-Me (cis)	S	–	DMA	1.15	5
1bb	5,7-di-Me (*R*,*R*; trans)	O	9-Cl	DMA	0.23	3
1bc	5,7-di-Me (*R*,*R*; trans)	S	9-Cl	DMA	0.48	3
1bd	5,7-di-Me (*S*,*S*; trans)	O	9-Cl	DMA	>5	3
1be	5,7-di-Me (*S*,*S*; trans)	S	9-Cl	DMA	>10	3
1bf	5-Me-7-keto	O	–	*n*-Pr	>250	4
1bg	4,7-di-Me (trans)	S	–	DMA	25.8	2
1bh	4,7-di-Me (cis)	S	–	DMA	>10	2
1bi	5,6-$(CH_2)_4$	O	–	–	>250	8
1bj	5,6-$(CH_2)_3$	O	–	–	>250	5
1bk	5,6-$CH_2C(=CH_2)CH_2$ (*S*)	S	9-Cl	–	>10	1
1bl	5,6-$CH_2C(=CHCH_3)CH_2$ (*S*) (6:1 *Z*:*E*)	S	9-Cl	–	3.76[f]	3
1bm	6,7-$(CH_2)_3$	S	9-Cl	–	>2	1
1bn	6,7-$(COCH_2CH_2)$	S	9-Cl	–	>250	2
1bo	6,7-$(CH_2)_4$	S	9-Cl	–	>2	1
1bp	7,8-$(CH_2)_2$	S	9-Cl	DMA	>2	1
1bq	5-Me (*S*)	S	8-Cl	DMA	0.005	20
1br	5-Me (*S*)	O	9-Cl	H	>250	2
1bs	5-Me (*S*)	O	9-Cl	DMA	0.18	2
1bt	5-Me (*S*)	S	9-Cl	DMA	0.043	53
1bu	5-Me (*S*)	S	9-Cl	CH_2-c-Pr	0.034	5
1bv	5-Me (*S*)	S	–	CH_2-c-Pr	0.060	5
1bw	5-Me	O	–	H	>250	3
1bx	5-Me	O	–	*n*-Pr	59.7	15
1by	5-Me	S	–	*n*-Pr	1.67	7
1bz	5-Me	O	–	2-MA	34.7	24

Table 1 (Continued)

no.	R	X	Y	Z	IC_{50},[a] μM	n[b]
1ca	5-Me	S	–	DMA	0.097	7
1cb	5-Me (*S*)	O	–	DMA	3.32	8
1cc	5-Me (*S*)	S	–	2-MA	0.026	5

[a] Mean value of effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1. Where determinations did not give an absolute numerical value, they were not included in the mean IC_{50} values listed. [b] Number of experiments run for a given compound. [c] Three of five tests indicated an IC_{50} of >184 μM. [d] Two of three tests indicated an IC_{50} of >180 μM. [e] Two of four tests indicated an IC_{50} of >30 μM. [f] Two of three tests indicated an IC_{50} of >160 μM.

Scheme 1. Methods A-1–A-5



Chemistry

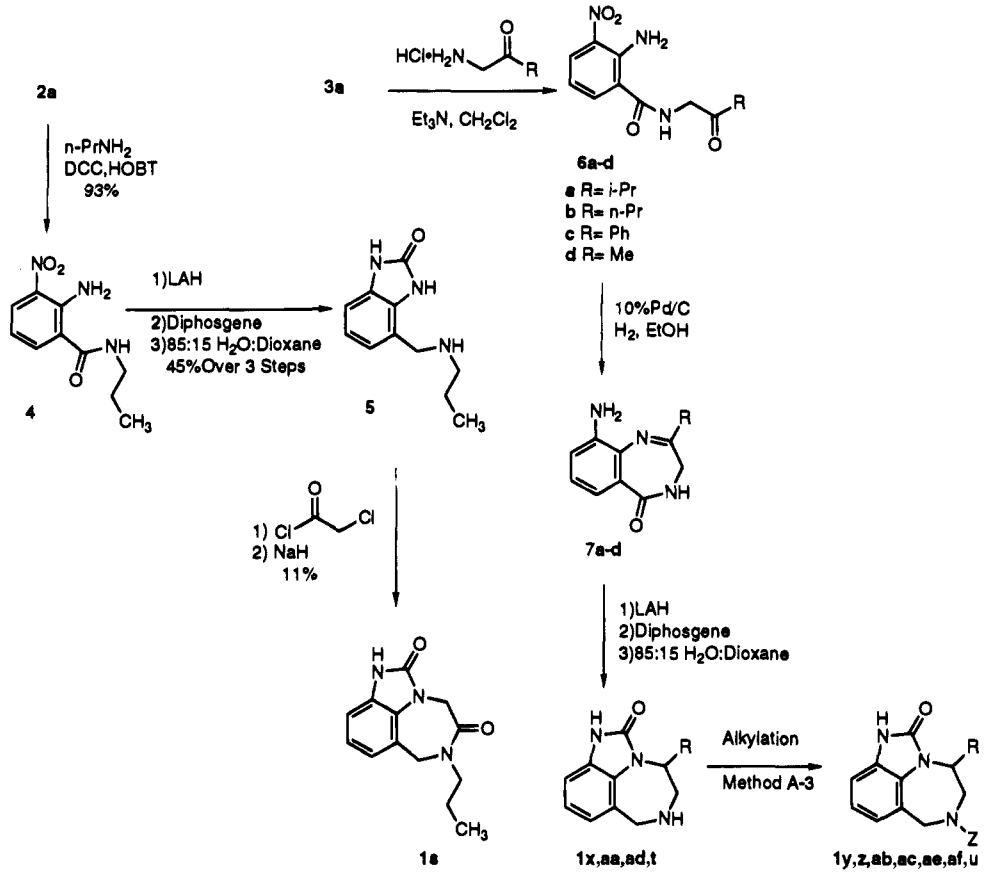
The number of varied substitutions explored in the 7-membered ring, both in terms of position of substitutions as well as functionality alterations (Table 1), resulted in the utilization of much diverse chemistry. This involved exploring 12 different synthetic routes (Schemes 1–9; methods A–L) in the generation of 67 novel, final targets, whose respective methods of syntheses are listed in Table 2.

Chemistry encompassed in Scheme 1 (methods A-1–A-5) was used mainly to prepare varied C-5 site substitution of **1**. The chemistry utilized for these compounds is reminiscent of our before-mentioned reports[2,3] on the preparation of the 5-Me analogues of **1**; therefore minimal commentary is necessary related to their preparation. With the exception of varying the appropriate starting material to place the different groups at C-5 of the final target **1**, and variations of some noteworthy purification conditions recorded in the Experimental Section, no significant changes were made from the previously published material. One other noteworthy point for Scheme 1 is that attempts to react secondary amines with acids **2** toward final targets such as **1bi,bj** by the otherwise standard 1,3-dicyclohexylcarbodiimide (DCC)-coupling reaction proved fruitless. The more reactive acid chlorides **3** were therefore employed which reacted cleanly with the secondary amines to generate their respective amide intermediates in high yield.

The 5-keto final compound **1s** (method B) was also prepared following, to an extent, related chemistry of the previously reported method A-1. A standard DCC coupling of *n*-propylamine to **2a** was used to generate **4**. Intermediate **4** was then treated with lithium aluminum hydride (LAH) to reduce both the nitro and amide functions in one pot. The resulting triamine was treated with 1 mol equiv of trichloromethyl chloroformate (diphosgene) to yield a carbamoyl chloride benzimidazolone intermediate which, in the same pot, was treated with an aqueous dioxane solution to hydrolyze the carbamoyl chloride to give desired intermediate amine **5**. This monoamine was reacted with chloroacetyl chloride to place the carbonyl group at the C-5 position of the desired final product. This acyclic benzimidazolone amide intermediate was treated with sodium hydride (NaH) to generate the reactive anion of the benzimidazolone. This anion readily cyclized to the 7-membered ring by a simple substitution of the alkyl chloride to give final product **1s**.

The secondary amines **1x,aa,ad,t** (method C), which contain racemic alkyl and aryl substitution in the C-4 position of **1**, were prepared by modifying the chemistry of the above-mentioned successful route for the C-5-substituted analogues. The main modification for the C-4-substituted analogues of **1** was that an amino ketone was used, rather than an amino acid, in the initial coupling reaction with acids **2** or acid chlorides **3** to generate keto amides **6a–d**. The R groups of these ketones correspond to the C-4 substituent of final products **1** which becomes self-evident after the conversions of **6a–d** to **7a–d**. These transformations entailed reducing the nitro groups of **6a–d** under a hydrogen

Scheme 2. Methods B and C

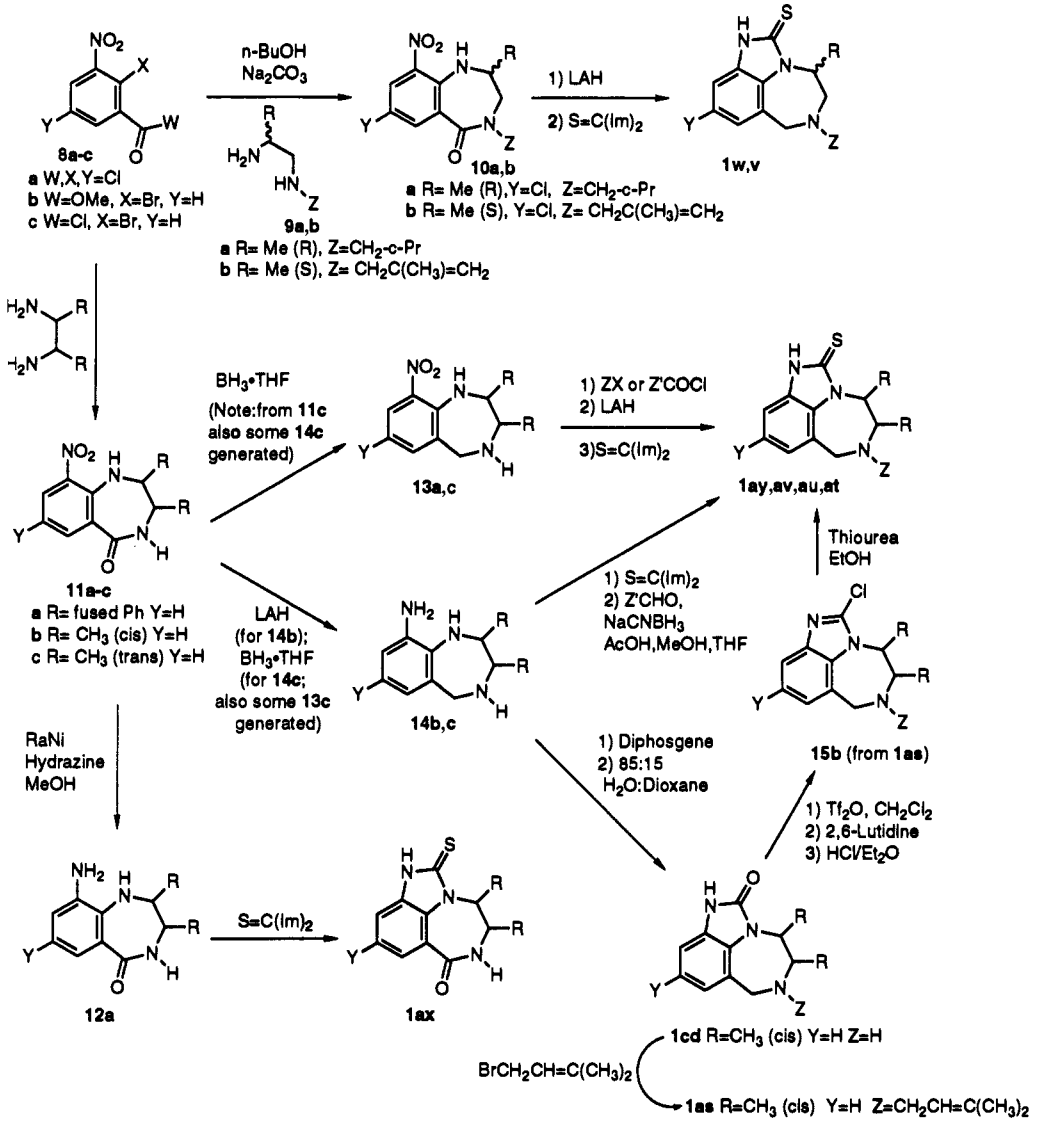


atmosphere in the presence of 10% Pd/C. The transient dianilino compounds were never isolated but rather readily cyclized in situ to yield intermediate compounds **7a–d**. These intermediates were treated with LAH which reduced both the imine and amide in one step. The resulting triamines were treated with diphosgene to yield the cyclic urea carbamoyl chlorides which, in the same pot, were treated with aqueous dioxane to hydrolyze the carbamoyl chlorides to yield the desired C-4-substituted secondary amines. These final secondary amines were then treated following the previously reported alkylation conditions[2] to yield the N-6-substituted final products **1y,z,ab,ac,ae,af,u**.

As previously mentioned, HIV-1 inhibitory stereoselectivity for the C-5 site of **1** has been noted with the *S* enantiomer proving more favorable than the *R* enantiomer. Once significant biological activity was noted for the racemic C-4-substituted series of **1**, the question arose whether there was significant biological stereoselectivity for either enantiomer in the C-4-substituted series. Rather than trying to resolve the racemic mixtures of C-4-substituted analogues generated by method C, an alternate stereospecific synthetic route was employed to prepare C-4 positional, pure enantiomers of **1** (method D). To prepare intermediates **9a,b**, the appropriate primary amine H_2N-Z was coupled with its respective optically pure sample of BOC-Ala-OH following standard DCC amide-forming reaction conditions. The resulting amides were treated with trifluoroacetic acid (TFA) at 0 °C to remove the BOC group and the resulting amide/amines treated with LAH to yield the desired diamine intermediates. These optically pure diamines were combined with the *n*-Bu ester of **8a**, which had been generated in situ, to yield respective intermediates **10a,b**. Most probably, **10a,b** are generated via a sequential reaction of nucleophilic aromatic substitution of **9** on the *n*-Bu ester of **8a** followed by an amide coupling, ring-closing reaction of the secondary amine with the ester. Intermediates **10** were then treated with LAH to reduce both the nitro and amide functions in one step. The resulting triamines were treated with thiocarbonyldiimidazole to yield their respective optically pure 4-substituted products **1w,v**.

Analogous chemistry to that explored in method D was used to prepare 4,5-disubstituted fused and nonfused products of **1** (method E). For example, 1,2-phenylenediamine was reacted with ester **8b** to generate the fused dibenzodiazepinone **11a**. Experimentation around selective reduction conditions of **11a** were investigated to add flexibility to subsequent chemistry culminating in diversity of the final products prepared. A selective Ra Ni/hydrazine reduction of the nitro group of **11a** generated the dianilino intermediate **12a**. This made it possible to do chemistry around the aniline groups, with the amide acting as a protecting group for the eventual N-6 amine of 1. In our reported case, we chose simply to cyclize the dianiline with thiocarbonyldiimidazole to yield final target **1ax**. A selective borane–tetrahydrofuran complex (BH_3·THF) reduction of the amide group of **11a** left the nitro group unscathed, generating amine **13a**. This method was chosen in lieu of the harsher LAH reduction conditions used in method D, which reduced the nitro and amide groups in one step. A selectively reduced intermediate such as **13a** avoided possible problematic selective alkylations or acylations, which may have arisen in the subsequent step with a fully reduced triamine akin to general structure **14**. Amine **13a** was easily acylated with cyclopropanecarbonyl chloride whose resulting amide

Scheme 3. Methods D–F



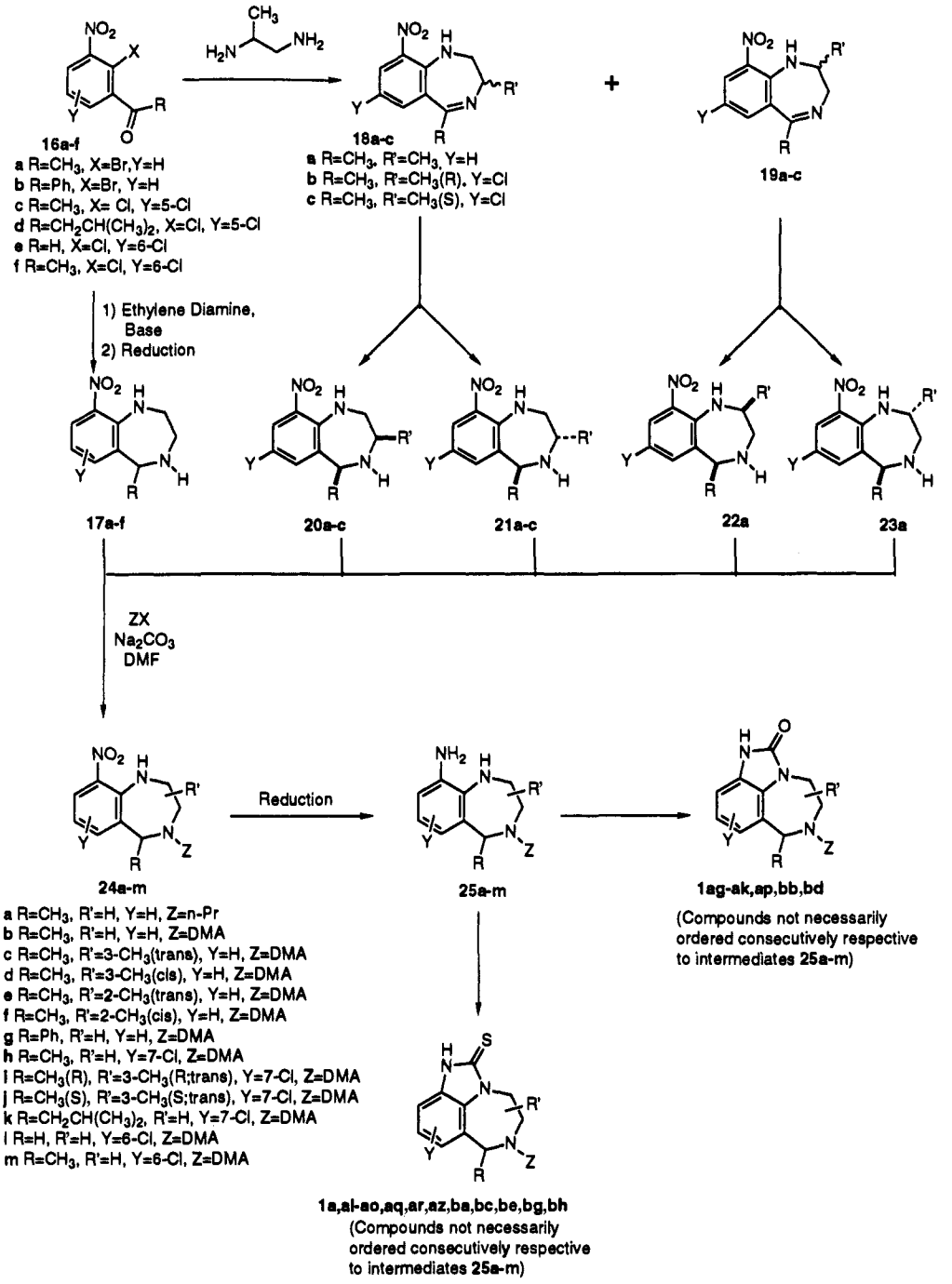
was treated with LAH to reduce the nitro and amide groups both in one step. The resulting triamine was then treated with thiocarbonyldiimidazole to yield final target **1ay**.

The synthetic method E was also used to prepare individually the *cis*- and *trans*-4,5-dimethyl-substituted final products of **1**. The previously mentioned synthetic method C could also have been used to prepare these targets, but method E was favored for the synthesis of these particular products. Method E had the advantage of being a stereospecific route, while method C would have involved stereoselective reductions and/or possibly cumbersome separation of isomers. Intermediates **11b,c** were prepared by reacting **8c** with meso-2,3-diaminobutane and D,L-2,3-diaminobutane, respectively. Various reduction conditions were also explored for **11b,c**. Treatment of intermediate **11b** with LAH gave the expected triamine **14b**, while treatment of **11c** with BH_3·THF under refluxing THF conditions led to a mixture of nitrodiamine **13c** and triamine **14c**, both in modest yields. Some further notable chemistry pursued via this route was performed on triamine **14c**. Intermediate **14c** was treated with thiocarbonyldiimidazole to generate an intermediate secondary amine benzimidazathione. We found this intermediate could be successfully converted via reductive amination to the final N-6-substituted target thiourea **1au**. This sequence complimented our previous work by adding another option to the methods available for preparing thioureas of final targeted thiones of **1**.

Related to final targeted thiones of **1**, problematic double-bond isomerizations of allylic side chains on the N-6 site of **1** has been noted[3] when preparing thioureas of **1** via an iminoyl chloride synthesis (method A-5). This isomerization occurred when phosphorus oxychloride ($POCl_3$) was used as a reagent in the iminoyl chloride-forming reaction. We therefore explored forming iminoyl chlorides by an alternate method (method F). The sequential treatment of the dimethylallyl N-6-substituted derivative **1as** with triflic anhydride (Tf_2O), 2,6-lutidine, and HCl led to iminoyl chloride **15b** with no detectable isomerization. This material was then easily converted to final product **1at** by treatment with thiourea.

Synthesis of C-7-substituted analogues of **1** (method G) entailed modifying the procedures of D and E, basically by substituting ketones **16a–f** as starting materials for esters and acid chlorides **8**. Ketones **16a–d,f** and aldehyde **16e** were prepared by following closely related published works cited in the Experimental Section. These carbonyl compounds were then treated with ethylenediamine and sodium cyanoborohydride ($NaBH_3CN$) to generate benzodiazepines **17a–f** which were then readily alkylated to generate their respective

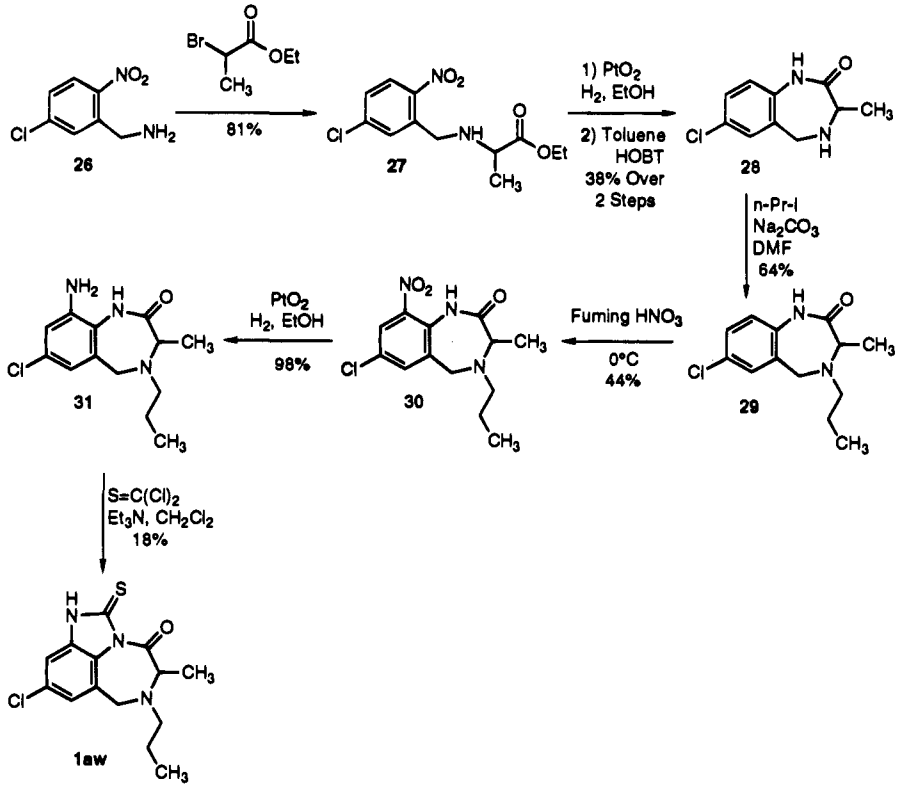
Scheme 4. Method G



intermediates of **24**. The nitro group of most of the intermediates for **24** was easily reduced with LAH to give their respective intermediates **25**. In some cases, where there was concern of potential dehalogenation of aromatic substituents by LAH, Ra Ni/hydrazine reduction conditions were used just as effectively. Intermediates **25** being converted to ureas of **1** were efficiently transformed with either diphosgene or 1,1′-carbonyldiimidazole. Intermediates **25** being converted to thioureas of **1** were also prepared by one of two methods. These two methods proved about equally effective and involved using either potassium ethylxanthate, which was generated in situ, or the commercially available 1,1′-thiocarbonyldiimidazole. Where amenable, one of these two direct methods of preparation for thioureas of **1** was pursued versus the less direct and more restrictive methods A-5 and F.

The remaining simple disubstituted final compounds of **1**, i.e., those containing 4,7 and 5,7 disubstitution, were also prepared following method G. The only alteration from the previously described method G was changing the coreactant of **16** from ethylenediamine to the nonsymmetrical 1,2-diaminopropane. The R substituent on **16** was maintained as Me for these reactions and, not surprisingly, yielded a mixture of both the 3,5- and 2,5-disubstituted benzodiazepines **18** and **19**. These intermediates were generated in a ratio of about 6:4, respectively, based on NMR, and fortunately were easily separable by simple chromatographic methods. Treatment of isolated products of **18** with $NaBH_3CN$ yielded a mixture of *cis*- and *trans*-3,5-benzodiazepines **20** and **21**, generally in a ratio of about 1:3.[6] This ratio was based on isolated yields which were accomplished utilizing preparative chromatography. Treatment of isolated **19a** with $NaBH_3CN$ yielded a mixture of *cis*- and *trans*-2,5-benzodiazepines **22a** and **23a** in a ratio of about 4:1,

Scheme 5. Method H



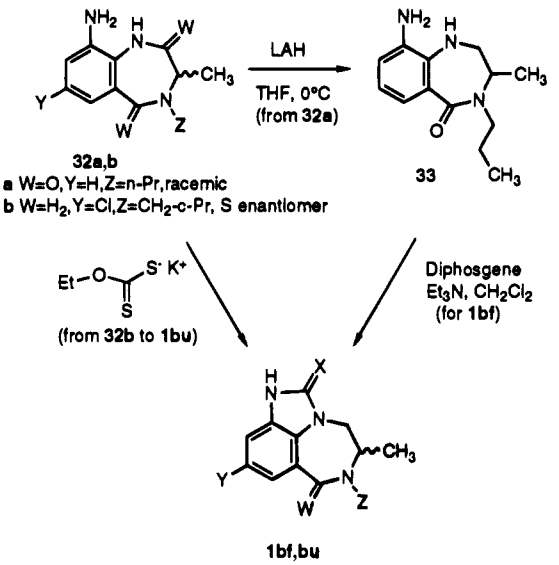
also based on isolated yields after chromatographic separation. As is obviously the case, pursuing identical chemistry starting with optically pure 1,2-diaminopropanes yielded similar ratios of optically pure benzodiazepines **18**–**21**. Further chemistry pursued on amines **20**–**23** was identical to that previously described for method G yielding final 4,7- and 5,7-disubstituted ureas and thioureas of **1**.

To prepare the 7-membered ring, disubstituted products of **1** containing a keto group as one of the substituents involved further chemical manipulation. Preparing the 4-keto 5-methyl-disubstituted analogue **1aw** involved a totally independent synthesis (method H). Alkylation of **26** with ethyl 2-bromopropionate gave **27**. The nitro group of **27** was reduced under a hydrogen atmosphere in the presence of platinum oxide (PtO_2) to yield an anilino intermediate which was subsequently cyclized to **28** in refluxing toluene with the aid of 1-hydroxybenzotriazole as an activating ester catalyst. Intermediate **28** was readily alkylated with 1-iodopropane to furnish **29** which was nitrated with fuming nitric acid (fuming HNO_3) to give **30**. The nitro group of **30** was reduced under a hydrogen atmosphere in the presence of PtO_2 to yield **31** which was treated with thiophosgene to generate the final target **1aw**.

Preparing the 5-methyl 7-keto analogue **1bf** involved exploiting selective reductive conditions different than those previously described (method I). It was found that treatment of C-2,C-5 diamides akin to **32a** with LAH at 0 °C led to selective monoreductions of the C-2 amide. For the case of **32a**, intermediate **33** was formed. Treatment of **33** with diphosgene readily gave desired target **1bf**.

Preparation of the 5,6-, 6,7-, and 7,8-fused disubstituted analogues of **1** entailed individualized syntheses. For the 5,6-fused ring olefinic compounds **1bk,bl**, this involved 6-step sequences (method J). Intermediate **34** was prepared by condensing *trans*-4-hydroxy-L-proline

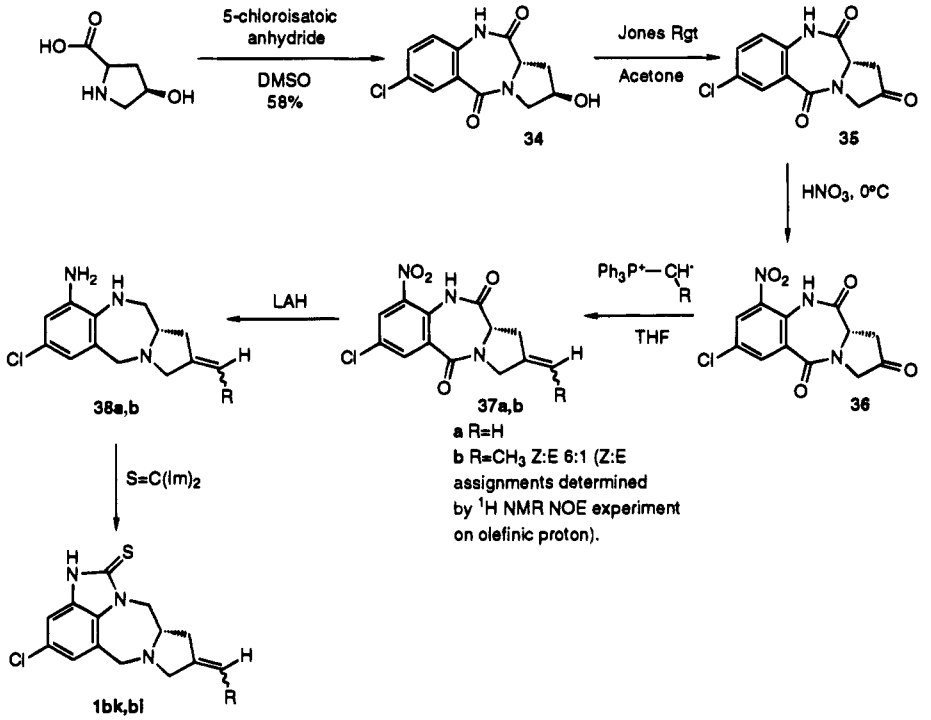
Scheme 6. Method I



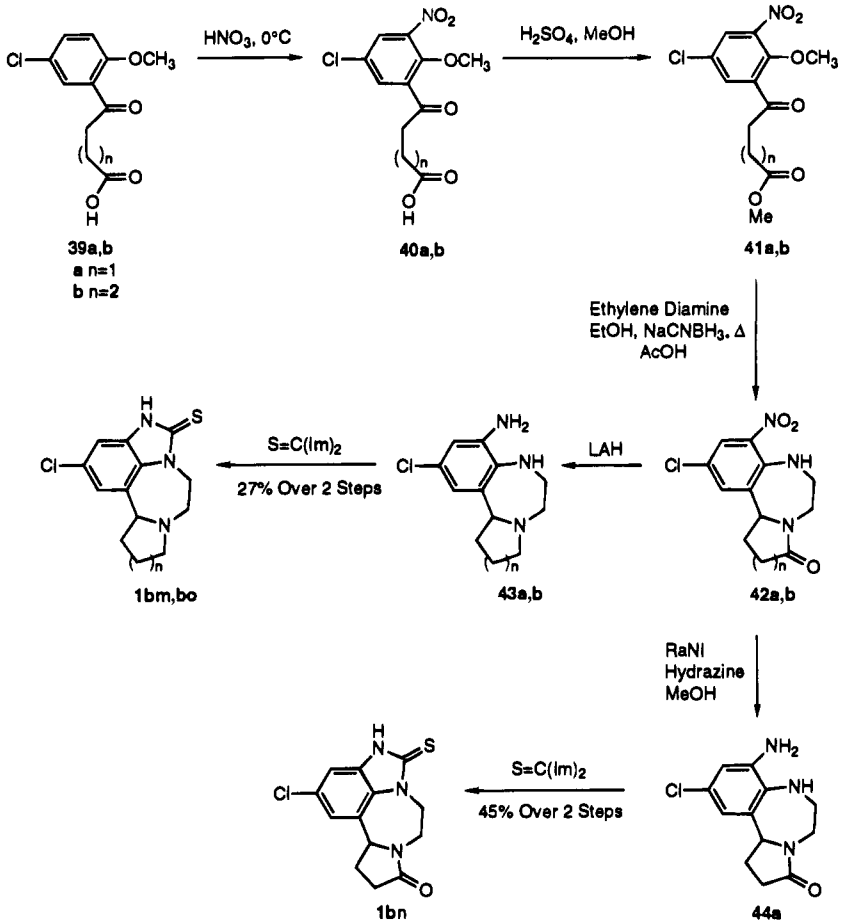
with 5-chloroisatoic anhydride. Oxidation of the alcohol moiety of **34** with Jones reagent led to ketone **35**. Treatment of **35** with fuming HNO_3 yielded **36** which was treated under Wittig reaction conditions with appropriate ylides to generate intermediates **37a,b**. Standard LAH reductions of these intermediates yielded triamines **38** which were converted to the final products **1bk,bl** with 1,1′-thiocarbonyldiimidazole.

Various 6,7-fused ring-substituted analogues of **1** were prepared via 5-step sequences (method K). Acids **39** were nitrated with fuming HNO_3 yielding acids **40** which were esterified under standard acidic methanolic conditions to the esters **41**. Treatment of these esters with ethylenediamine under reductive amination conditions resulted in a multistep one-pot reaction to yield the intermediate **42**. Various reductions and thiourea ring-forming reactions run sequentially on **42**, as previ-

Scheme 7. Method J



Scheme 8. Method K

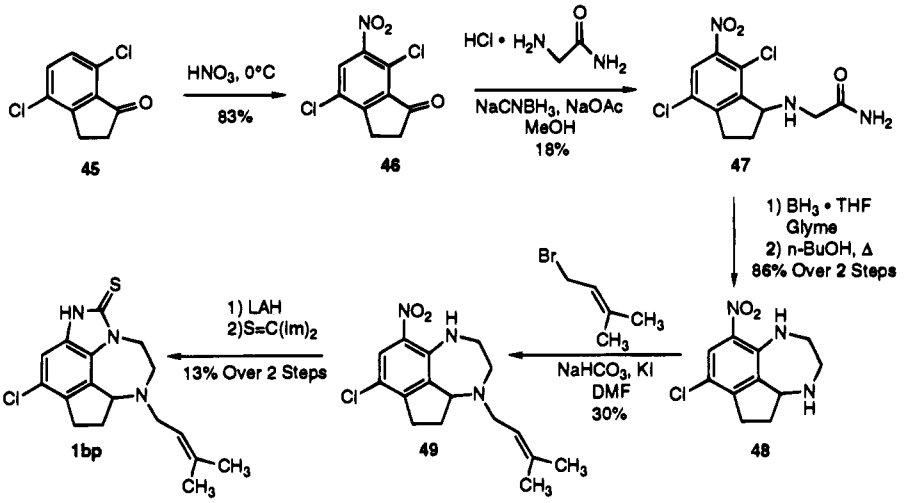


ously described for a number of TIBO analogues, resulted in desired 6,7-fused products **1bm,bo,bn**.

The sole 7,8-fused ring-substituted analogue of **1**, **1bp**, required a 5-step sequence (method L). Nitration of **45** gave ketone **46** which was treated under reductive amination conditions with glycinamide to provide intermediate **47**. The amide group of **47** was reduced with BH_3·THF to yield a primary amine which when warmed in refluxing *n*-BuOH cyclized to **48**. Alkylation of **48** furnished **49** which was sequentially treated with LAH and 1,1′-thiocarbonyldiimidazole to yield desired final product **1bp**.

The chemistry on the remaining analogues listed in Table 2, with the exception of **1bq**, has been reported

Scheme 9. Method L



in our previous publications. The chemistry utilized to prepare **1bq** will be described in our adjoining paper evaluating chemical and biological effects on **1** by varying aromatic substituents. These previously reported analogues of **1**, as well as **1bq**, have been listed in Table 2 solely for biological comparison to the newly reported analogues described above.

Results and Discussion

As mentioned in the introduction, the TIBO series of compounds **1** has demonstrated anti-HIV activity in primary and secondary screens as well as shown possible clinical efficacy against the HIV virus. However, for the series as a whole, including the compounds in this manuscript, the primary screen has supplied the initial results from which we have drawn our basic conclusions related to the series SAR. This primary screen, which has been previously described,[7] involved testing a compound's ability to inhibit the cytopathic effects of HIV-1 in MT-4 cells. These cells were infected with HIV-1 and incubated in the presence of various concentrations of the test compounds. The number of viable cells was then determined 5 days after infection by staining with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.[8] The reported values shown in Table 1 are the concentrations of each compound required to protect 50% (IC_{50}) of the MT-4 cells from cell death brought on by infection with HIV-1. The IC_{50}s reported as greater than a specified value are the highest concentration tested for that particular compound which failed to protect 50% of the MT-4 cells from the cytopathic effect of HIV-1. The reported IC_{50} values are the mean of a varied number of assays (n) for each analogue tested. The nature of the assay makes a determination of the standard deviations tenuous at best, although the values were usually quite consistent within the multiple determinations.

We began our study of the anti-HIV SAR around the 7-membered ring of **1** by evaluating variations solely at the C-5 site of **1**, where a methyl group resided in our original lead compounds. The simplest cases, the C-5 desmethyl compounds, were found to exhibit considerable HIV-1 inhibitory activity. Specifically, **1a,b** were quite active but significantly less than their corresponding 5-Me-substituted analogues, i.e., **1bq,-bt**, respectively. Interestingly, all other 5 positional, monoalkyl-substituted analogues of **1** proved less active, if not inactive, when directly compared to their respective 5-Me-substituted analogue: Me (**1bz**) > Et (**1d**) and Me (**1bs,bt**) > i-Pr (**1k,l**). Unfortunately, based on the available comparative data for **1p** (**1p** vs **1bz**), no definitive conclusions can be drawn about the 5 positional, monoaryl-substituted analogues of **1**. However, on the basis of the inactivity of the bulkier 5-i-Pr-substituted analogues of **1**, one might expect the activity for the 5-monoaryl-substituted analogues of **1** to prove less than favorable. Compiling these results suggests a tight size constraint for the C-5 site of **1** if significant anti-HIV activity is to be maintained. Any group larger than Me at this site resulted in loss of the desired biological activity, although Me substitution proved favorable over H substitution. Unrelated to size constraints, it was also found that replacing the 5-Me group of **1bx** with a carbonyl group (**1s**) resulted in loss of significant desired activity.

The C-4 position on the 7-membered ring of **1** was the next site explored with various monoalkyl and phenyl substitution changes. These C-4-substituted analogues proved to have significant HIV inhibitory activity and demonstrated a greater tolerance for larger substituents than for the above-mentioned C-5-substituted analogues of **1**. In fact, when comparing strictly the C-4-substituted compounds where X = O, we found that a bit of bulk or lipophilicity was desirable, with the i-Pr compound proving most active where direct comparisons could be made: Me (**1bz**) < i-Pr (**1z**) > n-Pr (**1ac**) ≫ Ph (**1af**). A comparison of this same active set of C-4-substituted compounds of **1** to their directly related C-5 Me-substituted analogue (**1bz**) showed the C-4-substituted compounds had comparable, or for **1z** possibly better, desired activity. Encouraged by these early findings, we prepared C-4 pure enantiomers of **1** to determine if there was biological stereospecificity for the C-4 site of **1**. We prepared the thioureas (X = S) of these pure enantiomers which, as previously mentioned, demonstrated early on in our studies to be better HIV inhibitors than the analogous ureas (X = O). We found that both the S enantiomer **1v** and the R enantiomer **1w** possessed significant desired activity. However, when these compounds were compared to their closest prepared C-5-substituted analogues, they proved considerably less active (**1w** ≪ **1bu** and **1w** ≪ **1cc**). We unfortunately did not complete work on a matching set

Table 2. Product Purification and Characterization

compd	synthesis[a]	formula[b]	purification[c]	yield, %	mp, °C
1a	G	$C_{15}H_{18}ClN_3S$	1% MeOH/CH_2Cl_2[d]	18	212–214
1b	A-5	$C_{15}H_{18}ClN_3S$	25% EtOAc/hexane[d]	11	214–215
1c	A-1	$C_{12}H_{15}N_3O$	CH_3CN	30	144–145.5
1d	A-3	$C_{16}H_{21}N_3O$	CH_3CN	57	116–118
1e	A-1	$C_{13}H_{17}N_3O$	CH_3CN	45	157.5–159.5
1f	A-3	$C_{17}H_{23}N_3O$	CH_3CN	65	137–143
1g	A-4	$C_{13}H_{17}N_3O$	CH_3CN	50	160–163
1h	A-3	$C_{18}H_{25}N_3O$	CH_3CN	73	126–129
1i	A-5	$C_{18}H_{25}N_3S$	2% MeOH/CH_2Cl_2; CH_3CN[d]	11	149–150
1j	A-2	$C_{13}H_{16}ClN_3O$	2% EtOH/CH_2Cl_2; CH_3CN[d]	21	180–182
1k	A-3	$C_{18}H_{24}ClN_3O$	2% EtOH/CH_2Cl_2; CH_3CN[d]	30	182–184
1l	A-5	$C_{18}H_{24}ClN_3S$	2% EtOH/CH_2Cl_2[d]	11	143–145
1m	A-1	$C_{13}H_{17}N_3O$	CH_3CN	24	156.5–159
1n	A-3	$C_{17}H_{23}N_3O$	CH_3CN	29	116–119
1o	A-1	$C_{16}H_{15}N_3O$	MeOH	13	245–246
1p	A-3	$C_{20}H_{21}N_3O$	CH_3CN	27	168.5–170
1q	A-1	$C_{12}H_{15}N_3O$	CH_3CN	48	153.5–158.5
1r	A-3	$C_{16}H_{21}N_3O$	EtOH	37	159–164
1s	B	$C_{13}H_{15}N_3O_2 \cdot 0.01CH_2Cl_2$	MeOH	11	259–262
1t	C	$C_{11}H_{13}N_3O \cdot 0.04CH_3OH$	MeOH	25	210.5–215
1u	A-3	$C_{15}H_{19}N_3O \cdot 0.05CH_3CN$	CH_3CN	62	134.5–138
1v	D	$C_{15}H_{18}ClN_3S$	1% EtOH/CH_2Cl_2[d]	13	170–172
1w	D	$C_{15}H_{18}ClN_3S$	1% EtOH/CH_2Cl_2; CH_3CN[d]	8	205–206
1x	C	$C_{13}H_{17}N_3O$	4% EtOH/CH_2Cl_2; CH_3CN[d]	20	162–165
1y	A-3	$C_{16}H_{23}N_3O$	3% EtOH/CH_2Cl_2; CH_3CN[d]	43	130.5–138
1z	A-3	$C_{17}H_{23}N_3O$	CH_3CN	42	138–142
1aa	C	$C_{13}H_{17}N_3O$	4% EtOH/CH_2Cl_2; CH_3CN[d]	35	157–158
1ab	A-3	$C_{16}H_{23}N_3O$	4% EtOH/CH_2Cl_2; CH_3CN[d]	38	115.5–117
1ac	A-3	$C_{17}H_{23}N_3O$	CH_3CN	54	123.5–127
1ad	C	$C_{16}H_{15}N_3O$[e]	4% EtOH/CH_2Cl_2; CH_3CN[d]	26	240–242.5
1ae	A-3	$C_{19}H_{21}N_3O \cdot 0.07CH_3CN$	4% EtOH/CH_2Cl_2; CH_3CN[d]	26	205–212
1af	A-3	$C_{20}H_{21}N_3O$[e]	CH_3CN	43	193–196.5
1ag	G	$C_{11}H_{13}N_3O$	1:8 MeOH:CH_2Cl_2; CH_3CN[d]	13	156–158
1ah	G	$C_{14}H_{19}N_3O$	1:15 MeOH:CH_2Cl_2; CH_3CN[d]	31	121.5–123.5
1ai	G	$C_{16}H_{21}N_3O$	7:3 EtOAc:hexane; CH_3CN[d]	8	98–121
1aj	G	$C_{16}H_{20}ClN_3O \cdot HCl$	1.5% MeOH/CH_2Cl_2(FB); HCl, Et_2O, *i*-PrOH[d]	11	249–250
1ak	G	$C_{16}H_{20}ClN_3O$	1:3 EtOAc:hexane; CH_3CN[d]	43	135–137
1al	G	$C_{14}H_{19}N_3S \cdot 0.1EtOH$	CH_3CN, then EtOH	25	175.5–177.5
1am	G	$C_{16}H_{21}N_3S$	1:1 EtOAc:hexane[d]	14	191–192.5
1an	G	$C_{16}H_{20}ClN_3S$[e]	CH_2Cl_2; MeOH[d]	23	178–179
1ao	G	$C_{16}H_{20}ClN_3S$	Et_2O/hexane[d]	59	190–191.5
1ap	G	$C_{19}H_{26}ClN_3O$	Et_2O/CH_2Cl_2; CH_3CN	22	133–135
1aq	G	$C_{19}H_{26}ClN_3S$	EtOAc/hexane; CH_3CN[d]	44	171–172
1ar	G	$C_{21}H_{23}N_3S$	25% EtOAc/hexane[d]	25	144–145
1as	A-3	$C_{17}H_{23}N_3O \cdot 0.04CH_2Cl_2 \cdot 0.06CH_3CN$	0.1% NH_4OH in 5% MeOH/CH_2Cl_2; CH_3CN[d]	11	150–152
1at	F	$C_{17}H_{23}N_3S$	0.1% NH_4OH in 3% MeOH/CH_2Cl_2; CH_3CN[d]	22	159–161
1au	E	$C_{16}H_{21}N_3S$[f]	0.1% NH_4OH in 5% MeOH/CH_2Cl_2; Et_2O[d]	18	132–135
1av	E	$C_{17}H_{23}N_3S$[e]	0.1% NH_4OH in 5% MeOH/CH_2Cl_2; EtOAc[d]	35	149–155
1aw	H	$C_{14}H_{16}N_3OS$	1:30 MeOH:CH_2Cl_2[d]	18	154–176
1ax	E	$C_{14}H_9N_3OS$[e]	MeOH	66	385–387
1ay	E	$C_{18}H_{17}N_3S$	25% EtOAc/hexane; CH_3CN[d]	24	173–175
1az	G	$C_{17}H_{23}N_3S$	1:20 MeOH:CH_2Cl_2; EtOH[d]	25	135–137
1ba	G	$C_{17}H_{23}N_3S$	1% MeOH/CH_2Cl_2; EtOH[d]	33	135–137
1bb	G	$C_{17}H_{22}ClN_3O$	1% MeOH/CH_2Cl_2; CH_3CN[d]	73	81–86
1bc	G	$C_{17}H_{22}ClN_3O$	100% CH_2Cl_2; CH_3CN[d]	24	163–164
1bd	G	$C_{17}H_{22}ClN_3O \cdot HCl$	2% MeOH/CH_2Cl_2(FB); *i*-PrOH	22	216–217
1be	G	$C_{17}H_{22}ClN_3S \cdot HCl$[e]	100% CH_2Cl_2(FB); *i*-PrOH[d]	16	212–213
1bf	I	$C_{14}H_{17}N_3O_2$	1:20 MeOH:CH_2Cl_2; CH_3CN[d]	15	236–237
1bg	G	$C_{17}H_{23}N_3S$	0.5% MeOH/CH_2Cl_2; EtOH[d]	27	182.5–183.5
1bh	G	$C_{17}H_{23}N_3S$	1% MeOH:CH_2Cl_2; EtOH[d]	51	178–180
1bi	A-1′	$C_{14}H_{17}N_3O \cdot 0.03\ CH_3NO_2$	CH_3NO_2	45	184.5–189
1bj	A-1′	$C_{13}H_{15}N_3O \cdot 0.2CH_2Cl_2$	CH_3NO_2	17	205–208.5
1bk	J	$C_{14}H_{14}ClN_3S$	1% MeOH:CH_2Cl_2[d]	31	250
1bl	J	$C_{15}H_{16}ClN_3O$[e]	3% MeOH:CH_2Cl_2; CH_3CN[d]	5	214
1bm	K	$C_{13}H_{14}ClN_3S$	45:55 EtOAc:hexane; CH_3CN[d]	27	252–254
1bn	K	$C_{13}H_{12}ClN_3OS$	rinsed with THF	45	>300 d
1bo	K	$C_{14}H_{16}ClN_3S$	1:1 EtOAc:hexane; CH_3CN[d]	12	263–265
1bp	L	$C_{17}H_{20}ClN_3S$[e]	1:1 EtOAc:hexane; CH_3CN[d]	13	200–201
1bu	I	$C_{15}H_{18}ClN_3S$	30:1 CH_2Cl_2:MeOH; CH_3CN[d]	19	171–174

[a] Method/reagent used to synthesize the product. [b] All products were analyzed for C, H, and N. [c] Products were crystallized and/or recrystallized from listed solvents. [d] Crude material flash chromatographed on silica gel eluting with identified solvent system prior to crystallization with listed solvent. [e] **1ad**, C: calcd, 72.43; found, 71.57. Exact mass MH^+ calcd: 266.1293. Found: 266.1295. Δ: 0.6 ppm. **1af**, C: calcd, 75.21; found, 74.61. Exact mass calcd: 319.1685. Found: 319.1674. Δ: 3.4 ppm. **1an**, C: calcd, 59.71; found, 59.09. Exact mass MH^+ calcd: 322.1145. Found: 322.1183. Δ: 11.8 ppm. **1av**, C: calcd, 67.74; found, 66.90. No sample remained for exact mass measurements. **1ax**, C: calcd, 62.91; found, 62.46. Exact mass calcd: 267.0466. Found: 267.0519. Δ: 19.8 ppm. **1be**, C: calcd, 54.84; found, 53.99. Exact mass MH^+ calcd: 336.1301. Found: 336.1315. Δ: 4.1 ppm. **1bl**, C: calcd, 58.91; found, 58.47. Exact mass calcd: 305.0754. Found: 305.0780. Δ: 8.5 ppm. **1bp**, C: calcd, 61.16; found, 60.67. Exact mass calcd: 333.1066. Found: 333.1100. Δ: 10.2 ppm. [f] C, H, N analysis not performed. Exact mass calcd: 287.1456. Found: 287.1449. Δ: 2.4 ppm.

of C-4-substituted enantiomers, so a direct comparison of relative biological activities between the *R* and *S* enantiomers can not be made.

The C-7 position on the 7-membered ring of **1** was also initially explored with various monoalkyl and phenyl substitution. We found that all the C-7 mono-Me-substituted urea and thiourea analogues of **1** prepared proved to be at least equally effective as inhibitors of HIV-1 as any other analogues of **1** synthesized. They proved more active than their associated desmethyl analogues when a direct comparison is made (**1an** > **1a** and **1ao** > **1b**) and about equally effective to their related C-5 Me-substituted urea (**1ak** = **1bs**) and thioureas (**1an** = **1bq**; **1ao** = **1bt**; **1am** = **1ca**; **1al** = **1by**). From the limited cases where larger groups occupied the C-7 position of **1**, we found no significant desired biological activity. This was true when C-7 was substituted with either an isobutyl group (**1ap,aq**) or a phenyl group (**1ar**).

As discussed above, the various monoalkyl substitutions at the C-4, C-5, or C-7 sites of **1** resulted in improved desired activity relative to their analogous unsubstituted compounds. We therefore chose to explore disubstituted variations around **1**, i.e., 4,5-, 4,7-, and 5,7-disubstituted analogues of **1**. We hoped this would enhance desired activity by combining substitutions in one molecule which had previously proven promising individually. Initially we prepared a complete series of 4,5-, 4,7-, and 5,7-dimethyl-substituted stereoisomers of **1**. This restricted the variation of **1** to strictly the relative positions of the dimethyl groups; therefore direct comparison of relative activities could be made. Unfortunately, the synergistic biological effect desired by disubstituting on the 7-membered ring was not realized, although some interesting trends were noted. Our best disubstituted analogue, **1az** (5,7-di-Me-*trans*), proved, at best, slightly better than its respective 5-mono-Me analogue, **1ca**. For the series of racemic dimethyl-substituted stereoisomers as a whole, in comparison to their respective 5-mono-Me analogue **1ca**, the following activity trends were noted, 5-mono-Me (**1ca**) ≤ 5,7-di-Me-*trans* (**1az**) > 5,7-di-Me-*cis* (**1ba**) ≥ 4,5-di-Me-*cis* (**1at**) > 4,7-di-Me-*cis* (**1bh**); 4,5-di-Me-*trans* (**1au**); 4,7-di-Me-*trans* (**1bg**). Inspired by the promising activity of the 5,7-di-Me-*trans* analogue **1az**, we prepared some additional 5,7-disubstituted analogues of **1**. Preparation of two sets of 5,7-di-Me-*trans*, enantiomerically pure analogues of **1** led to a number of unexpected SAR observations. Interesting, the (*R,R*)-5,7-di-Me-*trans*-substituted enantiomers **1bb,bc** were found to be significantly more active than their respective *S,S* enantiomers **1bd,be**. This is in contrast to the 5-mono-Me analogues of **1** where the *S* enantiomer has always demonstrated better activity than the respective *R* enantiomer. Also in contrast to the simple C-5-monomethylated analogues of **1**, the thiourea **1bc** with (*R,R*)-5,7-di-Me-*trans*-substitution seemed slightly less active than its respective urea analogue **1bb** (C-5 mono-Me: thiourea **1bt** > urea **1bs**]. Additionally, 9-Cl aromatic substitution on the 5,7-di-Me-substituted analogue of **1** significantly reduced the desired activity (**1bc** < **1az**) in contrast to the 5-mono-Me-substituted analogues (**1bt** ~ **1ca**). Unfortunately, these noted variances between the biological activities for the 5,7-di-Me-substituted versus their related 5-mono-Me-substituted analogues of **1** yielded 5,7-di-Me-substituted compounds showing less promise as HIV-1 inhibitors than the simpler 5-mono-Me-substituted analogues.

Proving no more promising was the 5,7-disubstituted analogue, **1bf**, created by adding a keto group at the C-7 site of **1bx**, which eliminated previously observed desired activity. Similarly, no desired activity was noted for the 4-keto 5-methyl-disubstituted analogue **1aw**.

Most of the discussion section thus far has dealt with the HIV inhibitory activity of analogues of **1** where the basic A, B, C ring system has not been altered. In addition to these compounds we also explored somewhat more distant derivatives where additional rings were fused onto **1**. This included a cursory look at hybridizing nevapirine,[9] another reported RT inhibitor of HIV-1, within our basic TIBO structure of **1** generating analogues **1ax,ay**. Neither of these compounds exhibited significant desired activity. We also examined various 5,6- (**1bi,bj,bl,bk**), 6,7- (**1bm,bo,bn**), and 7,8- (**1bp**) fused analogues of **1** with the hope of locking a favorable conformation of compounds which had previously exhibited significant HIV-1 inhibitory activity. Unfortunately, these modifications yielded analogues where all significant desired activity was lost.

In summary, we made systematic variations at the 4, 5, and 7 positions of **1** to study the anti-HIV-1 SAR of these compounds relative to the original lead compounds of **1**, which contained mono-Me substitution at the C-5 site. In addition to altering substituents at these sites, we also varied between mono- and disubstitution of these substituents on **1**. For the disubstituted analogues of **1**, both acyclic and ring-fused additions onto **1** were made. Evaluation of the biological results for these changes showed that the C-5 Me-substituted analogues of **1** maintained the highest desired activity, with the C-7 mono-Me-substituted analogues being the only others showing comparable activity. Although generally less active, the 4,5,7-unsubstituted, 4-mono-substituted, *cis*- and *trans*-5,7-di-Me-substituted, and *cis*-4,5-di-Me-substituted analogues of **1** also exhibited some significant desired activity. The remaining *trans*-4,5-di-Me-substituted, *cis*- and *trans*-4,7-di-Me-substituted, and all fused ring analogues of **1** possessed no noticeable desired activity. On the basis of these findings, we chose to maintain the C-5 mono-Me substituent on **1** when evaluating the anti-HIV SAR related to aromatic substitutions of **1**. These results are summarized in our adjoining and concluding paper on anti-HIV SAR related to **1**.

Experimental Section

All final products included in Table 2 were characterized by 360-MHz ^{1}H NMR (Bruker AM 360 WB), IR (Nicolet 60SX), mass spectra (Finnegan 3300), and elemental analyses. Unless otherwise specified, reported ^{1}H NMR's of intermediates were also run on the 360-MHz NMR. The elemental analyses were carried out by the internal Analytical Research Department of Janssen Research Foundation in Beerse, Belgium. Any final products which varied from the calculated percent values for C, H, or N by more than 0.4 were examined by exact mass measurements. These exact mass measurements were carried out by either the internal Spectroscopy Group of the R.W. Johnson Pharmaceutical Research Institute, Spring House, on a VG 7070 E high-resolution mass spectrometer or M-Scan, Inc., of West Chester, PA, on a VG Analytical ZAB 2-SE high-field mass spectrometer. All final products were also assayed for homogeneity by thin-layer chromatography on Whatman

MK6F (1 in. × 3 in. × 250 μm) silica gel plates. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. All reagents were commercially available unless specified. Table 2 also identifies the typical procedure followed to prepare each respective final product. Variance from these typical procedures is outlined below for all compounds where modifications were required.

Procedure Sequences for Method A-1–A-5. Procedure reaction conditions for methods A-1–A-5 have been previously reported in our earlier work related to the TIBO series of compounds.[2,3] Besides the obvious changes to appropriate starting materials, the procedures were not substantially altered. Notable vairations and/or additions to these procedures for compounds reported in this manuscript are listed below.

5-Ethyl-4,5,6,7-tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1c). A minor variation in the 6-step sequence for **1c** was the purification of its respective 9-amino-1,4-benzodiazepine-2,5-dione intermediate. This material was purified by trituration in MeOH.

4,5,6,7-Tetrahydro-5-(1-methylethyl)imidazo[4,5,1-*jk*]-[1,4]benzodiazepin-2(1*H*)-one (1e). A minor variation in the 6-step sequence for **1e** was the purification of its respective 9-amino-1,4-benzodiazepine-2,5-dione intermediate. This material was purified by trituration in 90:5 EtOAc:EtOH.

4,5,6,7-Tetrahydro-5-propylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1m). A minor variation in the 6-step sequence for **1m** was that its respective 9-amino-1,4-benzodiazepine-2,5-dione intermediate was used without purification.

4,5,6,7-Tetrahydro-5-phenylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1o). A minor variation in the 6-step sequence for **1o** was the purification of its respective 9-amino-1,4-benzodiazepine-2,5-dione intermediate. This material was purified by flash chromatography on a silica gel column eluting with 10:1 CH_2Cl_2:MeOH. The desired fractions were combined and concentrated under reduced pressure after which the residue was triturated in acetone.

2-Amino-3-nitrobenzoyl Chloride (3a). Under Ar, **2a**[10] (9.90 g, 0.054 mol) was added to thionyl chloride (20 mL, 0.274 mol) at room temperature and immediately brought to reflux. After 15 h the excess thionyl chloride was removed under reduced pressure, and the resulting yellow solid **3a** (100%) was used without further purification.

Procedure Sequence for Method B. 2-Amino-3-nitro-*N*-propylbenzamide (4). Under Ar at 0 °C 1,3-dicyclohexylcarbodiimide (DCC) (8.24 g, 0.04 mol) was added neat to a stirring solution of **2a** (7.08 g, 0.04 mol), *n*-$PrNH_2$ (3.29 mL, 0.04 mol), and 1-hydroxybenzotriazole hydrate (HOBT) (10.80 g, 0.08 mol) in THF (200 mL). After 1 h the reaction mixture was warmed to room temperature and stirred for an additional 16 h. The reaction mixture was then filtered and concentrated under reduced pressure. The concentrated residue was dissolved in CH_2Cl_2 (200 mL) and extracted twice with saturated aqueous $NaHCO_3$ (200 and 100 mL, respectively). The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 8.26 g (93%) of **4** as a yellow solid (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.8$). **4**: ^1H NMR ($CDCl_3$) δ 1.0 (s, 3H), 1.55–1.75 (m, 2H), 3.3–3.5 (q, 2H), 6.1 (bs, 1H), 6.6–6.7 (t, 1H), 7.6 (d, 1H), 8.1 (bs, 1H), 8.25 (d, 1H).

1,3-Dihydro-4-[(propylamino)methyl]-2*H*-benzimidazol-2-one (5). Under Ar at 0 °C **4** (3.35 g, 0.015 moL) was added neat over 10 min to a suspension of LAH (3.41 g, 0.90 moL) in THF (50 mL). After 1.5 h the reaction mixture was warmed to room temperature and stirred for 16 h. Then 1,4-dioxane (200 mL) was added to the reaction mixture after which the temperature was elevated to distill off the THF. The resulting mixture in dioxane was then maintained at reflux. After 48 h the reaction mixture was cooled to room temperature and the reaction quenched with H_2O (3.41 mL) followed by 15% NaOH (3.41 mL) and then H_2O (10.23 mL). The mixture was stirred for 1 h and then filtered. The resulting salts were digested in refluxing THF and then refiltered. The filtrates were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was immediately combined with 4-methylmorpholine (NMM) (4.94 mL, 0.045 mol) in CH_2Cl_2 (30 mL) and added over 10 min to a 0 °C solution of trichloromethyl chloroformate (1.80 mL, 0.015 mol) in CH_2Cl_2 (40 mL). After stirring for an additional 10 min, the mixture was concentrated under reduced pressure. A solution of 85:15 dioxane:H_2O (100 mL) was added to the resulting solid under Ar at room temperature and the resulting mixture warmed on a steam bath for 10 min. The resulting mixture was filtered through Dicalite. The filtrate was then basified with concentrated NH_4OH to give a brownish precipitate which was filtered and triturated with MeOH to give 1.32 g (43%) of **5** which was used for the subsequent reaction without further purification. However, an analytical sample of **5** was prepared by recrystallizing a 0.27-g sample of semipure **5** from MeOH (15 mL) to yield 0.13 g (21%) of pure **5** as a white solid, mp 219–222 °C, (TLC: 65:25:4 $CHCl_3$:MeOH:H_2O, $R_f = 0.15$). **5**: ^1H NMR (DMSO-d_6) δ 0.85 (t, 3H), 1.4–1.5 (m, 2H), 2.4 (t, 2H), 3.75 (s, 2H), 6.7–7.0 (m, 3H). Anal. ($C_{11}H_{15}N_3O$) C, H, N.

6,7-Dihydro-6-propylimidazo[4,5,1-*jk*][1,4]benzodiazepine-2,5(1*H*,4*H*)-dione (1s). Under Ar, chloroacetyl chloride (0.32 mL, 0.040 mol) in CH_2Cl_2 (10 mL) was added over 1 min to a 0 °C mixture of **5** (0.82 g, 0.040 mol) and Et_3N (0.56 mL, 0.040 mol) in CH_2Cl_2 (10 mL). The mixture was stirred for 30 min at 0 °C and then brought to reflux for an additional 30 min. The reaction mixture was then cooled to room temperature and extracted with 1 N HCl, saturated aqueous $NaHCO_3$, and then brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 0.72 g of an oil. A 0.65-g sample of this oil was dissolved in THF (3.5 mL) after which 50% NaH (0.122 g, 0.025 mol) was added neat at once at room temperature. After 1 h the reaction mixture was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The resulting solid was filtered from this biphasic system to yield 0.32 g (36%) of semipure **1s**. This material was further purified through trituration as described in Table 2 (TLC: 20:1 $CHCl_3$:MeOH, $R_f = 0.25$). **1s**: ^1H NMR (DMSO-d_6) δ 0.65–0.75 (t, 3H), 1.4–1.6 (m, 2H), 3.3–3.4 (t, 2H), 4.7–4.75 (s, 2H), 4.75–4.8 (s, 2H), 6.9–7.0 (s, 3H), 11.0 (s, 1H).

Typical Procedure Sequences for Method C. 2-Amino-*N*-(3-methyl-2-oxobutyl)-3-nitrobenzamide (6a). Under N_2, Et_3N (9.50 mL, 0.068 mol) in CH_2Cl_2 (15 mL) was added dropwise to a room temperature suspension of **3a** (6.85 g, 0.034 mol) and 1-amino-3-methylbutanone monohydrochloride[11] (4.7 g, 0.034 mol) in CH_2Cl_2 (85 mL). After stirring for 21 h the reaction mixture was washed with H_2O. The aqueous phase was rewashed with a second portion of CH_2Cl_2. The organic phases were combined and rewashed with H_2O, saturated aqueous $NaHCO_3$, and then brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 7.8 g of yellow solid. This material was warmed in refluxing EtOH (150 mL) and the undissolved solid filtered from the solution. The filtrate was concentrated to give 6 g (67%) of **6a** as a gummy solid which was used without further purification (TLC: 5% EtOH:CH_2Cl_2, $R_f = 0.75$; 1:1 EtOAc:hexane, $R_f = 0.5$). **6a**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.2 (d, 6H), 2.6–2.9 (m, 1H), 4.4 (d, 2H), 6.5–6.8 (t, 1H), 6.8–7.0 (bs, 1H), 7.65–7.8 (d, 1H), 8.0–8.4 (bs, 3H).

2-Amino-3-nitro-*N*-(2-oxopentyl)benzamide (6b). The desired product was prepared by following the procedure used for **6a** after substituting 1-amino-2-pentanone monohydrochloride[11] in place of 1-amino-3-methylbutanone monohydrochloride. Also the Et_3N solution was added to a 0 °C suspension of **3a** and amino ketone rather than a room temperature solution. Treatment of the semipure material also varied in that after the aqueous extractions the residue was warmed in refluxing EtOAc rather than refluxing EtOH to return a 89% yield of **6b** which was used without further purification.

***N*-(2-Amino-3-nitrobenzoyl)benzeneacetamide (6c).** The desired product was prepared by following the procedure used for **6a** after substituting 2-amino-1-phenylethanone in place of 1-amino-3-methylbutanone monohydrochloride. Also the Et_3N solution was added to a 0 °C suspension of **3a** and ketoamine rather than a room temperature solution. Also when the reaction mixture was partitioned between CH_2Cl_2 and H_2O, some solid precipitated which was filtered to give 4.2 g of solid. Upon completion of the extractions, an ad-

ditional 14.9 g of yellow solid was isolated. These two solid samples were combined and recrystallized from 1,2-dichloroethane to give 8.3 g (48%) of **6c** which was used without further purification.

2-Amino-3-nitro-*N*-(2-oxopropyl)benzamide (6d). The preparation of ketone **6d** varied from the standard procedure for **6a** in that a peptide-coupling procedure was utilized starting from **2a** rather than coupling with the acid chloride **3a**. This variation was not out of necessity but rather as an experimental comparison. Under Ar at room temperature DCC (11.32 g, 0.055 mol) in THF (50 mL) was added to **2a** (10 g, 0.055 mol) and HOBT (7.42 g, 0.055 mol) in THF (200 mL) followed by a solution of NMM (9.07 mL, 0.083 mol) in THF (50 mL). To the resulting solid mass was added a solution of 1-amino-2-propanone monohydrochloride (6.00 g, 0.055 mol) in DMF (300 mL) which led to a more fluid reaction mixture. Two additional portions of 1-amino-2-propanone monohydrochloride (1.5 g, 0.014 mol) and NMM (1.52 mL, 0.014 mol) were added in 24-h intervals. Then after stirring for an additional 24 h the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The concentrated residue was dissolved in CH_2Cl_2 and washed sequentially with H_2O twice, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 12 g of yellow solid. This material was recrystallized from EtOH to yield 8.34 g (64%) of **6d** which was used without further purification.

9-Amino-3,4-dihydro-2-(1-methylethyl)-5*H*-1,4-benzodiazepin-5-one (7a). At room temperature a mixture of **6a** (5.9 g, 0.022 mol) and 10% Pd/C (1.6 g) in EtOH (150 mL) was placed under a H_2 atmosphere at 50 psi for 26 h. Then an additional portion of 10% Pd/C (0.77 g) was added, and the reaction was continued. After an additional 24 h at room temperature, the reaction mixture was filtered through Dicalite and the filtered solid rinsed well with EtOH and CH_2Cl_2. The filtrate was concentrated under reduced pressure to give 4.64 g (97%) of yellow solid **7a** which was used without further purification (TLC: 5% EtOH:CH_2Cl_2, $R_f = 0.5$).

9-Amino-3,4-dihydro-2-propyl-5*H*-1,4-benzodiazepin-5-one (7b). At room temperature a mixture of **6b** (12 g, 0.045 mol) and 10% Pd/C (3.4 g) in EtOH (400 mL) was placed under a H_2 atmosphere at 50 psi for 24 h. The reaction mixture was then filtered through Dicalite and the filtered solid rinsed well with CH_2Cl_2 (300 mL). The filtrate was concentrated under reduced pressure to give 9 g (92%) of orange solid **7b** which was used without further purification.

9-Amino-3,4-dihydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (7c). At room temperature a mixture of **6c** (3.9 g, 0.013 mol) and 10% Pd/C (1.84 g) in EtOH (150 mL) was placed under a H_2 atmosphere at 50 psi for 15 h. Then an additional portion of 10% Pd/C (0.34 g) was added, and the reaction was continued. After another 24 h the mixture was filtered through Dicalite and the filtered solid rinsed well with CH_2Cl_2. This filtrate was combined with a filtrate from another run which had started with 4.6 g of **6c**. The combined filtrates were concentrated under reduced pressure to give 6.6 g (92%) of dark foam **7c** which was used without further purification.

9-Amino-3,4-dihydro-2-methyl-5*H*-1,4benzodiazepin-5-one (7d). At room temperature a mixture of **6d** (7.2 g, 0.030 mol) and 10% Pd/C (1.00 g) in EtOH was placed under a H_2 atmosphere at 50 psi for 7 h. Then an additional portion of 10% Pd/C (0.2 g) was added, and the reaction was continued. After another 24 h a third portion of 10% Pd/C was added, and the reaction was continued. After an additional 24 h at room temperature, the reaction mixture was heated to 40 °C for 24 h. The mixture was then filtered through Dicalite and the filtered solid rinsed well with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give 5.5 g (96%) of yellow gummy solid **7d** which was used without further purification.

4,5,6,7-Tetrahydro-4-(1-methylethyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1x). Under Ar powdered LAH (5.0 g, 0.13 mol) was added at room temperature to a suspension of **7a** (4.75 g, 0.022 mol) in dioxane (150 mL) and then heated to reflux for 6 days. After cooling to 0 °C, the reaction was quenched sequentially with H_2O (5 mL in 25 mL of THF), 3 N NaOH (5 mL), and H_2O (15 mL) after which the mixture was stirred at 0 °C for an additional 2 h. The mixture was then treated with $MgSO_4$, and filtered, and the resulting salts were rinsed with warm CH_2Cl_2 (200 mL). The filtrate was concentrated under reduced pressure to give 4.7 g of dark oil. This material was immediately combined with NMM (7.6 mL, 0.069 mol) in CH_2Cl_2 (50 mL) and added dropwise over 30 min to a 0 °C solution of trichloromethyl chloroformate (2.75 mL, 0.023 mol) in CH_2Cl_2 (100 mL) under Ar. After stirring for an additional 2.5 h the mixture was concentrated under reduced pressure. A solution of 85:15 dioxane:H_2O (100 mL) was added to the concentrated residue and the mixture warmed on a steam bath for 5 h. This mixture was washed twice with CH_2Cl_2, basified with concentrated NH_4OH, and then reextracted three times more with CH_2Cl_2. The latter three CH_2Cl_2 extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 3.2 g (63%) of crude **1x** as a foam which was further purified as described in Table 2. **1x**: ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 3H), 1.05 (d, 3H), 1.8–2.0 (bs, 1H), 2.3–2.45 (m, 1H), 3.0–3.1 (d, 1H), 3.6–3.7 (d, 1H), 4.05–4.15 (d, 1H), 4.2–4.25 (d, 1H), 4.25–4.35 (d, 1H), 6.7–6.8 (bs, 1H), 6.9–7.0 (bs, 2H), 10.0 (bs, 1H).

4,5,6,7-Tetrahydro-4-propylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1aa). The desired product was prepared by following the procedure used for **1x** except the LAH mixture was heated for 40 h instead of 6 days. Also the hydrolysis reaction concentrations were inverted from 85:15 dioxane:H_2O to 85:15 H_2O:dioxane.

4,5,6,7-Tetrahydro-4-phenylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1ad). The desired product was prepared by following the procedure used for **1x** except the LAH mixture was heated for 3 days instead of 6 days. Also the hydrolysis reaction concentrations were inverted from 85:15 dioxane:H_2O to 85:15 H_2O:dioxane.

4,5,6,7-Tetrahydro-4-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1t). The desired product was prepared by following the procedure used for **1x** except that **7d** (5.5 g, 0.029 mol) was added as a warm suspension in dioxane (200 mL) to a room temperature suspension of LAH (6 g, 0.16 mol) in dioxane (200 mL). This variation was not necessarily out of necessity but rather because of exploratory experimentation. Also, the LAH mixture was heated for 2 days instead of 6 days. In addition, the hydrolysis reaction concentrations were inverted from 85:15 dioxane:H_2O to 85:15 H_2O:dioxane.

Typical Procedure Sequences for Method D. 2,5-Dichloro-3-nitrobenzoyl Chloride (8a). Under Ar, 2,5-dichloro-3-nitrobenzoic acid (5.0 g, 0.021 mol) was added to thionyl chloride (10 mL, 0.13 mol) and the mixture was immediately warmed to reflux. After 24 h the excess thionyl chloride was removed under reduced pressure to give 4.74 g (89%) of residue solid **8a** which was used without further purification.

(*R*)-N^1-(Cyclopropylmethyl)-1,2-propanediamine (9a). Under Ar, DCC (26.9 g, 0.13 mol) was added neat to a 0 °C mixture of *N*-(*tert*-butoxycarbonyl)-D-alanine (25 g, 0.13 mol), (aminomethyl)cyclopropane (11.3 mL, 0.13 mol), and HOBT (35.1 g, 0.26 mol) in THF (300 mL). The reaction mixture was gradually warmed to room temperature and stirred for 16 h. The reaction mixture was then filtered and the solid rinsed with a small amount of THF. The filtrate was then dissolved in CH_3CN and cooled to 0 °C for 14 h. The resulting solid was filtered and the organic phase extracted with saturated aqueous $NaHCO_3$ and then brine. The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield 25.5 g (81%) of residue solid. This material was then added neat to 0 °C trifluoroacetic acid (TFA) (105 mL), and after 3 h at 0 °C, the excess TFA was removed under reduced pressure. The residual oil was dissolved into saturated aqueous $NaHCO_3$ which was then continuously extracted with CH_2Cl_2 for 16 h. The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 14.9 g (100%) of tan oil. This oil was dissolved in THF (100 mL) and slowly added to a room temperature suspension of LAH (11.4 g, 0.30 mol) in THF (100 mL). The reaction mixture was then warmed to reflux. After 16 h the reaction mixture was cooled to 0 °C and the reaction quenched

sequentially with H_2O (11.4 mL), 3 N NaOH (34.2 mL), and H_2O (11.4 mL). The resulting solid was filtered and rinsed with THF (25 mL). The combined filtrates were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 11.8 g (92%) of **9a** which was used without further purification.

(*S*)-*N*^{1}-(2-Methyl-2-propenyl)-1,2-propanediamine (9b). The desired product was prepared by following the procedure used for **9a** except *N*-(*tert*-butoxycarbonyl)-L-alanine was used in place of *N*-(*tert*-butoxycarbonyl)-D-alanine, (aminomethyl)-cyclopropane was replaced with 2-methylallylamine hydrochloride, and NMM was used as a base scavenger. Another variation from the procedure for **9a** was the workup for the intermediate BOC-Ala-NH-$CH_2C(CH_3)$=CH_2. This reaction mixture was filtered, concentrated, and dissolved in CH_2Cl_2 prior to the aqueous extractions to give an 85% yield of BOC-Ala-NH-$CH_2C(CH_3)$=CH_2. The TFA BOC removal yielded 49% of H_2N-Ala-NH-$CH_2C(CH_3)$=CH_2. The LAH reduction of this material yielded 49% of **9b** as a clear oil.

(−)-(*R*)-7-Chloro-4-(cyclopropylmethyl)-1,2,3,4-tetrahydro-2-methyl-9-nitro-5*H*-1,4-benzodiazepin-5-one (10a). Under Ar, **8a** (5.0 g, 0.020 mol) was added to a room temperature suspension of Na_2CO_3 (7.0 g, 0.066 mol) in *n*-BuOH (30 mL) and then warmed to reflux for 3 h. **9a** (2.6 g, 0.020 mol) was then added neat to the reaction mixture, and reflux was maintained for an additional 1 h. The mixture was then cooled to room temperature and filtered. The resulting solid was rinsed with a small amount of EtOH. The combined filtrates were concentrated under reduced pressure. The residual oil was flash chromatographed on a silica gel column eluting with 1% MeOH/CH_2Cl_2. The desired fractions were combined, concentrated, and crystallized from CH_3CN to give 2.93 g (47%) of **10a** as an orange solid, mp 78−80 °C. **10a**: ^{1}H NMR ($CDCl_3$) δ 0.3−0.4 (m, 2H), 0.5−0.65 (m, 2H), 1.0−1.5 (m, 1H), 1.35 (d, 3H), 3.15−3.25 (dd, 1H), 3.4−3.6 (m, 2H), 3.7−3.85 (dd, 1H), 4.0−4.15 (m, 1H), 8.1 (s, 1H), 8.3 (s, 1H), 8.3−8.4 (bs, 1H). Anal. ($C_{14}H_{16}ClN_3O_3$) C, H, N.

(+)-(*S*)-7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-(2-methyl-2-propenyl)-9-nitro-5*H*-1,4-benzodiazepin-5-one (10b). The desired product was prepared by following the procedure used for **10a**, except **10b** did not require recrystallization after purification by column chromatography, and isolated as an orange solid, mp 64−67 °C. Anal. ($C_{14}H_{16}ClN_3O_3$) C, H, N.

(−)-(*R*)-9-Chloro-6-(cyclopropylmethyl)-4,5,6,7-tetrahydro-4-methylimidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1w). Under Ar, **10a** (2.73 g, 8.83 mmol) in a small amount of 1,2-dimethoxyethane was added to a room temperature suspension of LAH (2.0 g, 52.70 mmol) in 1,2-dimethoxyethane (80 mL) and then warmed to reflux. After 14 h the mixture was cooled to 0 °C and the reaction quenched sequentially with H_2O (2.0 mL), 3 N NaOH (6 mL), and H_2O (2 mL). The resulting salts were filtered and rinsed with CH_2Cl_2. The combined filtrates were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The concentrated residue was dissolved in THF (50 mL), combined with 1,1′-thiocarbonyldiimidazole (1.73 g, 9.71 mmol) at room temperature, and then warmed to reflux for 1 h. The mixture was then added to EtOAc (10 mL) and washed thrice with H_2O (25 mL each). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified as described in Table 2. **1w**: ^{1}H NMR ($CDCl_3$) δ 0.2 (m, 2H), 0.6 (m, 2H), 0.9−1.0 (m, 1H), 1.5−1.6 (d, 3H), 2.45−2.55 (dd, 1H), 2.65−2.75 (dd, 1H), 2.9−3.0 (d, 1H), 3.3−3.4 (d, 1H), 3.8−3.9 (d, 1H), 4.2−4.3 (d, 1H), 5.0−5.1 (m, 1H), 6.9 (s, 1H), 7.1 (s, 1H), 10.0 (bs, 1H).

(+)-(*S*)-9-Chloro-4,5,6,7-tetrahydro-4-methyl-6-(2-methyl-2-propenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1v). The desired product was prepared by following the procedure used for **1w**, except the 1,1′-thiocarbonyldiimidazole thiourea ring-forming reaction for **1v** was heated for 3 h rather than 1 h.

Typical Procedure Sequences for Method E. 5,10-Dihydro-4-nitro-11*H*-dibenzo[*bc*][1,4]diazepin-11-one (11a). Under N_2, **8b**[2] (2.61 g, 0.010 mol), 1,2-phenylenediamine (1.08 g, 0.010 mol), and Na_2CO_3 (1.06 g, 0.010 mol) in *n*-BuOH (10 mL) were warmed to reflux. After 2 days the reaction mixture was cooled to 0 °C for about 0.5 h and then filtered after which the solid was rinsed with a small amount of *n*-BuOH and then MeOH. The filtered solid was then triturated in H_2O (30 mL), refiltered, and rinsed with an additional portion of H_2O (30 mL) and then Et_2O. After air-drying, there remained 1.94 g (76%) of copper-colored solid **11a**, mp 303−306 °C, which was used without further purification (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.4).

***cis*-1,2,3,4-Tetrahydro-2,3-dimethyl-9-nitro-5*H*-1,4-benzodiazepin-5-one (11b).** The desired product was prepared in a similar manner as **11a** after substituting meso-2,3-diaminobutane dihydrochloride in place of 1,2-phenylenediamine and **8c**[2] in place of **8b**. Also 3 mol excess of Na_2CO_3 was used, instead of 1 mol equiv as for **11a**, and the reaction mixture was heated for 1 day rather than 2 days. The reaction mixture was worked up by filtering off the resulting solid and concentrating the filtrate under reduced pressure. The concentrated residue was taken up in CH_2Cl_2, filtered, and reconcentrated under reduced pressure, and triturated with Et_2O to yield 58% of **11b** which was used without further purification.

***trans*-1,2,3,4-Tetrahydro-2,3-dimethyl-9-nitro-5*H*-1,4-benzodiazepin-5-one (11c).** The desired product was prepared in a similar manner as **11a** after substituting D,L-2,3-diaminobutane dihydrochloride in place of 1,2-phenylenediamine and **8c** in place of **8b**. Also 3 mol excess of Na_2CO_3 was used, instead of 1 mol equiv as for **11a**, and the reaction mixture was heated for 1 day rather than 2 days. The reaction mixture was worked up by concentrating the reaction mixture under reduced pressure and partitioning the residue between water and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an orange solid. This material was recrystallized from EtOAc to yield 43% of **11c** as an orange solid, mp 166−167 °C. Anal. ($C_{11}H_{13}N_3O_3$) C, H, N.

4-Amino-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (12a). Under N_2, NH_2NH_2·H_2O (0.45 mL, 9.2 mmol) was added over 15 min to a refluxing suspension of **11a** (0.38 g, 1.5 mmol) and RaNi (0.22 g) in MeOH (20 mL). The reaction mixture was refluxed for an additional 1 h and 40 min, cooled, and then filtered through Dicalite. The filtrate was concentrated under reduced pressure and triturated in Et_2O (5 mL) to give 0.27 g (80%) of **12a** as a pea green solid, mp 218−219 °C (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.35). **12a**: ^{1}H NMR (DMSO-d_6) δ 5.2 (s, 2H), 6.6−6.8 (m, 3H), 6.85−7.0 (m, 4H), 7.1 (d, 1H), 9.8 (s, 1H).

1,2-Dihydro-2-thioxobenzimidazo[7,1-*cd*][1,5]benzodiazepin-9(8*H*)-one (1ax). Under N_2, a mixture of **12a** (0.45 g, 2.0 mmol) and 1,1′-thiocarbonyldiimidazole (0.36 g, 2.0 mmol) in THF (20 mL) was warmed to reflux for 3 h. After cooling, the resulting solid was filtered off, rinsed with a small amount of THF, and then triturated in MeOH (10 mL) to give **1ax** as a yellow green solid. **1ax**: ^{1}H NMR (DMSO-d_6) δ 7.15−7.25 (m, 1H), 7.3−7.45 (m, 4H), 7.7−7.8 (m, 1H), 8.7−8.8 (d, 1H), 9.6 (s, 1H), 13.5−13.6 (bs, 1H).

10,11-Dihydro-4-nitro-5*H*-dibenzo[*bc*][1,4]diazepine (13a). Under Ar, BH_3·THF in THF (22 mL, 0.022 mol) was added over 5 min to a 0 °C semisuspension of **11a** (2.81 g, 0.011 mol) in THF (66 mL). After 2.5 h the reaction mixture was warmed to room temperature and stirred for an additional 18 h. The reaction mixture was then recooled to 0 °C and the reaction slowly quenched with 3 N HCl (22 mL) over 5 min. The resulting acidic mixture was then warmed to reflux on a steam bath for 1 h. The mixture was then again cooled to 0 °C, basified with 3 N NaOH, and extracted with CH_2Cl_2. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 2.42 g of crude product. This material was flash chromatographed on a silica gel column eluting with 30:1 CH_2Cl_2:MeOH. The desired fractions were combined and concentrated to give 1.04 g (40%) of **13a** as a dark, deep purple solid, mp 135−138 °C (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.8). **13a**: ^{1}H NMR ($CDCl_3$) δ 4.25 (s, 1H), 4.35 (s, 2H), 6.6−6.8 (m, 2H), 6.8−6.95 (m, 2H), 7.0 (d, 1H), 7.15 (d, 1H), 8.2 (d, 1H). Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

2,3-*trans*-2,3,4,5-Tetrahydro-2,3-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (13c). The desired product was prepared in a similar manner as **13a** after substituting **11c** in place of **11a**. Also 3.5 mol excess of BH_3·THF was used, instead of 2 mol equiv as for **13a**, and the reaction mixture was heated

at reflux for 4 days. The reaction mixture was worked up by quenching the reaction with water followed by 3 N NaOH. The resulting mixture was warmed to reflux for 3 h. The organic layer was then separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow oil. This material was flash chromatographed on a silica gel column eluting with 7% MeOH/CH_2Cl_2 containing 0.1% of NH_4OH. The desired fractions were combined and concentrated under reduced pressure to yield 5% of **13c** as an orange glass which was used without further purification.

7-(Cyclopropylmethyl)-6,7-dihydro-benz[*b*]imidazo-[4,5,1-*jk*][1,4]benzodiazepine-1(2*H*)-thione (1ay). Under Ar, cyclopropanecarbonyl chloride (0.18 mL, 2 mmol) in CH_2Cl_2 (2 mL) was added over 2 min to a 0 °C solution of **13a** (0.48 g, 2 mmol) in CH_2Cl_2 (15 mL). After 2 h, the reaction mixture was warmed to room temperature and stirred for an additional 16 h. The reaction mixture was then extracted with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 0.62 g (100%) of orange solid, mp 158–160 °C (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.85$). A sample of this material (0.56 g, 1.8 mmol) was added neat over 2 min to a 0 °C suspension of LAH (0.41 g, 10.8 mmol) in 1,2-dimethoxyethane (15 mL). After stirring for 25 min at room temperature, the mixture was warmed to room temperature for 0.5 h and then warmed to reflux. After 3 h the mixture was cooled to 0 °C and the reaction quenched sequentially with H_2O (0.41 mL), 3 N NaOH (0.41 mL), and H_2O (1.2 mL). After 15 min the reaction mixture was filtered and rinsed with a small amount of THF. The salts were digested in refluxing THF (20 mL) for 5 min and then refiltered. The combined filtrates were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a purplish oil. This material was combined with 1,1'-thiocarbonyldiimidazole (0.32 g, 1.8 mmol) in THF (10 mL) at room temperature and immediately brought to reflux. After 2 h the mixture was concentrated under reduced pressure and the residue partitioned between EtOAc and H_2O. The organic phase was dried over $MgSO_4$, filtered, and then adsorbed on silica gel. This material was flash chromatographed and further purified as described in Table 2 (TLC: 25% EtOAc:hexane, $R_f = 0.4$). **1ay**: ^1H NMR ($CDCl_3$) δ 0.05–0.15 (bd, 2H), 0.4–0.5 (bd, 2H), 0.8–0.9 (m, 1H), 2.7–2.95 (bs, 1H), 2.95–3.2 (bs, 1H), 4.2–4.5 (bd, 2H), 6.9–7.0 (d, 1H), 7.1–7.35 (m, 5H), 8.6–8.7 (d, 1H), 10.1–10.2 (bs, 1H).

4,5-*trans*-4,5,6,7-Tetrahydro-4,5-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1av). A mixture of **13c** (0.34 g, 1.54 mmol), 1-bromo-3-methyl-2-butene (0.23 g, 1.54 mmol), Na_2CO_3 (0.33 g, 3.08 mmol), and KI (0.26 g, 1.54 mmol) in DMF (10 mL) was stirred for 16 h at room temperature and then partitioned between EtOAc and H_2O. The organic phase was then washed with H_2O and brine, dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 0.34 g of orange oil. This material was flash chromatographed on a silica gel column eluting with 7% MeOH/CH_2Cl_2 containing 0.1% of NH_4OH. The desired fractions were combined and concentrated under reduced pressure to yield 0.18 g (40%) of an orange oil which crystallized upon standing. This material was dissolved in THF (10 mL), cooled to 0 °C, and treated with LAH (0.095 g, 2.49 mmol). The reaction mixture was then warmed gradually to reflux. After refluxing for 45 min the reaction mixture was cooled and the reaction quenched sequentially with H_2O (100 μL), 3 N NaOH (300 μL), and then H_2O (100 μL). After stirring for 30 min the mixture was filtered. The filtrate was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 0.17 g (theoretical weight, TW, 0.16 g) of orange oil. This material was combined with 1,1'-thiocarbonyldiimidazole (0.144 g, 0.810 mmol) in THF (5 mL) and warmed to reflux for 1 h. The reaction mixture was then partitioned between EtOAc and H_2O. The organic phase was then washed twice with H_2O and once with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 0.21 g of dark brown oil. This material was purified as described in Table 2. **1av**: ^1H NMR ($CDCl_3$) δ 1.05–1.15 (d, 3H), 1.4–1.5 (d, 3H), 1.7 (s, 3H), 1.8 (s, 3H), 3.1–3.3 (m, 3H), 4.1 (s, 2H), 4.9–5.0 (m, 1H), 5.3–5.4 (t, 1H), 6.8–6.9 (t, 1H), 7.0–7.15 (m, 2H), 9.8–9.9 (bs, 1H).

2,3-*cis*-2,3,4,5-Tetrahydro-2,3-dimethyl-1*H*-1,4-benzodiazepin-9-amine (14b). Under Ar a solution of **11b** (2.10 g, 8.93 mmol) in 1,4-dioxane (35 mL) was added to a 0 °C suspension of LAH (2.0 g, 53.6 mmol) in 1,4-dioxane (50 mL). The reaction mixture was then warmed to reflux. After 16 h heating was discontinued, and at room temperature the reaction was quenched sequentially with H_2O (2 mL), 3 N NaOH (6 mL), and H_2O (2 mL). The reaction mixture was then filtered and the filtrate concentrated under reduced pressure to yield 1.67 g (98%) of **14b** as a brown oil which was used without further purification. **14b** (crude): ^1H NMR ($CDCl_3$) δ 1.0–1.1 (d, 3H), 1.1–1.2 (d, 3H), 3.1–3.2 (m, 1H), 3.2–3.4 (bs, 2H), 3.6–3.7 (m, 1H), 3.8–3.9 (d, 1H), 4.1–4.2 (d, 1H), 6.5–6.6 (m, 1H), 6.6–6.7 (m, 2H).

2,3-*trans*-2,3,4,5-Tetrahydro-2,3-dimethyl-1*H*-1,4-benzodiazepin-9-amine (14c). The desired product was generated in the same reaction as for the preparation of **13c**. Intermediate **14c** was purified by flash chromatography as described in the experimental for **13c**. The desired fractions were combined and concentrated under reduced pressure to yield 8% of **14c** which was used without further purification.

4,5-*trans*-6-(Cyclopropylmethyl)-4,5,6,7-tetrahydro-4,5-dimethylimidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1au). Under Ar, **14c** (0.51 g, 2.67 mmol) and 1,1'-thiocarbonyldiimidazole (0.52 g, 2.94 mmol) in THF (20 mL) was warmed to reflux for 4 h. The reaction mixture was then partitioned between EtOAc and H_2O. The organic phase was then washed twice with H_2O and once with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 0.38 g (61%) of orange solid. A 0.216-g sample (0.921 mmol) of this material was combined with cyclopropanecarboxaldehyde (76 μL, 1.02 mmol), sodium cyanoborohydride (0.116 g, 1.85 mmol), and AcOH (53 μL, 0.921 mmol) in MeOH (10 mL) and THF (5 mL) and stirred for 2 days. The mixture was then neutralized with 3 N NaOH and filtered and the filtrate concentrated under reduced pressure. The concentrated residue was partitioned between 1 N NaOH and CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a brown oil. This material was purified as described in Table 2. **1au**: ^1H NMR ($CDCl_3$) δ 0.15–0.25 (d, 2H), 0.5–0.7 (m, 2H), 0.9–1.0 (m, 1H), 1.1–1.2 (d, 3H), 1.5–1.6 (d, 3H), 2.5–2.7 (m, 2H), 3.4–3.5 (m, 1H), 4.1–4.2 (dd, 2H), 4.9–5.0 (m, 1H), 6.9–7.0 (d, 1H), 7.0–7.2 (m, 2H), 9.8–9.9 (bs, 1H).

Procedure Sequence for Method F. *cis*-4,5,6,7-Tetrahydro-4,5-dimethylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1cd). **1cd** was prepared by reacting **14b** with trichloromethyl chloroformate in a similar manner as outlined for the preparation of **5**. The crude **1cd** was purified by flash chromatography on a silica gel column eluting with 7% MeOH/CH_2Cl_2 containing 0.1% of NH_4OH. The desired fractions were combined and concentrated under reduced pressure to yield 44% of **1cd** as a tan solid which was used without further purification.

4,5-*cis*-4,5,6,7-Tetrahydro-4,5-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1as). Alkylation of **1cd** following method A-3 yielded desired **1as** which was purified as described in Table 2.

4,5-*cis*-2-Chloro-4,5,6,7-tetrahydro-4,5-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine (15b). Under Ar, trifluoromethanesulfonic anhydride (0.36 mL, 2.14 mmol) was added neat to a −78 °C solution of **1as** (0.41 g, 1.43 mmol) in CH_2Cl_2 (25 mL). Upon completion of addition the reaction mixture was stirred for 10 min and then treated with 2,6-dimethylpyridine (0.33 mL, 2.86 mmol). After stirring for an additional 15 min at −78 °C, the reaction mixture was treated with HCl in Et_2O (0.26 g, 7.14 mmol in 9 mL) and then stirred for 15 min more. The reaction mixture was then poured into a saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and washed twice with CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure to give a brown oil. This material was purified by flash chromatography on a silica gel column eluting with 5% MeOH/CH_2Cl_2 containing 0.1% of NH_4OH. The desired fractions were combined and concentrated under reduced pressure to yield 0.22 g (51%) of **15b** which was used without further purification.

4,5-*cis*-4,5,6,7-Tetrahydro-4,5-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1at). Compound **15b** was treated with thiourea in EtOH following the reaction conditions employed in method A-5. Desired product **1at** was purified as described in Table 2. **1at**: ^{1}H NMR ($CDCl_3$) δ 1.3–1.4 (d, 3H), 1.5–1.6 (d, 3H), 1.65 (s, 3H), 1.7 (s, 3H), 3.1–3.4 (m, 3H), 3.8–3.9 (d, 1H), 4.4–4.5 (d, 1H), 5.0–5.1 (q, 1H), 5.2–5.3 (t, 1H), 6.8–6.9 (d, 1H), 7.0–7.2 (d, 2H), 9.4–9.5 (bs, 1H).

Typical Procedure Sequences for Method G. 1-(2-Bromo-3-nitrophenyl)ethanone (16a). The desired product was prepared following a literature procedure for the closely related 2-chloro-3-nitroacetophenone.[12] **16a** was isolated in 71% crude yield and used without further purification (TLC: 1:1 EtOAc:hexane, $R_f = 0.7$). **16a** (crude): ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.7 (s, 3H), 7.3–7.8 (m, 3H).

1-(2,5-Dichloro-3-nitrophenyl)ethanone (16c). This intermediate was prepared following the literature procedure cited for **16a** after substituting **8a** in place of **8c**. The crude reaction mixture was purified by HPLC on a silica gel column eluting with EtOAc/hexane. The desired fractions were combined and concentrated under reduced pressure to yield 40% of **16c** which was used without further purification.

1-(2,5-Dichloro-3-nitrophenyl)-3-methyl-1-butanone (16d). Under Ar, a solution of freshly prepared isopropylmagnesium bromide[13] in THF (164 mL containing 0.135 mol of reagent) was added slowly to a maintained 10 °C solution of monoethyl ester of isopropylmalonic acid (11.4 g, 65 mmol)[14] in THF (30 mL). Upon completion of addition the reaction mixture was cooled to 0 °C and treated over 30 min with a solution of **8a** (9.3 g, 36.5 mmol) in THF (20 mL). After stirring at 0 °C for 50 min, the reaction mixture was warmed to 30 °C and stirred for an additional 2 h. The mixture was then maintained at 0 °C overnight, treated with water (1.5 mL), and stirred for an additional 40 min. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between Et_2O and saturated aqueous NH_4Cl. The ether layer was then washed sequentially with H_2O, saturated aqueous $NaHCO_3$, and H_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 10.2 g of a viscous oil. This oil was combined with a solution of H_2SO_4 (1.8 mL, 32 mmol) and AcOH (34 mL) in H_2O (14.3 mL) and warmed to reflux for 12 h. Then an additional portion of AcOH (5 mL) was added, and heating was continued for an additional 4 h. The mixture was then concentrated under reduced pressure, treated with H_2O, and neutralized with $NaHCO_3$. The resulting aqueous solution was extracted with CH_2Cl_2. The organic phase was then washed sequentially with H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 7.6 g (75%) of **16d** as a dark viscous oil which was used without further purification.

1-(2,6-Dichloro-3-nitrophenyl)ethanone (16f). Under Ar, 2,6-dichloroacetophenone (99.0 g, 0.524 mol) was added to a −40 °C solution of concentrated HNO_3 (500 mL) in concentrated H_2SO_4 (500 mL). Upon completion of addition the reaction mixture was warmed to −4 °C and stirred for 1 h. The reaction mixture was poured onto ice and then extracted three times with CH_2Cl_2. The organic phases were combined, extracted with saturated aqueous $NaHCO_3$, dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 123.97 g (TW, 122.64 g) of **16f** which was used without further purification.

2,3,4,5-Tetrahydro-5-methyl-9-nitro-1*H*-1,4-benzodiazepine (17a). Under Ar, ethylenediamine (0.67 mL, 10 mmol) was added neat to a room temperature mixture of **16a** (1.99 g, 10 mmol) and $NaHCO_3$ (0.84 g, 10 mmol) in MeOH (50 mL). The mixture was immediately brought to reflux where it was maintained for 23 h. The reaction mixture was recooled to room temperature, and $NaBH_3CN$ (1.26 g, 20 mmol) was added neat. After stirring for 7 h the mixture was acidified to pH 7 with methanolic HCl. After stirring for an additional 15 h at room temperature, the reaction mixture was acidified further to pH < 2 with 3 N HCl, stirred for 0.5 h, and then concentrated under reduced pressure. The residue was then partitioned between 3 N NaOH and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 1.85 g (89%) of **17a** as a yellow oil which was used without further purification (TLC: 10:1 CH_2Cl_2:MeOH, $R_f = 0.25$). **17a**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.5 (d, 3H), 3.0–3.5 (m, 4H), 4.0–4.4 (m, 1H), 6.5–6.8 (t, 1H), 7.2–7.4 (d, 1H), 7.7–7.9 (bs, 1H), 7.9–8.1 (d, 1H).

2,3,4,5-Tetrahydro-9-nitro-5-phenyl-1*H*-1,4-benzodiazepine (17b). Under Ar, a mixture of ethylenediamine (3.3 mL, 49 mmol), **16b**[15] (15 g, 49 mmol), and $NaHCO_3$ (4.2 g, 49 mmol) in EtOH (200 mL) was warmed and then maintained at reflux for 24 h. The mixture was then concentrated under reduced pressure and the residue partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 15.11 g (TW, 13.10 g) of an orange solid. A 12.0-g sample of this material was redissolved in EtOH (500 mL), cooled to 0 °C, and treated portionwise slowly with $NaBH_4$ (5.0 g, 0.132 mol). Upon completion of addition the mixture was gradually warmed to room temperature and then stirred for an additional 3 h. The mixture was then concentrated under reduced pressure and partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 9.6 g (92%) of **17b** as a red oil which was used without further purification.

7-Chloro-2,3,4,5-tetrahydro-5-methyl-9-nitro-1*H*-1,4-benzodiazepine (17c). **17c** was prepared in a similar manner as **17a** after substituting **16c** in place of **16a**. **17c** was isolated in 96% yield from the reaction mixture and used without further purification.

7-Chloro-2,3,4,5-tetrahydro-5-(2-methylpropyl)-9-nitro-1*H*-1,4-benzodiazepine (17d). The imine for **17d** was prepared in a similar manner as **17a** after substituting **16d** in place of **16a** and *n*-BuOH in place of MeOH as the solvent. After heating the required 18 h to form the imine, the *n*-BuOH was removed under reduced pressure. The residue was diluted with MeOH and then treated with $NaBH_3CN$ in a similar manner as for **17a** to yield **17d** in 88% crude yield as a red solid which was used without further purification.

6-Chloro-2,3,4,5-tetrahydro-9-nitro-1*H*-1,4-benzodiazepine (17e). Under Ar **16e**[16] (5.0 g, 22.7 mmol) and ethylenediamine (1.52 g, 22.7 mmol) were combined in MeOH at room temperature. After 20 min $NaBH_3CN$ (1.72 g, 27.3 mmol) was added to the stirring mixture. After 16 h the reaction mixture was treated with 3 N HCl (20 mL), stirred for 1 h, and then treated with 3 N NaOH (40 mL). The resulting solution was extracted with CH_2Cl_2 after which the organic phase was dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 4.95 g of acyclic intermediate. This material was combined with Na_2CO_3 (2.09 g, 19.7 mmol) in *n*-BuOH (100 mL) and warmed to reflux. After 12 h the mixture was concentrated under reduced pressure. This material was purified by flash chromatography on a silica gel column eluting with 2% MeOH/CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to yield 0.80 g (16%) of **17e** which was used without further purification.

6-Chloro-2,3,4,5-tetrahydro-5-methyl-9-nitro-1*H*-1,4-benzodiazepine (17f). The imine for **17f** was prepared in a similar manner as **17d** after substituting **16f** in place of **16d**. After heating the required 6 h to form the imine, the *n*-BuOH was removed under reduced pressure. The residue was partitioned between H_2O and CH_2Cl_2; the organic phase was dried over K_2CO_3, filtered, and concentrated. This residue was dissolved in MeOH and treated with $NaBH_3CN$ in a similar manner as for **17a** to yield crude **17f**. This material was purified by flash chromatography on a silica gel column eluting with 2% and 5% MeOH/CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to yield 14.17 g (70%) of **17f** which was used without further purification.

2,3-Dihydro-3,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (18a). Under Ar, 1,2-diaminopropane (9.0 g, 0.121 mol) was added neat to a warm homogeneous solution of **16a** (29.6 g, 0.121 mol) and Na_2CO_3 (12.9 g, 0.121 mol) in *n*-BuOH (600 mL). The reaction mixture was then warmed to reflux for 4 h and concentrated under reduced pressure. The residue was partitioned between H_2O and CH_2Cl_2; the organic phase was dried over K_2CO_3, filtered, and concentrated to give 27.3 g. On the basis of ^{1}H NMR, there appeared to be a ratio isomer

of 6:4 **18a:19a**. This crude mixture of isomers was purified by preparative HPLC on a silica gel column eluting with 20% acetone:hexane. Isomer **18a** eluted in the front running fractions which were combined and concentrated under reduced pressure to yield 11.41 g (43%) of **18a** which was used without further purification (TLC: 1:1 acetone:hexane, R_f = 0.5). **18a**: ^{1}H NMR ($CDCl_3$) δ 1.4–1.5 (d, 3H), 2.4 (s, 3H), 3.55–3.65 (dd, 1H), 3.65–3.75 (dd, 1H), 3.85–3.95 (m, 1H), 6.65–6.75 (t, 1H), 7.5–7.6 (d, 1H), 8.2–8.3 (d, 1H), 8.5–8.6 (bs, 1H). Further elution with 30% acetone:hexane yielded isomer **19a** in the latter running fractions. These fractions were combined and concentrated under reduced pressure to yield 6.0 g (23%) of **19a** which was used without further purification (TLC: 1:1 acetone:hexane, R_f = 0.35). **19a**: ^{1}H NMR ($CDCl_3$) δ 1.3–1.4 (d, 3H), 2.4 (s, 3H), 3.5–3.6 (m, 1H), 3.85–3.95 (d, 1H), 4.1–4.2 (m, 1H), 6.7–6.8 (t, 1H), 7.55–7.65 (d, 1H), 8.2–8.3 (d, 1H), 8.3–8.4 (bs, 1H).

(*R*)-7-Chloro-2,3-dihydro-3,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (18b). Under Ar, NaOAc (39.54 g, 0.482 mol) was added to a room temperature mixture of (*R*)-1,2-diaminopropane dihydrochloride[17] (23.55 g, 0.160 mol) in *n*-BuOH (1.5 L). After stirring for 0.5 h, **16c** (36.40 g, 0.156 mol) in *n*-BuOH (0.5 L) was added, and the mixture was stirred for an additional 1 h at room temperature. The mixture was then warmed to reflux for 5 h after which it was concentrated under reduced pressure. The residue was suspended in CH_2Cl_2 which was sequentially washed with H_2O, 3 N NaOH, and brine. The organic phase was dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 38.86 g of red oil. This crude mixture of isomers was purified by preparative HPLC on a silica gel column eluting with 10% acetone:hexane. Isomer **18b** eluted in the front running fractions which were combined and concentrated under reduced pressure to yield 17.07 g (43%) of **18b** as a red oil which was used without further purification. Further elution with 15% acetone:hexane yielded isomer **19b** in the latter running fractions. These fractions were combined and concentrated under reduced pressure to yield 12.43 g (31%) of **19b**.

(*S*)-7-Chloro-2,3-dihydro-3,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (18c). This desired product was prepared following the procedure for **18b** after substituting (*S*)-1,2-diaminopropane dihydrochloride[17] in place of (*R*)-1,2-diaminopropane dihydrochloride. Also using a similar method of purification as for **18b** gave a 39% return of **18c**, which was used without further purification, as well as a 33% return of **19c**.

***cis*-2,3,4,5-Tetrahydro-3,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (20a).** Under Ar at room temperature, $NaBH_3CN$ (3.9 g, 62.2 mmol) was added neat to a solution of **18a** (11.35 g, 51.8 mmol) in MeOH (100 mL). After 16 h an additional portion of $NaBH_3CN$ (0.2 g, 3.18 mmol) was added to the reaction mixture along with some methanolic HCl. When TLC indicated the disappearance of **18a**, the reaction mixture was acidified to pH 1 with 3 N HCl. From this reaction mixture, 8.35 g of solid precipitate was collected which proved to be the crude HCl salt of **21a**. This material was recrystallized twice from MeOH to yield 4.05 g (30%) of pure **21a** as the HCl salt, mp 285–289 °C. Anal. ($C_{11}H_{15}N_3O_2$·HCl) C, H, N. All of the above filtrates were combined and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and aqueous 10% K_2CO_3. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 7.65 g of residue. This crude mixture of isomers was purified by preparative HPLC on a silica gel column eluting with 1:1 acetone:hexane. Isomer **20a** eluted in the front running fractions which were combined and concentrated under reduced pressure to yield 2.3 g (20%) of **20a** as an orange solid, mp 59–60 °C (TLC: 1:1 acetone:hexane, R_f = 0.25). **20a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (d, 3H), 1.42 (d, 3H), 2.07 (b, 1H), 2.53 (dd, 1H), 3.07 (m, 1H), 3.61 (dd, 1H), 3.90 (q, 1H), 6.84 (t, 1H), 7.45 (d, 1H), 7.56 (d, 1H), 7.87 (d, 1H). Anal. ($C_{11}H_{15}N_3O_2$) C, H, N. Residual **21a** eluted in the latter running fractions which were combined and concentrated under reduced pressure to yield an additional 3.36 g (29%) of free base **21a** as a viscous red oil (TLC: 1:1 acetone:hexane, R_f = 0.18). **21a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (d, 3H), 1.36 (d, 3H), 2.33 (b, 1H), 3.23 (m, 2H), 3.42 (dd, 1H), 4.37 (q, 1H), 6.72 (t, 1H), 7.36 (d, 1H), 7.87 (d, 1H), 7.96 (d, 1H). The combined total yield of **21a** as the HCl salt and the free base was 59%.

***trans*-2,3,4,5-Tetrahydro-3,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (21a).** The preparation of the desired product is described in the experimental for **20a**.

(3*R*)-*trans*-7-Chloro-2,3,4,5-tetrahydro-3,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (21b). The desired product was prepared in a similar manner as **21c** after substituting **18b** in place of **18c**. The workup varied in that in an attempt to prepare the free base sample of the reaction mixture by partitioning between 3N NaOH and CH_2Cl_2 some red solid precipitate was filtered from the biphasic mixture. This proved to be the HCl salt of **21b**. Continued basic extractions of this solid salt yielded 4.2 g (25%) of **21b** as a red oil in 96% purity (GLC) which was used without further purification. The original CH_2Cl_2 extract was concentrated under reduced pressure to give 12.4 g of oil, which consisted of a 2:1 mixture of **21b:20b**, and was not further purified.

(3*S*)-*trans*-7-Chloro-2,3,4,5-tetrahydro-3,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (21c). Under Ar at room temperature, $NaBH_3CN$ (4.70 g, 75.7 mmol) was added neat to a solution of **18c** (16.0 g, 63.1 mmol) in MeOH (160 mL). After 3 days, 3 N HCl (50 mL) was added to the mixture and the mixture stirred for an additional 1 h. The mixture was then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and aqueous 3 N NaOH. The organic phase was dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 16.9 g of residue. This crude mixture of isomers was purified by preparative HPLC on a silica gel column eluting with 15% acetone:hexane. Isomer **20c** eluted in the front running fractions which were combined and concentrated under reduced pressure to yield 3.95 g (25%) of **20c**. Further elution with 25% acetone:hexane yielded isomer **21c** in the latter running fractions. These fractions were combined and concentrated under reduced pressure to yield 10.43 g (65%) of **21c** which was used without further purification.

***cis*-2,3,4,5-Tetrahydro-2,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (22a).** Under Ar at room temperature, $NaBH_3CN$ (2.0 g, 32.9 mmol) was added neat to a solution of **19a** (6.00 g, 27.4 mmol) in MeOH (50 mL). After 16 h the reaction mixture was acidified to pH 1 with 3 N HCl and, after stirring for a short time, was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and aqueous 10% K_2CO_3. The organic phase was dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 6.01 g of residue. This crude mixture of isomers was purified by preparative HPLC on a silica gel column eluting with 1:1 acetone:hexane. Isomer **23a** eluted in the front running fractions which were combined and concentrated under reduced pressure to yield 0.84 g (14%) of **23a** which was used without further purification (TLC: 1:1 acetone:hexane, R_f = 0.17). **23a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (d, 3H), 1.45 (d, 3H), 2.41–2.49 (b, 1H), 2.56 (dd, 1H), 2.98 (dd, 1H), 3.12–3.22 (m, 1H), 3.87 (q, 1H), 6.90 (t, 1H), 7.15 (b, 1H), 7.69 (d, 1H), 7.90 (d, 1H). Isomer **22a** eluted in the latter running fractions which were combined and concentrated under reduced pressure to yield 3.86 g (64%) of **22a** which was used without further purification (TLC: 1:1 acetone:hexane, R_f = 0.08). **22a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (d, 3H), 1.33 (d, 3H), 2.51 (b, 1H), 2.79–2.87 (m, 2H), 3.60–3.69 (m, 1H), 4.30 (q, 1H), 6.81 (t, 1H), 7.42 (d, 1H), 7.47 (s, 1H), 7.91 (d, 1H).

***trans*-2,3,4,5-Tetrahydro-2,5-dimethyl-9-nitro-1*H*-1,4-benzodiazepine (23a).** The preparation of the desired product is described in the experimental for **22a**.

2,3,4,5-Tetrahydro-5-methyl-9-nitro-4-propyl-1*H*-1,4-benzodiazepine (24a). Under Ar, *n*-PrI (1.00 mL, 10 mmol) was added neat to a stirring room temperature mixture of **17a** (2.10 g, 10 mmol) and Na_2CO_3 (1.60 g, 15 mmol) in DMF (20 mL). The mixture was then warmed in an oil bath between 83 and 89 °C for 3 h. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between Et_2O and H_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 2.49 g (100%) of **24a** as a yellow-orange oil which was used without further purification (TLC: 10:1 CH_2Cl_2:MeOH, R_f = 0.4).

2,3,4,5-Tetrahydro-5-methyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24b). Under N_2, 1-bromo-3-methyl-2-butene (2.69 g, 18 mmol) was added neat over 20 s to a stirring room temperature mixture of **17a** (3.75 g, 15 mmol), Na_2CO_3 (2.39 g, 23 mmol), and KI (2.50 g, 15 mmol) in DMF (40 mL). After stirring for 22 h the reaction mixture was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 5.19 g (TW, 4.13 g) of yellowish-orange oil which was used without further purification.

***trans*-2,3,4,5-Tetrahydro-3,5-dimethyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (*E*)-2-Butenedioate (2:1) (24c).** The desired product was prepared in a similar manner as **24b** after substituting **21a** in place of **17a** and was used after reaction workup without further purification. A 0.25-g sample of **24c** was combined with fumaric acid (0.10 g, 0.86 mmol) in *i*-PrOH to yield a 0.25-g sample (72%) of **24c** as its 0.5 fumarate, mp 117−119 °C. Anal. ($C_{16}H_{23}N_3O_2{\cdot}C_2H_2O_2$) C, H, N.

***cis*-2,3,4,5-Tetrahydro-3,5-dimethyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24d).** The desired product was prepared in a similar manner as **24b** in ~100% yield, after substituting **20a** in place of **17a**, and was used after reaction workup without further purification.

***trans*-2,3,4,5-Tetrahydro-2,5-dimethyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24e).** The desired product was prepared in a similar manner as **24b** in ~100% yield, after substituting **23a** in place of **17a**, and was used after reaction workup without further purification.

***cis*-2,3,4,5-Tetrahydro-2,5-dimethyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24f).** The desired product was prepared in a similar manner as **24b** after substituting **22a** in place of **17a**. After the typical reaction workup, the crude residue was further purified by flash chromatography eluting with 1% MeOH:CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to give 70% of **24f** which was used without further purification.

2,3,4,5-Tetrahydro-4-(3-methyl-2-butenyl)-9-nitro-5-phenyl-1*H*-1,4-benzodiazepine (24g). The desired product was prepared in a similar manner as **24b** after substituting **17b** in place of **17a**. After the typical reaction workup, the crude residue was further purified by flash chromatography on a silica gel column eluting with 3% EtOH:CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to give 65% of **24g** which was used without further purification. A 0.69-g sample of **24g** was combined with fumaric acid (0.29 g, 2.48 mmol) in EtOH to yield a 0.66-g sample of **24g** as its fumarate salt, mp 101−102 °C. Anal. ($C_{20}H_{23}N_3O_2{\cdot}C_4H_4O_4$) C, H, N.

7-Chloro-2,3,4,5-tetrahydro-5-methyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24h). The desired product was prepared in a similar manner as **24b** after substituting **17c** in place of **17a**. After the typical reaction workup, the crude residue was further purified by HPLC on a silica gel column eluting with 2% EtOAc:CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to give 47% of **24h** which was used without further purification.

(3*R*)-*trans*-7-Chloro-2,3,4,5-tetrahydro-3,5-dimethyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24i). The desired product was prepared in a similar manner as **24b** after substituting **21b** in place of **17a**. After the typical reaction workup, the crude residue was further purified by flash column chromatography on a silica gel column eluting with 1% MeOH:CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to give 93% of **24i** as a red oil which was used without further purification.

(3*S*)-*trans*-7-Chloro-2,3,4,5-tetrahydro-3,5-dimethyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24j). The desired product was prepared in a similar manner as **24b** in 95% yield, after substituting **21c** in place of **17a**, and was used after reaction workup without further purification.

7-Chloro-2,3,4,5-tetrahydro-4-(3-methyl-2-butenyl)-5-(2-methylpropyl)-9-nitro-1*H*-1,4-benzodiazepine (24k). The desired product was prepared in a similar manner as **24b** after substituting **17d** in place of **17a**. After the typical reaction workup, the crude residue was further purified by flash column chromatography on a silica gel column eluting with a 3:97 EtOAc:hexane system. The desired fractions were combined and concentrated under reduced pressure to give 43% of **24k** as a red oil which was used without further purification.

6-Chloro-2,3,4,5-tetrahydro-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24l). The desired product was prepared in a similar manner as **24b** after substituting **17e** in place of **17a**. After the typical reaction workup, the crude residue was further purified by flash column chromatography on a silica gel column eluting with CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to give 40% of **24l** which was used without further purification.

6-Chloro-2,3,4,5-tetrahydro-5-methyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24m). The desired product was prepared in a similar manner as **24b** in 96% yield, after substituting **17f** in place of **17a**, and was used after reaction workup without further purification.

2,3,4,5-Tetrahydro-5-methyl-4-propyl-1*H*-1,4-benzodiazepin-9-amine (25a). Under N_2, **24a** (2.49 g, 10 mmol) in THF (40 mL) was added over 12 min to a 0 °C suspension of LAH (1.52 g, 40 mmol) in THF (50 mL). The mixture was gradually warmed to room temperature and then warmed to reflux. After refluxing for 1.5 h the reaction mixture was cooled to 0 °C and the reaction quenched sequentially with H_2O (1.52 mL), 3 N NaOH (1.52 mL), and H_2O (4.56 mL). The reaction mixture was then warmed to room temperature, stirred for an additional 2 h, and then filtered. The filtered salts were digested in THF (75 mL) and then refiltered. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (60 mL), dried over $MgSO_4$, filtered, and reconcentrated under reduced pressure to yield 1.86 g (85%) of **25a** as a brownish-red oil which was used without further purification (TLC: 5:1 $CHCl_3$:MeOH, R_f = 0.2).

Intermediates 25b−g,j,l,m. The desired products were prepared in yields ranging from 91 to 100% following the procedure of **25a**, after substituting the appropriate starting material for **24a**, and were used after reaction workups without further purification.

7-Chloro-2,3,4,5-tetrahydro-5-methyl-4-(3-methyl-2-butenyl)-1*H*-1,4-benzodiazepin-9-amine (25h). Under Ar, hydrazine monohydrate (1.0 g, 21.8 mmol) in MeOH (3 mL) was added over 20 min to a refluxing suspension of **24h** (1.34 g, 4.3 mmol) and Ra Ni (0.49 g) in MeOH (22 mL). After an additional 1.5 h of refluxing, the reaction mixture was filtered cautiously through Dicalite. The filtrate was concentrated under reduced pressure to yield 1.39 g (100%) of **25h** as a reddish oil which was used without further purification.

(3*R*)-*trans*-9-Amino-7-chloro-2,3,4,5-tetrahydro-3,5-dimethyl-4-(3-methyl-2-butenyl)-1*H*-1,4-benzodiazepine (25i). The desired product was prepared in 97% yield following the procedure of **25h**, after substituting **24i** for **24h**, and was used after reaction workup without further purification.

9-Amino-7-chloro-2,3,4,5-tetrahydro-4-(3-methyl-2-butenyl)-5-(2-methylpropyl)-1*H*-1,4-benzodiazepine (25k). The desired product was prepared in 99% yield following the procedure of **25h**, after substituting **24k** for **24h**, and was used after reaction workup without further purification.

4,5,6,7-Tetrahydro-7-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1ag). The desired product was prepared in a similar manner as **5**, after substituting **17a** in place of **4**, and was purified as described in Table 2.

4,5,6,7-Tetrahydro-7-methyl-6-propylimidazo[4,5,1-*jk*]-[1,4]benzodiazepin-2(1*H*)-one (1ah). Under Ar, trichloromethyl chloroformate (0.26 mL, 2.12 mmol) in CH_2Cl_2 (15 mL) was added over 4 min to a 0 °C solution of **25a** (0.93 g, 4.25 mmol) and NMM (0.93 mL, 8.5 mmol) in CH_2Cl_2 (30 mL). After 0.5 h the mixture was extracted with saturated aqueous $NaHCO_3$. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 0.90 g of crude product which was purified as described in Table 2 (TLC: 5:1 $CHCl_3$:MeOH, R_f = 0.75). **1ah**: ^{1}H NMR ($CDCl_3$) δ 0.9−1.0 (t, 3H), 1.4−1.5 (d, 3H), 1.5−1.65 (m, 2H), 2.6−2.75 (m, 2H), 3.05−3.15 (d, 1H), 3.5−3.6 (t, 1H), 3.8−3.9 (t, 1H),

4.1–4.2 (d, 1H), 4.25–4.35 (q, 1H), 6.6–6.7 (d, 1H), 6.8–6.9 (d, 1H), 6.9–7.0 (m, 1H), 9.0–9.1 (bs, 1H).

4,5,6,7-Tetrahydro-7-methyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1ai). The desired product was prepared following the procedure for **1ah**, after substituting **25b** in place of **25a**, and was purified as described in Table 2.

9-Chloro-4,5,6,7-tetrahydro-7-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1ak). Under Ar, **25h** (0.71 g, 2.5 mmol) and 1,1'-carbonyldiimidazole (0.45 g, 2.8 mmol) in THF (25 mL) was stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure and the residue combined with EtOAc and sequentially washed with H_2O twice, dilute aqueous AcOH, H_2O twice, and brine. The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 0.72 g of crude product which was further purified as described in Table 2.

(5*R*)-*trans*-9-Chloro-4,5,6,7-tetrahydro-5,7-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1bb). The desired product was prepared following the procedure for **1ah** after substituting **25i** in place of **25a** and reversing the addition order, i.e., the amine solution was added to the phosgene equivalent. The final product was purified as described in Table 2.

(+)-(5*S*)-*trans*-9-Chloro-4,5,6,7-tetrahydro-5,7-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one Monohydrochloride (1bd). The desired product was prepared following the procedure for **1ah** after substituting **25j** in place of **25a** and reversing the addition order, i.e., the amine solution was added to the phosgene equivalent. The final product was purified as described in Table 2.

9-Chloro-4,5,6,7-tetrahydro-6-(3-methyl-2-butenyl)-7-(2-methylpropyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2-(1*H*)-one (1ap). The desired product was prepared in a similar manner as **1ak** after substituting **25k** in place of **25h**. Also the reaction mixture was warmed at reflux for 3 h before concentrating the reaction under reduced pressure. The concentrated residue was combined with EtOAc and sequentially washed with dilute aqueous AcOH, dilute aqueous $NaHCO_3$, H_2O, and brine. The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **1ap** which was further purified as described in Table 2.

8-Chloro-4,5,6,7-tetrahydro-7-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (1aj). The desired product was prepared following the procedure for **1ah** after substituting **25m** in place of **25a** and reversing the addition order, i.e., the amine solution was added to the phosgene equivalent. The final product was purified as described in Table 2.

4,5,6,7-Tetrahydro-7-methyl-6-propylimidazo[4,5,1-*jk*]-[1,4]benzodiazepine-2(1*H*)-thione (1al). KOH (0.32 g) was added to a room temperature solution of **25a** (0.93 g, 4.25 mmol) in EtOH (5 mL) and H_2O (1 mL). CS_2 (0.34 mL, 5.65 mmol) was added to the resulting solution. After stirring for 10 min the reaction mixture was warmed to 90 °C for 1 h under Ar. After cooling to room temperature the reaction mixture was diluted with H_2O (5.6 mL) and then AcOH (0.47 mL). The reaction mixture was then filtered. The filtered solid was partitioned between dilute NH_4OH and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 500 mg of crude product which was further purified as described in Table 2 (TLC: 10:1 CH_2Cl_2:MeOH, $R_f = 0.5$). 1al: ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H), 1.4–1.5 (d, 3H), 1.5–1.65 (m, 2H), 2.55–2.75 (m, 2H), 3.1–3.2 (d, 1H), 3.6–3.7 (t, 1H), 4.0–4.1 (t, 1H), 4.3–4.4 (q, 1H), 4.65–4.75 (d, 1H), 6.85–7.15 (m, 3H), 10.4 (bs, 1H).

4,5,6,7-Tetrahydro-7-methyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1am). The desired product was prepared following the procedure for **1al**, after substituting **25b** in place of **25a**, and was purified as described in Table 2.

***trans*-4,5,6,7-Tetrahydro-5,7-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1az).** Under Ar, **25c** (4.8 g, 14.5 mmol) and 1,1'-thiocarbonyldiimidazole (3.9 g, 22.4 mmol) in THF (100 mL) were warmed to reflux for 0.5 h. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between EtOAc and H_2O. The organic phase was then washed twice with H_2O and once with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was further purified as described in Table 2. **1az**: ^1H NMR (400 MHz, CD_3OD) δ 1.29 (d, 3H), 1.35 (s, 3H), 1.47 (d, 3H), 1.70 (s, 3H), 3.03 (dd, 1H), 3.18 (dd, 1H), 3.86–3.92 (m, 2H), 4.49 (q, 1H), 4.66–4.74 (m, 1H), 5.14–5.22 (m, 1H), 6.91 (d, 1H), 7.07 (d, 1H), 7.12 (t, 1H).

Final Products 1ba,bg,bh,ar,ao,bc,be,a,an. The desired products were prepared following the procedure for **1az**, after substituting the respective diamines **25d–j,l,m** in place of **25c**, and were purified as described in Table 2. **1ba**: ^1H NMR (400 MHz, CD_3OD) δ 1.30 (d, 3H), 1.47 (s, 3H), 1.65 (d, 6H), 3.03–3.15 (m, 2H), 3.31–3.36 (m, 1H), 4.09 (dd, 1H), 4.19 (q, 1H), 4.80 (dd, 1H), 5.18 (t, 1H), 6.94 (d, 1H), 7.09–7.15 (m, 2H).

9-Chloro-4,5,6,7-tetrahydro-6-(3-methyl-2-butenyl)-7-(2-methylpropyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1aq). The desired product was prepared following the procedure for **1az**, after substituting **25k** in place of **25c** and varying the solvent from THF to benzene. The final product was purified as described in Table 2.

Procedure Sequence for Method H. Ethyl *N*-[(5-Chloro-2-nitrophenyl)methyl]alanine (27). Under Ar, **26**[18] (44.27 g, 0.238 mol), ethyl 2-bromopropionate (33.92 mL, 0.261 mol), and Na_2CO_3 (14.1 g, 0.133 mol) were combined in DMF (600 mL) at room temperature and immediately placed in a bath whose temperature was raised to 80 °C over 20 min. After 1 h at 80 °C, heating was discontinued, and the mixture was concentrated under reduced pressure. The residue was suspended in Et_2O which was washed three times with H_2O and then with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 59.91 g of crude product. This material was swirled in EtOH (130 mL) and filtered. The filtrate was concentrated under reduced pressure to yield 55.03 g (81%) of **27** which was used without further purification (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.85). **27**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.1–1.5 (m, 6H), 2.1–2.5 (bs, 1H), 3.2–3.6 (m, 1H), 4.0–4.4 (m, 4H), 7.2–8.0 (m, 3H).

7-Chloro-1,3,4,5-tetrahydro-3-methyl-2*H*-1,4-benzodiazepin-2-one (28). At room temperature a mixture of **27** (22 g, 0.077 mol) and PtO_2 (2 g) in EtOH (120 mL) was placed under a H_2 atmosphere at 43 psi for 3 h. The reaction mixture was filtered through Dicalite and the filtrate concentrated under reduced pressure to give 20.87 g (TW, 19.69 g) of oil (TLC: 20:1 CH_2Cl_2:MeOH, $R_f = 0.45$). This oil was combined with HOBT (5.71 g, 42.3 mmol) in toluene (300 mL) and warmed to reflux for 3 days. After cooling, the resulting solid was filtered and rinsed with a small amount of toluene to yield 11.18 g of tannish solid. An attempt to flash chromatograph this material on a silica gel column eluting with 1:4 MeOH: CH_2Cl_2 proved less than promising in separating desired **28** from residual HOBT. Therefore a 6.06-g sample was stirred in saturated aqueous $NaHCO_3$ (70 mL). After 0.75 h the suspension was filtered and rinsed with a small amount of ice cold H_2O to yield 3.31 g (38%) of **28** (TLC > 95%) which was used without further purification. A small sample was further purified by trituration in CH_2Cl_2 to yield pure **28** as a white solid, mp 186–188 °C (TLC: 5:1 $CHCl_3$:MeOH, $R_f = 0.7$). **28**: ^1H NMR (DMSO-d_6) δ 1.05–1.15 (d, 3H), 2.9–3.0 (bs, 1H), 3.3–3.4 (m, 1H), 3.7–3.85 (m, 2H), 7.0 (d, 1H), 7.25–7.35 (m, 2H), 9.8 (s, 1H). Anal. ($C_{10}H_{11}ClN_2O$) C, H, N.

7-Chloro-1,3,4,5-tetrahydro-3-methyl-4-propyl-2*H*-1,4-benzodiazepin-2-one (29). Under Ar, *n*-PrI (2.23 mL, 23 mmol) was added neat to a stirring room temperature mixture of **28** (4.00 g, 19 mmol) and Na_2CO_3 (2.02 g, 19 mmol) in DMF (30 mL). The mixture was then warmed in an oil bath between 83 and 89 °C for 24 h. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between CH_2Cl_2 and H_2O. The organic phase was then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an off-white solid. This solid was triturated in Et_2O (20 mL), filtered, and rinsed with Et_2O (10 mL) to yield 3.07 g (64%) of **29** (TLC > 95%) which was used without further purification. A small sample was

further purified by an additional trituration in Et_2O to yield pure **29** as a white solid, mp 137–139 °C (TLC: 5:1 $CHCl_3$:MeOH, R_f = 0.85; 20:1 CH_2Cl_2:MeOH, R_f = 0.4). **29**: ^1H NMR ($CDCl_3$) δ 0.85–0.95 (t, 3H), 1.3–1.4 (d, 3H), 1.4–1.6 (m, 2H), 2.35–2.45 (m, 1H), 2.5–2.6 (m, 1H), 3.5–3.6 (m, 1H), 3.8–4.0 (dd, 2H), 6.8–6.9 (d, 1H), 7.2–7.3 (m, 2H), 7.8–7.9 (s, 1H). Anal. ($C_{13}H_{17}ClN_2O$) C, H, N.

7-Chloro-1,3,4,5-tetrahydro-3-methyl-9-nitro-4-propyl-2*H*-1,4-benzodiazepin-2-one (30). Over 10 min, **29** (2.77 g) was added neat to fuming HNO_3 which was stirring at 0 °C. After an additional 0.5 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for an additional 16 h. The reaction mixture was then slowly added to ice (100 g) with stirring. The resulting ice cold mixture was basified with 3 N NaOH and extracted with three portions of CH_2Cl_2 (100 mL each). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 2.74 g of yellowish solid. This crude residue was adsorbed on silica gel and further purified by flash column chromatography on a silica gel column eluting with 25% EtOAc/hexane. The desired fractions were combined and concentrated under reduced pressure to give 1.43 g (44%) of **30** as a yellow solid, mp 161–164 °C (TLC: 5:1 $CHCl_3$:MeOH, R_f = 0.85; 20:1 CH_2Cl_2:MeOH, R_f = 0.45). **30**: ^1H NMR ($CDCl_3$) δ 0.9–1.0 (t, 3H), 1.2–1.3 (d, 3H), 1.45–1.65 (m, 2H), 2.3–2.4 (m, 1H), 2.55–2.65 (m, 1H), 3.3–3.4 (m, 1H), 3.7–3.95 (dd, 2H), 7.5 (s, 1H), 8.1 (s, 1H), 9.2 (s, 1H). Anal. ($C_{13}H_{16}ClN_3O_3$) C, H, N.

9-Amino-7-chloro-1,3,4,5-tetrahydro-3-methyl-4-propyl-2*H*-1,4-benzodiazepin-2-one (31). At room temperature a mixture of **30** (0.53 g, 1.78 mmol) and PtO_2 (0.06 g) in EtOH (12 mL) was placed under a H_2 atmosphere at 38 psi for 5.5 h. The reaction mixture was then filtered through Dicalite and the filtrate concentrated under reduced pressure to give 0.47 g (98%) of **31** (TLC > 95%) which was used without further purification. A small sample was further purified by trituration in EtOH to yield pure **31** as an off-white solid, mp 197.5–198.5 °C (TLC: 5:1 $CHCl_3$:MeOH, R_f = 0.7; 20:1 CH_2Cl_2:MeOH, R_f = 0.25). **31**: ^1H NMR ($CDCl_3$) δ 0.9–1.0 (t, 3H), 1.2–1.3 (d, 3H), 1.45–1.6 (m, 2H), 2.3–2.4 (m, 1H), 2.5–2.6 (m, 1H), 3.3–3.4 (m, 1H), 3.7 (s, 2H), 3.9 (s, 2H), 6.65 (s, 1H), 6.75 (s, 1H), 7.5 (bs, 1H). Anal. ($C_{13}H_{18}ClN_3O$) C, H, N.

9-Chloro-2,5,6,7-tetrahydro-5-methyl-6-propyl-2-thioxoimidazo[4,5,1-*jk*][1,4]benzodiazepin-4(1*H*)-one (1aw). Under N_2, a solution of thiophosgene (0.13 mL, 1.76 mmol) in CH_2Cl_2 (7 mL) was added over 5 min to a stirring 0 °C mixture of **31** (0.47 g, 1.76 mmol) and Et_3N (0.49 mL, 3.52 mmol) in CH_2Cl_2 (80 mL). The final reaction mixture was stirred an additional 10 min at 0 °C and then extracted with saturated aqueous $NaHCO_3$. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.70 g of crude product which was purified as described in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.4). **1aw**: ^1H NMR ($CDCl_3$) δ 0.8–0.9 (t, 3H), 1.4–1.5 (m, 5H), 2.35–2.6 (m, 2H), 3.9–4.0 (q, 1H), 4.1–4.35 (dd, 2H), 7.0 (s, 1H), 7.15 (s, 1H), 10.9–11.1 (bs, 1H).

Procedure Sequence for Method I. 9-Amino-3-methyl-4-propyl-1*H*-1,4-benzodiazepine-2,5(3*H*,4*H*)-dione (32a). At room temperature a solution of ethyl 2-bromopropionate (12.98 mL, 0.1 mol) and *n*-$PrNH_2$ (16.44 mL, 0.2 mol) in Et_2O (70 mL) was stirred for 72 h. The mixture was then filtered, and the resulting salts were rinsed with a small amount of Et_2O. The combined filtrates were concentrated under reduced pressure to give 15.91 g (100%) of a clear liquid. An 8.65-g sample of this liquid, along with Et_3N (7.56 mL, 54 mmol), in CH_2Cl_2 (40 mL) at 0 °C was treated with a semisuspension of **3a** (10.83 g, 54 mmol) in CH_2Cl_2 (90 mL) over 10 min. After 5 additional min the reaction mixture was warmed to room temperature and stirred for an additional 1 h. The reaction mixture was then extracted sequentially with H_2O, saturated aqueous $NaHCO_3$, 2 N citric acid, and then saturated aqueous $NaHCO_3$ once again. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 19.14 g of yellow solid. This material and 10% Pd/C (2.0 g) in EtOH (100 mL) were placed under a H_2 atmosphere at 46 psi. After 2 h, the reaction mixture was filtered through Dicalite, an additional portion of 10% Pd/C (2.0 g) was combined with the filtrate, and the reaction mixture was again placed under a H_2 atmosphere at 51 psi. After 17 h the reaction mixture was again filtered through Dicalite and concentrated under reduced pressure. The resulting oil was placed under vacuum (25 mmHg) and warmed to 205 °C for 2 h. After cooling, the residue was purified by flash chromatography on a silica gel column eluting with 20:1 CH_2Cl_2:MeOH. The desired fractions were combined and concentrated under reduced pressure to give 4.60 g (34%) of **32a** which was used without further purification (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.25).

(*S*)-9-Amino-7-chloro-4-(cyclopropylmethyl)-2,3,4,5-tetrahydro-3-methyl-1*H*-1,4-benzodiazepine (32b). The desired product was prepared following our previously reported work[3] after substituting the appropriate enantiospecific starting material alanine methyl ester hydrochloride for the racemic mixture used in our previous report.

9-Amino-2,3-dihydro-3-methyl-4-propyl-1*H*-1,4-benzodiazepin-5(4*H*)-one (33). Under Ar, **32a** (1.24 g, 5 mmol) was added neat to a 0 °C suspension of LAH (1.15 g, 30 mmol) in THF (35 mL). After the mixture had stirred at 0 °C for 4.5 h, the reaction was quenched sequentially with H_2O (1.15 mL), 3 N NaOH (1.15 mL), and H_2O (3.45 mL). After stirring for an additional 45 min the salts were filtered. The salts were digested in warm THF (60 mL) and then refiltered. The combined filtrates were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **33** as an oil which was used without further purification (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.4).

4,5-Dihydro-5-methyl-6-propylimidazo[4,5,1-*jk*][1,4]benzodiazepine-2,7(1*H*,6*H*)-dione (1bf). The above residual oil **33** was combined with Et_3N (0.695 mL, 5 mmol) in CH_2Cl_2 (30 mL), cooled to 0 °C, and treated with a solution of trichloromethyl chloroformate (0.30 mL, 2.5 mmol) in CH_2Cl_2 (20 mL) over 15 min. Five minutes after completion of addition the reaction mixture was washed sequentially with H_2O, 3 N HCl, and saturated aqueous $NaHCO_3$. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.98 g of crude **1bf** which was further purified as described in Table 2 (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.3). **1bf**: ^1H NMR ($CDCl_3$) δ 0.95–1.05 (t, 3H), 1.1–1.2 (d, 3H), 1.65–1.85 (m, 2H), 3.4–3.6 (m, 1H), 3.7–3.9 (m, 2H), 4.0–4.1 (m, 1H), 4.4–4.65 (dd, 1H), 7.1–7.2 (t, 1H), 7.2–7.3 (d, 1H), 7.9–8.0 (d, 1H), 10.2–10.3 (s, 1H).

(+)-(*S*)-9-Chloro-6-(cyclopropylmethyl)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1bu). The desired product was prepared following the procedure for **1al**, after substituting **32b** in place of **25a**, and was purified as described in Table 2.

Procedure Sequence for Method J. (2*R*)-*cis*-7-Chloro-2,3-dihydro-2-hydroxy-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10*H*,11a*H*)-dione (34). A mixture of *trans*-4-hydroxy-L-proline (20.42 g, 0.16 mol) and 5-chloroisatoic anhydride (28.0 g, 0.16 mol) in DMSO (300 mL) was warmed at 120 °C for 5 h. After cooling, the mixture was poured into H_2O (1400 mL). The resulting mixture was cooled in an ice bath to yield white crystals which were filtered and dried to give 37.05 g of crude product. This material was recrystallized from H_2O (600 mL) to yield 25.04 g (58%) of **34** as a white solid, mp 137–138 °C (TLC: 5% (10% NH_4OH/MeOH)/CH_2Cl_2, R_f = 0.26). **34**: ^1H NMR (DMSO-d_6) δ 1.9–2.0 (m, 1H), 2.55–2.65 (m, 1H), 3.45–3.55 (dd, 1H), 3.6–3.7 (d, 1H), 4.25–4.35 (m, 2H), 5.2 (d, 1H), 7.15–7.2 (d, 1H), 7.6 (d, 1H), 7.75 (s, 1H), 10.7 (s, 1H).

(+)-(11a*S*)-7-Chloro-1,3,10,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione (35). Jones reagent[19] (35 mL) was added portionwise over 1 h to a 0 °C solution of **34** (22.15 g, 84 mmol) in acetone (800 mL). The mixture was then warmed to room temperature and stirred for an additional 16 h. *i*-PrOH (10 mL) was then added after which the reaction mixture was concentrated under reduced pressure. The residue was treated with H_2O and then filtered. The solid was rinsed with H_2O which after drying gave 13.0 g of white solid **35** which was used without further purification. A small sample was further purified by recrystallization from *i*-PrOH/$CHCl_3$ to yield pure **35** as a white solid, mp 268–270 °C (TLC: 5% (10% NH_4OH/MeOH)/CH_2Cl_2, R_f = 0.57). **35**: ^1H

NMR (DMSO-d_6) δ 2.85–2.95 (dd, 1H), 3.15–3.25 (d, 1H), 3.85–3.95 (d, 1H), 4.1–4.2 (d, 1H), 4.65–4.75 (dd, 1H), 7.15–7.25 (d, 1H), 7.65–7.7 (d, 1H), 7.8 (s, 1H), 10.8 (s, 1H). Anal. ($C_{12}H_9ClN_2O_3$) C, H, N.

(+)-(11a*S*)-7-Chloro-9-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11(3*H*,10*H*,11a*H*)-trione (36). Under Ar, **35** (11.50 g, 43 mmol) was added neat over 30 min to 0 °C fuming nitric acid. After stirring for an additional 5 h at 0 °C, the reaction mixture was added slowly to ice (600 g). The resulting solid was filtered and rinsed with a small amount of H_2O. After drying the resulting solid under high vacuum at 50 °C for 16 h, there remained 11.04 g (82%) of **36** which was used without further purification (TLC: 5% (10% NH_4OH/MeOH)/CH_2Cl_2, $R_f = 0.76$). **36**: ^1H NMR (DMSO-d_6) δ 2.85–2.95 (dd, 1H), 3.1–3.2 (d, 1H), 3.9–4.15 (dd, 1H), 4.1–4.2 (d, 1H), 4.8–4.9 (d, 1H), 8.1 (s, 1H), 8.4 (s, 1H), 10.5 (s, 1H).

(+)-(11a*S*)-7-Chloro-2,3-dihydro-2-methylene-9-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10*H*,11a*H*)-dione (37a). Under Ar, 80% NaH (1.88 g, 65 mmol) was added to a room temperature suspension of methyltriphenylphosphonium bromide (23.0 g, 65 mmol) in THF (600 mL). After warming and maintaining the mixture at reflux for 3 h, **36** (5.0 g, 16 mmol) in THF (800 mL) was added slowly to the hot mixture. After an additional 1.5 h at reflux the reaction mixture was cooled and filtered. The filtrate was concentrated under reduced pressure and the residue partitioned between EtOAc (600 mL) and H_2O (500 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 27 g of dark brown oil. This crude residue was purified by flash column chromatography on a silica gel column eluting with MeOH:CH_2Cl_2 solutions starting with 0% MeOH and increasing incrementally by 0.5% up to 1%. The desired fractions were combined and concentrated under reduced pressure to give 2.50 g (51%) of **37a**, mp 165–167 °C (TLC: 2% MeOH/CH_2Cl_2, $R_f = 0.73$). **37a**: ^1H NMR (DMSO-d_6) δ 2.75–2.85 (m, 1H), 3.15–3.25 (d, 1H), 4.1–4.3 (dd, 2H), 4.5–4.6 (d, 1H), 5.1–5.2 (d, 2H), 8.15 (s, 1H), 8.4 (s, 1H), 10.4 (s, 1H). Anal. ($C_{13}H_{10}ClN_3O_4$) C, H, N.

[11a*S*(*E* + *Z*)]-7-Chloro-2-ethylidene-2,3-dihydro-9-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10*H*,11a*H*)-dione (37b). The desired product was prepared in a similar manner as **37a** after substituting ethyltriphenylphosphonium bromide in place of methyltriphenylphosphonium bromide. The crude residue was purified by flash column chromatography on a silica gel column eluting with MeOH:CH_2Cl_2 solutions starting with 0% MeOH and increasing incrementally by 0.5% up to 2%. The desired fractions were combined and concentrated under reduced pressure to give a 39% yield of **37b** as a 6:1 *Z*:*E* mixture of isomers, mp 178–184 °C. Anal. ($C_{14}H_{12}ClN_3O_4$) C, H, N. **37b**, major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (d, 3H), 2.80–2.87 (m, 1H), 3.42 (d, 1H), 4.20 (d, 1H), 4.31 (s, 2H), 5.59–5.63 (m, 1H), 8.26 (d, 1H), 8.30 (d, 1H), 9.76 (s, 1H).

(11a*S*)-7-Chloro-2,3,5,10,11,11a-hexahydro-2-methylene-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-9-amine (38a). Under Ar, **37a** (2.0 g, 65 mmol) was added neat to a 0 °C suspension of LAH (2.50 g, 65.8 mmol) in THF (200 mL). After stirring for 0.5 h at 0 °C, the mixture was gradually warmed to reflux. After 5 h the mixture was recooled to 0 °C and the reaction quenched sequentially with EtOAc, MeOH, H_2O, 3 N NaOH, and H_2O. After stirring for an additional 30 min, the salts were filtered. The salts were digested in warm THF (60 mL) and then refiltered. The combined filtrates were concentrated under reduced pressure, and the residue was partitioned between $CHCl_3$ and H_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1.80 g (TW, 1.62 g) of **38a** as a reddish-brown semisolid which was used without further purification (TLC: 10% MeOH/$CHCl_3$, $R_f = 0.56$).

[11a*S*(*E* + *Z*)]-7-Chloro-2-ethylidene-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-9-amine (38b). The desired product was prepared by following the procedure for **38a** after substituting **37b** in place of **37a** to give **38b** in ~100% yield as a reddish semisolid.

(10a*S*)-4-Chloro-6,8,9,10,10a,11-hexahydro-9-methyleneimidazo[4,5,1-*jk*]pyrrolo[2,1-*c*][1,4]benzodiazepine-1(2*H*)-thione (1bk). The desired product was prepared following the procedure for **1al** after substituting **38a** in place of **25a**. The other variations were that the reaction was run at room temperature and the mixture was stirred for 18 h prior to simply filtering off the crude product and rinsing it with Et_2O. The crude product was purified as described in Table 2. **1bk**: ^1H NMR (DMSO-d_6) δ 2.3–2.4 (m, 2H), 2.9–3.0 (dd, 1H), 3.1–3.2 (m, 1H), 3.2–3.4 (d, 1H), 3.7–3.8 (m, 2H), 4.2–4.3 (d, 1H), 4.7–4.8 (d, 1H), 4.9–5.0 (d, 2H), 7.1 (s, 2H), 13.0 (bs, 1H).

(+)-[10a*S*(*E* + *Z*)]-4-Chloro-9-ethylidene-6,8,9,10,10a,-11-hexahydroimidazo[4,5,1-*jk*]pyrrolo[2,1-*c*][1,4]benzodiazepine-1(2*H*)-thione (1bl). The desired product was prepared following the procedure for **1al** after substituting **38b** in place of **25a**. The other variations were that the reaction was run at room temperature and the mixture was stirred for 18 h prior to simply filtering off the crude product and rinsing it with Et_2O. The crude product was purified as described in Table 2.

Procedure Sequence for Method K. 5-Chloro-2-methoxy-γ-oxobenzenebutanoic Acid (39a). The desired product was prepared following a previously published procedure.[20] However a minor variation was pursued in the workup. After the aqueous HCl quench of the initial reaction, the resulting biphasic mixture was extracted with CH_2Cl_2. The organic phase was separated and washed with an aqueous $NaHCO_3$ solution. This aqueous solution was treated slowly with 3 N HCl until acidic. The resulting solid was filtered, rinsed with H_2O, and air-dried to give **39a** in 41% yield.

5-Chloro-2methoxy-∂-oxobenzenepentanoic Acid (39b). The desired product was prepared following the literature procedure used for **39a** after substituting glutaric anhydride for succinic anhydride. The above noted variations in the workup for **39a** were also pursued in this workup to give **39b** as a white solid in 29% yield.

5-Chloro-2-methoxy-3-nitro-γ-oxobenzenebutanoic Acid (40a). Under Ar, **39a** (14.0 g, 57.85 mmol) was added neat over 2 min to 0 °C fuming HNO_3 (140 mL). After 0.75 h the solution was poured into ice (660 g) with stirring. The resulting solid was filtered, rinsed with a small amount of ice cold H_2O, and air-dried to yield 11.36 g (68%) of **40a** as a brown-tinted solid which was used without further purification (TLC: 5:1 CH_2Cl_2:MeOH, $R_f = 0.65$; 1:1 EtOAc:hexane, $R_f = 0.05$). **40a**: ^1H NMR (DMSO-d_6) δ 2.6 (t, 2H), 3.2 (t, 2H), 3.8 (s, 3H), 8.0 (s, 1H), 8.3 (s, 1H).

5-Chloro-2-methoxy-3-nitro-∂-oxobenzenepentanoic Acid (40b). Under Ar, **39b** (18.36 g, 71.7 mmol) was added neat over 20 min to 0 °C fuming HNO_3 (184 mL). After an additional 1.25 h at 0 °C, the reaction solution was poured into ice (865 g) with stirring. The resulting mixture was extracted with CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 20.28 g (94%) of **40b** as a yellow oil which was used without further purification.

Methyl 5-Chloro-2-methoxy-3-nitro-γ-oxobenzenebutanoate (41a). A mixture of **40a** (10 g, 34.84 mmol) and concentrated H_2SQ_4 (0.5 mL) in MeOH (400 mL) was warmed to reflux. After 16 h the solution was concentrated under reduced pressure and partitioned between CH_2Cl_2 and H_2O. The organic phase was further washed with saturated $NaHCO_3$ and then brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 7.13 g (68%) of **41a** as a brown oil which crystallized upon standing. This material was used without further purification (TLC: 5:1 CH_2Cl_2:MeOH, $R_f = 0.99$; 1:1 EtOAc:hexane, $R_f = 0.8$). **41a**: ^1H NMR ($CDCl_3$) δ 2.7–2.8 (m, 2H), 3.2–3.3 (m, 2H), 3.75 (s, 3H), 3.95 (s, 3H), 7.7 (s, 1H), 7.9 (s, 1H).

Methyl 5-Chloro-2-methoxy-3-nitro-∂-oxobenzenepentanoate (41b). The desired product was prepared in a similar manner as **41a** after substituting **40b** in place of **40a** as a starting material. Also the crude product was further purified by flash column chromatography on a silica gel column eluting with 20% EtOAc/hexane to give 34% of **41b** as a yellow oil which was used without further purification.

10-Chloro-1,6,7,11b-tetrahydro-8-nitro-3*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-3(2*H*)-one (42a). Under Ar, $NaBH_3CN$ (2.98 g, 47.38 mmol) was added to a room temperature solution of **41a** (7.13 g, 23.69 mmol), ethylenediamine (1.42 g,

23.69 mmol), and AcOH (2.84 g, 47.38 mmol) in EtOH (240 mL) after which the reaction mixture was warmed to reflux. After 21 h the reaction mixture was cooled to room temperature and treated with methanolic HCl to pH <3. After stirring for 6 h the mixture was concentrated under reduced pressure, and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 5.75 g of dark brownish oil. This material was crystallized from EtOH (50 mL) to yield 2.27 g (35%) of **42a** as an orange-copper-colored solid, mp 166–168 °C (TLC: 5:1 CH_2Cl_2:MeOH, R_f = 0.75; 80:20:5 $CHCl_3$:MeOH:HCOOH, R_f = 0.8). **42a**: ^{1}H NMR ($CDCl_3$) δ 2.35–2.5 (m, 4H), 3.4–3.5 (m, 1H), 3.65–3.75 (m, 1H), 3.75–3.95 (m, 2H), 5.1–5.2 (m, 1H), 7.4 (s, 1H), 8.1 (s, 1H), 8.25–8.35 (bs, 1H). Anal. ($C_{12}H_{12}ClN_3O_3$) C, H, N.

2-Chloro-6,7,10,11,12,12a-hexahydro-4-nitropyrido[1,2-*d*][1,4]benzodiazepin-9(5*H*)-one (42b). The desired product was prepared in a similar manner as **42a** after substituting **41b** in place of **41a**. Also the procedure varied in that the reaction mixture was warmed at reflux for 4 days before cooling and treating with methanolic HCl to pH <3. The purification varied from **42a** in that the crude material was flash chromatographed on a silica gel column eluting with 1:25 MeOH:CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to give 23% of **42b** as a copper-colored oil which was used without further purification.

8-Amino-10-chloro-1,2,3,6,7,11b-hexahydro-5*H*-pyrrolo-[1,2-*d*][1,4]benzodiazepine (43a). Under N_2, **42a** (0.56 g, 2 mmol) was added neat to a 0 °C suspension of LAH (0.46 g, 12 mmol) in THF (20 mL). After stirring for 0.5 h at 0 °C, the mixture was gradually warmed to reflux. After 5 h the mixture was recooled to 0 °C and the reaction quenched sequentially with H_2O (0.46 mL), 3 N NaOH (0.46 mL), and H_2O (1.38 mL). After stirring for an additional 30 min, the salts were filtered. The salts were digested in warm THF and then refiltered. The filtrates were combined, and the resulting solution containing **43a** was used in the subsequent step without further manipulation (TLC: 5:1 CH_2Cl_2:MeOH, R_f = 0.1).

2-Chloro-5,6,7,9,10,11,12,12a-octahydropyrido[1,2-*d*]-[1,4]benzodiazepin-4-amine (43b). The desired product was prepared in a similar manner as **43a** after substituting **42b** as the starting material in place of **42a**.

2-Chloro-7,8,10,11,12,12a-hexahydroimidazo[4,5,1-*jk*]-pyrrolo[1,2-*d*][1,4]benzodiazepine-5(4*H*)-thione (1bm). Under N_2, 1,1′-thiocarbonyldiimidazole (0.36 g, 2 mmol) was added to the resulting solution of **43a** and warmed to reflux for 3 h. The reaction mixture was then concentrated under reduced pressure and the crude product purified as described in Table 2 (TLC: 5:1 CH_2Cl_2:MeOH, R_f = 0.7). **1bm**: ^{1}H NMR (DMSO-d_6) δ 1.7–1.9 (m, 3H), 2.55–2.65 (m, 2H), 2.75–2.85 (t, 1H), 3.15–3.25 (t, 1H), 3.35–3.45 (m, 1H), 3.55–3.7 (m, 2H), 4.5–4.6 (d, 1H), 6.95 (s, 1H), 7.1 (s, 1H), 13.0 (s, 1H).

2-Chloro-7,8,11,12,13,13a-hexahydro-10*H*-imidazo[4,5,1-*jk*]pyrido[1,2-*d*][1,4]benzodiazepine-5(4*H*)-thione (1bo). The desired product was prepared in a similar manner as **1bm**, after substituting **43b** as the starting material in place of **43a**, and was purified as described in Table 2.

8-Amino-10-chloro-1,6,7,11b-tetrahydro-3*H*-pyrrolo-[1,2-*d*][1,4]benzodiazepin-3(2*H*)-one (44a). The desired product was prepared in 100% yield following the procedure of **25h**, after substituting **42a** for **24h**, and was used after reaction workup without further purification (TLC: 80:20:5 $CHCl_3$:MeOH:HCOOH, R_f = 0.65).

2-Chloro-4,5,7,8,12,12a-hexahydro-5-thioxoimidazo[4,5,1-*jk*]pyrrolo[1,2-*d*][1,4]benzodiazepin-10(11*H*)-one (1bn). Under Ar, 1,1′-thiocarbonyldiimidazole (0.27 g, 1.5 mmol) was added to **44a** (0.38 g, 1.5 mmol) in THF (20 mL) and warmed in an oil bath at 80 °C for 2 h. After cooling the resulting solid was filtered and rinsed with MeOH to yield 0.20 g (45%) of **1bn** as a tan solid (TLC: 80:20:5 $CHCl_3$:MeOH:HCOOH, R_f = 0.7). **1bn**: ^{1}H NMR (DMSO-d_6) δ 1.9–2.1 (m, 1H), 2.3–2.45 (m, 2H), 2.7–2.8 (m, 1H), 3.45–3.55 (t, 1H), 3.7–3.8 (t, 1H), 4.15–4.25 (d, 1H), 4.6–4.7 (d, 1H), 5.15–5.25 (t, 1H), 7.1 (s, 1H), 7.15 (s, 1H), 13.0–13.1 (bs, 1H).

Procedure Sequence for Method L. 4,7-Dichloro-2,3-dihydro-1*H*-inden-1-one (45). The desired product was prepared as previously described[21] after substituting 3-chloropropionic acid as the starting material for β-propiolactone to yield **45** in 57% yield.

4,7-Dichloro-2,3-dihydro-6-nitro-1*H*-inden-1-one (46). Over 0.33 h under Ar, **45** (41.89 g, 0.209 mol) was added neat to 0 °C fuming HNO_3 (420 mL). After 0.5 h the solution was added to ice (1.5 kg). The precipitated solid was filtered and rinsed with four portions of H_2O (100 mL each). After air-drying the resulting 39.98 g (80%) of off-white **46** was used without further purification (TLC: 1:1 EtOAc:hexane, R_f = 0.8). **46**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.8–3.0 (m, 2H), 3.0–3.3 (m, 2H), 8.0–8.1 (s, 1H).

2-[(4,7-Dichloro-2,3-dihydro-6-nitro-1*H*-inden-1-yl)amino]acetamide (47). Under Ar, $NaBH_3CN$ (11.31 g, 0.18 mol) was added to a room temperature solution of **46** (22.05 g, 0.09 mol), glycinamide hydrochloride (9.90 g, 0.09 mol), and NaOAc (14.77 g, 0.18 mol) in MeOH (500 mL) after which the reaction mixture was warmed to reflux. After 2 days the reaction mixture was cooled to room temperature and treated over 20 min with 3 N HCl (120 mL). After stirring for 4 h the mixture was basified with 3 N NaOH and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 15.44 g of brownish oil. This material was triturated with 1:1 acetone/hexane to yield 4.80 g (18%) of **47** as a solid which was used without further purification (TLC: 1:1 EtOAc:hexane, R_f = 0.3; 90:10:1 CH_2Cl_2:MeOH:NH_4OH, R_f = 0.45). **47**: ^{1}H NMR (DMSO-d_6) δ 2.05–2.15 (m, 1H), 2.2–2.3 (m, 1H), 2.6–2.7 (bd, 1H), 2.9–3.0 (m, 1H), 3.1 (d, 2H), 3.15–3.25 (m, 1H), 4.4–4.5 (bs, 1H), 7.05–7.15 (bs, 1H), 7.2–7.3 (bs, 1H), 8.2 (s, 1H).

7-Chloro-2,3,4,4a,5,6-hexahydro-9-nitro-1*H*-indeno[1,7-*ef*][1,4]diazepine (48). Over 15 min, BH_3·THF in THF (37.42 mL, 37.42 mmol) was added to a room temperature suspension of **47** (3.78 g, 12.48 mmol) in 1,2-dimethoxyethane (110 mL) under Ar. After 3 days at room temperature, the reaction mixture was warmed to 60 °C for an additional 1 day. The reaction mixture was then cooled to 0 °C and treated with MeOH (55 mL) followed by 3 N HCl (55 mL). After 5 h, the reaction was basified with 3N NaOH (60 mL) and the mixture slightly concentrated under reduced pressure. The resulting concentrated aqueous solution was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 4.96 g of oil (TLC: 90:10:1 CH_2Cl_2:MeOH:NH_4OH, R_f = 0.25). This material was combined with NaOAc (1.13 g, 13.73 mmol) in *n*-BuOH (50 mL) and warmed to reflux. After 16 h the mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 2.72 g (86%) of **48** as a brown-orange solid which was used without further purification (TLC: 90:10:1 CH_2Cl_2:MeOH:NH_4OH, R_f = 0.5; 20:1 CH_2Cl_2:MeOH, R_f = 0.3). **48**: ^{1}H NMR (DMSO-d_6) δ 1.6–1.75 (m, 1H), 2.35–2.45 (m, 1H), 2.6–2.9 (m, 4H), 3.1–3.25 (m, 2H), 3.8–3.9 (m, 1H), 4.45–4.55 (bs, 1H), 7.9 (s, 1H), 8.2 (bs, 1H).

7-Chloro-2,3,4,4a,5,6-hexahydro-4-(3-methyl-2-butenyl)-9-nitro-1*H*-indeno[1,7-*ef*][1,4]diazepine (49). Under N_2, 1-bromo-3-methyl-2-butene (0.96 g, 6.45 mmol) was added neat to a stirring, room temperature mixture of **48** (1.36 g, 5.38 mmol), $NaHCO_3$ (0.45 g, 5.38 mmol), and KI (0.89 g, 5.38 mmol) in DMF (25 mL). After stirring for 16 h the reaction mixture was partitioned between Et_2O and H_2O. The aqueous phase was reextracted with a second portion of Et_2O. The organic phases were combined and washed with H_2O and then brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 1.2 g of black oil. This crude material was flash chromatographed on a silica gel column eluting with 1:35 MeOH:CH_2Cl_2. The desired fractions were combined and concentrated under reduced pressure to give 0.52 g (30%) of **49** as an orange oil which was used without further purification (TLC: 20:1 CH_2Cl_2:MeOH, R_f = 0.4; 5:1 CH_2Cl_2:MeOH, R_f = 0.8).

9-Chloro-4,5,6,6a,7,8-hexahydro-6-(3-methyl-2-butenyl)cyclopent[*ef*]imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (1bp). The nitro group of **49** was reduced to the amine following the procedure for **43a** after substituting **49**

for **42a**. The resulting amine THF solution (TLC: 5:1 CH_2Cl_2:MeOH, R_f = 0.5) was treated with **1** mol equiv of 1,1'-thiocarbonyldiimidazole and warmed to reflux for 3 h. The reaction mixture was then concentrated under reduced pressure and partitioned between EtOAc and H_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield crude product which was further purified as described in Table 2 (TLC: 25% EtOAc:hexane, R_f = 0.4). **1bp**: ^{1}H NMR ($CDCl_3$) δ 1.7 (s, 3H), 1.8 (s, 3H), 1.95–2.05 (m, 1H), 2.45–2.55 (m, 1H), 2.7–2.8 (t, 1H), 2.8–2.95 (m, 1H), 3.0–3.1 (m, 1H), 3.1–3.2 (m, 1H), 3.35–3.5 (t, 2H), 3.65–3.75 (t, 1H), 4.0–4.1 (m, 1H), 4.7–4.8 (d, 1H), 5.3–5.4 (bs, 1H), 7.0 (s, 1H), 9.8–9.9 (bs, 1H).

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References

(1) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M.; Breslin, H.; Raeymaekers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellenkens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. Potent and selective inhibition of HIV-1 replication *in vitro* by a novel series of TIBO derivatives. *Nature* **1990**, *343*, 470–474.

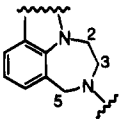
(2) Kukla, M.; Breslin, H.; Pauwels, R.; Fedde, C.; Miranda, M.; Scott, M.; Sherrill, R.; Raeymaekers, A.; Van Gelder, J.; Andries, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) Derivatives. *J. Med. Chem.* **1991**, *34*, 746–751.

(3) Kukla, M.; Breslin, H.; Diamond, C.; Grous, P.; Ho, C. Y.; Miranda, M.; Rodgers, J.; Sherrill, R.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L.; Janssen, M. A. C.; Janssen, P. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) Derivatives. 2. *J. Med. Chem.* **1991**, *34*, 3187–97.

(4) De Clercq, E. HIV-1-Specific RT Inhibitors: Highly Selective Inhibitors of Human Immunodeficiency Virus Type 1 that Are Specifically Targeted at the Viral Reverse Transcriptase. *Med. Res. Rev.* **1993**, *13* (3), 229–258.

(5) Pialoux, G.; Youle, B.; DuPont, B.; Gazzard, B.; Cauwenbergh, G.; Stoffels, P.; Davies, S.; De Saint Martin, J.; Janssen, P. Pharmacokinetics of R 82913 in patients with AIDS or AIDS-related complex. *Lancet* **1991**, *338*, 140–143.

(6) The relative stereochemistry of dimethylated intermediates **20**–**23** (Scheme 4) and related final products was assigned on the basis of detailed NMR examination of **20a**, **21a**, **22a**, **23a**, and **1ba,az**. These studies involved closely examining Dreiding models while evaluating ^{1}H NMR NOE difference data and, when applicable, ^{1}H NMR H–H coupling data. A summary of the key observations follows. The ^{1}H NMR interaction distinguishing **20a** from **21a** was the NOE between H-3 and H-5 (see generic structure below for numbering used in this discussion) seen for **20a** which indicated a cis diequatorial configuration of methyl groups. In addition, the final products **1ba,az** resulting from intermediates **20a** and **21a**, respectively, were also examined. In **1ba**, 1,3-diaxial NOE's between H-3 and H-5 were observed, while for **1az** an NOE was observed between H-3 and the C-5 methyl group. Differentiating **22a** (cis, axial–equitorial, methyl groups) from **23a** (trans, equatorial–equatorial, methyl groups) required a combination of observations. NOE's were noted from the overlapped H-3's to both methyl groups at C-2 and C-5 in **22a**, whereas in **23a**, the diequitorial arrangement of the methyl groups dictates that only the C-2 methyl gave an NOE to distinguishable H-3's. As confirmation of the diequatorial array of methyls in **23a**, a 1,3-diaxial NOE was observed between H-3 and H-5.



(7) Pauwels, R.; De Clercq, E.; Desmyter, J.; Balzarini, J.; Goubau, P.; Herdewijn, P.; Vandeputte, M. Sensitive and rapid assay on MT-4 cells for detection of antiviral compounds against the AIDS virus. *J. Virol. Methods* **1987**, *16*, 171–185.

(8) Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds. *J. Virol. Methods* **1988**, *20*, 309.

(9) Hargrave, K.; Proudfoot, J.; Grozinger, K.; Cullen, E.; Kapadia, S.; Patel, U.; Fuchs, V.; Mauldin, S.; Vitous, J.; Behnke, M.; Klunder, J.; Pal, K.; Skiles, J.; McNeil, D.; Rose, J.; Chow, G.; Skoog, M.; Wu, J.; Schmidt, G.; Engel, W.; Eberlein, W.; Saboe, T.; Campbell, S.; Rosenthal, A.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridobenzo- and Dipyridodiazepinones. *J. Med. Chem.* **1991**, *34*, 2231–2241.

(10) James, C.; Kenner, J.; Stubbings, W. Note on the Preparation of certain Iodo-compounds. *J. Chem. Soc.* **1920**, *117*, 773–776.

(11) Matsumoto, K.; Suzuki, M.; Iwasaki, T.; Miyoshi, M.; Okumura, K. New Convenient Syntheses of alpha-C-Acylamino Acids and alpha-Amino Ketones. *J. Org. Chem.* **1973**, *38*, 3571–3575.

(12) Scrowston, R.; Cooper, J. Substitution Reactions of Benzo[*b*]-thiophen Derivatives. Part III. Nitration of Benzo[*b*]thiophen-2-carboxylic Acid and its 3-Methyl Derivative. *J. Chem. Soc. C* **1971**, 3405–3409.

(13) Ireland, R.; Marshall, J. A. New Synthetic Method For The Preparation Of alpha-substituted beta-ketoesters. *J. Am. Chem. Soc.* **1959**, *81*, 2907–2908.

(14) Reported: Corey, E. The Mechanism of the Decarboxylation of alpha, beta- and beta, gamma-Unsaturated Malonic Acid Derivatives and the Course of Decarboxylative Condensation Reactions in Pyridine. *J. Am. Chem. Soc.* **1952**, *74*, 5897–5905. Prepared following procedure: Strube, R. Ethyl *tert*-Butyl Malonate. In *Organic Syntheses*; Rabjohn, N., Ed.; John Wiley and Sons: New York, 1963; Collect. Vol. IV, pp 417–419.

(15) Hori, M.; Kataoka, T.; Ohno, K.; Toyoda, T. Reactivities of 9-Phenylxanthylium and 9-Phenylthioxanthylium Salts in Electrophilic and Nucleophilic Reactions. I. Nitration. *Chem. Pharm. Bull.* **1973**, *21* (6), 1272–1281.

(16) Deinet, A. Methods for the Control of Plant Growth. U.S. Patent 3,223,515, December 14, 1965.

(17) Miller, D.; Hsu, F. L.; Ruffolo, R., Jr.; Patil, P. Stereochemical Studies of Adrenergic Drugs. Optically Active Derivatives of Imidazolines. *J. Med. Chem.* **1976**, *19*, 1382–1384.

(18) Celnik, K.; Jankowske, Z. Synthesis and properties of some 2-nitrobenzylamine derivatives. *Pol. J. Chem.* **1978**, *52* (5), 947–951.

(19) Djerassi, C.; Engle, R. R.; Bowers, A. The Direct Conversion of Steroidal Δ^5-3β-Alcohols to Δ^5- and Δ^4-3-Ketones. *J. Org. Chem.* **1956**, *21*, 1547–1549.

(20) Huffman, J. A. New Synthetic Route to Methoxytetralones. *J. Org. Chem.* **1959**, *24*, 1759–1763.

(21) Marechal, E.; Oliver, M. Etude de monomeres halogenes et de leur polymerisation cationique. IV.-Preparation, homopolymerisation et copolymerisation cationiques du (dichloro-4,7 indene). (Study of halogenated monomers and their cationic polymerization. IV. Preparation, homopolymerization and cationic copolymerization of (dichloro-4,7 indene).) *Bull. Soc. Chim. Fr.* **1974**, 699–700.

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