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 (TlBO) Derivatives. 4

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In previous papers, we have described the discovery of a new series of compounds, 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-ones, TlBO (**1** and **1a**), with potent anti-HIV-1 activity and the synthesis of analogues to better define the structure–activity relationships (SAR) in terms of changes in substituents at the N-6 position and variations of the five-membered urea ring as well as the seven-membered diazepine ring. This paper describes the synthesis of TlBO analogues with various substituents on the aromatic ring and their SAR in terms of anti-HIV-1 properties. Substituents on the 8-position furnished the most rewarding results and gave a large improvement in potency versus the parent compound. These included halogen, thiomethyl, and methyl. Analogues like 8-cyano, -methoxy, and -acetylene were equipotent, while 8-amino, -acetylamino, -dimethylamino, and -nitro were inactive (Table 1). Substituents at the 9-position tended to have little effect on activity, and 10-substituents decreased activity. The 8-chloro compound **6a** with $IC_{50} = 0.0043\ \mu M$ is currently under clinical development.

Introduction

In our previous publications[1-3] we reported a series of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]-benzodiazepin-2(1*H*)-ones (TlBO) exhibiting potent anti-HIV-1 activity. The mechanism of action of this series of compounds was elucidated[5] and found to be allosteric inhibition of viral reverse transcriptase with subsequent retardation of viral replication. Our initial medicinal chemistry and structure–activity relationship (SAR) efforts were directed toward several fronts: (1) the synthesis of a large variety of substituents at the N-6 position, (2) the alteration of the five-membered urea ring, and (3) variation, or substitution, of the seven-membered diazepine ring. As a result of these efforts, the lead compound **1a** (Table 1) was discovered and found to inhibit HIV-1 virus replication with an IC_{50} of 0.034 μM, comparable to AZT. This paper will describe the synthesis and SAR of variation of the aromatic ring substitutions and the resulting further improvement of anti-HIV-1 activity.

Chemistry

Variation of the aromatic ring portion of TlBO compounds was accomplished mostly through the generation of several key intermediates: the 8- and 9-halogens and the 8- and 9-nitro compounds. These intermediates were then further elaborated to a large series of TlBO analogues. A number of target compounds described in this article were synthesized employing previously developed synthetic schemes[2,3] depending on the availability of starting materials.

As indicated in Scheme 1 the 8-chloro (**6a**) and 8-fluoro (**6b**) analogues were prepared conveniently from the commercial 2,6-dihalobenzaldehydes. Nitration of the dihalides with a mixture of nitric acid and sulfuric acid gave the respective nitrobenzaldehyde **2** in 95% yields. The aldehydes were then reacted with L-alaninamide under reductive amination conditions to yield **3**. Reduction of the amides with borane in THF gave the nitrobenzodiazepines **4**. Alkylation with dimethylallyl bromide and subsequent reduction of the nitro function with Raney nickel and hydrazine gave the triamines **5**. The thiourea ring was then generated with 1,1'-thiocarbonyldiimidazole to give the target compounds **6a,b**. A similar synthetic scheme in which nitrobenzoic acid derivatives were used as starting material for the preparation of **1** and **1a** was reported by K. A. Parker.[4] The fluoronitro intermediate **4b** served as a convenient source of 8-thioether and 8-ethers as outlined in Scheme 1, by displacement of the 8-fluoro with alkoxides and thioalkoxide affording **4c–e** in high yield.

Another convenient route for generating a variety of 8-substituted analogues involved NBS bromination of the *t*-BOC-protected tricycle **7** at low temperature (−35 °C) in chloroform to give the 8-bromo intermediate **8a** (Scheme 2). This reaction gave a mixture of 8-bromo (**8a**), 10-bromo (**9**), and 8,10-dibromo compounds. These were separated by reverse phase liquid chromatography in modest yields and identified by NMR spectroscopic analysis (NOE). The 8-bromo **8a** was then deprotected with TFA and subsequently N-alkylated to provide **10e**. Treatment of **10e** with triflic anhydride, lutidine, and ethereal HCl and subsequent refluxing in ethanolic thiourea provided **10f**. The versatility of intermediate **8a** was further demonstrated with the successful syn-

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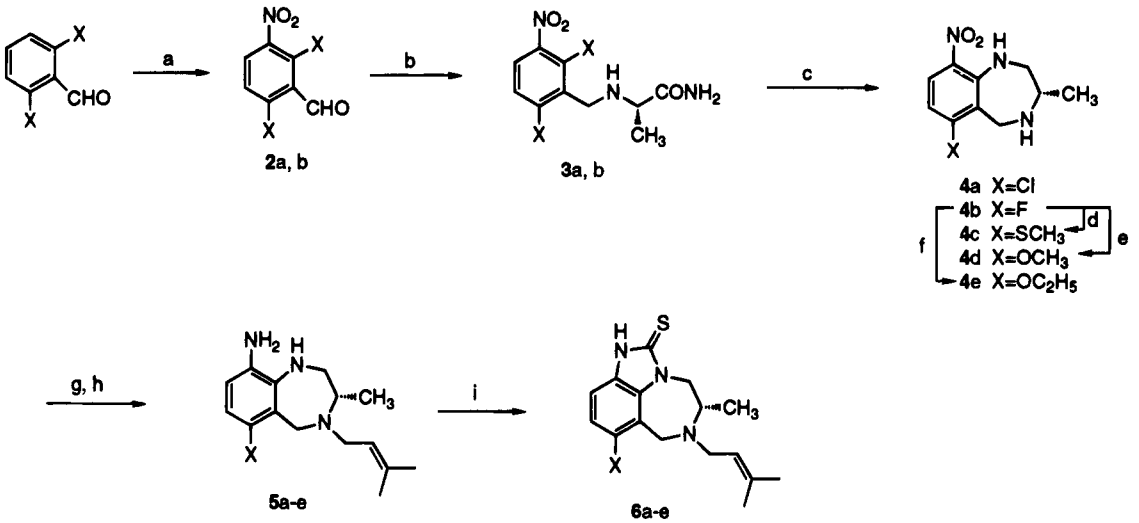
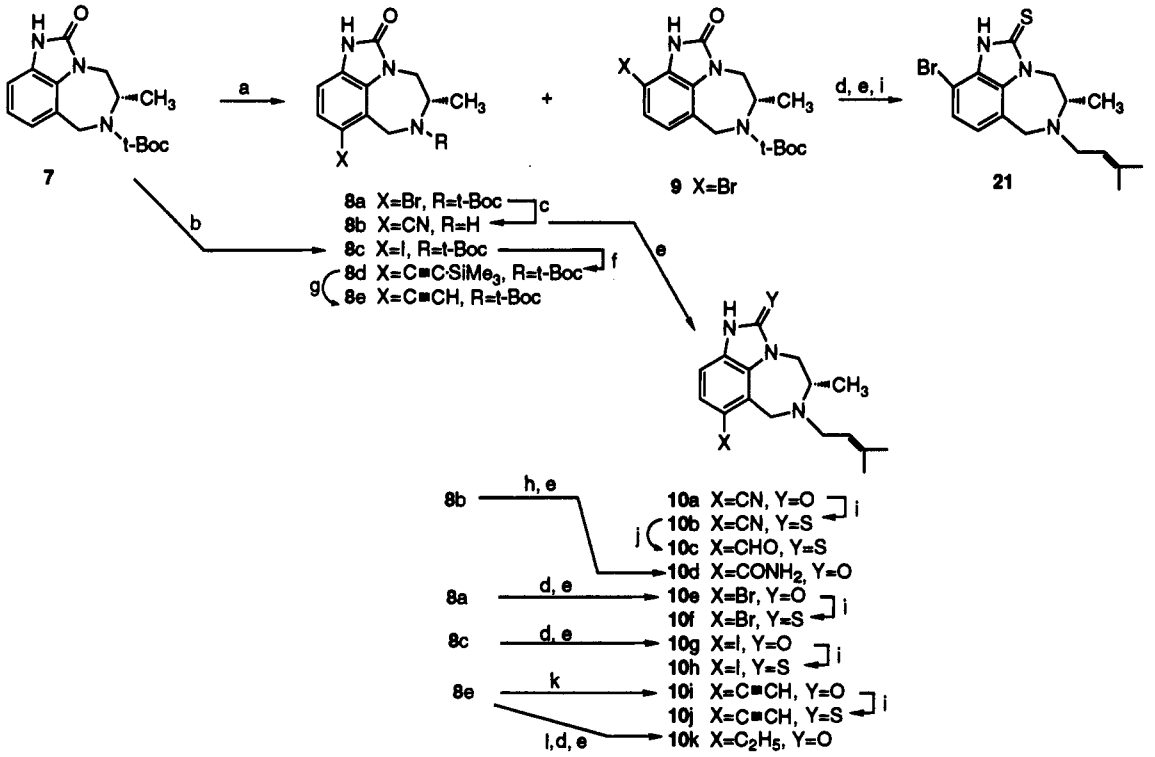
Scheme 1[a]



[a] (a) H_2SO_4/HNO_3; (b) L-alaninamide HCl, NaOAc, $NaCNBH_3$; (c) (1) BH_3·THF, (2) NaOAc, Δ; (d) CH_3SNa/DMF; (e) K_2CO_3/CH_3OH; (f) K_2CO_3/EtOH; (g) $(CH_3)_2C{=}CHCH_2Br$, Na_2CO_3, KI; (h) Ra Ni, H_2NNH_2, or LAH/THF; (i) $Im_2C{=}S$.

Scheme 2[a]

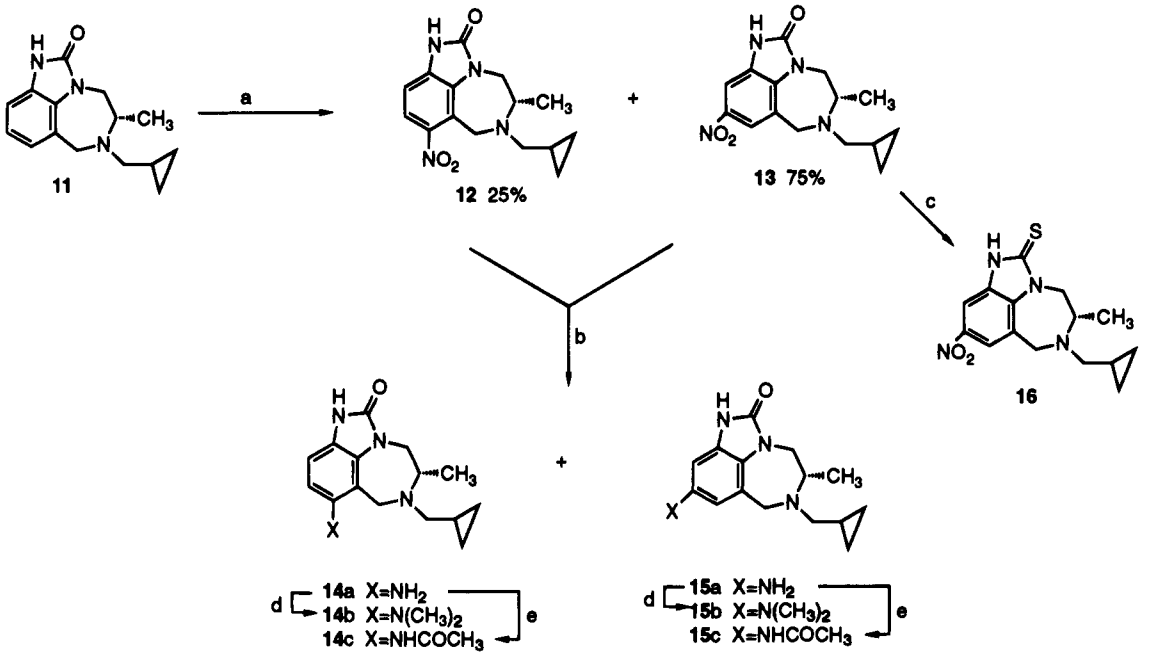


[a] (a) NBS/$CHCl_3$; (b) $TI(OAc)_3$, ICl, CH_2Cl_2; (c) CuCN, DMF; (d) TFA; (e) $ClCH_2CH{=}C(CH_3)_2$, Na_2CO_3, DMF; (f) (trimethylsilyl)acetylene, $Pd(Ph_3)_4$, CuI, Et_3N, THF; (g) K_2CO_3, MeOH; (h) H_2SO_4, NaCl; (i) (1) Tf_2O, lutidine, ethereal HCl; (2) thiourea/EtOH/Δ; (j) DIBAL, HOAc; (k) (1) TMSOTf, *i*-Pr_2EtN; (2) $ClCH_2CH{=}C(CH_3)_2$, Na_2CO_3, DMF; (l) NH_4HCO_2, Pd/C, MeOH.

thesis of several 8-substituted analogues, such as 8-cyano, 8-carboxamide, and 8-carboxaldehyde derivatives. Nucleophilic displacement of the 8-bromo group with cuprous cyanide in DMF gave the 8-cyano **8b** in high yield with concomitant loss of the *t*-BOC protecting group. Compound **8b** was converted to the target benzimidazolone **10a** in one step and then to the thione **10b** using the triflic anhydride procedure described above. The aldehyde **10c** was obtained by DIBAL reduction of the nitrile in methylene chloride at −70 °C. Treatment of **8b** with sulfuric acid in the presence of sodium chloride followed by alkylation gave the carboxamide **10d** in 65% yield.

The 8-iodo analogue **8c** was obtained by treating the unsubstituted tricycle **7** with thallium acetate followed by iodine monochloride at −70 °C in methylene chloride. This reaction gave a mixture of 8-iodo and 9-iodo products in a ratio of 6:1. The iodo intermediate **8c** was isolated and purified by liquid chromatography in 48% yield. Compound **8c** served as a useful synthetic intermediate leading to acetylene analogues **10i,j** as well as the 8-ethyl **10k**. Coupling of **8c** with (trimethylsilyl)acetylene under Sonogashira conditions[6] gave the (trimethylsilyl)acetylene **8d** in 74% yield. Removal of trimethylsilyl protecting group with K_2CO_3/MeOH gave acetylene **8e** in 91% yield. Removal of the *t*-BOC group from **8e** was accomplished with trimethylsilyl triflate and diisopropylethylamine in methylene chloride at

Scheme 3[a]



[a] (a) Fuming HNO_3, 0 °C; (b) Ra Ni, NH_2NH_2, MeOH; (c) (1) $POCl_3$, (2) thiourea, EtOH; (d) 37% HCHO, $NaCNBH_3$; (e) CH_3COCl, THF.

room temperature. Attempted removal of the *t*-BOC group with trimethylsilyl iodide or trimethylsilyl iodide with diisopropylamine under the same condition gave a mixture of the desired free amine and the corresponding 8-vinyl iodide, a side product from the addition of HI to the acetylene group. Alkylation gave the benzimidazolone **10i** which was converted to the thione **10j** using the triflic anhydride procedure.

In Scheme 3 the 8-amino and 9-amino analogues were prepared by nitration of the previously reported[3] benzimidazolone **11** in fuming nitric acid at low temperature (−60 °C). The nitration gave a mixture of 9-nitro and 8-nitro regioisomers in a 75:25 ratio which were separated by recrystallizations from acetonitrile. The position of the nitro group was established by NMR spectroscopic analysis (NOE) in $CDCl_3$. Reduction of the nitro group with Ra Ni/NH_2NH_2 gave the amines **14a** and **15a** which were subsequently converted to the alkylamines **14b** and **15b** and the amides **14c** and **15c**.

A number of final target compounds were synthesized using previously published reaction sequences.[2] In each case, the known nitroaminobenzoic acid[7,8] was used as the starting material and converted in seven steps to the desired final compounds **10l,m**, **18a,b**, and **19a,b** in 12%, 0.15%, 6.8%, 2.2%, 18%, and 10%, overall yields, respectively. Additionally, the known 5-fluoroisatoic anhydride[9] and 5,10-dichloroisatoic anhydride[9] were employed for the preparation of 9-fluoro and 9,10-dichloro analogues by the isatoic anhydride procedure described in a previous paper.[3] The 9-fluoro **17** was obtained in seven steps with 3.4% overall yield. Similarly the 9,10-dichloro **20** was obtained in 2.4% overall yield.

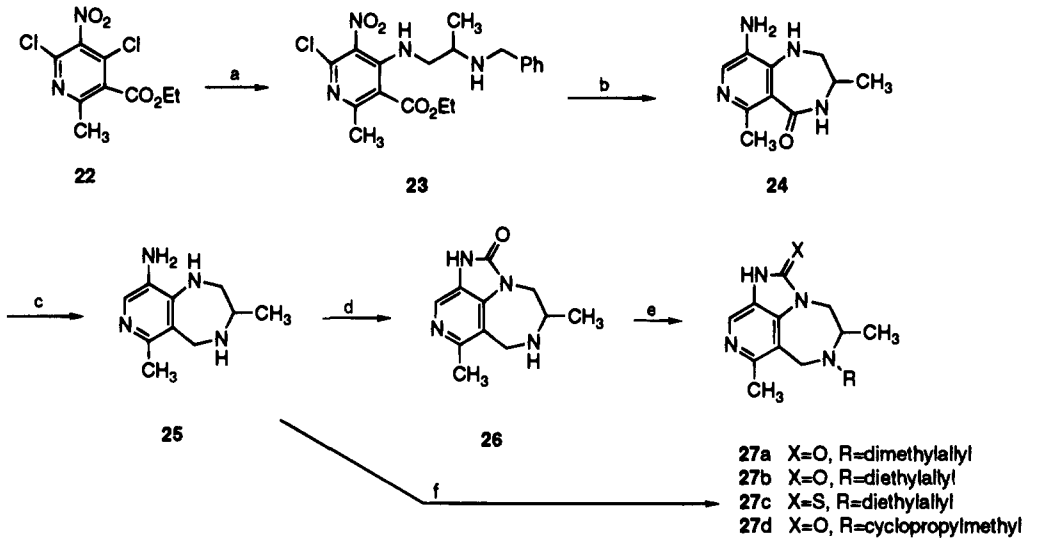
The racemic pyridyl analogues **27** were synthesized in five steps as shown in Scheme 4. Alkylation of the known chloronitropyridine[11] **22** with N^2-(phenylmethyl)-1,2-propanediamine gave **23** in 69% yield. Catalytic dehalogenation of **23** followed by refluxing in sodium ethanolate furnished the lactam **24** in 45% overall yield. Reduction of the lactam with LAH followed by condensation with diphosgene gave the imidazolone **26** which was alkylated to the targets **27a,b,d**.

Results and Discussion

As discussed in earlier papers on the TlBO series of compounds, **1** and **1a** exhibited potent anti-HIV-1 activity in primary and secondary screens as well as showed some possible efficacy in early clinical trials. The primary screen results displayed in Table 1 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.[12,13] 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 effects of HIV-1.

As indicated in Table 1, we have synthesized a large number of compounds in which the aromatic substituents of the molecule were varied. Previously we reported that in **1** and **1a** the dimethylallyl group was the optimal side chain at the N-6 position and that the thiourea ring was considerably more active than the corresponding urea ring. Consequently in our synthetic efforts, we maintained the dimethylallyl side chain constant as often as possible for SAR purposes. However, in several cases, due to synthetic requirements cyclopropylmethyl was the side chain instead. In the aromatic substituted analogues described in this paper, the thioureas (thiones) were also, without exception, more active than their urea counterparts as can be seen from Table 1 (cf. **10a** vs **10b**, **10e** vs **10f**, **10g** vs **10h**, **10i** vs **10j**, **10l** vs **10m**, **13** vs **16**, and **19a** vs **19b**). A range of 1.3−68-fold increase in activity was observed

Scheme 4[a]



[a] (a) $H_2NCH_2CH(CH_3)NHBzl$, Et_3N, MeOH; (b) (1) 10% Pd/C, NH_4HCO_2, MeOH, Δ, (2) NaOEt, Δ; (c) BH_3·THF, TMSCl, THF; (d) $Cl_3COCOCl$, NMM, CH_2Cl_2; (e) alkylating agent, Na_2CO_3, KT, DMF; (f) diethylallyl bromide, Na_2CO_3, KI, DMF, $Im_2C{=}S$.

when oxygen was replaced by sulfur. Among the aromatic substituted analogues, substituents on the 8-position gave the most interesting results and a large improvement in potency versus the parent compound. The 8-halogen-substituted compounds were among the most active analogues in this series, viz., 8-chloro, **6a** (IC_{50} = 0.0043 μM), 8-fluoro, **6b** (IC_{50} = 0.0058 μM), and 8-bromo, **10f** (IC_{50} = 0.0030 μM). The exception was 8-iodo, **10h**, which exhibited only modest activity. This may be due to the steric bulk of the iodine atom. The 8-thiomethyl analogue, **6c**, showed good activity and was about 10 times more active than the 8-methoxy analogue **6d**, possibly due to the more lipophilic nature of the thiomethyl group versus the methoxy group. The 8-ethoxy, **6e**, was less active than both **6c,d**, again suggesting a steric factor may be operating. The fact that the 8-methyl analogue, **10l**, was quite active in contrast to the 8-ethyl, **10k**, which was totally inactive, further implied that there may be a rather limited steric bulk tolerance at this portion of the molecule. The 8-cyano (**10b**), 8-methoxy (**6d**), and 8-acetylene (**10j**) were equipotent as compared to the parent compound **1**, while the amino, aminoacetyl, dimethylamino, and nitro analogues were inactive.

A variety of 8-substituted analogues were synthesized, and the SAR that emerged seemed to suggest that neither electron-donating nor electron-withdrawing properties of the substituents were the main factor for the increased activity observed since widely variant substituents such as Cl, CN, CH_3, OCH_3, and SCH_3 have comparable potency. On the other hand, the most active compounds seemed inevitably to contain a lipophilic group with limited bulk at the 8-position (such as 8-F, 8-Cl, 8-Br, 8-SCH_3, and 8-CH_3). Substituents at the 9-position tended to have little effect on activity compared to **1**, and the limited number of 10-position substituents examined (compounds **19a,b** and **21**) consistently showed decreased activity. Substitution of heteroaromatics for the benzene ring portion of the molecules generally gave inactive compounds. The pyridyl analogues **27** and the previously reported pyrimidinyl analogue[14] were inactive or much less active.

In summary, we made variations at the 8-, 9-, and 10-positions of the aromatic ring portion of TlBO to better define the SAR in this series of compounds. Substituents at the 8-position gave the most interesting and large improvement of anti-HIV-1 activity. The increased activity was probably not related to electronic effects of the substituents but rather to the lipophilic character and the size of the substituents. Substituents at the other two positions tended to give compounds with equipotent or decreased activity. The 8-chloro analogue **6a** (IC_{50} = 0.0043 μM) exhibited a 10-fold increase in activity over the lead compound **1a** and was chosen for further development.

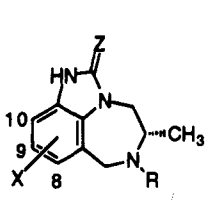
Experimental Section

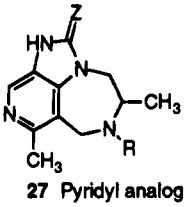
All final products included in Table 1 were characterized by 360-MHz ^1H NMR (Bruker AM 360 WB), IR (Nicolet 60SX), mass spectra (Finnegan 3300), and elemental analyses. Some of the intermediates were analyzed by mp, MS, or NMR. The elemental analyses were carried out by the internal Analytical Research Department of Janssen Research Foundation in Beerse, Belgium. 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.

2-[(2,6-Dichloro-3-nitrobenzyl)amino]propionamide (3a). To a solution of L-alaninamide HCl (8.42 g, 0.0498 mol) and sodium acetate (12.26 g, 0.149 mol) in 100 mL of methanol was added 2,6-dichloro-3-nitrobenzaldehyde (10.96 g, 0.0498 mol). After 0.5 h, $NaBH_3CN$ (3.77 g, 0.0598 mol) in 10 mL of MeOH was added and the solution was stirred at room temperature for 45 min. It was acidified to pH 1 with 3 N HCl and allowed to stir at room temperature for 16 h before the solvent was evaporated. The residue was basified with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried with K_2CO_3, and concentrated to give 14.06 g of crude product. Recrystallization with 2-propanol gave 10.29 g (71%) of pure **3a**: mp 128–129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 7 Hz, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.65–1.75 (s, 1H, NH), 3.25–3.32 (q, 1H, CH), 4.10–4.12 (q, 2H, CH_2), 5.40 (s, 1H, NH), 7.06 (s, 1H, NH), 7.50 (d, 1H, ArH), 7.70 (d, 1H, ArH); MS/MH^+ (CI, CH_4) m/z 292.

(S)-6-Chloro-2,3,4,5-tetrahydro-3-methyl-9-nitro-1*H*-1,4-benzodiazepine (4a). To a solution of **3a** (10.03 g, 0.0343 mol) in 400 mL of glyme and under argon was added 1 M BH_3·THF (103 mL, 0.103 mol). The reaction mixture was

Table 1. Variation of Aromatic Substituents and Inhibition of HIV-1 Replication





27 Pyridyl analog

no.	X	Z	R	formula	mp °C	IC_{50},[a] μM	n[b]	purification[c] (% yield)
1[d]	H(R82150)	S	DMA[e]			0.044		
1a[f]	9-Cl(R82913)	S	DMA			0.034		
6a	8-Cl(R86183)	S	DMA	$C_{16}H_{20}ClN_3$	160–161	0.0043	57	
6b	8-F	S	DMA	$C_{16}H_{20}FN_3S$	178	0.0058	1	CH_2Cl_2 (43)
6c	8-SCH_3	S	DMA	$C_{17}H_{23}N_3S_2$	134	0.0050	1	
6d	8-OCH_3	S	DMA	$C_{17}H_{23}N_3OS$·HCl	243.6	0.0339	1	
6e	8-OEt	S	DMA	$C_{18}H_{25}N_3OS$	146	0.0959	1	
10a	8-CN	O	DMA	$C_{17}H_{20}N_4O$	145	1.1396	2	
10b	8-CN	S	DMA	$C_{17}H_{20}N_4S$	173	0.0563	2	
10c	8-CHO	S	DMA	$C_{17}H_{21}N_3OS$·HCl·0.6H_2O	185	0.188	1	
10d	8-$CONH_2$	O	DMA	$C_{17}H_{22}N_4O_2$[g]	243.2	6.36	1	
10e	8-Br	O	DMA	$C_{16}H_{20}BrN_3O$	123–124	0.0473	2	
10f	8-Br	S	DMA	$C_{16}H_{20}BrN_3S$	157–159	0.003	14	+, CH_3CN (23.1)
10g	8-I	O	DMA	$C_{16}H_{20}IN_3O$	132	0.088	1	CH_3CN (63)
10h	8-I	S	DMA	$C_{16}H_{20}IN_3S$[h]	175	0.0474	1	+, CH_3CN (23)
10i	8-C≡CH	O	DMA	$C_{18}H_{21}N_3O$	122	0.4376	1	CH_3CN (48)
10j	8-C≡CH	S	DMA	$C_{18}H_{21}N_3S$	153.5	0.0296	1	+, CH_3CN (11.6)
10k	8-CH_2CH_3	O	DMA	$C_{18}H_{25}N_3O$·HCl	219.5	>5.94	1	
10l	8-CH_3	O	DMA	$C_{17}H_{23}N_3O$	134–136	0.989	10	CH_3CN (53)
10m	8-CH_3	S	DMA	$C_{17}H_{23}N_3S$	146–149	0.0136	11	+, CH_3CN (13.6)
13	9-NO_2	O	CPM[i]	$C_{15}H_{18}N_4O_3$	189–190	33.43	3	
14a	8-NH_2	O	CPM	$C_{15}H_{20}N_4$	205–207	849	3	
14b	8-$N(CH_3)_2$	O	CPM	$C_{17}H_{23}N_3S$	143–144	6.65	1	
14c	8-$NHCOCH_3$	O	CPM	$C_{17}H_{23}N_3O$	230–231	>796	1	
15a	9-NH_2	O	CPM	$C_{15}H_{20}N_4O$	186–188	60.55	7	
15b	9-$N(CH_3)_2$	O	CPM	$C_{17}H_{24}N_4O$·0.08CH_2Cl_2	215–217	6.65	1	
15c	9-$NHCOCH_3$	O	CPM	$C_{17}H_{22}N_4O_2$	241–242	159	3	
16	9-NO_2	S	CPM	$C_{15}H_{18}N_4O_2S$[j]	204–206	2.45	2	
17	9-F	S	DMA	$C_{16}H_{20}FN_3S$	171.5–173.5	0.0250	8	+, CH_3CN (37)
18a	9-CF_3	O	DMA	$C_{17}H_{20}F_3N_3O$	121–122	5.919	5	+ (80)
18b	9-CF_3	S	DMA	$C_{17}H_{20}F_3N_3S$	146–148	0.485	5	+, CH_3CN (33)
18c[k]	9-CH_3	O	DEA[l]	$C_{19}H_{27}N_3O$[m]	101–104	0.3142	6	CH_3CN (12)
19a	10-OCH_3	O	DMA	$C_{17}H_{23}N_3O_2$	142–145	6.63	1	(67)
19b	10-OCH_3	S	DMA	$C_{17}H_{23}N_3OS$	190	4.725	2	+, CH_3CN (58)
20	9,10-diCl	S	DMA	$C_{16}H_{19}Cl_2N_3S$	167–170	0.0255	5	+, EtOAc (40.9)
21	10-Br	S	DMA	$C_{16}H_{20}BrN_3S$·0.1CH_2Cl_2	140–142	1.075	2	+, CH_3CN (34)
				Pyridyl Analogues[n]				
27a		O	DMA	$C_{16}H_{22}N_4O$	195–196	872	1	
27b		O	DEA	$C_{18}H_{26}N_4O$·0.1CH_2Cl_2	217–219	>2	1	
27c		S	DEA	$C_{18}H_{26}N_4S$	239–242	0.243	2	
27d		O	CPM	$C_{15}H_{20}N_4O$·0.55H_2O	172–175	596	3	
AZT						0.0041		

[a] Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 virus or highest concentration tested which did not achieve 50% protection. [b] Number of experiments run for a given compound. [c] Purification method for compounds whose experimentals were not included. If a silica gel chromatography was done on the crude product, it is indicated by a "+". The solvent used for recrystallization follows. [d] See refs 1 and 2. [e] DMA = 3,3-dimethylallyl or 3-methyl-2-butenyl. [f] See ref 3. [g] C: calcd, 64.95; found, 65.57. N: calcd, 17.82; found, 17.05. [h] C: calcd, 46.49; found, 45.44. N: calcd, 10.17; found, 9.75. [i] CPM = cyclopropylmethyl. [j] C: calcd, 56.59; found, 53.55. N: calcd, 17.60; found 16.57. [k] Racemic. [l] DEA = 3,3-diethylallyl. [m] Elemental analysis not done. [n] Racemic compounds.

stirred at room temperature for 72 h. Methanol (180 mL) was added dropwise, 180 mL of 3 N HCl was added slowly, and then the reaction mixture was stirred at room temperature for 48 h. The solution was made basic with 200 mL of 3 N NaOH, and the organic layer was separated. The solution was extracted with CH_2Cl_2, which was then dried (K_2CO_3) and evaporated. The residue was taken up in 100 mL of *n*-BuOH, and NaOAc (3.0 g, 0.0366 mol) was added. The reaction mixture was refluxed under argon for 72 h. The solvent was removed, and the residue was dissolved in CH_2Cl_2, washed with a $NaHCO_3$ solution, and dried with K_2CO_3 and the solvent removed. The crude product was purified by flash chromatography on silica gel (1% MeOH/CH_2Cl_2) to give 5.4 g of product which was combined with 2.59 g of fumaric acid in methanol to give 3.80 g of pure fumarate salt. The base was freed with 3 N NaOH and CH_2Cl_2 to give 3.73 g (45%) of **4a**: mp 94–96 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 1.01 (d, J = 7 Hz, 3H, CH_3), 2.70–2.80 (br m, 1H), 3.10–3.25 (m, 2H), 3.60–3.70 (m, 1H), 3.94 (d, J = 17 Hz, 1H, $ArCH_2N$), 4.20 (d, J = 17 Hz, 1H, $ArCH_2N$), 6.74–6.77 (d, 1H, ArH), 7.86–7.88 (d, 1H, ArH), 8.27 (m, 1H, NH); MS MH^+ (CI, CH_4) *m/z* 242.

(+)-(*S*)-6-Fluoro-2,3,4,5-tetrahydro-3-methyl-9-nitro-1*H*-1,4-benzodiazepine (4b). To a flask under argon containing 2-[(2,6-difluoro-3-nitrobenzyl)amino]propionamide (24.46 g, 0.0944 mol) was added 283 mL (0.283 mol) of a 1 M solution of BH_3·THF in THF. The solution was stirred at room temperature for 0.5 h, refluxed for 4.5 h, and stirred at room temperature overnight. A faint spot of starting material remained by TLC, so the solution was refluxed for an additional 1 h, the solution cooled to room temperature, 250 mL of MeOH added dropwise, and 330 mL of 3 N HCl added dropwise. The solution was allowed to stir at room tempera-

ture overnight. The organic solvents were evaporated, and the remaining aqueous layer was filtered, made basic with 3 N NaOH, and extracted with CH_2Cl_2. The extracts were dried with K_2CO_3 and evaporated. The residue (15.6 g) was dissolved in 100 mL of methanol and stirred with 13.5 g of K_2CO_3 at room temperature over the weekend. A small percentage of uncyclized intermediate remained, so the solution was refluxed for 1 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, washed with water, dried with K_2CO_3, and evaporated to give 14.65 g of red oil. A flash chromatography eluting with 1% MeOH:CH_2Cl_2 gave 7.67 g (36%) of product as a red oil.

(*S*)-2,3,4,5-Tetrahydro-3-methyl-6-(methylthio)-9-nitro-1*H*-1,4-benzodiazepine (4c). A mixture of **4b** (1.66 g, 0.00738 mol) and CH_3SNa (0.57 g, 0.00812 mol) in DMF (20 mL) was stirred under Ar at room temperature overnight. Additional CH_3SNa (0.2 g) in DMF (20 mL) was added, and the mixture was stirred at room temperature overnight. The mixture was refluxed for 2 h and evaporated. The residue was dissolved in CH_2Cl_2, washed with $NaHCO_3$, and evaporated to yield 1.94 g, mp 92–94 °C.

(*S*)-6-Chloro-2,3,4,5-tetrahydro-3-methy-4-(3-methyl-2-butenyl)-1*H*-1,4-benzodiazepin-9-amine (5a). A 1.80-g (0.0074 mol) sample of **4a** was treated with 3-methyl-2-butenyl bromide (1.37 g, 0.0894 mol) in DMF (18 mL) in the presence of Na_2CO_3 (1.21 g, 0.0114 mol) and KI (1.24 g, 0.00745 mol) at room temperature for 16 h to give 2.60 g of crude material after workup which was purified by flash chromatography on silica gel (2% MeOH/CH_2Cl_2) to give 1.93 g of pure *N*-dimethylallyl derivative. To a cooled mixture of LAH (0.90 g, 0.0238 mol) in THF (25 mL) was added the *N*-dimethylallyl derivative (1.84 g, 0.00595 mol) dissolved in 25 mL of THF. The reaction mixture was heated to reflux for 8 h and cooled to 0 °C, and 0.9 mL of H_2O in 50 mL of THF was added slowly followed by 0.9 mL of 3 N NaOH and 2.7 mL of H_2O. The precipitate was filtered and washed with THF and the solvent removed to give 1.75 g of **5a** as a red oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6 Hz, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.00–3.40 (m, 7H), 3.80–3.90 (br s, 1H), 4.0 (d, J = 16 Hz, 1H, $ArCH_2N$), 4.25 (d, J = 16 Hz, 1H, $ArCH_2N$), 5.30 (t, 1H), 6.55 (d, 1H), 6.69 (d, 1H); MS MH^+ (CI, CH_4) *m/z* 280.

(*S*)-6-Fluoro-2,3,4,5-tetrahydro-3-methyl-4-(3-methyl-2-butenyl)-1*H*-1,4-benzodiazepin-9-amine (5b). To a solution of **4b** (3.0 g, 0.0133 mol) in DMF (30 mL) were added dimethylallyl bromide (2.15 g, 0.0140 mol), sodium carbonate (2.12 g, 0.02 mol), and potassium iodide (2.21 g, 0.0133 mol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed, and the residue was dissolved in CH_2Cl_2, washed with H_2O, and dried over K_2CO_3 and the solvent removed. The resulting residue was flash chromatographed on silica gel (1% MeOH/CH_2Cl_2) to give 3.30 g (85%) of product as a red oil. To a mixture of 3.20 g (0.0109 mol) of this red oil and wet Raney Ni (~1.0 g) in MeOH (150 mL) under argon was added dropwise $NH_2NH_2{\cdot}H_2O$ (8 mL). Addition was stopped when the yellow color of the solution disappeared. The solvent was removed, and the residue was taken up in ether, washed with H_2O and brine, and dried over K_2CO_3 and the ether removed to give 2.78 g of the diamine **5b**.

(+)-(*S*)-8-Chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (6a). To a solution of **5a** (1.75 g, 0.00595 mol) in THF (35 mL) was added thiocarbonyldiimidazole (1.40 g, 0.00714 mol). The reaction mixture was refluxed for 0.5 h, the solvent was removed, and the residue was flash chromatographed on silica gel (0.5% CH_3OH/CH_2Cl_2). One recrystallization from absolute EtOH gave 1.03 g (54%) of pure **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.8 Hz, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.10–3.27 (m, 2H), 3.50–3.60 (m, 1H), 4.20 (d, J = 17 Hz, 1H, $ArCH_2N$), 4.23–4.30 (dd, 1H, NCH_2CH), 4.42 (d, J = 17 Hz, 1H, $ArCH_2N$), 4.55–4.60 (dd, 1H, NCH_2-CH), 5.22 (t, 1H), 7.01 (d, 1H), 7.17 (d, 1H), 10.15 (s, 1H).

(−)-(*S*)-4,5,6,7-Tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-8-(methylthio)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (6c). A mixture of **4c** (2.14 g, 0.00817 mol), 3-methyl-2-butenyl bromide (1.46 g, 0.0098 mol), KI (1.36 g, 0.00817 mol), and Na_2CO_3 (1.3 g, 0.01226) in DMF (20 mL) was stirred under Ar at room temperature for 48 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, washed with water, dried (K_2CO_3), and evaporated. The residue was purified by column chromatography over silica gel (eluent: 2-propanone/hexane, 1/9). The pure fractions were collected and evaporated to yield 1.04 g (40%). The alkylated product (1.04 g, 0.0032 mol) in 50 mL of methanol and Ra Ni (0.25 g) in 50 mL of methanol were refluxed under argon. Hydrazine hydrate (0.97 mL, 0.0199 mol) was added dropwise over a 30-min period. The mixture was filtered through Decalite and evaporated. The residue was taken up in CH_2Cl_2, washed with water, dried (K_2CO_3), and evaporated to give 0.96 g (0.0033 mol) of the amino compound which was dissolved in 40 mL of THF, and 1,1′-thiocarbonyldiimidazole (0.78 g, 0.004 mol) was added. The mixture was refluxed for 45 min under Ar. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, washed with water, dried (K_2CO_3), and evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2 and then CH_3OH/CH_2Cl_2, 2/98). The pure fractions were concentrated (0.83 g) and crystallized from CH_3OH to yield 0.35 g (32%).

1,1-Dimethylethyl (+)-(*S*)-1,2,4,5,6,7-Hexahydro-5-methyl-2-oxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-6-carboxylate (7). (+)-(*S*)-4,5,6,7-Tetrahydro-5-methylimidazo-[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-one (7.4 g, 36.7 mmol) in CH_3CN (500 mL) was cooled to −35 °C before *t*-BOC anhydride (24.8 g, 113.8 mmol) and DMAP(0.45 g, 0.1 mmol) were added neat. The mixture was allowed to reach room temperature, and after 12 h, the reaction mixture was concentrated to a solid residue. The solid residue was flash chromatographed (CH_2Cl_2/MeOH, 99/1). The pure fractions were concentrated and dissolved in MeOH (100 mL). K_2CO_3 (10 g) was added, the mixture was stirred at room temperature for 3 h and concentrated, and the residue was partitioned between ethyl acetate/water. The organic phase was dried over sodium sulfate and concentrated to give solid residue **7** (6.4 g, 57.7%): mp 196–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.50 (m, 12H, $4CH_3$), 3.37–3.95 (m, 1H), 4.15–4.25 (dd, 0.5H), 4.25–4.35 (dd, 0.5H), 4.51–4.69 (m, 2H), 4.80–4.90 (m, 0.5H), 4.90–5.0 (d, 0.5H), 6.8–7.0 (m, 3H), 8.90–9.90 (d, 1H, NH). Anal. ($C_{16}H_{21}N_3O_3$) C,H,N.

1,1-Dimethylethyl (−)-(*S*)-8-Bromo-1,2,4,5,6,7-hexahydro-5-methyl-2-oxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-6-carboxylate (8a). A solution of **7** (5.43 g, 17.9 mmol) in 150 mL of $CHCl_3$ was cooled to −35 °C. NBS (2.29 g, 17.9 mmol) was added neat. After 6 h the reaction mixture was allowed slowly to reach room temperature, where it was kept for an additional 12 h. The reaction mixture was concentrated, and the solid was chromatographed (LC, reverse phase) to give 2.10 g of **8a** (30.7%): mp 235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05–1.30 (m, 12H, $4CH_3$), 3.70–3.92 (m, 1H), 4.02–4.20 (m, 1H), 4.30–4.5 (m, 0.5H), 4.5–4.82 (m, 2H), 4.90–5.80 (d, 0.5H), 6.78 (d, 1H), 7.12 (d, 1H), 11.0 (s, 1H). Anal. ($C_{16}H_{20}BrN_3O_3$) C,H,N.

(+)-(*S*)-1,2,4,5,6,7-Hexahydro-5-methyl-2-oxoimidazo-[4,5,1-*jk*][1,4]benzodiazepine-8-carbonitrile (8b). A mixture of **8a** (20.0 g, 0.0526 mol) and CuCN (46.9 g, 0.526 mol) in DMF (100 mL), under argon, was heated to reflux for 16 h. The reaction mixture was poured into 100 mL of 20% NaCl solution at 60 °C. This mixture was stirred for 1 h. The solution was neutralized with 3 N HCl (pH = 7) and extracted (constant liquid/liquid extraction) overnight with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated. The residue (5.4 g, 45% yield) was purified by flash chromatography on silica gel. The pure fractions were collected and evaporated. The residue was crystallized from CH_3CN to give 2.8 g (23.3%) of **8b**: mp 274 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (d, 3H), 2.76–2.90 (m, 1H), 3.0–3.15 (m, 1H), 4.50–4.62 (dd, 2H), 4.25–4.40 (d, 1H), 6.98 (d, 1H), 7.40 (d, 1H), 11.45 (s, 1H). Anal. ($C_{12}H_{12}N_4O$) C,H,N.

1,1-Dimethylethyl (−)-(*S*)-1,2,4,5,6,7-Hexahydro-8-iodo-5-methyl-2-oxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-6-carboxylate (8c). A solution of **7** (3.60 g, 0.0119 mol) in CH_2Cl_2 (100 mL) was cooled to −70 °C under argon flow.

$Tl(OAc)_3$ (5.34 g, 0.01307 mol) was added. Then a solution of iodochloride (1.93 g, 0.0119 mol) in CH_2Cl_2 (100 mL), cooled to −70 °C, was added over a period of 1 h to the reaction mixture. Stirring was continued for 6 h at −70 °C. Then, the reaction mixture was allowed to reach room temperature. Stirring was continued at room temperature for 12 h. Saturated aqueous $NaHSO_3$ (100 mL) was added. The organic layer was separated, washed with water, separated again, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by liquid chromatography (eluent: CH_3OH/water, 70/30). The fractions containing the pure product were evaporated. The residue was crystallized from CH_3CN (15 mL) and dried (overnight, vacuum, 60 °C) to yield 2.43 g (48%) of **8c**: mp 220.5−222 °C; ^1H NMR (400 MHz, $CDCl_3$) ∂ 1.07−1.36 (m, 12H), 3.45−3.70 (m, 1H), 4.0−4.25 (m, 1H), 4.25−4.70 (m, 2H), 4.70−5.0 (m, 1H), 6.45 (d, 1H), 7.20 (d, 1H), 11.45 (s, 1H). Anal. ($C_{16}H_{20}IN_3O_3$) C,H,N.

1,1-Dimethylethyl (−)-(*S*)-1,2,4,5,6,7-Hexahydro-5-methyl-2-oxo-8-[(trimethylsilyl)ethynyl)]imidazo[4,5,1-*jk*][1,4]-benzodiazepine-6-carboxylate (8d). A mixture of **8c** (1.0 g, 0.00233 mol), triethylamine (5 mL), and THF (5 mL) was stirred under N_2 for 15 min. (Trimethylsilyl)acetylene (0.78 mL, 0.00558 mol) was added followed by $Pd(PPh_3)_4$ (0.27 g, 0.023 mol) and CuI (0.04 g, 0.023 mol). The mixture was stirred for 5 days before it was filtered and partitioned between EtOAc/water. The organic layer was washed twice with water and once with a saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue (1.24 g) was purified by column chromatography over silica gel (eluent: EtOAc/hexane, 50/50). The pure fractions were concentrated to give 0.77 g (83%) of product which was crystallized from CH_3CN and dried under high vacuum at 60 °C for 3 days to yield 0.27 g of **8d**: mp 209.5 °C; ^1H NMR (400 MHz, DMSO-d_6) ∂ 0.22 (s, 9H), 1.15−1.40 (m, 12H), 3.75−3.85 (t, 1H), 4.10−4.20 (dd, 1H), 4.55−4.65 (m, 1H), 4.80−4.85 (d, 1H), 6.80 (d, 1H), 7.05 (d, 1H), 11.45 (s, 1H).

1,1-Dimethylethyl (*S*)-8-Ethynyl-1,2,4,5,6,7-hexahydro-5-methyl-2-oxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-6-carboxylate (8e). A mixture of **8d** (0.43 g, 0.00108 mol) and K_2CO_3 (0.74 g, 0.00539 mol) in methanol (10 mL) was stirred overnight at room temperature. The reaction mixture was evaporated. The residue was stirred in H_2O/CH_2Cl_2. The solid was filtered off. The solid was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH, 93/7). The pure fractions were collected and evaporated. The residue (0.18 g) was crystallized from CH_3CN and dried (high vacuum, room temperature, 5 days followed by drying under high vacuum at 60 °C) to yield 0.047 g (13.3%) of **8e**: mp 300 °C. Anal. ($C_{18}H_{21}N_3O_3 \cdot 0.1CH_2Cl_2$) C,H,N.

(+)-(*S*)-1,2,4,5,6,7-Hexahydro-5-methyl-6-(3-methyl-2-butenyl)-2-oxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-8-carbonitrile (10a). A mixture of **8b** (1.5 g, 0.0065 mol), dimethylallyl bromide (0.83 mL, 0.0072 mol), Na_2CO_3 (0.76 g, 0.0072 mol), KI (1.2 g, 0.0072 mol), and DMF (10 mL) was combined at room temperature under argon. The reaction mixture was stirred for 3 h at room temperature and concentrated. The residue was partitioned between water and CH_2Cl_2. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated. The residue (oil) was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH, 97/3). The pure fractions were collected and evaporated. The residue was crystallized from CH_3CN (5 mL). The crystals were collected on filter and dried (vacuum, overnight, 60 °C) to yield 1.3 g (68%) of **10a**: ^1H NMR (400 MHz, $CDCl_3$) ∂ 1.30 (d, 3H), 1.45 (s, 3H), 1.75 (s, 3H), 3.10−3.27 (m, 2H), 3.50−3.58 (m, 1H), 3.85−3.95 (m, 1H), 4.12 (d, 1H), 4.21 (d, 1H), 4.48 (d, 1H), 5.25 (t, 1H), 7.10 (d, 1h), 7.40 (d, 1H), 10.15 (s, 1H).

(+)-(*S*)-1,2,4,5,6,7-Hexahydro-5-methyl-6-(3-methyl-2-butenyl)-2-thioxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-8-carbonitrile (10b). A solution of **10a** (1.07 g, 0.0036 mol) in CH_2Cl_2 (75 mL) was cooled to −78 °C under argon flow. Then trifluoromethanesulfonic acid anhydride (0.67 mL, 0.0040 mol) was added neat at −78 °C, and after 15 min, lutidine was added (0.84 g, 0.0072 mol) at −78 °C. Another 15 min later, ethereal HCl (20 mL) was added at −78 °C. Stirring at this temperature was continued for 0.5 h. Saturated aqueous $NaHCO_3$ was added to the cold reaction mixture to neutralize the reaction. Then, this mixture was allowed to warm up to room temperature. The mixture was extracted twice with CH_2Cl_2 (50 mL). The organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue (oil) was dissolved in ethanol (5.0 mL), thiourea (2.7 g, 0.036 mol) was added, and this mixture was refluxed overnight. The cooled reaction mixture was evaporated, and the residue was partitioned between H_2O/CH_2Cl_2. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated. The residue (oil) was purified by flash chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH, 98/2). The pure fractions were collected and evaporated. The residue was crystallized from CH_3CN. The crystals were filtered off and dried (overnight, vacuum, 60 °C) to yield 0.450 g (40%) of **10b**: ^1H NMR (400 MHz, $CDCl_3$) ∂ 1.30 (d, 3H), 1.45 (s, 3H), 1.75 (s, 3H), 3.10−3.27 (m, 2H), 3.50−3.62 (m, 1H), 4.20−4.32 (m, 2H), 4.48−4.60 (m, 2H), 5.20 (t, 1H), 7.18 (d, 1H), 7.42 (d, 1H), 11.40 (s, 1H).

(−)-(*S*)-1,2,4,5,6,7-Hexahydro-5-methyl-6-(3-methyl-2-butenyl)-2-thioxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-8-carboxaldehyde Hydrochloride Hydrate (10:10:6) (10c). A solution of **10b** (0.30 g, 0.00056 mol) in THF (150 mL) under Ar was cooled to −78 °C, and DIBAL/CH_2Cl_2 (2.88 mL, 0.288 mol) was added. After 30 min, glacial acetic acid (5 mL) was added, the solution was allowed to reach room temperature, and water (5 mL) was added. The methylene chloride layer was separated and washed with a saturated aqueous $NaHCO_3$ solution, brine, and water. The solvent was evaporated, and the oily residue was dissolved in diethyl ether and treated with ethereal HCl (10 mL). The precipitate was filtered off, crystallized from CH_3CN (5 mL), and dried in vacuo overnight at room temperature to yield 0.21 g (65%) of **10c**: ^1H NMR (400 MHz, DMSO-d_6) ∂ 1.38−1.50 (m, 3H), 1.58 (s, 3H), 1.75 (s, 3H), 3.80−4.0 (m, 2H), 4.0−4.10 (br s, 1H), 4.27−4.72 (m, 1.5H), 4.70 (s, 1H), 5.10 (s, 0.5H), 5.30−5.50 (m, 2H), 7.40 (d, 1H), 7.80−7.90 (m, 1H), 10.10 (m, 1H), 11.0 (s, 0.5H), 11.66 (s, 0.5H), 13.4−13.65 (d, 1H).

(−)-(*S*)-1,2,4,5,6,7-Hexahydro-5-methyl-6-(3-methyl-2-butenyl)-2-oxoimidazo[4,5,1-*jk*][1,4]benzodiazepine-8-carboxamide (10d). NaCl (0.5 g) was added to a mixture of **8b** (0.51 g, 0.00224 mol) in concentrated H_2SO_4 (5 mL) under Ar, and the mixture was heated at 80 °C for 2 h. The mixture was brought to room temperature, poured onto ice, and neutralized with NH_4OH until pH 7. The precipitate was filtered off, washed with water, crystallized from CH_3CN (5 mL), and dried in vacuo at 60 °C to give 0.36 g (65%) of the deprotected carboxamide. A mixture of the carboxamide (0.36 g, 0.00146 mol), dimethylallyl bromide (0.19 g, 0.0016 mol), Na_2CO_3 (0.17 g, 0.0016 mol), KI (0.27 g, 0.0011 mol), and DMF (3 mL) was stirred under Ar at room temperature for 3 h. The solvent was evaporated, and the residue was partitioned between water and $CHCl_3$. The organic layer was separated, washed with a saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. The oily residue was purified by column chromatography over silica gel ($CHCl_3/CH_3OH$, 97/3). The pure fractions were collected and evaporated. The residue was crystallized from CH_3CN (5 mL) and dried under high vacuum at 60 °C overnight to yield 0.26 g (57%) of **10d**: ^1H NMR (400 MHz, DMSO-d_6) ∂ 1.10 (d, 3H), 1.35 (s, 3H), 1.65 (s, 3H), 2.98−3.20 (m, 2H), 3.65−3.75 (m, 1H), 3.95−4.20 (m, 2H), 4.30−4.38 (d, 1H), 5.10 (t, 1H), 6.80 (d, 2H), 7.10 (d, 1H), 7.20 (s, 1H), 7.55 (s, 1H), 10.95 (s, 1H).

(+)-(*S*)-8-Bromo-1,2,4,5,6,7-hexahydro-5-methyl-6-(3-methyl-2-butenyl)-2-oxoimidazo[4,5,1-*jk*][1,4]benzodiazepine (10e). To cooled (0 °C) TFA under argon was slowly added **8a** (2.0 g, 5.24 mmol) neat. The solution was stirred at 0 °C for 2 h. The reaction mixture was concentrated to a residue oil. DMF (200 mL) was added followed by dimethylallyl bromide (0.66 mL, 5.76 mmol), Na_2CO_3 (3.0 g, 28.3 mmol), and KI (0.96 g, 5.76 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated to a residue solid and partitioned between water/ethyl acetate. The organic phase was washed with

saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The oil was crystallized from acetonitrile (5 mL) and dried overnight under high vacuum (60 °C) to yield 1.5 g (81.8%) of **10e**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, 3H), 1.45 (s, 3H), 1.72 (s, 3H), 3.10–3.28 (m, 2H), 3.4–3.55 (m, 1H), 3.82–3.92 (dd, 1H), 4.10–4.19 (d, 2H), 4.32–4.51 (d, 1H), 5.25 (t, 1H), 6.82 (d, 1H), 7.21 (d, 1H), 9.80 (s, 1H).

(−)-(*S*)-8-Ethyl-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one Monohydrochloride (10k). A mixture of **8e** (1.0 g, 3.06 mmol), NH_4HCO_2 (1.93 g, 30.6 mmol), and Pd/C (10%) (1.0 g) in MeOH (75 mL) was refluxed for 1 h. After cooling to room temperature, the reaction mixture was filtered through Dicalite and evaporated, leaving 0.43 g of colorless glass. This material was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated, leaving 0.43 g of white foam which was used for the next reaction. A mixture of the white foam obtained above (0.43 g, 0.00130 mol) in TFA (10 mL) was stirred at 0 °C for 2 h. The reaction mixture was evaporated and the residue alkylated as previously described to yield crude **10k** (oil, 0.35 g, 90%). This was dissolved in diethyl ether, and ethereal HCl (2 mL) was added. The precipitate was filtered and recrystallized from 2-propanol, and the crystals were filtered and dried (60 °C, high vacuum, 3 days) to yield 1.35 g (63%) of **10k**: ^1H NMR (400 MHz, DMSO-d_6) δ 1.02–1.16 (m, 3H), 1.38–1.60 (m, 6H), 1.80 (s, 3H), 2.50–2.62–3.28 (m, 2H), 3.82–3.92 (t, 1H), 3.92–4.60 (m, 2H), 4.06–4.30 (m, 1.3H), 4.30–4.48 (m, 1H), 4.48–4.60 (m, 1H), 5.45 (t, 1H), 6.82–6.92 (dd, 2H), 10.04–11.2 (m, 1.6H).

(+)-(*S*)-6-(Cyclopropylmethyl)-5-methyl-8-nitro-4,5,6,7-tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (12) and (+)-(*S*)-6-(Cyclopropylmethyl)-5-methyl-9-nitro-4,5,6,7-tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (13). Over about 45 min, 11[3] (2.75 g, 0.0106 mol) was added neat portionwise to fuming nitric acid (30 mL) at −60 to −50 °C (bath temperature) under Ar with stirring. After all the solid dissolved, the mixture was stirred at −50 °C for an additional 30 min. The mixture was then slowly poured into ~400 mL of ice/H_2O. The resulting solution was made basic by adding a 50% NaOH solution and then saturated aqueous $NaHCO_3$ until pH = 8. The nitro compound precipitated out. It was collected on a filter and dried under vacuum at 50 °C for 16 h. NMR ($CDCl_3$) indicated that the sample was a mixture of **12** and **13** (25:75). A 0.50-g sample of the crude mixture was crystallized three times in CH_3CN to yield ~150 mg of yellow solid **13** which was dried under vacuum at 50 °C for 16 h.

(+)-(*S*)-8-Amino-6-(cyclopropylmethyl)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (14a) and (+)-(*S*)-9-Amino-6-(cyclopropylmethy)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]-benzodiazepin-2(1*H*)-one (15a). To a refluxing mixture of Ra Ni (1.6 g) and hydrazine hydrate (15.0 mL, 0.031 mol) in methanol (200 mL) was added portionwise **13** (12.4 g, 0.041 mol) which contained about 25% **12**. The yellow color of the starting material slowly discharged during the addition. After the addition was completed, the mixture was refluxed for 20 min. The mixture was cooled and the Ra Ni removed by filtration (Celite). The solvent was removed to give 11.20 g of a crude brown oil. TLC showed two spots, one major and one minor (10% MeOH/CH_2Cl_2). The crude oil was triturated with ~40 mL of CH_3CN to give a brown solid (8.5 g) which was taken up in $CHCl_3$ and washed with H_2O to remove some water soluble material. The $CHCl_3$ was removed and the residue triturated in 40 mL of CH_3CN to give 5.5 g of solid **15a**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.00–0.12 (m, 2H), 0.42–0.58 (m, 2H), 0.80–0.90 (m, 1H), 1.25 (d, 3H), 2.20–2.30 (m, 1H), 2.55–2.65 (m, 1H), 3.42–3.55 (s, 3H), 3.60–3.75 (m, 1H), 3.95–4.05 (dd, 1H), 4.05–4.15 (d, 1H), 4.35–4.45 (d, 1H), 6.15 (s, 1H), 6.30 (s, 1H), 8.5 (s, 1H). The mother liquors were combined, and the solvent was removed to give 4.85 g of reddish brown solid which was a mixture of **14a** and **15a** (about 50:50). This material was purified by flash chromatography on silica gel, eluting the column with 1% (10% NH_4OH/MeOH)–CH_2Cl_2 which was increased to 3% and finally 5% (10% NH_4OH/MeOH)–CH_2Cl_2. The fractions containing **14a** were combined, and the solvent was removed to give 1.25 g of pure **14a** which was dried at 50 °C for 16 h: ^1H NMR (400 MHz, DMSO-d_6) δ 0.00 (m, 2H), 0.39–0.48 (m, 2H), 0.80–0.90 (m, 1H), 1.12 (d, 3H), 2.20–2.30 (m, 1H), 2.48–2.58 (m, 1H), 3.30–3.45 (m, 1H), 3.60–3.68 (m, 1H), 3.75–3.80 (m, 2H), 4.10 (d, 1H), 4.42 (s, 2H), 6.32 (d, 1H), 6.55 (d, 1H), 10.32 (s, 1H, NH).

(+)-(*S*)-6-(Cyclopropylmethy)-8-(dimethylamino)-5-methyl-4,5,6,7-tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (14b). To a solution of **14a** (0.272 g, 0.001 mol) in 80 mL of CH_3CN and 2.0 mL of 37% formaldehyde was added sodium cyanoborohydride (0.19 g, 0.003 mol). The reaction mixture was stirred for 15 min at room temperature, and then 8 drops of glacial acetic acid was added. The mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was basified by adding 20 mL of saturated aqueous K_2CO_3 solution. The resulting mixture was extracted with ether and dried (Na_2SO_4) and the solvent removed to give 230 mg of oil. NMR showed it was a mixture of desired product and *N*-hydroxymethyl compound. It was taken up with 10 mL of concentrated HCl, heated to reflux for 3 h, and then cooled and basified with solid K_2CO_3. The mixture was partitioned between ether (~100 mL) and water, the organic layer dried (Na_2SO_4), and the ether removed to yield 200 mg of an oil. It was purified by flash column chromatography on silica gel, eluting the column with CH_2Cl_2 and then 2% (10% NH_4OH/MeOH)–CH_2Cl_2. Fractions containing the pure product were combined, and the solvent was removed to yield an oil; trituration with CH_3CN gave a white solid product (80 mg).

(+)-(*S*)-6-(Cyclopropylmethyl)-4,5,6,7-tetrahydro-5-methyl-9-nitroimidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (16). A mixture of **13** (1.0 g, 0.0033 mol) in 70 mL of $POCl_3$ (0.75 mol) was heated in an oil bath maintained at 90–100 °C for 20 h. During the heating, the mixture slowly went into solution. The solvent ($POCl_3$) was removed under reduced pressure. The residue was neutralized with Na_2CO_3 solution to pH ~ 8 and extracted with 800 mL of ether. The ether layer was dried (Na_2SO_4) and removed to give 0.52 g of gummy solid. The gummy solid was taken up in 40 mL of EtOH, and 0.50 g of thiourea (0.0065 mol) was added. The mixture was heated to reflux for 2 h. The precipitated yellow solid was collected on a filter and dried to give 320 mg as the HCl salt. The HCl salt was treated with saturated $NaHCO_3$ solution, extracted with ~50 mL of $CHCl_3$, and dried (Na_2SO_4) and the $CHCl_3$ solvent removed to yield 200 mg of yellow solid which was purified by flash chromatography on silica gel eluting the column with 0.5% MeOH/CH_2Cl_2 and then 1% MeOH/CH_2Cl_2. The fractions containing pure product were combined, and the solvent was removed to yield 153 mg of pure **16**.

(+)-(*S*)-9-Acetamido-6-(cyclopropylmethy)-5-methyl-4,5,6,7-tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (15c). To a solution of **15a** (0.32 g, 0.0012 mol) in THF (30 mL) was added acetyl chloride (0.093 g, 0.0012 mol) at room temperature with stirring. The mixture was stirred for 16 h. The solvent was removed, and the residue was made basic by adding a saturated solution of Na_2CO_3. The product was extracted into 40 mL of $CHCl_3$ and dried (Na_2SO_4), and the solvent was removed to yield 250 mg of crude solid. This solid was purified by flash column chromatography on silica gel, eluting the column with CH_2Cl_2 first and then 1% up to 3% MeOH/CH_2Cl_2. The fractions containing the desired product were combined, and the solvent was removed to yield 180 mg of pure **15c** (49%). The sample was dried under high vacuum at 50 °C for 16 h. **15c**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (m, 2H), 0.35–0.55 (m, 2H), 0.75–0.85 (m, 1H), 1.20 (d, 3H), 2.20 (s, 3H), 2.15–2.25 (m, 1H), 2.55–2.65 (m, 1H), 3.40–3.50 (m, 1H), 3.50–3.62 (m, 1H), 3.80–3.90 (dd, 1H), 4.05 (d, 1H), 4.30 (d, 1H), 6.80 (s, 1H), 7.45 (s, 1H), 9.70 (s, 1H).

Ethyl 6-Chloro-2-methyl-5-nitro-4-[[2-[(phenylmethyl)-amino]propyl]amino]-3-pyridinecarboxylate Monohydrochloride (23). To a refluxing solution of **22** (94.6 g, 0.339 mol), triethylamine (67 mL, 0.484 mol), and methanol (700 mL) was added a solution of $H_2NCH_2CH(CH_3)NHBzl$ (55.59 g, 0.339

mol) in 250 mL of methanol over 30 min. After refluxing for 15 min, the solvent was removed. The resulting gum was triturated with EtOAc, and the salts were filtered off. Evaporation gave 180.7 g of brown oil. This oil was triturated with ether, filtered, and acidified with ethereal HCl. The resulting yellow precipitate was filtered off and recrystallized from CH_3CN to give 104 g (69% yield) of a pale yellow product.

9-Amino-2,3-dihydro-3,6-dimethyl-1*H*-pyrido[4,3-*e*]-1,4-diazepin-5(4*H*)-one (24). A solution of **23** (40 g, 90.3 mmol), 10% Pd/C (40 g), and ammonium formate (57 g, 90.3 mmol) in methanol (800 mL) was refluxed for 6 h. After cooling to room temperature, the reaction mixture was filtered thrugh Dicalite and evaporated, leaving 23.5 g of a yellow solid. This material was taken up in ethanol (200 mL) and filtered. The filtrate was added to a solution of NaOEt prepared from 12 g (52.2 mmol) of sodium and 500 mL of ethanol. After refluxing overnight, the reaction mixture was cooled to room temperature, filtered, neutralized with concentrated HCl to pH = 8, and filtered. Evaporation gave 14.74 g of a yellow solid. Crystallization from MeOH gave 9.5 g of product as a yellow solid (51% yield), mp 87 °C softened, 120 °C dec.

9-Amino-2,3,4,5-tetrahydro-3,6-dimethyl-1*H*-pyrido-[4,3-*e*]-1,4-diazepine Dihydrochloride (25). To a suspension of **24** (7.80 g, 37.9 mmol) in THF (150 mL) was added BH_3·THF (180 mL, 189 mmol) dropwise by addition funnel. Gas evolution was observed and the compound dissolved to give a yellow solution. After addition of TMSCl (24 mL, 189 mmol), the reaction mixture was refluxed overnight. After the mixture cooled to room temperature, the reaction was quenched by dropwise addition of MeOH (40 mL). The reaction mixture was then refluxed for 1 h, cooled to room temperature, and filtered. The resulting pale yellow solid was refluxed in 2-propanol (300 mL) for 1 h, filtered, and dried at 60 °C under high vacuum for 2 h to give 8.54 g (82%) of a pale yellow solid. A sample was recrystallized from IPA/MeOH and dried over the weekend at 60 °C under high vacuum. **25**: mp 300 °C dec; ^{1}H NMR (400 MHz, $DMSOd_6$) ∂ 1.316 (d, J = 6.5 Hz, 3H), 2.50 (s, 3H), 4.25 (d, 1H), 4.40 (d, 1H), 5.7 (s, 2H), 7.50 (s, 1H), 7.75 (s, 1H), 9.20–10.5 (br d, 2H), 13.7 (br s, 1H); MS MH^+ (FAB) m/z 193.

4,5,6,7-Tetrahydro-5,8-dimethylimidazo[4,5,1-*jk*]pyrido-[3,4-*f*][1,4]diazepin-2(1*H*)-one Dihydrochloride (26). To a 0 °C suspension of **25** (8.04 g, 30.3 mmol) and *N*-methylmorpholine (15.5 mL, 141 mmol) in methylene chloride (400 mL) was added trichloromethyl chloroformate (4.67 mL, 38.7 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. After evaporating, the residue was refluxed in 15% H_2O/dioxane for 1.5 h. The solvent was then evaporated and refluxed with 2-propanol (200 mL). Filtration gave 5.18 g of a pale powder (67%) as the HCl salt, mp 300 °C dec.

4,5,6,7-Tetrahydro-5,8-dimethyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1-*jk*]pyrido[3,4-*f*][1,4]diazepin-2(1*H*)-one (27a). A mixture of **26** (0.55 g, 2.16 mmol), dimethylallyl bromide (0.26 mL, 2.16 mmol), Na_2CO_3 (0.69 g, 6.48 mmol), and KI (0.36 g, 2.16 mmol) in DMF (30 mL) was stirred for 3 days at room temperature. After partitioning between CH_2Cl_2 and dilute aqueous NaOH, the aqueous phase was extracted with CH_2Cl_2 (4×). The combined organic phases were dried (K_2CO_3) and evaporated, leaving a pale yellow foam. Trituration with CH_3CN gave 0.231 g of white crystalline product which was dried overnight under high vacuum at room temperature (37% yield). **27a**: ^{1}H NMR (400 MHz, DMSO-d_6) ∂ 1.15 (d, J = 7 Hz, 3H), 1.35 (s, 3H), 1.70 (s, 3H), 2.28 (s, 3H), 3.0–3.1 (m, 1H), 3.15–3.22 (m, 1H), 3.40–3.50 (m, 1H), 3.68–3.75 (m, 1H), 3.70–3.85 (m, 1H), 3.90 (d, 1H), 4.50 (d, 1H), 5.18 (t, 1H), 7.90 (s, 1H), 11.0 (br, s, 1H).

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