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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. \_\_\_\_\_ S. \_\_\_\_\_ D. \_\_\_\_\_

Ref: Expediente No. 00.065.062

Solicitud de patente titulada: "LOS INHIBIDORES TRICICLICOS DE POLI (ADP-RIBOSA) POLIMERASAS".

Solicitante: AGOURON PHARMACEUTICALS INC, y CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED.

**RESPUESTA AL OFICIO No. 9705 NOTIFICADO POR FIJACION EN LISTA No. 418,**  
**DE FECHA 20 DE OCTUBRE 2005, (EXAMEN DE BUSQUEDA DE**  
**ANTERIORIDADES)**

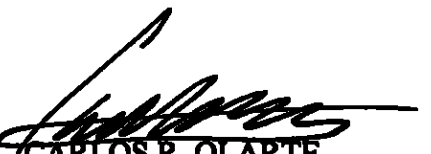
CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito dar respuesta al auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486. Consecuentemente, me permito presentar los siguientes documentos solicitados por el Examinador:

|   |                                                                                                                                                                                                                                                                                                       |         |
|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1 | KUKLA MJ, BRESLIN HJ, DIAMOND CJ, GROUS PP, HO CY, MIRANDA M, RODGERS JD, SHERRILL RG, DE CLERCQ E, PAUWELS R, ET AL.<br>"Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo [4,5,1-jk][1,4]benzodiazepin-2(1H)-on e (TIBO) derivatives. 2."<br>J Med Chem. 1991 34(11):3187-97. | ANEXO A |
|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|

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|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 2 | BRESLIN HJ, KUKLA MJ, LUDOVICI DW, MOHRBACHER R, HO W, MIRANDA M, RODGERS JD, HITCHENS TK, LEO G, GAUTHIER DA, ET AL.<br>"Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo [4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) derivatives. 3."<br>J Med Chem. 1995. 38(5):771-93.                                                                                      | ANEXO B |
| 3 | DATABASE CHEMABS. Online<br>CHEMOCAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US.<br>GENESTE, P. ET AL.<br>"Studies of the Imidazo 4,5,1-jk : 1,4 benzodiazepine and imidazo 1,5,4-ef : 1,5 benzodiazepine series"<br>Retrieved from SIN<br>Database accession no. 88:182987<br>XP002162228<br>RNs '66996-64-3 '66596-57-4 '66596-6<br>& EUR. J. MED. CHEM. – CHIM. THER. (1978) 13 (1): 53-9. | ANEXO C |
| 4 | DATABASE CHEMABS. Online<br>CHEMOCAL ABSTARCTS SERVICE, COLUMBUS, OHIO, US.<br>HAERTER. H. P. ET. AL.<br>"Schmidt reaction of tetrahydroquinolone derivates"<br>Retrieved from SIN<br>Database accession no. 85: 32967<br>XPO02162229<br>RNs '59705-04-3 59705-05-4<br>& CHIMIA (1976) 30 (2): 50-2                                                                                      | ANEXO D |
| 5 | GATTA, FRANCO ET AL<br>"Derivates of 1-phenyl-2-methyl-4, 5-dihydro-6H-pyrrolo 3, 2, 1-ij-6-quinolinone. I"<br>CHIM THER. (1973). 8(4),455-8                                                                                                                                                                                                                                             | ANEXO E |

Atentamente,

  
CARLOS R. OLARTE  
C.C. No. 79.782.747 de Bogotá  
T.P. 74.295

Anexos: Anexo A  
Anexo B  
Anexo C  
Anexo D  
Anexo E

sphere for 2 h, solids were filtered using analytical grade Celite, and the filtrate was concentrated to furnish 1.56 g (86%) of 2 as an amorphous white solid: NMR ( $D_2O$ )  $\delta$  1.17-1.80 (m, 12 H), 2.11 (s, 3 H), 2.33-2.93 (m, 8 H), 3.15 (t, 4 H,  $J = 7$ ), 3.33 (s, 3 H), 3.48-3.84 (m, 16 H). Anal. ( $C_{27}H_{40}N_4O_{11}$ ) C, H, N.

11,22,33-Trihydroxy-1,18,33,36,34-pentaoxa-11,18,23,27,32-pentazena-2,3,8,38,39,42-hexaoxatritetrasecantane (3). Compound 23 (2.0 g, 1.8 mmol) was debenzoylated by the method of 2 to furnish 1.35 g (80%) of 3 as an amorphous solid. A sample of 3 (0.845 g) was passed through Sephadex LH-20 eluting with EtOH to afford an analytical sample (0.766 g) of 3: NMR ( $D_2O$ )  $\delta$  1.10-1.79 (m, 12 H), 2.33-2.93 (m, 8 H), 3.15 (t,

4 H,  $J = 7$ ), 3.33 (s, 3 H), 3.47-3.85 (m, 24 H), 4.38 (s, 2 H). Anal. ( $C_{28}H_{44}N_4O_{14}$ ) C, H, N.

**Acknowledgment.** Support was provided by National Institutes of Health Grant No. HL-42817.

**Registry No.** 2, 135638-91-4; 3, 135638-92-5; 7, 139246-21-2; 14, 135638-92-3; 15, 135638-93-4; 16, 135638-94-5; 17, 135638-95-6; 18, 135638-96-7; 19, 135638-97-8; 20, 135638-98-9; 21, 135638-99-0; 22, 135638-99-3; 23, 135658-31-8;  $PbCH_3ONHBOC$ , 79723-21-7; succinic anhydride, 109-30-5; 3,6,9-trioxadecanoyl tosylate, 63821-74-8; 3,6,9-trioxadecanoyl chloride, 63881-16-3; iron, 7439-89-6.

## Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-8-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) Derivatives. 2

Michael J. Kukla,<sup>1</sup> Henry J. Breslin,<sup>1</sup> Craig J. Diamond,<sup>1</sup> Phillip P. Gross,<sup>1</sup> Chih Y. Ho,<sup>1</sup> Milton Miranda,<sup>1</sup> James D. Rodgers,<sup>1</sup> Ronald G. Sherrill,<sup>1</sup> Erik De Clercq,<sup>1</sup> Rudi Pauwels,<sup>1</sup> Koen Andries,<sup>1</sup> Luc J. Moens,<sup>1</sup> Marcel A. C. Janssen,<sup>1</sup> and Paul A. J. Janssen<sup>1</sup>

Janssen Research Foundation, Spring House, Pennsylvania 19477, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroederstraat 10, B-3000 Leuven, Belgium, and Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium. Received April 1, 1991

In the first paper of this series a new structure with anti-HIV-1 activity was disclosed and analogues were synthesized to explore the structure-activity relationship of changes in the substituent (R) attached at the N-6 position of 2. This study describes the syntheses and anti-HIV-1 testing of analogues with variations of the five-membered urea ring of the 4,5,6,7-tetrahydro-8-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) structures. Although many different rings were synthesized to replace the cyclic urea of TIBO, most were found to be inactive in inhibiting the replication of the HIV-1 virus in MT-4 cells. The exceptions were replacement of the urea oxygen with sulfur or selenium to give the corresponding thio- or selenoanalogues. These were found to be more active than the oxygen counterparts. A small series of analogues was synthesized and tested which allowed direct comparison of urea and thiourea derivatives. Without exception, the latter were always more active than the former. The most active compound of this series (8d) was found to inhibit the HIV-1 virus with an  $IC_{50}$  of 0.012  $\mu M$  which is comparable to that of AZT.

### Introduction

In previous publications<sup>1,2</sup> we described the discovery of a new series of compounds, 4,5,6,7-tetrahydro-8-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one derivatives, that were assigned the acronym TIBO derivatives. The initial lead compounds, represented by structure 9, were found to specifically inhibit replication of HIV-1 virus, the causative agent for AIDS (acquired immune deficiency syndrome). The first paper in this series<sup>1</sup> described variation of the N-6 substituent and the resultant structure-activity relationships (SAR). Although these compounds had specific and consistent activity against HIV-1 virus, there was a need to find compounds with a higher level of potency. The best compound from the previous paper had activity comparable to DDI (2',3'-dideoxyinosine), which is currently undergoing clinical evaluation, but AZT (Zidovudine), the only approved drug against AIDS, was >2800 times as effective as our best analogue in blocking replication of the HIV-1 virus in the cellular assay used to determine relative potency. This publication describes efforts to systematically alter the 5-ring urea portion of the tricyclic TIBO structure 9 to determine the effects these changes might have on the relative potency of the resultant analogues to block HIV-1 replication.

### Chemistry

In addition to the synthetic methods previously described<sup>1</sup> to obtain the basic ring system of the TIBO series, Scheme 1 illustrates an efficient and versatile synthesis of several analogues and intermediates. Chloroisatoic anhydride (1) is treated with alanine methyl ester hydrochloride in pyridine under reflux.<sup>3</sup> Although the *l* isomer is pictured, the scheme has been carried out with both the *d* isomer and racemic material as well. The aromatic chloro substituent in 2 acts as a convenient block to para nitration in the next step, yet can be readily removed (step 8) if desired. Treatment of 2 with cold fuming nitric acid gave a 92% yield of 3. Reduction of 3 with lithium aluminum hydride (LAH) in refluxing glyme served to reduce both the carbonyl and the nitro functionalities to yield triamine 4. This material was specifically monoalkylated

<sup>1</sup> Janssen Research Foundation, Pennsylvania.

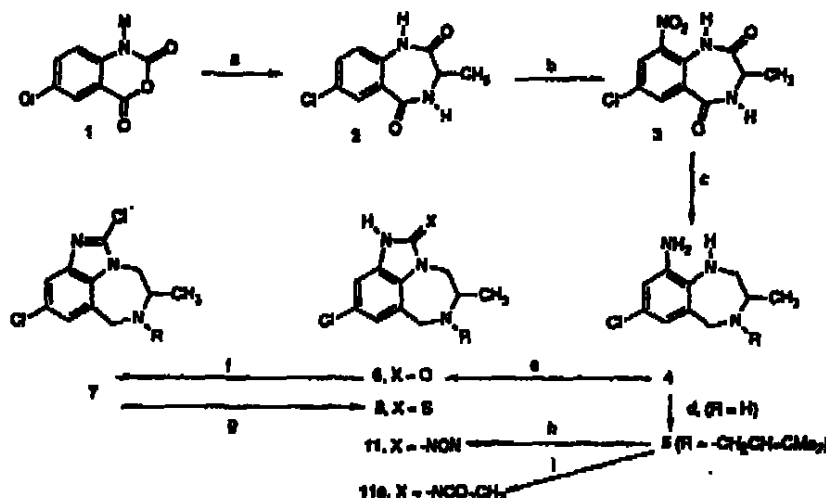
<sup>2</sup> Katholieke Universiteit Leuven.

<sup>3</sup> Janssen Research Foundation, Belgium.

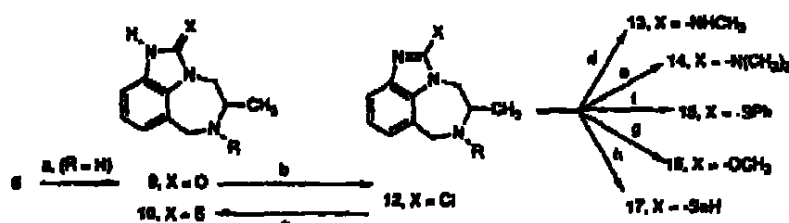
(1) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M.; Breslin, H.; Roeymans, A.; Van Gelder, J.; Wostenborghs, R.; Heynants, J.; Schellekens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. Potent and selective inhibition of HIV-1 replication *in vitro* by a novel series of TIBO derivatives. *Nature* 1990, 345, 470-474.

(2) Kukla, M.; Breslin, H.; Pauwels, R.; Fedde, C.; Miranda, M.; Scott, M.; Sherrill, R.; Roeymans, 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-8-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) Derivatives. *J. Med. Chem.* 1991, 34, 748-761.

(3) Kim, D. Improved Synthesis of 1,4-Benzodiazepine-2,6-diones. *J. Heterocycl. Chem.* 1975, 12, 1323.

Scheme I<sup>a</sup>

<sup>a</sup> (a) Alanine methyl ester-HCl, pyridine, reflux; (b) fuming nitric acid, 0 °C; (c) LAH, glyme, reflux; (d)  $\text{ClCH}_2\text{CH}=\text{CHMe}$ ,  $\text{Na}_2\text{CO}_3$ , KI, DMF; (e)  $\text{Cl}_2\text{COCOCl}$ , N-methyl morpholine,  $\text{CH}_2\text{Cl}_2$ , 0 °C; (f)  $\text{POCl}_3$ ,  $\text{Na}_2\text{CO}_3$ , 80–110 °C; (g) thiourea, EtOH, reflux; (h)  $(\text{PhO})_2\text{C}=\text{NCN}$ , IPrOH; (i)  $\text{CH}_3\text{OC}(\text{NH})\text{NHCO}_2\text{CH}_3$ ,  $\text{CHCl}_3/\text{HOAc}$ .

Scheme II<sup>a</sup>

<sup>a</sup> (a) 10% Pd/C,  $\text{NH}_4\text{HCO}_3$ , IPrOH/ $\text{H}_2\text{O}$ ; (b)  $\text{POCl}_3$ ,  $\text{Na}_2\text{CO}_3$ , 80–110 °C; (c) thiourea, EtOH, reflux; (d) 40% aq  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ , MeOH, reflux; (e) 40% aq  $\text{HN}(\text{CH}_2)_3$ , MeOH, reflux; (f)  $\text{PhSH}$ , NaOH, MeOH/ $\text{H}_2\text{O}$ , reflux; (g) Na, MeOH; (h)  $\text{H}_2\text{NC}=\text{SeNH}_2$ , EtOH.

to give 5 by addition of less than 1 equiv of alkylating agent to a cold (0–5 °C) solution of 4 and monitoring the extent of reaction, as well as formation of dialkylated product. As the latter became significant the reaction was halted with the ratio of 4:5 ca. 1:2. The product 5 was isolated by column chromatography. By the previously described procedures,<sup>3</sup> 4 and 5 were converted to the corresponding benzimidazolones, 6. As mentioned above, the chlorine in 6 ( $R = \text{H}$ ) was readily removed by palladium-catalyzed reduction using ammonium formate as the source of hydrogen.<sup>4</sup> Conversion of ones (8 or 9) to thiones (8 or 10), when R was not hydrogen, was accomplished in a two-step procedure. Treatment of 6 with phosphorus oxychloride at elevated temperatures gave intermediate 7 in ca. 60% yields. Literature studies<sup>5</sup> of the reaction of benzimidazolone with  $\text{POCl}_3$  had shown that bubbling HCl through the heated mixture increased the reaction rate. In this case, when R was an allylic side chain, especially 3,3-dimethylallyl, that procedure caused an increase in the amount of side products presumably arising from addition and subsequent elimination of HCl to give isomeric olefin side chains.

Intermediate 5 was treated with diphenyl cyanocarbonimidate<sup>6</sup> to give 11 or with methyl (iminomethoxymethyl)carbamate<sup>7</sup> to obtain guanidine derivative 11a (Scheme I).

Imino chloride 12, synthesized by the same method used to obtain 7, was a useful starting point for analogues 13–17 (Scheme II). The displacements to form 13–15 all seemed to require the presence of water, since in each case the reactions run under anhydrous conditions were unsuccessful. On the other hand, when 16 was prepared with commercial NaOMe, presumably contaminated with NaOH, a significant amount of hydrolysis product ( $X = \text{OH}$ ) was formed, while freshly prepared reagent did not generate this side product.

Another approach to target structures (Scheme III) was to reduce dilactam 2 to the corresponding benzodiazepine followed by selective acylation of the more basic nitrogen. Nitration followed by chemical reduction of the amide and nitro groups gave 19, which was used to synthesize analogues 20–22. Use of reactive reagents like sulfonyl chloride or sulfonyl amide chloride failed to give 20 from 19,

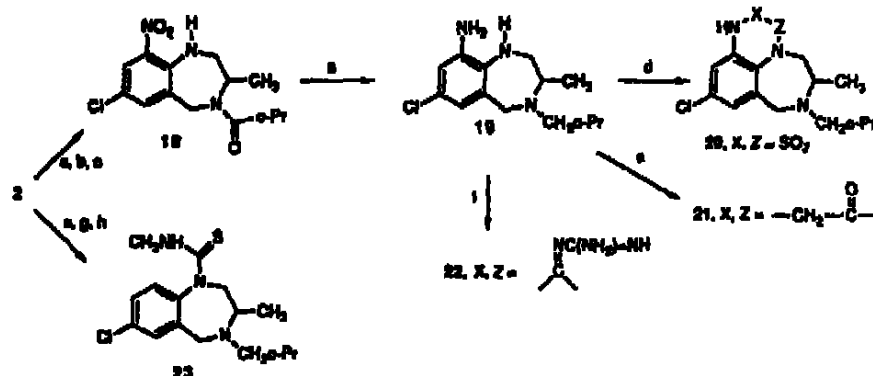
(4) Anwar, M.; Sharman, D.; Roney, J.; Spatola, A. Applications of Ammonium Formate Catalytic Transfer Hydrogenation. 8. Analysis of Catalyst, Donor Quantity, and Solvent Effects Upon the Efficacy of Dechlorination. *J. Org. Chem.* 1989, 54, 1284–9.

(5) Harrison, D.; Ralph, J. T.; Smith, A. C. B. Some 1- and 2-Halogenobenzimidazolones. *J. Chem. Soc.* 1963, 2930–7.

(6) Webb, R.; Labaw, C. Diphenyl Cyanocarbonimidate. A versatile Synthon for the Construction of Heterocyclic Systems. *J. Heterocycl. Chem.* 1982, 19, 1205–6. Diphenyl Cyanocarbonimidate and Dichlorodiphenylmethane as Synthons for the Construction of Heterocyclic Systems of Medicinal Interest. *Ibid.* 1987, 24, 275–8.

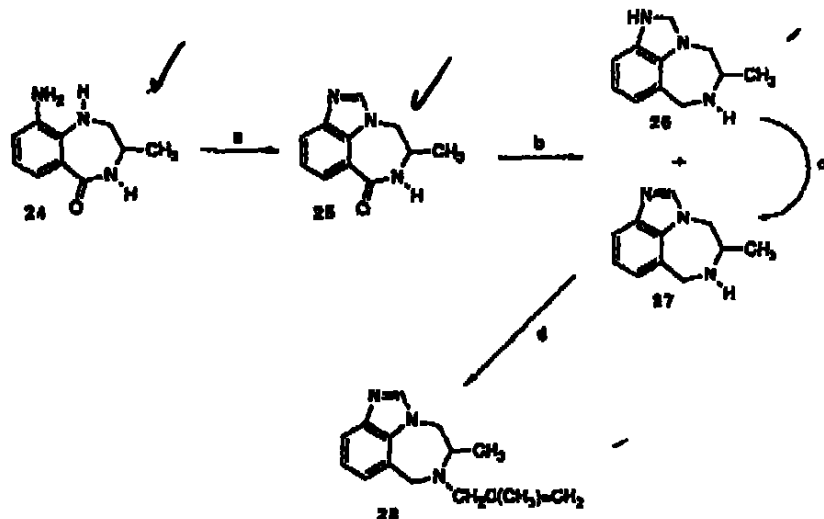
(7) Hamprecht, G.; Acker, R.; Haedcke, E. Substituierte 1,2,4,6-Thiatrisiazin-1,1-dioxide, ihre Herstellung und Struktur. *Liebigs Ann. Chem.* 1965, 12, 2363–70.

## Scheme III\*



\* (a) LAH, glyme; (b) *o*-PrCOCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (c) fuming HNO<sub>3</sub>; (d) H<sub>2</sub>NSO<sub>2</sub>NH<sub>2</sub>, 185 °C; (e) BrCH<sub>2</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>; (f) H<sub>2</sub>NCN, conc HCl, 80 °C; (g) BrCH<sub>2</sub>-Pr, Na<sub>2</sub>CO<sub>3</sub>, DMF; (h) CH<sub>3</sub>NCS, iPrOH.

## Scheme IV\*



\* (a) Formamidine acetate; (b) LAH, glyme, reflux; (c) air; THF; (d) ClCH<sub>2</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>, KI, Na<sub>2</sub>CO<sub>3</sub>, DMF.

whereas heating 19 neat with sulfamide gave 20, albeit in low yield. On the other hand, 19 react readily with bromoacetic acid at ambient temperature to give 21. Interestingly, none of the isomeric material with the carbonyl and methylene interchanged, which would result from alkylation of the ring amine, was detected. Biurethane derivative 22 came from reaction of 19 with cyanamide in concentrated hydrochloric acid.

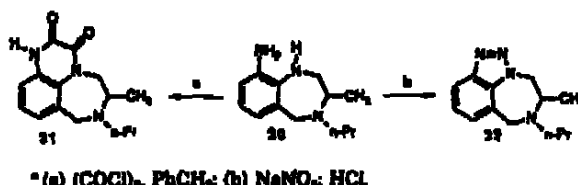
In a three-step procedure (Scheme III), 2 was reduced to the benzodiazepine as before, specifically alkylated at the secondary amine versus the anilino nitrogen, and then reacted with methyl thiocyanate at the latter amine. This led to acyclic thiourea analogue 23.

Benzimidazole derivative 28 was obtained from 24<sup>2</sup> (Scheme IV) by reaction with formamidine acetate. The seven-membered-ring nitrogen of 24 had been rendered nonbasic as a lactam. Subsequent reduction of that carbonyl by LAH also reduced the heterocycle to dihydrobenzimidazole 26, which was readily air oxidized to 27 by stirring a THF solution in an open flask.

Intermediate 30, akin to 19, was reacted with oxalyl chloride or nitrous acid (Scheme V) to form dicarbonyl analogue 31 or triazine 32, respectively.

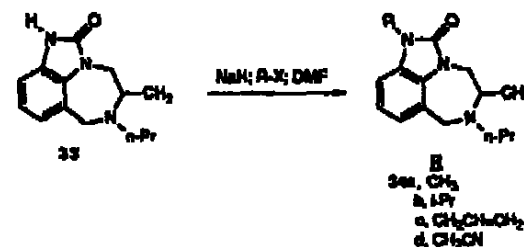
A short series of compounds alkylated on the benzimidazolone nitrogen, 34a-d, was obtained (Scheme VI)

## Scheme V\*



\* (a) (COCl)<sub>2</sub>, PhCH<sub>3</sub>; (b) NaNO<sub>2</sub>, HCl.

## Scheme VI

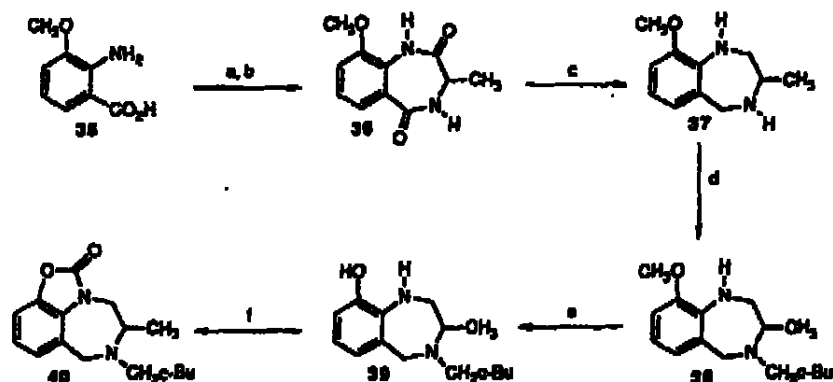


by deprotonating 33 with sodium hydride in the presence of the appropriate alkylating agent.

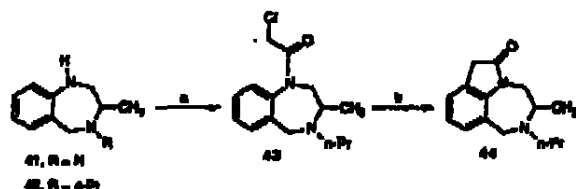
Replacing that same benzimidazolone nitrogen with oxygen was accomplished by the procedure shown in

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Scheme VII<sup>a</sup>

<sup>a</sup> (a) Alanine methyl ester, DCC, HBT, NMM; (b) 200 °C, neat; (c) BH<sub>3</sub>, THF; (d) BrCH<sub>2</sub>-Bu, Na<sub>2</sub>CO<sub>3</sub>, KI, DMF; (e) BBBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (f) urea, 200 °C.

Scheme VIII<sup>a</sup>

<sup>a</sup> (a) ClCH<sub>2</sub>COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (b) AlCl<sub>3</sub>, 175 °C.

**Scheme VII.** 3-Methoxyanthranilic acid (35) was coupled with alanine methyl ester followed by cyclization to give diacetam 36. Initial attempts to reduce 36 with LAH gave multiple products; the major was from demethylation of the methyl ether to give the phenol analogue of 37. Attempts to selectively alkylate the benzylic amine of this phenol product or to form the desired benzoxazolone with diphenyls were unsuccessful. Subsequently, reduction of the diacetam 36 to diamine 37 was carried out smoothly with borane. This in turn was selectively alkylated to 38 and converted to phenol 39 with boron tribromide. The final target benzoxazolone 40 was obtained by carbonylating 39 in a melt with urea.

The synthesis of 44 (Scheme VIII), the corresponding carbon replacement of the secondary nitrogen in the five-membered ring of 9, began with selective alkylation of diamine 41 with *n*-propyl iodide to yield 42. Compound 42 was acylated with chloroacetyl chloride and the intermediate chloride 43 was cyclized to 44 with aluminum chloride at elevated temperatures.

A series of analogues in which the benzimidazolone tertiary nitrogen of 9 was replaced by carbon is exemplified in Scheme IX. Intermediate 45, available through a Gassman oxindole synthesis,<sup>9</sup> was alkylated with chloroacetone to yield oxindole 46. Limited reduction of 46 with zinc dust in acidic media removed the thiomethyl group to give 47. However, reduction of 46 with Raney nickel in *tert*-butyl alcohol resulted in desulfurization, reduction of the nitrile, and subsequent intramolecular reductive amination of the resultant primary amine with the ketone to furnish the desired ring system 48. NOE studies indicated that 48 is a single diastereomer with the 3- and 5-position protons of the chiral centers in a *cis* relationship. Alkylation of 48 was accompanied by epimerization of the

oxindole ring to give a 3:1 mixture (<sup>1</sup>H NMR) of products 49. Conversion of 49 to thione 50 was accomplished with Lawesson's reagent and chlorination of 49 with phosphorus oxychloride yielded chloroxindole 51. The stereochemistry of 50 was determined by <sup>1</sup>H NMR to be a 3:2 mixture of diastereomers. Dehalogenation of 51 to indole derivative 52 was accomplished with palladium on carbon. Treatment of 49 with base in the presence of dimethyl sulfoxide resulted in  $\alpha$  oxidation to alcohol 53.

## Results and Discussion

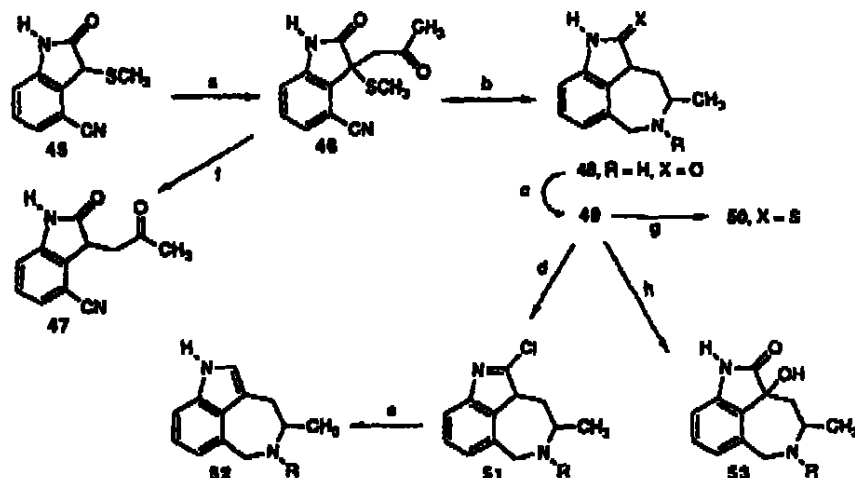
The ability of the compounds reported in this paper to block replication of HIV-1 was determined in MT-4 cells as described previously.<sup>9</sup> The cells were either infected with HIV-1 or mock infected and incubated in the presence of various concentrations of the test compounds. The number of viable cells was then determined 5 days after infection by staining with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.<sup>10</sup> The reported values shown in Tables I and II are the concentrations of each compound required to protect 50% (IC<sub>50</sub>) of the MT-4 cells from cell death brought on by infection with HIV-1 virus. The IC<sub>50</sub>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. In some cases, higher testing concentrations than those shown were precluded because the tested compounds were toxic to the control or mock-infected cells. The IC<sub>50</sub> determinations or evaluations of activity for each compound reported in the tables were assayed in duplicate and the IC<sub>50</sub> values are reported as an average of those determinations. 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.

As indicated in Table I, we have made a large range of variations of the five-membered-ring urea portion of the tricyclic TIBO structures. In general, this part of the molecule has proven to be extremely important to the activity of the TIBO series. The majority of these alterations have led to complete loss of activity, although the

(9) Gassman, P.; Van Bergen, T. Oxindoles. A New, General Method of Synthesis. *J. Am. Chem. Soc.* 1976, 98, 560A-17.

(9) Pauwels, R.; De Clercq, E.; Desmyter, J.; Balzarini, J.; Cochen, P.; Herdewijn, P.; Vandepitte, 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.

(10) 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.

Scheme IX<sup>a</sup>

<sup>a</sup> (a) Chloro acetone,  $K_2CO_3$ , KI, DMF; (b) Raney Ni,  $t$ -BuOH; (c) R-X, KI,  $Na_2CO_3$ , DMF; (d)  $POCl_3$ , reflux; (e) 10% Pd/C, EtOH,  $Et_3N$ ; (f) Zn dust, HOAc, THF; (g) Lawesson Reagent, BHT,  $PhCH_3$ ; (h)  $K_2CO_3$ , DMSO,  $H_2O$ .

Table I. Testing of 5-Ring Variations To Inhibit HIV-1 Replication

| no. | X-Y-Z                                     | 5-<br>config | arom<br>sub | R                              | IC <sub>50</sub> <sup>a</sup><br>μM |
|-----|-------------------------------------------|--------------|-------------|--------------------------------|-------------------------------------|
| 9a  | HC-(C=O)-N                                | ±            |             | DMA <sup>b</sup>               | 9.5                                 |
| 10a | HN-(C=S)-N                                | ±            |             | DMA                            | 0.097                               |
| 11  | HNC(=NCN)-N                               | S            | 9-Cl        | DMA                            | >250                                |
| 11a | N=C(NHCO <sub>2</sub> CH <sub>3</sub> )-N | S(+)         | 9-Cl        | DMA                            | >10                                 |
| 13  | N=C(NHCH <sub>3</sub> )-N                 | ±            |             | DMA                            | >250                                |
| 14  | N=C(NMe <sub>2</sub> )-N                  | ±            |             | DMA                            | >250                                |
| 15  | N=C(SPh)-N                                | ±            |             | DMA                            | >50                                 |
| 16  | N=C(OCH <sub>3</sub> )-N                  | ±            |             | DMA                            | >250                                |
| 17  | HN-(C=Se)-N                               | S(+)         | 9-Cl        | DMA                            | 0.018                               |
| 20  | HN-SO <sub>2</sub> -N                     | ±            | 9-Cl        | CH <sub>3</sub> - <i>n</i> -Pr | >10                                 |
| 21  | HN-CH <sub>2</sub> -(C=O)-N               | ±            | 10-Cl       | CH <sub>3</sub> - <i>n</i> -Pr | >10                                 |
| 22  | HN-C=N(C(NH <sub>2</sub> )-NH)-N          | ±            | 9-Cl        | CH <sub>3</sub> - <i>n</i> -Pr | >50                                 |
| 23  | acyclic<br>(Me-NH-(C=S)-N)                | S(-)         | 7-Cl        | CH <sub>3</sub> - <i>n</i> -Pr | >10                                 |
| 25  | N=C-N                                     | ±            |             | 2-MA <sup>c</sup>              | >2                                  |
| 31  | HN-(C=O)-(C=O)-N                          | ±            |             | <i>n</i> -Pr                   | >250                                |
| 32  | N=N-N                                     | ±            |             | <i>n</i> -Pr                   | >10                                 |
| 34a | Me-N-(C=O)-N                              | ±            |             | <i>n</i> -Pr                   | >250                                |
| 34b | iPr-N-(C=O)-N                             | ±            |             | <i>n</i> -Pr                   | >250                                |
| 34c | allyl-N-(C=O)-N                           | ±            |             | <i>n</i> -Pr                   | >50                                 |
| 34d | NCCH <sub>3</sub> -N-(C=O)-N              | ±            |             | <i>n</i> -Pr                   | >250                                |
| 40  | O-(C=O)-N                                 | ±            |             | CH <sub>3</sub> - <i>n</i> -Bu | >2                                  |
| 44  | CH <sub>3</sub> -(C=O)-N                  | ±            |             | <i>n</i> -Pr                   | >250                                |
| 49  | HN-(C=O)-CH                               | ±            |             | 2-MA                           | >50                                 |
| 50a | HN-(C=S)-CH                               | ±            |             | 2-MA                           | >10                                 |
| 50b | HN-(C=S)-CH                               | ±            |             | A <sup>d</sup>                 | >250                                |
| 51  | HN-C(Cl)=C                                | ±            |             | <i>n</i> -Pr                   | >50                                 |
| 52  | HN-CH=C                                   | ±            |             | <i>n</i> -Pr                   | >250                                |
| 53  | HN-(C=O)-CH(OH)                           | ±            |             | 2-MA                           | >250                                |

<sup>a</sup> 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. <sup>b</sup> DMA = 3,3-dimethylallyl or 3-methyl-2-butenyl. <sup>c</sup> 2-MA = 2-methylallyl or 2-methyl-2-propenyl. <sup>d</sup> A = allyl.

replacement of the urea (one) with a thiourea (thione), as indicated in Tables I and II, has yielded much more potent derivatives. In fact, there seems to be a need for the intact ring, since the analogue 23, which includes all the necessary elements of the most active compounds but in an acyclic

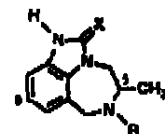
array, is inactive. On the other hand, two replacements of the 5-ring with a 6-ring by insertion of a methylene (21) or another carbonyl (31) also proved to be inactive.

A limited number of changes in the 1-position (X in Table I structures), which included alkylation of the urea nitrogen (34a-d) or replacement of the nitrogen with oxygen (40) or carbon (44), have all led to inactive derivatives. Possibly the NH is necessary for hydrogen bonding either at nitrogen or through tautomerization at the 2-position carbonyl.

Because the 3-position (Z in Table I structures) is a ring juncture, the only logical change was to exchange carbon for nitrogen as indicated in analogues 49-53. Again, the products of these alterations proved to be inactive compounds, including 49 and 50, which are the direct carbon analogues of active structures 9 and 10.

The 2-position (Y in Table I structures) is where the greatest number of variations have been investigated. Analogues with replacements of the carbonyl carbon with nitrogen to give triazine 32 and sulfur dioxide to give sulfonamide 20 or deletion of the oxygen as encompassed in imidazole 23 all failed to protect the test cells from the HIV-1 infection. However, replacement of the carbonyl oxygen with the other group VI elements, sulfur (10a) and selenium (17), led to compounds with much higher potency. A number of other variations along that theme proved unsuccessful, including cyanamide derivative 11, which in the histamine H-2 blockers had been a potent isosteric replacement for a thiourea.<sup>11</sup> Additionally, guanidines (13 and 14), biguanidine (22), carbamate (11a), O-methylated urea (16), and S-phenylated thiourea (15) were also inactive variations.

These observations give the impression that the heteroatom attached to the 2-position, either oxygen, sulfur, or selenium, is directly involved in the binding of these inhibitors to HIV-1 reverse transcriptase (see below). This is further borne out by the limitations of the heteroatom attached at the 2-position. As previously mentioned, analogues with a nitrogen attachment (11, 11a, 13, 14, and 22) were completely devoid of activity. At this point, it is not clear whether the lack of activity is the result of the electronegativity differences, imparted basicity of nitrogen versus the group VI elements, or the fact that the nitrogen derivatives all have the added bulk of attached substituents.

Table II. Comparison of *One* versus *Thione* Derivatives in Inhibition of HIV-1 Replication


| R                                              | <i>S</i> -config | arom<br>sub | X = O |                                  | X = S |                                  | ratio<br>(O/S) <sup>b</sup> |
|------------------------------------------------|------------------|-------------|-------|----------------------------------|-------|----------------------------------|-----------------------------|
|                                                |                  |             | no.   | IC <sub>50</sub> <sup>a</sup> μM | no.   | IC <sub>50</sub> <sup>a</sup> μM |                             |
| DMA <sup>c</sup>                               | ±                |             | 9a    | 9.8 (16)                         | 10a   | 0.097 (6)                        | 101                         |
| CH <sub>2</sub> - <i>c</i> -Pr                 | <i>S</i> (+)     |             | 9b    | 10.0 (5)                         | 10b   | 0.06 (5)                         | 167                         |
| 2-MA <sup>d</sup>                              | <i>S</i> (+)     |             | 9c    | 15.2 (17)                        | 10c   | 0.026 (6)                        | 584                         |
| <i>n</i> -Pr                                   | ±                |             | 9d    | 80.0 (15)                        | 10d   | 1.7 (7)                          | 36                          |
| CH <sub>2</sub> - <i>c</i> -Bu                 | <i>S</i> (+)     | 9-Cl        | 9e    | 0.35 (7)                         | 10e   | 0.026 (8)                        | 13                          |
| DMA                                            | <i>S</i> (+)     | 9-Cl        | 9b    | 0.18 (2)                         | 10b   | 0.039 (53)                       | 6                           |
| CH <sub>2</sub> CH <sub>2</sub> - <i>c</i> -Pr | <i>S</i> (+)     | 9-Cl        | 9c    | 2.2 (3)                          | 10c   | 0.42 (4)                         | 5                           |
| DEA <sup>e</sup>                               | <i>S</i> (+)     | 9-Cl        | 9d    | 0.029 (7)                        | 10d   | 0.012 (5)                        | 2                           |
| DMA                                            | <i>R</i> (-)     | 9-Cl        | 9e    | 4.2 (6)                          | 10e   | 0.39 (5)                         | 11                          |
| AZT                                            |                  |             |       |                                  |       | 0.004                            |                             |
| DDC                                            |                  |             |       |                                  |       | 0.137                            |                             |
| DDI                                            |                  |             |       |                                  |       | 8.5                              |                             |

<sup>a</sup> Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 virus. This is a mean of multiple IC<sub>50</sub> determinations, the number of which is included in parentheses. <sup>b</sup> Ratio of the IC<sub>50</sub> of one versus thione analogues. <sup>c</sup> DMA = 3,3-dimethylallyl or 3-methyl-2-butenyl. <sup>d</sup> 2-MA = 2-methylallyl or 2-methyl-2-propenyl. <sup>e</sup> DEA = 3,3-diethylallyl or 3-ethyl-2-pentenyl.

Table II lists a series of analogues and their IC<sub>50</sub> in blockade of HIV-1 replication, which allows comparison of the *one* and *thione* derivatives. The list includes a variety of N-8 substituents,<sup>2</sup> compounds with or without a 9-chloro substituent, and racemic, *R*, or *S* configurations at the 5-position. Looking at this data, a few trends are apparent which warrant mention. Without exception, the *thiones* are more potent than the corresponding *ones* in the MT-4 cell assay, which is exemplified by the ratios (see Table II) being >1 in all cases. However, the ratios are not consistent within the limited series and range from 2 to 584.

There are some obvious differences between the oxygen and sulfur TIBO derivatives which might help to explain the differences in activity. As indicated earlier, the proton of the secondary urea seems to be necessary for activity. The relative pK<sub>a</sub>s of the urea proton versus the thiourea proton might be an indication of the propensity of the proton to form a hydrogen bond in binding at a receptor. Although we have not measured the pK<sub>a</sub>s in our compounds, Brown has found<sup>13</sup> that, in the case of the simple thiobenzimidazolone versus benzimidazolone, the acidity of the sulfur analogue (pK<sub>a</sub> = 10.24) is significantly higher than that of the oxygen analogue (pK<sub>a</sub> = 11.95).

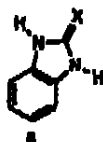
One might speculate that the active form of the TIBO structures that interacts with the reverse transcriptase (see later discussion) is the hydroxy (54b) or thiol (55b) tautomer of the urea or thiourea, respectively. Although we

series of *ones* and *thiones*, in either case the tautomerization presumably lies far to the side of the carbonyl (54a) or thiocarbonyl (55a) with the hydroxy or thiol constituting a minor contribution to the character of the molecules. However, a crystallographic study of thiobenzimidazolone<sup>14</sup> suggests that there is approximately 80% double bond character in the C-S bond, much less than would be expected for the C-O bond in benzimidazolone. Furthermore, measurement of the dipole moment of thiobenzimidazolone<sup>14</sup> indicates that there may be a significant contribution of the dipole form 55c, whereas the oxygen analogue is very close to the calculated value for the double bond tautomer 54a.

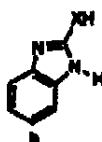
Another obvious difference between the oxygen and sulfur analogues is the size of the atoms and the subsequent length of the C-O versus C-S bonds. The latter is naturally longer and may help to span a distance more efficiently in a binding site.

Another unexplained trend in Table II is that the compounds with a 9-Cl substituent seem, within the limited series, to have smaller ratios of relative potency of the *ones* to *thiones* than the nonhalogenated analogues. In other words, the oxygen and sulfur analogues are much closer in relative potency with the presence of the 9-Cl. Possibly the reasons for the activity differences discussed here will be clearer as we make further analogues in this series.

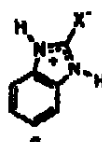
A discussion of some preliminary studies to ascertain the mechanism by which the TIBO series blocks HIV-1 replication has been published<sup>1</sup> and a more detailed discussion followed.<sup>15</sup> The conclusions of those studies were that these compounds, like AZT and other 2',3'-dideoxynucleoside analogues, act by inhibiting reverse transcrip-



54, X = O



54, X = S



have no experimental determinations within the reported

- (11) Durant, G.; Emmett, J.; Capelin, C.; Miles, P.; Parsons, M.; Prain, H.; White, G. Cyanoguanidine-Thiourea Equivalences in the Development of the Histamine H<sub>2</sub>-Receptor Antagonist, Clamidine. *J. Med. Chem.* 1977, 20, 901-6.  
(12) Brown, D. Some 2-Substituted Linear Naphthimidazoles. *J. Chem. Soc.* 1958, 1974-7.

- (13) Form, G.; Raper, R.; Downie, T. The crystal and molecular structure of 2-mercaptobenzimidazole. *Acta Crystall.* 1976, B32, 345-8.

- (14) Benzimidazoles and Congeneric Tricyclic Compounds. Preston, P., Ed.; An Interscience Publication; New York: John Wiley & Sons, 1981; p 354.

- (15) Debyser, Z.; Patwala, R.; Andries, K.; Deemster, J.; Kukla, M.; Janssen, P.; De Clercq, E. An antiviral target on reverse transcriptase of human immunodeficiency virus type 1 revealed by tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one and -thione derivatives. *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88, 1451-1455.

## Anti-HIV-1 Activity of TIBO Derivatives

tase, but unlike the latter, TIBO compounds are specific for HIV-1 and do not interfere with HIV-2 or other viral reverse transcriptases. Additionally, AZT and related compounds, by virtue of their nucleoside structures, are phosphorylated by cellular kinases. The resultant nucleotides are incorporated into the growing DNA chain by the reverse transcriptase during transcription of RNA to DNA by the RNA-dependent DNA polymerase. This leads to chain termination, halt of DNA formation, and consequent inhibition of HIV-1 replication. The compounds of the present series, on the other hand, do not require prior phosphorylation to inhibit reverse transcriptase. The TIBO compounds apparently block HIV-1 reverse transcriptase in a specific and unique manner. The exact nature of the inhibition is currently under study.

## Experimental Section

All final products included in the tables were characterized by 300-MHz  $^1\text{H}$  NMR (Bruker AM 300WB, reported in ppm relative to TMS), IR (Nicolet 80SX), and mass spectra (Finnigan 3300) as well as elemental analyses. The latter were performed by the Internal Analytical Research Department of Janssen Research Foundation in Beerse, Belgium. All final products were assayed for homogeneity by thin-layer chromatography on Whatman MK6F (1 × 3 in × 250  $\mu\text{m}$ ) silica gel plates. Melting points were determined on a Thomas-Hoover capillary immersion apparatus or a Mel-Temp hot stage and are uncorrected.

(+)-(S)-7-Chloro-3,4-dihydro-3-methyl-1*H*-1,4-benzodiazepine-2,5-dione (1). Chloroacetic anhydride (1; 41.49 g, 0.31 mol) and *L*-alanine methyl ester hydrochloride (31.4 g, 0.235 mol) were combined in 110 mL of pyridine under argon. The mixture was heated under reflux for 10 h, then it was allowed to cool to ambient temperature and stirred another 12 h before it was filtered, and the collected solid was rinsed with water. The solid was rinsed with EtOH and then Et<sub>2</sub>O to yield 24.77 g (52%) of white solid (mp 285–287 °C), which was used without further purification.

(+)-(S)-7-Chloro-3,4-dihydro-3-methyl-9-oxo-1*H*-1,4-benzodiazepine-2,5-dione (2). Fuming nitric acid (94 mL) was cooled with an ice bath under argon before addition of 2 (24.56 g) over 27 min. The mixture was stirred for 3.5 h at 0 °C and then it was slowly added to 450 g of ice with stirring. The precipitated solid was isolated on a filter and washed with a small amount of water. It was air-dried at room temperature overnight to yield 27.84 g (85%) of yellow solid (mp 240–242 °C), which was used without further purification.

(S)-7-Chloro-2,3,4,5-tetrahydro-3-methyl-1*H*-1,4-benzodiazepine-9-amine (4) (R = H). To a stirred, cooled (ice bath) suspension of 1AH (18.2 g, 0.48 mol) in glyme (300 mL) under nitrogen was added neat 3 over 90 min. The mixture was stirred another 2 h at 0 °C and then slowly brought to reflux and maintained for 40 h. It was then recooled with an ice bath and quenched with careful sequential addition of 18.2 mL of H<sub>2</sub>O in 54 mL of THF, 18.2 mL of 15% NaOH, and 54.8 mL of H<sub>2</sub>O. The mixture was warmed to ambient temperature and stirred for 1 h before the solid was filtered off. The solid was digested with 200 mL of hot THF and refiltered. The combined filtrates were concentrated under vacuum, and the resultant oil was used without further purification to synthesize 5 (R = CH<sub>2</sub>CH=CHMe) or 5 (R = H).

7-Chloro-2,3,4,5-tetrahydro-3-methyl-4-(3-methyl-3-butenyl)-1*H*-1,4-benzodiazepine-9-amine (5) (R = CH<sub>2</sub>CH=CHMe). To a stirred solution of 4 (R = H) (221.6 g, 1.047 mol) in 3.24 L of DMF under nitrogen were added KI (173.8 g, 1.047 mol) and Na<sub>2</sub>CO<sub>3</sub> (165.1 g, 1.538 mol). The reaction was cooled to 0–5 °C, and 1-chloro-3-methyl-2-butene (76.7 g, 0.733 mol) in DMF (850 mL) was added dropwise over 2 h. After 18 h at 0–5 °C another portion of 1-chloro-3-methyl-2-butene (16.4 g, 0.167 mol) in 176 mL of DMF was added over 0.5 h, and finally after 0.5 h, a third portion of 1-chloro-3-methyl-2-butene (16.4 g, 0.167 mol) in 176 mL of DMF was added over 0.25 h. The reaction was monitored by GLC throughout to compare the relative amounts of desired product, starting material, and dialkylated product. The final ratio was 4.3:2.4:1, respectively. The mixture was poured into

Table III. Product Purification and Characterization

| no.  | formula <sup>a</sup>                                                                                                   | purification <sup>b</sup>             | mp, °C      | % yield |
|------|------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------|---------|
| 5(a) | C <sub>11</sub> H <sub>17</sub> ClN <sub>2</sub> O                                                                     | CH <sub>2</sub> OH                    | 199–200     | 23      |
| 5(S) | C <sub>11</sub> H <sub>17</sub> ClN <sub>2</sub> O                                                                     | CH <sub>2</sub> CN                    | 199.5–200   | 39      |
| 5(R) | C <sub>11</sub> H <sub>17</sub> ClN <sub>2</sub> O                                                                     | CH <sub>2</sub> CN                    | 199–201     | 48      |
| 6a   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> O                                                                     | + CH <sub>2</sub> CN                  | 137         | 64      |
| 6b   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> O                                                                     | CH <sub>2</sub> CN                    | 132.5–138   | 71      |
| 6c   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> O                                                                     | + CH <sub>2</sub> CN                  | 134–127     | 60      |
| 6d   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> O·HCl                                                                 | + EtOH/<br>Et <sub>2</sub> O          | 237 dec     | 92      |
| 6e   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> O                                                                     | CH <sub>2</sub> CN                    | 132–133.5   | 46      |
| 8a   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> S                                                                     | + CH <sub>2</sub> CN                  | 208–207     | 78      |
| 8b   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> S                                                                     | +                                     | 178–181.5   | 11      |
| 8c   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> S                                                                     | +                                     | 178–179     | 81      |
| 8d   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> S·HCl                                                                 | + EtOH/<br>Et <sub>2</sub> O          | >280        | 84      |
| 8e   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> S                                                                     | +                                     | 183–184     | 12      |
| 9b   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O                                                                       | +                                     | 112–114     | 43      |
| 10a  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> S <sup>c</sup>                                                          | +                                     | 124.5–126.5 | 53      |
| 10b  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> S <sup>d</sup>                                                          | +                                     | 190–202     | 32      |
| 10c  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> S                                                                       | +                                     | 134–138     | 24      |
| 10d  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> S <sup>e</sup>                                                          | + CH <sub>2</sub> CN                  | 149–151     | 20      |
| 11   | C <sub>11</sub> H <sub>17</sub> ClN <sub>2</sub>                                                                       | CH <sub>2</sub> CN                    | 181–184     | 28      |
| 11a  | C <sub>11</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>                                                        | +                                     | 140         | 22      |
| 13   | C <sub>11</sub> H <sub>17</sub> N <sub>2</sub> ·H <sub>2</sub> O                                                       | H <sub>2</sub> O/CH <sub>2</sub> OH   | 100–105     | 45      |
| 14   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> ·1.5C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>                        | <i>i</i> -PrOH                        | 173.5–175.5 | 15      |
| 15   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> S                                                                       | + CH <sub>2</sub> CN                  | 87–90       | 53      |
| 16   | C <sub>11</sub> H <sub>17</sub> N <sub>2</sub> O·1.5C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>                       | <i>i</i> -PrOH                        | 137–138.5   | 30      |
| 17   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> S <sub>2</sub>                                                        | <i>i</i> -PrOH                        | 175 dec     | 64      |
| 20   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> SO <sub>2</sub> <sup>f</sup>                                          | + CH <sub>2</sub> CN                  | 204–205.5   | 11      |
| 21   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> O                                                                     | +                                     | 149–152     | 33      |
| 22   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> ·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>                         | EtOH                                  | 203.5–205.5 | 25      |
| 23   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> S·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>                        | EtOH/Et <sub>2</sub> O                | 177–179     | 75      |
| 25   | C <sub>11</sub> H <sub>17</sub> N <sub>2</sub> O                                                                       | <i>i</i> -PrOH                        | 253–255     | 34      |
| 27   | C <sub>11</sub> H <sub>17</sub> N <sub>2</sub> ·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>                           | EtOH                                  | 203–204.5   | 92      |
| 28   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> ·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub> ·<br>0.2Et <sub>2</sub> O | CH <sub>2</sub> CN                    | 130–133     | 76      |
| 31   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub>                                                          | + <i>i</i> -PrOH                      | 213.5–215.5 | 20      |
| 32   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> ·HCl·0.2H <sub>2</sub> O                                                | + EtOH                                | 223–225     | 48      |
| 34a  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O                                                                       | CH <sub>2</sub> CN/H <sub>2</sub> O   | 186–8       | 64      |
| 34b  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub> S                        | DMK/Et <sub>2</sub> O                 | 178–180     | 38      |
| 34c  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub> S                        | <i>i</i> -PrOH                        | 182–187     | 62      |
| 34d  | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O                                                                       | + hex                                 | 83–86       | 51      |
| 40   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>                          | EtOH                                  | 147–150     | 17      |
| 44   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O·C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>                          | <i>i</i> -PrOH                        | 180–182     | 20      |
| 46   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> S                                                        | EtOAc                                 | 228–230     | 52      |
| 47   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub>                                                          | + EtOH                                | 178–180     | 83      |
| 48   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O                                                                       | EtOAc                                 | 164–168     | 25      |
| 49   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O                                                                       | + EtOAc                               | 185–187     | 48      |
| 50a  | C <sub>17</sub> H <sub>23</sub> N <sub>2</sub> S <sup>g</sup>                                                          | + CH <sub>2</sub> OH                  | 120 dec     | 34      |
| 50b  | C <sub>15</sub> H <sub>19</sub> N <sub>2</sub> S                                                                       | + CH <sub>2</sub> OH                  | 122 dec     | 14      |
| 51   | C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub> ·HCl                                                                  | <i>i</i> -PrOH/<br>CH <sub>2</sub> OH | >280        | 28      |
| 52   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> ·HCl                                                                    | + <i>i</i> -PrOH                      | 245–247     | 57      |
| 53   | C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·<br>C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>    | + EtOH                                | 227–230     | 40      |

<sup>a</sup> All compounds were analyzed for C, H, N. <sup>b</sup> Purification method: If a silica gel chromatography was done on the crude product, it is indicated by a "+"; the solvent used for recrystallization follows. <sup>c</sup> C: calcd, 68.88; found, 68.34. <sup>d</sup> C: calcd, 68.90; found, 68.48. <sup>e</sup> C: calcd, 64.33; found, 63.98. <sup>f</sup> C: calcd, 67.52; found, 68.12. <sup>g</sup> C: calcd, 51.29; found, 50.48. <sup>h</sup> C: calcd, 71.59; found, 70.03. <sup>i</sup> H: calcd, 7.74; found, 7.25.

3.66 L of CH<sub>2</sub>Cl<sub>2</sub> and 2.4 L of H<sub>2</sub>O, and the layers were separated. The aqueous was extracted with another 1.25 L of CH<sub>2</sub>Cl<sub>2</sub>. The combined organics were washed 7 times with a total of 4.8 L of H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to yield 217.7 g of crude product. This was column chromatographed on silica gel with toluene/2-propanol (98:2) as eluent to give 89 g of product which was rechromatographed on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/EtOH/MeOH saturated with NH<sub>3</sub> (95:5:1) as eluant to yield 54.5 g of oil. This was triturated with hexane (130 mL) at room temperature and cooled to 0 °C before the solid product was isolated on a filter and dried under vacuum at 30 °C to yield 54.7 g of 5.

(S)-2,9-Dichloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5-*b*]1,4-benzodiazepine (7).

**Typical Procedure (R = H).** A stirred mixture of **6** (2.0 g, 7 mmol) and  $\text{Na}_2\text{CO}_3$  (0.75 g, 7 mmol) in  $\text{POCl}_3$  (30 mL) under nitrogen was heated at 95 °C for 28 h. The mixture was concentrated on a rotary evaporator and the residue treated with 150 mL of saturated  $\text{NaHCO}_3$  and extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were washed with saturated  $\text{NaHCO}_3$  and then brine, dried with  $\text{MgSO}_4$ , and concentrated to yield 1.6 g of dark residue **7** that was used without further purification.

**(+)-(S)-9-Chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepine-2-(1H)-thione (8).** Typical Procedure (R = H). Crude **7** (1.6 g) was dissolved in 30 mL of EtOH before addition of solid thiourea (1.5 g). The stirred mixture was heated at 95 °C under nitrogen for 24 h. It was concentrated under vacuum; the residue was diluted with saturated  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3x). The combined extracts were washed with saturated  $\text{NaHCO}_3$  and then brine, dried with  $\text{MgSO}_4$ , and concentrated to yield 1.35 g of yellow foam. Flash chromatography on silica gel with 40% EtOAc/hexane as eluent gave 0.87 g of pale yellow solid. This was triturated with a few milliliters of ice-cold  $\text{CH}_3\text{CN}$  to yield 0.56 g of off-white solid **8**.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.3 (d, 3 H,  $\text{CH}_3$ ), 1.45 (s, 3 H,  $\text{CH}_3$ ), 1.74 (s, 3 H,  $\text{CH}_3$ ), 3.08–3.18 (m, 1 H), 3.15–3.25 (m, 1 H), 3.5–3.6 (m, 1 H), 4.05 (d, 1 H), 4.15 (dd, 1 H), 4.5 (dd, 1 H), 5.2 (t, 1 H), 6.89 (s, 1 H), 7.08 (s, 1 H), 10.1 (s, 1 H).

**(+)-(S)-4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepine-2(1H)-one (9) (R = H).** Ammonium formate (5 g) in 15 mL of  $\text{H}_2\text{O}$  and then solid **8** (R = H, 5.0 g) were added to a suspension of 10% Pd/C (1.0 g) in 500 mL of *i*-PrOH under argon. After 20 h the reaction was filtered through Dicalite and the catalyst washed with MeOH. The filtrate was concentrated to a tan solid that was redissolved in 100 mL of  $\text{H}_2\text{O}$  and neutralized with the addition of 50 mL of saturated aqueous  $\text{NaHCO}_3$  and heated on a steam bath. A white solid (3.7 g, 87%) separated, which was isolated after cooling: mp 200–202 °C.

**(-)-(S)-[18-Chloro-1,2,4,5,6,7-hexahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepine-3-ylidene]amino]formonitrile (11).** **5** (1.0 g, 3.6 mmol) and diphenyl cyanocarbonimidate (Aldrich; 0.85 g, 3.6 mmol) were combined in *i*-PrOH (50 mL) under nitrogen and heated under reflux for 24 h. The mixture was concentrated on a rotary evaporator and the residue partitioned between  $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$ . The organic layer was washed with saturated  $\text{NaHCO}_3$  and then brine, dried with  $\text{MgSO}_4$ , and concentrated to a clear oil. This was triturated with a few milliliters of ice-cold  $\text{CH}_3\text{CN}$ . The crystals were collected, washed with cold  $\text{CH}_3\text{CN}$ , and dried to yield 0.33 g (26%): mp 151–154 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.38 (d, 3 H,  $\text{CH}_3$ ), 1.47 (s, 3 H,  $\text{CH}_3$ ), 1.75 (s, 3 H,  $\text{CH}_3$ ), 3.1 (dd, 1 H), 3.2 (dd, 1 H), 3.48–3.58 (m, 1 H), 3.9 (dd, 1 H), 4.02 (d, 1 H), 4.1 (dd, 1 H), 4.3 (d, 1 H), 5.2 (t, 1 H), 6.85 (s, 1 H), 7.2 (s, 1 H), 12.2 (s, 1 H).

**(+)-(S)-Methyl [5-Chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepine-2-yl]carbamate (11a).** **5** (2.79 g, 10 mmol), methyl (iminomethoxymethyl)carbamate (2.0 g, 15 mmol), and glacial acetic acid (3 g, 50 mmol) were combined in  $\text{CHCl}_3$  (70 mL) and heated under reflux. After 17 h an additional portion of methyl (iminomethoxymethyl)carbamate (0.66 g, 5 mmol) was added and reflux continued over a few days. The cooled reaction mixture was washed with  $\text{H}_2\text{O}$  and then dilute  $\text{NH}_4\text{OH}$ , dried with  $\text{MgSO}_4$ , and concentrated. The residue was chromatographed on silica gel (5% MeOH/ $\text{CH}_2\text{Cl}_2$ ). The pure fractions were concentrated and dissolved in diisopropyl ether before addition of *i*-PrOH/HCl to give a solid HCl salt which was washed with  $\text{CH}_3\text{CN}$  to yield 1.9 g. This material was dissolved in  $\text{H}_2\text{O}$  and the free base liberated with addition of  $\text{NH}_4\text{OH}$  and extracted into  $\text{CH}_2\text{Cl}_2$ . The organic layer was concentrated and the residue chromatographed on silica gel (2% MeOH/ $\text{CH}_2\text{Cl}_2$ ). The pure fractions were concentrated, and the solid residue was washed with diisopropyl ether to yield 0.8 g (22%): mp 140 °C.

**4,5,6,7-Tetrahydro-N,5-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepine-2-amine (13)** (Same Procedure for 14). Crude **12** (0.55 g) was suspended in a mixture of 40% aqueous  $\text{H}_2\text{NCH}_3$  (Aldrich; 10 mL) and MeOH (5 mL) under  $\text{N}_2$  and heated at 85 °C (bath temperature) for 25 h. Another 2 mL of  $\text{H}_2\text{NCH}_3$  solution was added and heating continued for 7 h. The mixture was allowed to cool and a white solid

separated which was collected and recrystallized from  $\text{H}_2\text{O}/\text{CH}_3\text{OH}$  to yield 0.28 g (48%): mp 100–105 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.32 (d, 3 H,  $\text{CH}_3$ ), 1.4 (s, 3 H,  $\text{CH}_3$ ), 1.53 (s, 3 H,  $\text{CH}_3$ ), 3.08–3.25 (m, 5 H), 3.57–3.67 (m, 1 H), 4.12 (d, 1 H), 4.25 (d, 1 H), 5.22 (m, 1 H), 6.72 (d, 1 H), 47.02 (t, 1 H), 7.37 (d, 1 H).

**(±)-4,5,6,7-Tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-2-(phenylthio)imidazo[4,5,1-jk][1,4]benzodiazepine (18).** Thiophenol (2 mL), followed by 30 mL of  $\text{H}_2\text{O}$ , and then NaOH (1.0 g, 25 mmol) were added to a solution of crude **12** (1.0 g, 3.5 mmol) in MeOH (70 mL). The mixture was stirred at ambient temperature for 24 h before another portion of thiophenol (1 mL) was added and the mixture heated to 50 °C. After 3 h the mixture was concentrated to remove the MeOH. The aqueous residue was further diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (2x). The organics were washed with  $\text{H}_2\text{O}$  and then brine, dried with  $\text{MgSO}_4$ , and concentrated to 1.5 g of crude product. This was flash chromatographed on silica gel (25% EtOAc/hexane) to yield 0.68 g of solid that was recrystallized from  $\text{CH}_3\text{CN}$  to yield 0.23 g (18%) of white solid: mp 57–60 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.18 (d, 3 H,  $\text{CH}_3$ ), 1.45 (s, 3 H,  $\text{CH}_3$ ), 1.72 (s, 3 H,  $\text{CH}_3$ ), 3.1 (dd, 1 H), 3.2 (dd, 1 H), 3.42–3.52 (m, 1 H), 4.1 (d, 1 H), 4.15 (dd, 1 H), 4.28 (dd, 1 H), 4.34 (d, 1 H), 5.22 (s, 1 H), 6.98 (d, 1 H), 7.15 (t, 1 H), 7.23–7.4 (m, 5 H), 7.6 (d, 1 H).

**4,5,6,7-Tetrahydro-5-methoxy-6-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepine (E)-2-Butenesulfonate (23)** (18). Sodium (0.4 g, 17 mmol) was added to cold MeOH (25 mL) under  $\text{N}_2$ . Crude **12** was added to the cold solution, which was then heated to reflux. After 5.5 h the mixture was concentrated and the residue partitioned between  $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$  (2x). The organics were washed with  $\text{H}_2\text{O}$  and then brine, dried with  $\text{MgSO}_4$ , and concentrated to an oil (1.1 g) that was flash chromatographed on silica gel (4% EtOAc/hexane) to yield 0.3 g of colorless oil. This oil was dissolved in *i*-PrOH and added to a hot solution of fumaric acid (1.5 equiv) in *i*-PrOH. On cooling of the solution, white crystals separated, collected, and washed with cold  $\text{CH}_3\text{CN}$  and then Et<sub>2</sub>O to yield 0.31 g (30%): mp 137–138.5 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.2 (d, 3 H,  $\text{CH}_3$ ), 1.38 (s, 3 H,  $\text{CH}_3$ ), 1.71 (s, 3 H,  $\text{CH}_3$ ), 3.06 (dd, 1 H), 3.19 (dd, 1 H), 3.5–3.6 (m, 1 H), 3.9 (dd, 1 H), 4.0–4.2 (m, 6 H), 5.18 (t, 1 H), 6.77 (d, 1 H), 7.0 (t, 1 H), 7.25 (d, 1 H).

**(+)-(S)-9-Chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepine-2-(1H)-selenone (17).** This material was synthesized by the same procedure used to make **8** (R =  $\text{CH}_2\text{CH}=\text{CH}_2$ ) except that selenocurea was used in place of thiourea. The crude product was recrystallized from *i*-PrOH to yield **17** (64%): mp 178 °C dec.

**(±)-7-Chloro-4-(cyclopropylcarbonyl)-2,3,4,5-tetrahydro-3-methyl-9-nitro-1H-1,4-benzodiazepine (18).** At 0 °C under argon a suspension of **2** (22.46 g, 0.1 mol) in 400 mL of glyme was added to a suspension of LAH (0.49 g, 0.25 mol) in 100 mL of glyme. The reaction was heated to reflux for 19 h and then cooled and quenched with the addition of 20.5 mL of 3 N NaOH solution. THF (125 mL) was added and the mixture heated under reflux for 45 min before the solids were filtered off and rinsed thrice with THF. The combined filtrates were evaporated to yield 20.49 g (>100%) of product which was used without further purification. The diamine (20.02 g, 0.102 mol) and Et<sub>3</sub>N (14.22 mL, 0.102 mol) were dissolved in 400 mL of  $\text{CH}_2\text{Cl}_2$  and cooled to 0 °C before dropwise addition of cyclopropanecarbonyl chloride in 150 mL of  $\text{CH}_2\text{Cl}_2$  over 35 min under argon. The mixture was allowed to warm to ambient temperature. After 72 h the mixture was washed with saturated  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtered, and concentrated to yield 28.59 g (>100%) of amorphous yellow solid which was used without further purification. That material (23.07 g) was added over 30 min to fuming nitric acid (75 mL) cooled to 0 °C. After another 35 min at 0 °C the solution was slowly added to 700 g of ice with stirring. The precipitated solid was filtered and washed with 700 mL of ice water to yield, after drying, 23.87 g (57%) of yellow solid **18**, which was used without purification.

**(±)-7-Chloro-4-(cyclopropylmethyl)-2,3,4,5-tetrahydro-3-methyl-1H-1,4-benzodiazepine-9-amine (19).** Solid **18** (18.54 g, 0.08 mol) was added over 45 min to a suspension of LAH (13.7 g, 0.28 mol) in 350 mL of glyme cooled to 0 °C. The reaction was then stirred at ambient temperature for 2 h and heated under

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reflux for 17 h before it was quenched with the careful sequential addition of 13.7 mL of  $H_2O$  in 41 mL of THF, 19.7 mL of 15% NaOH solution, and 41 mL of  $H_2O$ . The solid salts were filtered off and digested with 100 mL of boiling THF for 5 min and refiltered. The combined filtrates were concentrated to yield 14.18 g of brown oil 19 that was used without further purification.

(±)-9-Chloro-6-(cyclopropylmethyl)-4,5,6,7-tetrahydro-8-methyl-1*H*-1,2,5-thiadiazolo[4,3,2-*jk*][1,4]benzodiazepine-5*S,S*-Dioxide (20). Sulfuryl diarside (0.46 g, 4.75 mmol) and 19 (1.28 g, 4.75 mmol) were combined under  $N_2$  and immediately placed in an oil bath at 130 °C, which was then heated to 185 °C over 10 min. After 1 h the mixture was cooled and flash chromatographed on silica gel ( $CH_2Cl_2$ /MeOH 10:1) to yield 0.17 g (11%) of product which was triturated with  $CH_2CN$  to yield 44 mg of 20 as a tan solid: mp 204–205.5 °C. At ambient temperature the  $^1H$  NMR spectrum of 20 was poorly resolved, but when heated to 70 °C the peaks sharpened:  $^1H$  NMR (360 MHz,  $DMSO-d_6$ )  $\delta$  0.15–0.3 (m, 2 H), 0.5–0.6 (m, 2 H), 0.9–1.06 (m, 1 H), 1.3 (d, 3 H,  $CH_3$ ), 2.6–2.8 (m, 2 H), 3.45 (dd, 2 H), 3.6 (dd, 2 H), 3.65–3.75 (m, 1 H), 4.1 (d, 1 H), 6.6 (s, 2 H).

(±)-10-Chloro-7-(cyclopropylmethyl)-1,2,5,6,7,8-hexahydro-6-methyl-3*H*-pyrazino[2,3,4-*jk*][1,4]benzodiazepine-3-one (21). Bromosuccinic acid (1.06 g, 4 mmol) and 19 (1.06 g, 4 mmol) were combined in  $CH_2Cl_2$  (8 mL) and stirred at ambient temperature for 7 days. Some MeOH was added to bring separated solid back into solution before the mixture was added to saturated  $NaHCO_3$  solution and extracted with  $CH_2Cl_2$ . The organic layer was dried with  $MgSO_4$  and concentrated to 0.62 g of brown solid that was flash chromatographed on silica gel ( $CH_2Cl_2$ /MeOH 80:3) to yield 0.4 g (33%) of 21 as an off-white solid: mp 149–152 °C;  $^1H$  NMR (360 MHz,  $CDCl_3$ )  $\delta$  0.1 to 0.1 (m, 2 H), 0.4–0.55 (m, 2 H), 0.75–0.9 (m, 1 H), 1.15 (d, 3 H,  $CH_3$ ), 2.52 (d, 2 H), 3.25–3.4 (m, 1 H), 3.5 (dd, 1 H), 3.75 (d, 1 H), 3.87 (dd, 1 H), 4.35 (d, 2 H), 6.58 (s, 1 H), 6.59 (s, 1 H).

(±)-*N*-(9-Chloro-6-(cyclopropylmethyl)-1,2,4,5,6,7-hexahydro-6-methylimidazo[4,5,1-*jk*]benzodiazepine-2-ylidene)-guanidine (*E*)-2-Butenedioate (1:1) (22). Cyanamide (0.26 g, 8.25 mmol) in 3.5 mL of  $H_2O$  was added over 20 s to a mixture of 19 in 1.28 mL of concentrated HCl. The mixture was heated at 90 °C for 2 h, cooled to 0 °C, basified with saturated  $NaHCO_3$ , and extracted with  $CH_2Cl_2$ . The organic phase was dried with  $MgSO_4$  and concentrated to 1.82 g of black oil that was flash chromatographed on silica gel ( $CH_2Cl_2$ /MeOH 7:1) to yield 0.62 g of clear tan oil. The oil was dissolved in 8 mL of EtOH and added to 0.23 g of fumaric acid in 7 mL of EtOH to yield 0.47 g (26% based on cyanamide) of 22 as a white fumarate salt: mp 203–205.5 °C.

(-)-(*S*)-7-Chloro-4-(cyclopropylmethyl)-2,3,4,5-tetrahydro-*N*,3-dimethyl-1*H*-1,4-benzodiazepine-1-carbothioamide (*E*)-2-Butenedioate (1:1) (23). As previously described (see preparation of 18), 2(8) was reduced. The resultant diamine (9.63 g, 50 mmol) and  $Na_2CO_3$  (5.3 g, 50 mmol) were combined in 50 mL of DMF and heated to 90 °C before dropwise addition of cyclopropylthiomethane over 8 min. The mixture was heated another 5 h and then stirred at ambient temperature for 11 h before it was added to 500 mL of  $H_2O$  and extracted with  $CHCl_3$ . The organic layer was washed with  $H_2O$  (3x) and then brine, dried with  $MgSO_4$ , and concentrated to yield 11.12 g of tan oil (85% pure by GLC) that was used without further purification. A solution of this material (9.4 g, 37.5 mmol) in 75 mL of *i*-PrOH was heated to 90 °C under argon, while methyl thioisocyanate (Aldrich; 2.84 g, 38.8 mmol) was added dropwise. The reaction was heated at 80 °C for 11 h (an additional 1.0 g (13.7 mmol) of MeNCS was added after 8 h). The reaction was concentrated and the orange gum was flash chromatographed on silica gel (MeOH/ $CH_2Cl_2$  0:100 to 3:97). A 5.36-g sample of purified product was converted to a malate salt in Et<sub>2</sub>O/*i*-PrOH to give 4.9 g which was recrystallized from Et<sub>2</sub>O/*i*-PrOH to yield 4.47 g: mp 177–179 °C;  $^1H$  NMR (360 MHz,  $DMSO-d_6$ , 70 °C)  $\delta$  0.25–0.4 (m, 2 H), 0.57–0.7 (m, 2 H), 1.06–1.2 (m, 1 H), 1.25 (d, 3 H,  $CH_3$ ), 2.6–2.75 (m, 1 H), 2.75–2.9 (m, 1 H), 2.92 (d, 3 H,  $CH_3$ ), 3.62–3.77 (m, 1 H), 4.05 (d, 1 H), 3.82–4.15 (m, 1 H), 4.42 (d, 1 H), 4.35–4.7 (m, 1 H), 6.06 (s, 2 H), 7.24 (d, 1 H), 7.3–7.45 (m, 1 H), 7.45–7.55 (m, 1 H), 7.60 (d, 1 H).

(±)-8,6-Dihydro-6-methylimidazo[4,5,1-*jk*][1,4]benzodiazepine-7(4*H*)-one (24). A mixture of 24<sup>1</sup> (7.64 g, 0.04 mol)

and formamidine acetate (8.32 g, 0.08 mol) was quickly heated to 145 °C and maintained for 1 h before cooling. The resultant solid was triturated with 150 mL of hot  $CH_2CN$ , cooled, filtered, and triturated with 150 mL of hot *i*-PrOH to yield 2.7 g (34%) of 24. A small sample was further purified by recrystallization in *i*-PrOH to yield a light tan solid: mp 253–255 °C.

4,5,6,7-Tetrahydro-6-methylimidazo[4,5,1-*jk*][1,4]benzodiazepine (*E*)-2-Butenedioate (1:1) (27). Neat 25 (2.23 g, 11 mmol) was added to a stirred suspension of LAH (1.88 g, 44 mmol) in 150 mL of glyme at 0 °C under argon. After 2 h at 0 °C the mixture was heated under reflux for 18 h before it was allowed to cool and quenched with careful sequential addition of 1.7 mL of  $H_2O$  in 5 mL of THF, 1.7 mL of 16% NaOH solution, and 5.1 mL of  $H_2O$ . The salts were filtered and digested with 100 mL of hot THF and refiltered. The combined filtrates were dried over  $MgSO_4$  and concentrated to yield 1.91 g of solid which proved to be a 2:1 mixture of 26 and 27. The former could be separated and purified by recrystallization with  $CH_2CN$ . The mixture was converted to pure 27 by stirring a THF solution open to the atmosphere at ambient temperature for 16 h. A small sample of 27 was purified by adding an EtOH solution to 1 equiv of fumaric acid in EtOH to yield a white fumaric acid salt: mp 203–204.5 °C;  $^1H$  NMR (360 MHz,  $DMSO-d_6$ )  $\delta$  1.2 (d, 3 H,  $CH_3$ ), 1.7 (d, 3 H,  $CH_3$ ), 2.92 (d, 1 H), 3.2 (d, 1 H), 3.53–3.63 (m, 1 H), 4.1 (d, 1 H), 4.15 (d, 1 H), 4.2 (dd, 1 H), 4.42 (dd, 2 H), 4.75 (s, 1 H), 4.85 (s, 1 H), 6.65 (s, 2 H), 6.92 (d, 1 H), 7.1 (t, 1 H), 7.5 (d, 1 H), 8.13 (s, 1 H).

5,6,7,8-Tetrahydro-6-methyl-7-propyl-1*H*-pyrazino[3,2,1-*jk*][1,4]benzodiazepine-2,3-dione (31). A solution of 30 (0.99 g, 4.5 mmol), prepared by methods described in ref 1, in 45 mL of toluene was added to a solution of oxalyl chloride (0.39 mL, 4.5 mmol) in 90 mL of toluene before the reaction was heated to reflux. After 2 h the mixture was cooled, and the solid was filtered and washed with a small amount of toluene followed by Et<sub>2</sub>O to yield 1.18 g of brown solid. This was dissolved in  $CH_2Cl_2$ , washed with saturated  $NaHCO_3$ , dried with  $MgSO_4$ , and concentrated. The residue was flash chromatographed on silica gel ( $CH_2Cl_2$ /MeOH 20:1) to yield 0.24 g (20%) of off-white solid that was recrystallized from *i*-PrOH to give 130 mg of white solid 31: mp 213.6–215.5 °C;  $^1H$  NMR (360 MHz,  $CDCl_3$ )  $\delta$  0.82 (t, 3 H,  $CH_3$ ), 1.2 (d, 3 H,  $CH_3$ ), 1.32–1.52 (m, 2 H), 2.4–2.6 (m, 2 H), 3.22–3.32 (m, 1 H), 3.9 (d, 1 H), 4.07–4.28 (m, 1 H), 4.38 (d, 1 H), 4.8 (d, 1 H), 6.95 (d, 1 H), 7.1 (t, 1 H), 7.2 (d, 1 H).

4,5,6,7-Tetrahydro-6-methyl-6-propyl-1,2,3-triazolo[4,5,1-*jk*][1,4]benzodiazepine Monohydrochloride (32). Sodium nitrite (0.24 g, 3.5 mmol) was added over 15 s to a cold (0 °C) solution of 30 (0.06 g, 3 mmol) in 30 mL of 3 N HCl. The mixture was stirred cold for 1 h before it was basified with 3 N NaOH and extracted with  $CH_2Cl_2$ . The organic phase was dried with  $MgSO_4$  and concentrated, and the residual oil was flash chromatographed on silica gel (EtOAc/hexane 1:1) to yield 390 mg (49%) of oil. This was dissolved in 5 mL of EtOH and combined with 0.14 mL of concentrated HCl. The white solid HCl salt of 32 was filtered and dried to yield 290 mg: mp 223–225 °C;  $^1H$  NMR (360 MHz,  $DMSO-d_6$ /D<sub>2</sub>O)  $\delta$  0.9 (t, 3 H,  $CH_3$ ), 1.5 (d, 3 H,  $CH_3$ ), 1.7–1.88 (m, 2 H), 3.0–3.18 (m, 1 H), 3.18–3.35 (m, 1 H), 4.38–4.53 (m, 1 H), 4.6–4.96 (m, 2 H), 4.95–5.2 (m, 2 H), 7.52 (t, 1 H), 7.6 (d, 1 H), 8.12 (d, 1 H).

4,5,6,7-Tetrahydro-6-methyl-2-oxo-6-propylimidazo[4,5,1-*jk*][1,4]benzodiazepine-1(2*H*)-acetonitrile (34a-d). The procedure is typified by 34d. Sodium hydride (0.118 g, 3 mmol) and 33 (0.75 g, 3.08 mmol) were combined in 45 mL of DMF under argon at ambient temperature. After 1 h, bromoacetonitrile (0.341 mL, 4.9 mmol) was added and stirring continued another 45 min before the mixture was concentrated. The residue was partitioned between Et<sub>2</sub>O and  $CH_2Cl_2$ . The organic phase was washed with brine, dried with  $MgSO_4$ , and concentrated to an oil that was flash chromatographed on silica gel (3–5% EtOH/ $CH_2Cl_2$ ). The solid product was triturated with hexane to yield 0.59 g (51%) of off-white 34d: mp 83–85 °C;  $^1H$  NMR (360 MHz,  $CDCl_3$ )  $\delta$  0.9 (s, 3 H), 1.38 (d, 3 H,  $CH_3$ ), 1.4–1.6 (m, 2 H), 2.42–2.8 (m, 2 H), 3.4–3.52 (m, 1 H), 3.83 (dd, 1 H), 4.05 (d, 1 H), 4.1 (dd, 1 H), 4.82 (s, 2 H), 6.9 (d, 1 H), 7.0 (d, 1 H), 7.1 (t, 1 H).

3,4-Dihydro-9-methoxy-3-methyl-1*H*-1,4-benzodiazepine-2,5-dione (35). *N*-Methylmorpholine (11 mL, 0.1 mol) was added to a solution of 2-amino-3-methoxybenzoic acid (16.7 g, 0.1 mol),

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( $\pm$ )-alanine methyl ester hydrochloride (13.9 g, 0.1 mol), and 1-hydroxybenzotriazole (27 g, 0.3 mol) in 400 mL of THF under  $N_2$  at ambient temperature. The mix was cooled to 0 °C before addition of neat liquid dicyclohexylcarbodiimide (30.8 g, 0.1 mol). The reaction was stirred at ambient temperature for 4 days before it was filtered and the filtrate concentrated. The residue was partitioned between EtOAc/saturated aqueous  $NaHCO_3$ ; the organic phase was dried with  $MgSO_4$  and concentrated to yield 23.99 g of brown oil. The oil was heated under a Dean-Stark trap (to collect displaced MeOH) in an argon atmosphere at 200 °C for 3 h. It was cooled and triturated with 75 mL of hot *i*-PrOH, cooled, filtered, and washed with cold *i*-PrOH to yield 12.6 g (57%) of off-white 36, which was used without further purification.

**2,3,4,5-Tetrahydro-8-methoxy-3-methyl-1*H*-1,4-benzodiazepine (37).** Borane (1 M in THF, 272 mL, 0.27 mol) was added to a cold (0 °C) solution of 36 (12 g, 0.054 mol) in 300 mL of THF. After 5 min the solution was heated to reflux. After 3 days the solution was recooled to 0 °C and quenched with slow addition of 270 mL of 3 N HCl. When the addition was complete, the mixture was heated on a steam bath for 30 min, cooled, and basified with 325 mL of 15% aqueous NaOH. It was then extracted with  $CH_2Cl_2$  (2 $\times$ ), which was then washed with brine, dried with  $MgSO_4$ , and concentrated to yield 6.53 g (62%) of 37 as a brown oil, which solidified on standing and was used without further purification.

**4-(Cyclobutylmethyl)-2,3,4,5-tetrahydro-3-methyl-1*H*-1,4-benzodiazepine-8-ol (39).** Diamine 37 was monoalkylated to 38 under standard conditions (see ref 1) in 71% yield. The crude 38 (2.6 g, 10 mmol) was dissolved in 225 mL of  $CH_2Cl_2$  before addition of boron tribromide (14.1 mL, 14 mmol) over 1 min, under  $N_2$ . After 24 h, MeOH (20 mL) was added carefully to the mixture and it was stirred for 1 h and concentrated. The residue was partitioned between  $CH_2Cl_2$  (2 $\times$ ) and saturated aqueous  $NaHCO_3$ . The organics were dried with  $Na_2SO_4$  and concentrated to yield 2.51 g (>100%) of 39 as a brown oil which was used directly in the next step.

**6-(Cyclobutylmethyl)-4,5,6,7-tetrahydro-5-methyl-2*H*-oxazolo[5,4,3-*jk*]1,4-benzodiazepine-2-one (E)-2-Butenedioate (1:1) (40).** Urea (0.6 g, 10 mmol) and 39 (1.23 g, 5 mmol) were combined under nitrogen and immediately placed in an oil bath at 155 °C, heated to 200 °C over 20 min, and maintained for another 20 min. The mixture was allowed to cool and partitioned between  $CH_2Cl_2$  (2 $\times$ ) and  $H_2O$ . The organics were dried with  $MgSO_4$  and concentrated onto silica gel added to the solution. The silica gel was placed atop a flash column and eluted with EtOAc/hexane (15:85) to yield 230 mg (17%) of 40 as a clear yellow oil. A sample was dissolved in EtOH and added to 1 equiv of fumaric acid in EtOH to give, after filtration, the acid addition salt as a white solid: mp 147–150 °C, resolidifies and remelts 173–195 °C;  $^1H$  NMR (360 MHz, DMSO- $d_6$ )  $\delta$  1.17 (d, 3 H,  $CH_3$ ), 1.47–1.67 (m, 2 H), 1.72–1.9 (m, 2 H), 1.9–2.03 (m, 2 H), 2.4–2.55 (m, 2 H), 2.56–2.7 (m, 1 H), 3.73 (dd, 1 H), 3.89 (dd, 1 H), 4.02 (d, 1 H), 4.1 (d, 1 H), 6.62 (s, 2 H), 6.95 (d, 1 H), 7.03 (t, 1 H), 7.18 (d, 1 H).

**1,2,3,4-Tetrahydro-3-methyl-3-propylpyrrole[3,2,1-*jk*]1,4-benzodiazepine-6(7*H*)-one (E)-2-Butenedioate (1:1) (44).** Diamine 41<sup>16</sup> was alkylated under standard conditions to give 42 (3.17 g, 15.5 mmol) which was dissolved in 30 mL of  $CH_2Cl_2$  and cooled to 0 °C under argon before addition of chloroacetyl chloride (1.24 mL, 15.5 mmol) in 30 mL of  $CH_2Cl_2$  over 2 min. After 15 min the reaction mixture was washed with saturated aqueous  $NaHCO_3$  (2 $\times$ ). The organics were dried with  $MgSO_4$  and concentrated to yield 4.63 g (>100%, 4.37 g theoretical) of 43 as an oil used without further purification. The total amount (4.37 g, 15.5 mmol) was placed under argon before addition of solid  $AKCl_3$  over 1 min. The mixture was slowly heated to ca. 170 °C over 1 h and maintained for 20 h. It was cooled and the resultant black glass was dissolved by the careful addition of 200 g of ice with swirling. The aqueous solution was basified with 3 N aqueous NaOH and extracted with  $CH_2Cl_2$ . The organic phase was dried with  $MgSO_4$  and concentrated to 4.34 g of black oil that was flash

chromatographed on silica gel by elution with  $CH_2Cl_2$ /MeOH (30:1) to yield 1.15 g. This was rechromatographed to give 0.74 g (19.5%) of 44 as a clear yellow oil. A sample was dissolved in Et<sub>2</sub>O and added to 1 equiv of fumaric acid in EtOH. The fumaric salt of 44 was isolated and recrystallized from *i*-PrOH to give a white solid: mp 180–182 °C;  $^1H$  NMR (360 MHz,  $CDCl_3$ )  $\delta$  0.8 (s, 3 H), 1.08 (d, 3 H,  $CH_3$ ), 1.32–1.45 (m, 2 H), 2.4 (t, 2 H), 3.05–3.2 (m, 1 H), 3.67 (s, 2 H), 3.85 (dd, 1 H), 3.73 (d, 1 H), 3.98 (dd, 1 H), 4.3 (d, 1 H), 6.62 (s, 2 H), 6.9 (t, 1 H), 7.0 (d, 1 H), 7.1 (d, 1 H).

**2,3-Dihydro-3-(methylthio)-2-oxo-3-(2-oxopropyl)-1*H*-indole-4-carbonitrile (46).** A mixture of 45<sup>17</sup> (80.6 g, 0.395 mol), chloroacetone (31.4 mL, 0.395 mol), potassium carbonate (54.6 g, 0.395 mol), and potassium iodide (55.6 g, 0.395 mol) in 1.6 L of DMF was stirred at ambient temperature for 5 h before it was partitioned between  $H_2O$  and EtOAc. The organic layer was washed with  $H_2O$  (3 $\times$ ) and then brine, dried with  $MgSO_4$ , and partially concentrated. Crystallization from solution yielded 63.9 g (62%) of 46: mp 228–230 °C.

**2,3-Dihydro-2-oxo-3-(2-oxopropyl)-1*H*-indole-4-carbonitrile (47).** Zinc dust (135 g, 2.0 mol) and 46 (26.7 g, 0.103 mol) in 750 mL of THF and 26 mL of acetic acid were refluxed for 2 h. The mixture was filtered and concentrated to a solid residue that was triturated with *i*-BuOMe (2 $\times$ ) and recrystallized from absolute EtOH to yield 18.3 g (83%) of 47 as a tan solid. A sample was further purified by flash chromatography on silica gel ( $CH_2Cl_2$ /MeOH 9:1) followed by recrystallization from EtOAc to give a pale pink powder: mp 178–180 °C.

**1,2a,3,4,5,6-Hexahydro-4-methyl-2*H*-azepino[5,4,3-*cd*]indole-2-one (48).** Raney nickel (400 g, Fluka) was washed with *i*-BuOH (3 $\times$ ) before it was mixed with 46 (27.8 g, 0.107 mol) in 1 L of *i*-BuOH and refluxed for 1.5 h. The hot solvent was decanted off the nickel which was further washed with hot *i*-BuOH (5 $\times$ ). The combined washes were concentrated to yield 7.62 g of solid that was triturated with EtOAc to yield 5.51 g (25%) of 48 as a pale pink solid. A sample was further purified by recrystallization from EtOAc: mp 164–166 °C.

**1,2a,3,4,5,6-Hexahydro-4-methyl-5-(2-methyl-2-propenyl)-2*H*-azepino[5,4,3-*cd*]indole-2-one (49) (R = 2-MA).** A mixture of 48 (19.0 g, 60.7 mmol), chloro-2-methyl-2-propene (6.5 mL, 66.8 mmol), KI (11.1 g, 66.8 mmol), and  $Na_2CO_3$  (32 g, 304 mmol) in DMF (200 mL) were stirred at ambient temperature for 2 days before it was partitioned between  $H_2O$ /EtOAc. The organic phase was washed with  $H_2O$  and then brine, dried with  $Na_2SO_4$ , and concentrated to yield 10 g of brown oil. This was flash chromatographed on silica gel ( $CH_2Cl_2$ /MeOH/ $NH_4OH$  93:5:0.1) to yield 7.51 g (48%) of 49 as a yellow solid. A sample was further purified by recrystallization from EtOAc to give a pale yellow solid: mp 165–167 °C;  $^1H$  NMR (360 MHz, DMSO- $d_6$ )  $\delta$  1.2 (s, 3 H), 1.3–1.4 (m, 1 H), 1.55 (s, 3 H,  $CH_3$ ), 1.82 (d, 1 H), 2.85 (d, 1 H), 3.4–3.5 (m, 1 H), 3.55 (dd, 1 H), 3.88 (d, 1 H), 3.98 (d, 1 H), 4.62 (s, 1 H), 4.78 (s, 1 H), 6.6 (d, 1 H), 6.7 (d, 1 H), 7.07 (t, 1 H), 10.86 (s, 1 H).

**1,2a,3,4,5,6-Hexahydro-4-methyl-5-(2-methyl-2-propenyl)-2*H*-azepino[5,4,3-*cd*]indole-2-thione (50) (R = 2-MA).** Lawesson's reagent (1.07 g, 2.69 mmol; Aldrich), 49 (R = 2-MA, 0.83 g, 2.23 mmol), and BHT (ca. 2 mg) in 20 mL of toluene were refluxed for 2 h. Filtration gave 1.37 g of brown solid that was flash chromatographed on silica gel ( $CH_2Cl_2$ /MeOH/ $NH_4OH$  93:7:0.1) to give 0.67 g of green glass that was crystallized from MeOH to yield 150 mg (24%) of 50: mp 120 °C dec.

**2-Chloro-3,4,5,6-tetrahydro-4-methyl-5-propyl-1*H*-azepino[5,4,3-*cd*]indole Monohydrochloride (51) (R = *n*-Pr).**  $POCl_3$  (5 mL) and 49 (R = *n*-Pr, 0.6 g) were heated under reflux for 5 h. The mixture was allowed to cool and added to ice cold saturated aqueous  $NaHCO_3$  and  $CH_2Cl_2$ . After 0.5 h the organic layer was dried with  $Na_2SO_4$  and concentrated to a green oil that was flash chromatographed on silica gel ( $CH_2Cl_2$ /MeOH/ $NH_4OH$  93:7:0.1) to give 180 mg (28%) of pale yellow solid 51. This was dissolved in Et<sub>2</sub>O, and Et<sub>2</sub>O saturated with HCl was added. The precipitated solid was recrystallized from *i*-PrOH/MeOH to yield

(16) Kim, D.; Baum, T. Derivatives of Tetrahydro-1,4-benzodiazepines as Potential Antihypertensive Agents. *J. Med. Chem.* 1977, 20, 209–212.

(17) Gessman, P.; Gilbert, D.; Tien-Yau, L. Substituent Effects on the Carbon-13 Spectra of Oxindoles. *J. Org. Chem.* 1977, 42, 1340–4.

100 mg of white crystalline 51-HCl: mp ca. 230 °C dec.  
 3,4,5,6-Tetrahydro-4-methyl-5-propyl-1*H*-azepino[5,4,3-*cd*]indole Monohydrochloride (52) (*R* = *n*-Pr). A mixture of 51 (*R* = *n*-Pr, 0.15 g), 10% Pd/C (0.15 g), and Et<sub>3</sub>N (10 drops) in 20 mL of EtOH was placed on a Parr shaker under 28 psi of hydrogen for 2 h. It was then filtered through Dicalite and concentrated to a yellow glass. Flash chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH 93:7:0.1) gave 80 mg (87%) of 52 as a yellow solid. This was dissolved in EtOAc and ethereal HCl added. The precipitated solid was recrystallized from *i*-PrOH to yield 30 mg of 52-HCl as white crystals: mp 245-247 °C. Protonation of 52 by HCl formed a mixture of diastereomers in a 2:1 ratio as seen in the <sup>1</sup>H NMR. Where protons were separated in the spectrum, the chemical shift of the minor diastereomer is indicated in parentheses, but the proton count of both isomers are combined. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>): δ 0.8 (t, 3 H, CH<sub>3</sub>), 1.52 (1.42) (d, 3 H, CH<sub>3</sub>), 1.66-1.9 (m, 2 H), 2.75-2.9 (2.9-3.02) (m, 1 H), 3.02-3.4 (m, 3 H), 4.06-4.15 (3.87-3.97) (m, 1 H), 4.57-4.82 (m, 2 H), 6.92-7.02 (m, 1 H), 7.02-7.13 (m, 1 H), 7.32 (7.23) (s, 1 H), 7.38 (t, 1 H), 10.34 (s, 1 H), 11.31 (11.18) (s, 1 H).  
 3,4,5,6-Tetrahydro-3*a*-hydroxy-4-methyl-5-(3-methyl-3-propenyl)-2*aH*-azepino[5,4,3-*cd*]indol-2(1*H*)-one Monohydrochloride Ethanolate (1:1) (53) (*R* = 2-MA). A mixture of 49 (*R* = 2-MA, 0.5 g, 1.95 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.84 g, 3.9 mmol) in 9 mL of DMSO and 1 mL of H<sub>2</sub>O was stirred overnight at

ambient temperature and open to the atmosphere. It was then partitioned between aqueous NaHSO<sub>4</sub> solution and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous phase was saturated with NaCl, basified with 3 N NaOH to pH 10, and repeatedly extracted (7×) with CH<sub>2</sub>Cl<sub>2</sub>. The combined organics were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was flash chromatographed on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH 93:7:0.1) to give a green oil which was taken up in Et<sub>2</sub>O and precipitated with ethereal HCl. Recrystallization from EtOH gave 0.24 g (40%) of 53-HCl-EtOH as pale green crystals: mp 227-230 °C.

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## Synthesis and Ocular Antihypertensive Activity of New Imidazolidine Derivatives Containing a $\beta$ -Blocking Side Chain

D. Huber,<sup>1</sup> J. D. Ehrhardt,<sup>1</sup> N. Decker,<sup>1</sup> J. Himber,<sup>2</sup> G. Andermann,<sup>1</sup> and G. Leclerc<sup>3,4</sup>

Institut de Pharmacologie (UA 889 CNRS), Equipe de Pharmacochimie, Faculté de Médecine, 11, rue Humann, 67000 Strasbourg, France, Laboratoires ALCON, Recherches et Développement, BP 18, 68340 Kayserberg, France, and Faculté de Médecine et de Pharmacie, Université Joseph Fourier, Avenue du Verdun, 38240 Meylan, France. Received March 21, 1991

The syntheses of new phenylimidazolidine derivatives (3-6)<sup>1</sup> containing a propanolamine oxime or an oxypropanolamine moiety attached either to the aromatic or to the imidazolidine ring are described. These compounds were evaluated for potential ocular antihypertensive activity in  $\alpha$ -sympatrically-induced ocular hypertension in rabbits. These compounds represent a unique series of effective ocular antihypertensive agents that despite possessing structural characteristics of  $\beta$ -blockers and of imidazolidine derivatives, exhibit weak  $\alpha$ - and  $\beta$ -adrenergic agonist and antagonist activities. These findings may be of significant therapeutic importance in the medical management of glaucoma.

Adrenergic receptors are classified into  $\alpha$ - and  $\beta$ -adrenergic receptors<sup>2</sup> and further subdivided into  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$ .<sup>3-5</sup> Most of them have already been found in eye tissues. Physiological and biochemical studies support the importance of  $\alpha$ - and  $\beta$ -adrenergic receptors in the regulation of IOP<sup>7,8</sup> (intraocular pressure). Even though the distribution of these receptor subpopulations in eye tissues has not yet been completely delineated, data indicate that the receptors in the ciliary body, which modulate aqueous humor production, are mainly of  $\alpha_2$  and  $\beta_2$  type.<sup>9-13</sup>  $\alpha$ -Adrenergic agonists<sup>14-17</sup> and  $\beta$ -adrenergic antagonists<sup>18</sup> are known to have a favorable effect on the IOP in open-angle glaucoma.  $\beta$ -Adrenoceptor antagonists, widely used in glaucoma therapy, are presumed to lower IOP by decreasing aqueous humor formation, mainly by affecting membrane permeability.<sup>19</sup>  $\alpha$ -Agonists and especially clonidine were shown to decrease aqueous humor formation by constriction of afferent ciliary process blood vessels.<sup>9</sup> On another hand, it has been reported that the resistance of aqueous humor outflow was decreased by clonidine.<sup>17,20-23</sup> Prazosin, an antagonist which has a high specificity for the  $\alpha_1$  receptors, lowers IOP in animal models.<sup>23,24</sup> However, prazosin is not a very effective

hypotensive agent because it also reduces aqueous humor outflow, thus negating the benefit of reduction of aqueous

- (1) Leclerc, G.; Huber, D.; Himber, J.; Andermann, G. U.S. Patent 4,801,617, 1989.
- (2) Alquist, R. P. *Am. J. Physiol.* 1948, 183, 594.
- (3) Lands, A. M.; Arnold, A.; McAuliff, J. P.; Luqueño, P. P.; Brown, J. G., Jr. *Nature* 1967, 214, 597.
- (4) Glomann, H.; Hornung, R.; Prosek, P. J. *Cardiol. Pharmacol.* 1988, 2, 8303.
- (5) Van Zwieten, E. A.; Timmermans, P. B. M. W. M. *Pharm. Weekbl., Sci. Ed.* 1982, 161.
- (6) Timmermans, P. B. M. W. N.; Schoop, A. M. G.; Knaak, Eur. J. Pharmacol. 1981, 70, 7.
- (7) Pottar, D. E. *Pharmacol. Rev.* 1981, 33, 133.
- (8) Leopold, I. H.; Diamas, E. *Annu. Rev. Pharmacol. Toxicol.* 1982, 22, 401.
- (9) Marek, F. J.; Cavario, S. J. *Arch. Ophthalmol.* 1978, 96, 1111.
- (10) Wes, M. B.; Molinoff, P. B. *Invest. Ophthalmol. Vis. Sci.* 1987, 28, 420.
- (11) Neufeld, A. H.; Page, E. D. *Invest. Ophthalmol. Vis. Sci.* 1977, 16, 1118.
- (12) Carvantes, Y. C.; Hernandez, H. H. J. *Toxicol. Ocul. Toxicol.* 1986, 5, 186.
- (13) Nathanson, J. A. *Invest. Ophthalmol. Vis. Sci.* 1981, 21, 798.
- (14) Ralli, R. *Acta Ophthalmol.* 1975, 135, 37.
- (15) Allen, K. C.; Langham, M. E. *Invest. Ophthalmol. Vis. Sci.* 1978, 15, 818.
- (16) Krieglstein, G. K.; Langham, M. E.; Loychecker, W. *Invest. Ophthalmol. Vis. Sci.* 1978, 17, 149.

<sup>1</sup> Institut de Pharmacologie.

<sup>2</sup> Laboratoires ALCON.

<sup>3</sup> Université Joseph Fourier.

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

Henry J. Breslin,<sup>\*,†</sup> Michael J. Kukla,<sup>†</sup> Donald W. Ludovici,<sup>†</sup> Richard Mohrbacher,<sup>†</sup> Winston Ho,<sup>†</sup> Milton Miranda,<sup>†</sup> James D. Rodgers,<sup>†</sup> T. Kevin Hitchans,<sup>†</sup> Gregory Leo,<sup>†</sup> Diane A. Gauthier,<sup>†</sup> Chih Y. Ho,<sup>†</sup> Malcolm K. Scott,<sup>†</sup> Erik De Clercq,<sup>‡</sup> Rudi Pauwels,<sup>‡</sup> Koen Andries,<sup>‡</sup> Marcel A. C. Janssen,<sup>§</sup> and Paul A. J. Janssen<sup>†</sup>

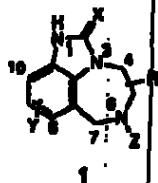
Janssen Research Foundation, Spring House, Pennsylvania 19477, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroederstraat 10, B-3000 Leuven, Belgium, and Janssen Research Foundation, Turnhoutseweg 30, B-3340 Beerse, Belgium

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4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jh*][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-*jh*][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).<sup>1</sup> 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.



Our previous medicinal chemistry publications<sup>2,3</sup> 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.<sup>4</sup> A phase I clinical study of **1bt** on 22 late stage AIDS patients run over a 50 week period has also recently been reported.<sup>5</sup> 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.

\* Address correspondence to this author at: Janssen Research Foundation, Welsh and McKean Roads, Spring House, PA 19477.

<sup>†</sup> Janssen Research Foundation, PA.

<sup>‡</sup> Katholieke Universiteit Leuven.

<sup>§</sup> Janssen Research Foundation, Belgium.

<sup>\*</sup> Present affiliation: R. W. Johnson Pharmaceutical Research Institute, Spring House, PA.

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

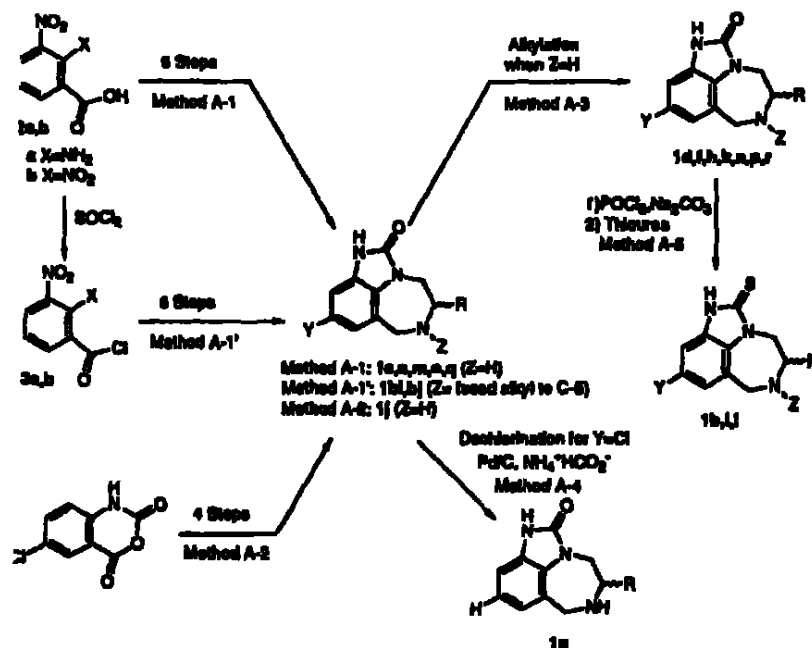
| no. | R                                                                       | X | Y    | Z                     | IC <sub>50</sub> , nM | n <sup>a</sup> |
|-----|-------------------------------------------------------------------------|---|------|-----------------------|-----------------------|----------------|
| 1a  | H                                                                       | S | 8-Cl | DMA                   | 0.048                 | 2              |
| 1b  | H                                                                       | S | 9-Cl | DMA                   | 0.18                  | 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  | 5,6-di-Me                                                               | O | -    | H                     | >250                  | 5              |
| 1r  | 5,6-di-Me                                                               | O | -    | 2-MA                  | 23.1 <sup>c</sup>     | 6              |
| 1s  | 5-keto                                                                  | O | -    | n-Pr                  | >250                  | 2              |
| 1t  | 4-Me                                                                    | O | -    | H                     | >250                  | 6              |
| 1u  | 4-Me                                                                    | O | -    | 2-MA                  | 32.1                  | 5              |
| 1v  | 4-Me (S)                                                                | S | 9-Cl | 2-MA                  | 0.67                  | 5              |
| 1w  | 4-Me (S)                                                                | S | 9-Cl | CH <sub>2</sub> -c-Pr | 2.18                  | 6              |
| 1x  | 4-i-Pr                                                                  | O | -    | H                     | >250                  | 2              |
| 1y  | 4-i-Pr                                                                  | O | -    | n-Pr                  | 73.3 <sup>d</sup>     | 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 <sub>2</sub> -c-Pr | 13.4                  | 1              |
| 1av | 4,5-di-Me (trans)                                                       | S | -    | DMA                   | 14.3 <sup>e</sup>     | 5              |
| 1aw | 4-keto 5-Me                                                             | S | 9-Cl | n-Pr                  | >50                   | 1              |
| 1ax | 7-oxo-1,6-benzo                                                         | S | -    | H                     | >250                  | 1              |
| 1ay | 4,6-benzo                                                               | S | -    | CH <sub>2</sub> -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-''-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-(C <sub>12</sub> ) <sub>1</sub>                                     | O | -    | -                     | >250                  | 8              |
| 1bj | 5,6-(C <sub>12</sub> ) <sub>2</sub>                                     | O | -    | -                     | >250                  | 5              |
| 1bk | 5,6-Cl <sub>2</sub> C(-CH <sub>2</sub> )CH <sub>2</sub> (S)             | S | 9-Cl | -                     | >10                   | 1              |
| 1bl | 5,6-Cl <sub>2</sub> C(-CHCH <sub>2</sub> )CH <sub>2</sub> (S) (6:1 Z:E) | S | 9-Cl | -                     | 3.78 <sup>f</sup>     | 3              |
| 1bm | 6,7-(C <sub>12</sub> ) <sub>2</sub>                                     | S | 9-Cl | -                     | >2                    | 1              |
| 1bn | 6,7-(C <sub>12</sub> )CH <sub>2</sub> CH <sub>2</sub>                   | S | 9-Cl | -                     | >250                  | 2              |
| 1bo | 6,7-(C <sub>12</sub> ) <sub>1</sub>                                     | S | 9-Cl | -                     | >2                    | 1              |
| 1bp | 7,8-(C <sub>12</sub> ) <sub>2</sub>                                     | 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 <sub>2</sub> -c-Pr | 0.034                 | 5              |
| 1bv | 5-Me (S)                                                                | S | -    | CH <sub>2</sub> -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 <sub>50</sub> <sup>a</sup> $\mu$ M | n <sup>b</sup> |
|-----|----------|---|---|------|---------------------------------------|----------------|
| 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              |

<sup>a</sup> 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<sub>50</sub> values listed. <sup>b</sup> Number of experiments run for a given compound. <sup>c</sup> Three of five tests indicated an IC<sub>50</sub> of >184  $\mu$ M. <sup>d</sup> Two of three tests indicated an IC<sub>50</sub> of >180  $\mu$ M. <sup>e</sup> Two of four tests indicated an IC<sub>50</sub> of >30  $\mu$ M. <sup>f</sup> Two of three tests indicated an IC<sub>50</sub> of >180  $\mu$ M.

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.

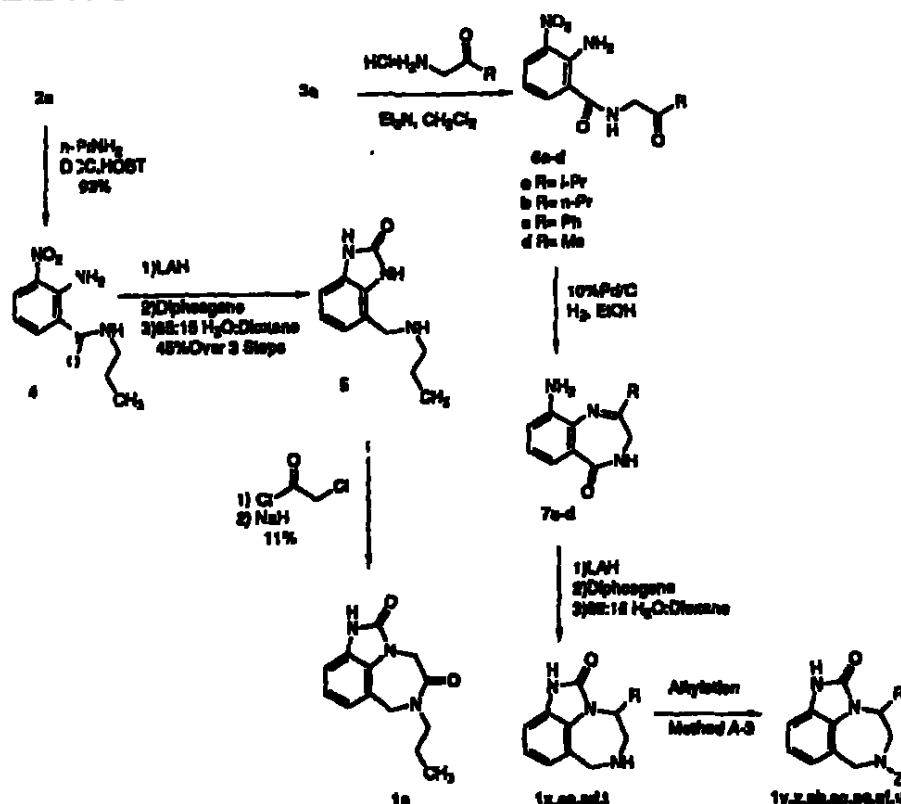
Chemistry encompassed in Scheme 1 (methods A-1-A-5) was used mainly to prepare varied C-5 site substitution of 1. The chemistry utilized for these compounds is reminiscent of our before-mentioned reports<sup>2,3</sup> on the preparation of the 5-Me analogues of 1; therefore minimal commentary is necessary 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 1b, l, j 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 E and C

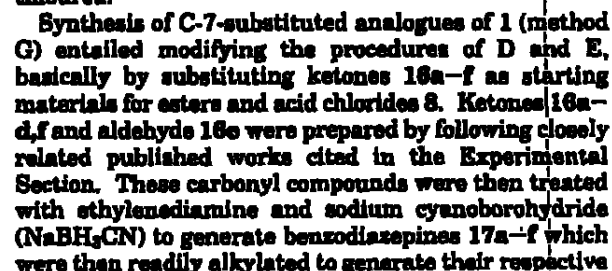


atmosphere in the presence of 10% Pd/C. The transient dianilino compound, were never isolated but rather readily cyclized *in situ* to yield intermediate compounds 7a-d. These intermediates were treated with LAH which reduced both the imine and amide in one step. The resulting triamines were treated with diposgene 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<sup>2</sup> to yield the N-6-substituted final products 1y,x,ab,ac,ae,af,u.

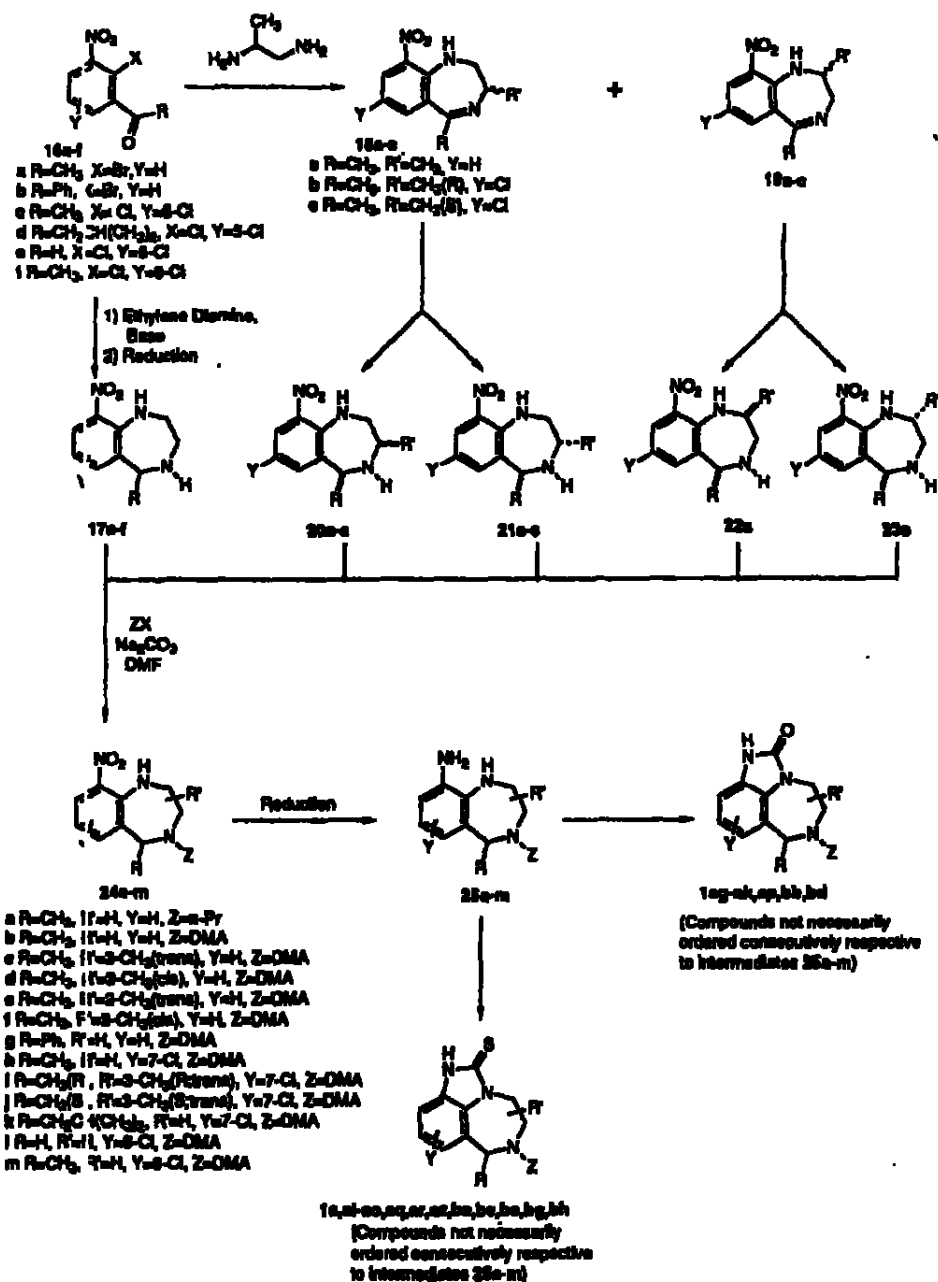
As previously mentioned, HIV-1 inhibitory stereoselectivity for the C-5 site of 1 has been noted with the *S* enantiomer proving more favorable than the *R* enantiomer. Once significant biological activity was noted for the racemic C-4-substituted series of 1, the question arose whether there was significant 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  $\text{H}_2\text{N}-\text{Z}$  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 non-fused 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  $\text{Ra Ni}$ /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 ( $\text{BH}_3/\text{THF}$ ) 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 4. Method G

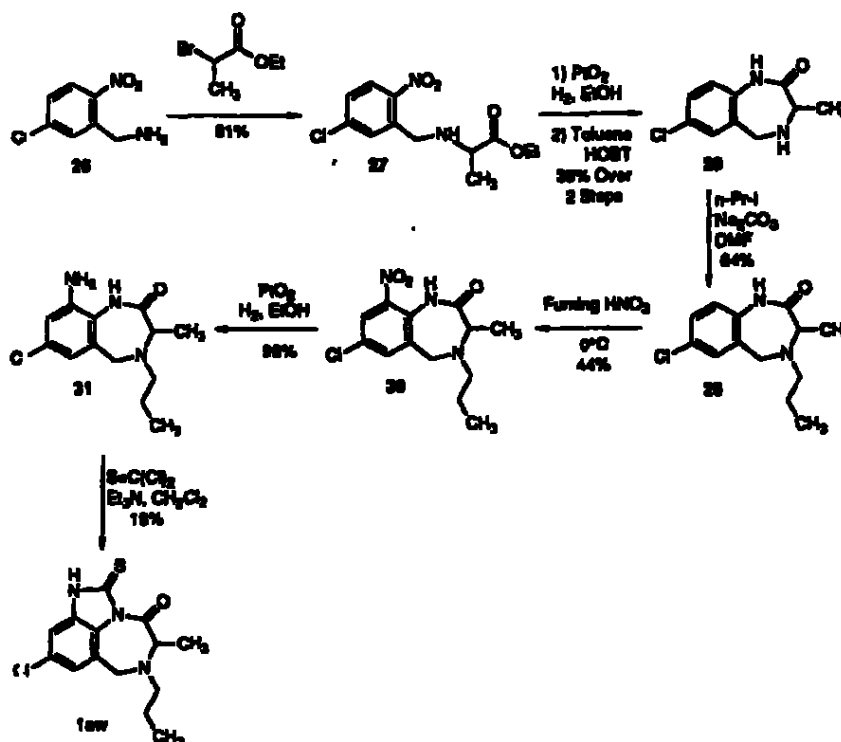


intermediates of 24. The nitro group of most of the intermediates for 24 was easily reduced with LAH to give their respective intermediates 25. In some cases, where there was concern of potential dehalogenation of aromatic substituents by LAH, Ra Ni/hydrasine reduction conditions were used just as effectively. Intermediates 25 being converted to ureas of 1 were efficiently transformed with either diphosgene or 1,1'-carbonyldiimidazole. Intermediates 25 being converted to thio-ureas 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<sub>4</sub>CN yielded a mixture of *cis*- and *trans*-3,5-benzodiazepines 20 and 21, generally in a ratio of about 1:3.<sup>6</sup> This ratio was based on isolated yields which were accomplished utilizing preparative chromatography. Treatment of isolated 19a with NaBH<sub>4</sub>CN yielded a mixture of *cis*- and *trans*-2,5-benzodiazepines 22a and 23a in a ratio of about 4:1.

## Scheme 5. Method H



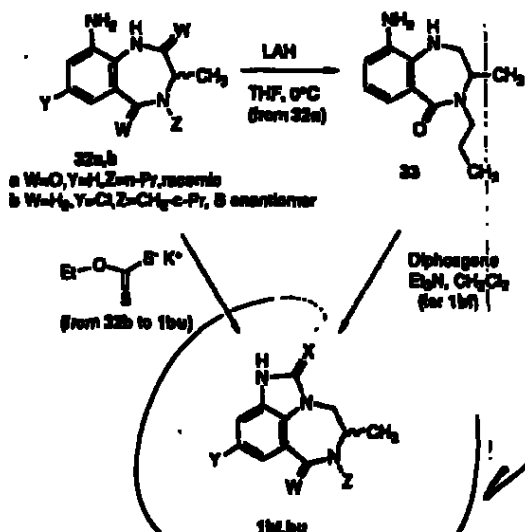
also based on isolated yields after chromatographic separation. As is obviously the case, pursuing identical chemistry starting with optically pure 1,2-diaminopropanes yielded similar ratios of optically pure benzodiazepines 18–21. Further chemistry pursued on amines 20–23 was identical to that previously described for method G yielding final 4,7- and 5,7-disubstituted uras 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 ( $\text{PtO}_2$ ) to yield an aniline 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  $\text{HNO}_3$ ) to give 30. The nitro group of 30 was reduced under a hydrogen atmosphere in the presence of  $\text{PtO}_2$  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

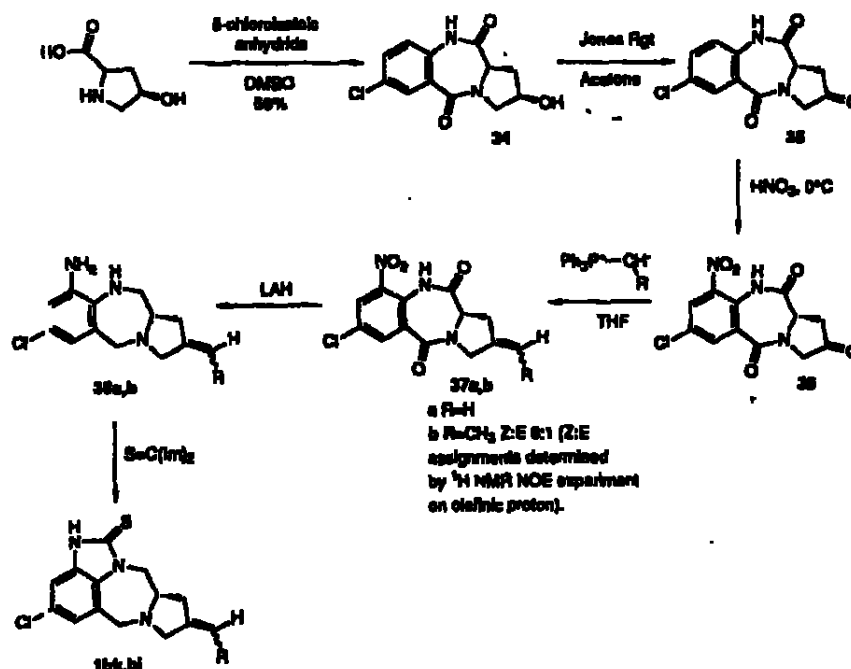
## Scheme 6. Method I



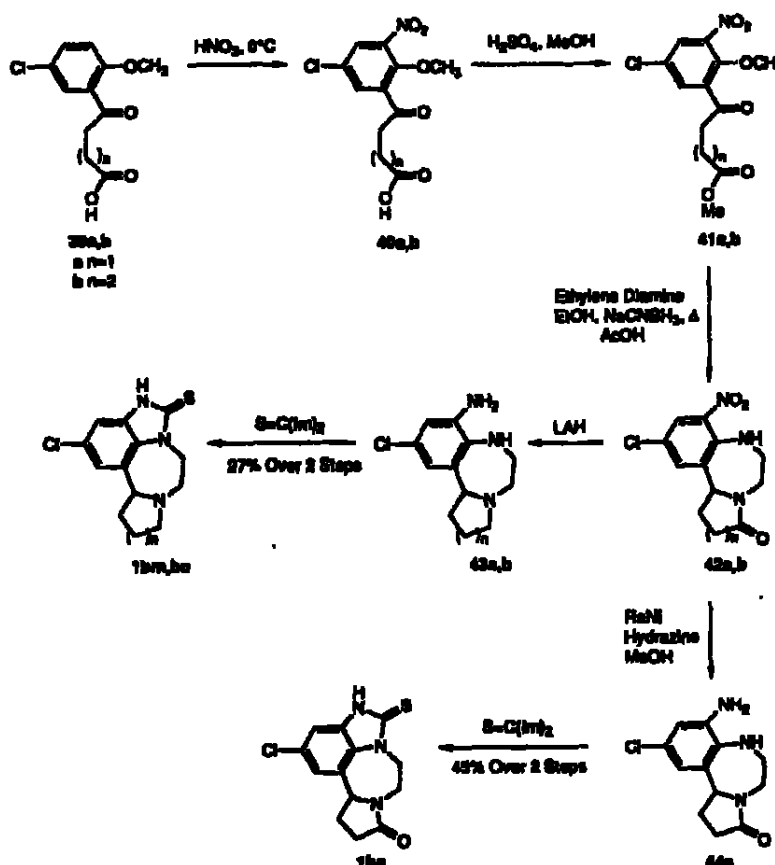
with 5-chloroisatoic anhydride. Oxidation of the alcohol moiety of 34 with Jones reagent led to ketone 35. Treatment of 35 with fuming  $\text{HNO}_3$  yielded 36 which was treated under Wittig reaction conditions with appropriate ylides to generate intermediates 37a,b. Standard LAH reductions of these 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  $\text{HNO}_3$  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:



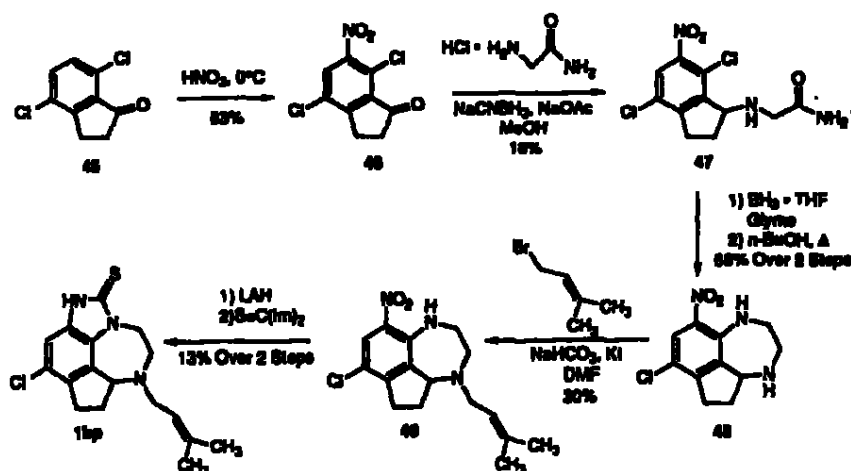
ously described for a number of TIBO analogues, resulted in desired 11,7-fused products 1bm,bo,ba.

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 glycineamide to provide intermediate 47. The amide group of 47 was reduced with

BH<sub>3</sub>·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 3. 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,<sup>7</sup> 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.<sup>8</sup> The reported values shown in Table 1 are the concentrations of each compound required to protect 50% (IC<sub>50</sub>) of the MT-4 cells from cell death brought on by infection with HIV-1. The IC<sub>50</sub>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<sub>50</sub> 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 demethyl 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 (1bx) > Et (1d) and Me (1bs, bt) > *i*-Pr (1k, l). Unfortunately, based on the available comparative data for 1p (1p vs 1bx), 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 (1bx) < *i*-Pr (1x) > *n*-Pr (1ao) > 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 (1bx) showed the C-4-substituted compounds had comparable, or for 1x 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 <sup>a</sup> | formula <sup>b</sup>                                                                                                       | purification <sup>c</sup>                                                                            | yield, % | mp, °C      |
|-------|------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------|-------------|
| 1a    | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 1% MeOH/CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>                                                 | 18       | 212–214     |
| 1b    | A-5                    | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 25% EtOAc/hexane <sup>d</sup>                                                                        | 11       | 214–215     |
| 1c    | A-1                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 30       | 144–145.5   |
| 1d    | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 57       | 116–118     |
| 1e    | A-1                    | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 45       | 157.5–159.5 |
| 1f    | A-3                    | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 65       | 137–143     |
| 1g    | A-4                    | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 50       | 160–163     |
| 1h    | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 73       | 126–129     |
| 1i    | A-5                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 2% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 11       | 149–150     |
| 1j    | A-2                    | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O                                                                         | 2% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 21       | 180–182     |
| 1k    | A-3                    | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O                                                                         | 2% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 30       | 182–184     |
| 1l    | A-5                    | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 2% EtOH/CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>                                                 | 11       | 143–145     |
| 1m    | A-1                    | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 24       | 158.5–159   |
| 1n    | A-3                    | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 29       | 116–119     |
| 1o    | A-1                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | MeOH                                                                                                 | 13       | 245–246     |
| 1p    | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 27       | 188.5–170   |
| 1q    | A-1                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 48       | 153.5–155.5 |
| 1r    | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | EtOH                                                                                                 | 37       | 159–164     |
| 1s    | B                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·0.01CH <sub>2</sub> Cl <sub>2</sub>                         | MeOH                                                                                                 | 11       | 259–262     |
| 1t    | C                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·0.04CH <sub>2</sub> OH                                      | MeOH                                                                                                 | 25       | 210.5–215   |
| 1u    | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·0.05CH <sub>2</sub> CN                                      | CH <sub>2</sub> CN                                                                                   | 62       | 134.5–138   |
| 1v    | D                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 1% EtOH/CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>                                                 | 13       | 170–172     |
| 1w    | D                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 1% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 8        | 205–206     |
| 1x    | C                      | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O                                                                           | 4% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 20       | 162–165     |
| 1y    | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | 3% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 43       | 130.5–138   |
| 1z    | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 42       | 138–142     |
| 1aa   | C                      | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O                                                                           | 4% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 35       | 157–158     |
| 1ab   | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | 4% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 38       | 115.5–117   |
| 1ac   | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | CH <sub>2</sub> CN                                                                                   | 64       | 123.5–127   |
| 1ad   | C                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sup>d</sup>                                                              | 4% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 26       | 240–242.5   |
| 1ae   | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·0.07CH <sub>2</sub> CN                                      | 4% EtOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 26       | 205–212     |
| 1af   | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sup>d</sup>                                                              | CH <sub>2</sub> CN                                                                                   | 43       | 193–198.5   |
| 1ag   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | 1:8 MeOH:CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                           | 13       | 156–158     |
| 1ah   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | 1:15 MeOH:CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                          | 31       | 121.5–123.5 |
| 1ai   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O                                                                           | 7:3 EtOAc:hexane; CH <sub>2</sub> CN <sup>d</sup>                                                    | 8        | 98–121      |
| 1aj   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O·HCl                                                                     | 1.5% MeOH/CH <sub>2</sub> Cl <sub>2</sub> (FB); HCl, Et <sub>2</sub> O, <i>i</i> -PrOH <sup>d</sup>  | 11       | 249–250     |
| 1ak   | C                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O                                                                         | 1:3 EtOAc:hexane; CH <sub>2</sub> CN <sup>d</sup>                                                    | 43       | 135–137     |
| 1al   | C                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·0.1EtOH                                                     | CH <sub>2</sub> CN, then EtOH                                                                        | 25       | 175.5–177.5 |
| 1am   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 1:1 EtOAc:hexane <sup>d</sup>                                                                        | 14       | 191–192.5   |
| 1an   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S <sup>d</sup>                                                            | CH <sub>2</sub> Cl <sub>2</sub> ; MeOH <sup>d</sup>                                                  | 23       | 178–179     |
| 1ao   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | Et <sub>2</sub> O/hexane <sup>d</sup>                                                                | 59       | 190–191.5   |
| 1ap   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O                                                                         | Et <sub>2</sub> O/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN                               | 22       | 133–135     |
| 1aq   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | EtOAc/hexane; CH <sub>2</sub> CN <sup>d</sup>                                                        | 44       | 171–172     |
| 1ar   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 25% EtOAc/hexane <sup>d</sup>                                                                        | 25       | 144–146     |
| 1as   | A-3                    | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·0.04CH <sub>2</sub> Cl <sub>2</sub> ·0.06CH <sub>2</sub> CN | 0.1% NH <sub>4</sub> OH in 5% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup> | 11       | 150–162     |
| 1at   | F                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 0.1% NH <sub>4</sub> OH in 5% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup> | 22       | 159–161     |
| 1au   | E                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S <sup>d</sup>                                                              | 0.1% NH <sub>4</sub> OH in 5% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; Et <sub>2</sub> O <sup>d</sup>  | 18       | 132–135     |
| 1av   | E                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S <sup>d</sup>                                                              | 0.1% NH <sub>4</sub> OH in 5% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; EtOAc <sup>d</sup>              | 36       | 149–155     |
| 1aw   | H                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> OS                                                                          | 1:30 MeOH:CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>                                               | 18       | 154–176     |
| 1ax   | E                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> OS <sup>d</sup>                                                             | MeOH                                                                                                 | 66       | 385–387     |
| 1ay   | F                      | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> S                                                                           | 25% EtOAc/hexane; CH <sub>2</sub> CN <sup>d</sup>                                                    | 24       | 173–175     |
| 1az   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 1:20 MeOH:CH <sub>2</sub> Cl <sub>2</sub> ; EtOH <sup>d</sup>                                        | 25       | 135–137     |
| 1ba   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 1% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; EtOH <sup>d</sup>                                          | 33       | 135–137     |
| 1bb   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O                                                                         | 1% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 73       | 81–86       |
| 1bc   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O                                                                         | 100% CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                               | 24       | 163–164     |
| 1bd   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O·HCl                                                                     | 2% MeOH/CH <sub>2</sub> Cl <sub>2</sub> (FB); <i>i</i> -PrOH                                         | 22       | 216–217     |
| 1be   | G                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S·HCl <sup>d</sup>                                                        | 100% CH <sub>2</sub> Cl <sub>2</sub> (FB); <i>i</i> -PrOH <sup>d</sup>                               | 16       | 212–213     |
| 1bf   | I                      | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>                                                              | 1:20 MeOH:CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                          | 15       | 236–237     |
| 1bg   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 0.5% MeOH/CH <sub>2</sub> Cl <sub>2</sub> ; EtOH <sup>d</sup>                                        | 27       | 182.5–183.5 |
| 1bh   | G                      | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> S                                                                           | 1% MeOH:CH <sub>2</sub> Cl <sub>2</sub> ; EtOH <sup>d</sup>                                          | 51       | 178–180     |
| 1bi   | A-1 <sup>d</sup>       | C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> ·0.08 CH <sub>3</sub> NO <sub>2</sub>                        | CH <sub>3</sub> NO <sub>2</sub>                                                                      | 45       | 184.5–189   |
| 1bj   | A-1 <sup>d</sup>       | C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·0.2CH <sub>2</sub> Cl <sub>2</sub>                          | CH <sub>2</sub> NO <sub>2</sub>                                                                      | 17       | 205–208.5   |
| 1bk   | J                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 1% MeOH:CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>                                                 | 31       | 230         |
| 1bl   | J                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> O <sup>d</sup>                                                            | 3% MeOH:CH <sub>2</sub> Cl <sub>2</sub> ; CH <sub>2</sub> CN <sup>d</sup>                            | 5        | 214         |
| 1bm   | K                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 45:55 EtOAc:hexane; CH <sub>2</sub> CN <sup>d</sup>                                                  | 37       | 252–254     |
| 1bn   | K                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> OS                                                                        | riased with THF                                                                                      | 45       | >300 d      |
| 1bo   | K                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 1:1 EtOAc:hexane; CH <sub>2</sub> CN <sup>d</sup>                                                    | 12       | 263–265     |
| 1bp   | L                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S <sup>d</sup>                                                            | 1:1 EtOAc:hexane; CH <sub>2</sub> CN <sup>d</sup>                                                    | 13       | 200–201     |
| 1bu   | I                      | C <sub>21</sub> H <sub>19</sub> ClN <sub>3</sub> S                                                                         | 30:1 CH <sub>2</sub> Cl <sub>2</sub> :MeOH; CH <sub>2</sub> CN <sup>d</sup>                          | 19       | 171–174     |

<sup>a</sup> Method/reagent used to synthesize the product. <sup>b</sup> All products were analyzed for C, H, and N. <sup>c</sup> Products were crystallized and/or recrystallized from listed solvents. <sup>d</sup> Crude material flash chromatographed on silica gel eluting with identified solvent system prior to crystallization with listed solvent. <sup>e</sup> 1ad, C: calcd, 73.43; found, 71.57. Exact mass MH<sup>+</sup> calcd: 266.1293. Found: 266.1295. Δ: 0.6 ppm. 1af, C: calcd, 73.21; found, 74.61. Exact mass calcd: 319.1685. Found: 319.1674. Δ: 3.4 ppm. 1am, C: calcd, 59.71; found, 59.09. Exact mass MF<sup>+</sup> calcd: 322.1145. Found: 322.1153. Δ: 11.8 ppm. 1av, C: calcd, 67.74; found, 68.90. 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, 53.79. Exact mass MH<sup>+</sup> calcd: 336.1301. Found: 336.1315. Δ: 4.1 ppm. 1bl, C: calcd, 55.91; found, 55.47. Exact mass calcd: 305.0754. Found: 305.0780. Δ: 8.5 ppm. 1bp, C: calcd, 61.16; found, 60.67. Exact mass calcd: 333.1068. Found: 333.1100. Δ: 10.3 ppm. <sup>f</sup> C, H, N analysis not performed. Exact mass calcd: 287.1486. Found: 287.1449. Δ: 2.4 ppm.

## Anti-HIV-1 Activity of TBO Derivatives. 3

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 or 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 thiourea (1an = 1lq; 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, 1ax (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 analogues 1ca, the following activity trends were noted, 5-mono-Me (1ca) ≤ 5,7-di-Me-*trans* (1ax) > 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 1ax, 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,be were found to be significantly more active than their respective *S,S* enantiomers 1bd,ba. 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 < 1ax) 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 nevirapine,<sup>9</sup> another reported RT inhibitor of HIV-1, within our basic TBO 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 looking 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 380-MHz <sup>1</sup>H NMR (Bruker AM 380 WB), IR (Nicolet 80SX), mass spectra (Finnegan 3300), and elemental analyses. Unless otherwise specified, reported <sup>1</sup>H NMR's of intermediates were also run on the 380-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. x 3 in. x 25  $\mu$ m) 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.<sup>2,3</sup> Besides the obvious changes to appropriate starting materials, the procedures were not substantially altered. Notable variations 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-jh][1,4]benzodiazepin-2(1H)-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-1-(1-methylethyl)imidazo[4,5,1-jh][1,4]benzodiazepin-2(1H)-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-1-propylimidazo[4,5,1-jh][1,4]benzodiazepin-2(1H)-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-1-phenylimidazo[4,5,1-jh][1,4]benzodiazepin-2(1H)-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<sub>2</sub>Cl<sub>2</sub>: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<sup>10</sup> (9.90 g, 0.064 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) (5.24 g, 0.04 mol) was added neat to a stirring solution of 2a (7.08 g, 0.04 mol), *n*-PrNH<sub>2</sub> (3.29 mL, 0.04 mol), and 1-hydroxybenzotriazole hydrate (HOBT) (10.80 g, 0.08 mol) in THF (20 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<sub>2</sub>Cl<sub>2</sub> (200 mL) and extracted twice with saturated aqueous NaHCO<sub>3</sub> (200 and 100 mL, respectively). The organic phase was then dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to yield 8.26 g (93%) of 4 as a yellow solid (TLC: 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R*<sub>f</sub> = 0.8). 4: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.0 (s, 3H), 1.55–1.7 (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]-2H-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<sub>2</sub>O (3.41 mL) followed by 15% NaOH (3.41 mL) and then H<sub>2</sub>O (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<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting oil was immediately combined with 4-methylmorpholine (NMM) (4.94

mL, 0.045 mol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and added over 10 min to a 0 °C solution of trichloromethyl chloroformate (1.80 mL, 0.015 mol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL). After stirring for an additional 10 min, the mixture was concentrated under reduced pressure. A solution of 85:15 dioxane:H<sub>2</sub>O (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<sub>4</sub>OH 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: 85:25:4 CHCl<sub>3</sub>:MeOH:H<sub>2</sub>O, *R*<sub>f</sub> = 0.15). 5: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  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<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O) C, H, N.

**6,7-Dihydro-6-propylimidazo[4,5,1-jh][1,4]benzodiazepine-2,5(1H,4H)-dione (1a).** Under Ar, chloroacetyl chloride (0.32 mL, 0.040 mol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added over 1 min to a 0 °C mixture of 5 (0.82 g, 0.040 mol) and Et<sub>3</sub>N (0.56 mL, 0.040 mol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>, and then brine. The organic phase was dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (10 mL). The resulting solid was filtered from this biphasic system to yield 0.32 g (36%) of semipure 1a. This material was further purified through trituration as described in Table 2 (TLC: 20:1 CHCl<sub>3</sub>:MeOH, *R*<sub>f</sub> = 0.25). 1a: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  0.85–0.75 (t, 3H), 1.4–1.6 (m, 2H), 3.3–3.4 (t, 2H), 4.7–4.76 (q, 2H), 4.75–4.8 (s, 2H), 6.9–7.0 (s, 3H), 11.0 (s, 1H).

**Typical Procedure Sequences for Method C. 3-Amino-N-(3-methyl-2-oxobutyl)-3-nitrobenzamide (6a).** Under N<sub>2</sub>, Et<sub>3</sub>N (9.50 mL, 0.068 mol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added dropwise to a room temperature suspension of 3a (6.85 g, 0.034 mol) and 1-amino-3-methylbutanone monohydrochloride<sup>11</sup> (4.7 g, 0.034 mol) in CH<sub>2</sub>Cl<sub>2</sub> (85 mL). After stirring for 21 h the reaction mixture was washed with H<sub>2</sub>O. The aqueous phase was rewash with a second portion of CH<sub>2</sub>Cl<sub>2</sub>. The organic phases were combined and rewash with H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, and then brine, dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>, *R*<sub>f</sub> = 0.75; 1:1 EtOAc:hexane, *R*<sub>f</sub> = 0.5). 6a: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>11</sup> in place of 1-amino-3-methylbutanone monohydrochloride. Also the Et<sub>3</sub>N 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-(3-Amino-3-nitrobenzoyl)benzamide (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<sub>3</sub>N solution was added to a 0 °C suspension of 3a and ketamine rather than a room temperature solution. Also when the reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O, some solid precipitated which was filtered to give 4.3 g of solid. Upon completion of the extractions, an ad-

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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, 0.085 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 (8.00 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  $\text{CH}_2\text{Cl}_2$  and washed sequentially with  $\text{H}_2\text{O}$  twice, saturated aqueous  $\text{NaHCO}_3$ , and brine. The organic phase was then dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to give 12 g of yellow solid. This material was recrystallized from EtOH to yield 8.34 g (84%) of **6d** which was used without further purification.

**9-Amino-3,4-dihydro-2-(1-methylethyl)-5H-1,4-benzodiazepin-5-one (7a).** At room temperature a mixture of **6a** (5.9 g, 0.022 mol) and 0% Pd/C (1.8 g) in EtOH (150 mL) was placed under a  $\text{H}_2$  atmosphere at 50 psi for 26 h. Then an additional portion of 0% 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  $\text{CH}_2\text{Cl}_2$ . 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: $\text{CH}_2\text{Cl}_2$ ,  $R_f$  = 0.5).

**9-Amino-3,4-dihydro-2-propyl-5H-1,4-benzodiazepin-5-one (7b).** At room temperature a mixture of **6b** (12 g, 0.045 mol) and 10% Pd/C (3.0 g) in EtOH (400 mL) was placed under a  $\text{H}_2$  atmosphere at 50 psi for 24 h. The reaction mixture was then filtered through Dicalite and the filtered solid rinsed well with  $\text{CH}_2\text{Cl}_2$  (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-5H-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  $\text{H}_2$  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  $\text{CH}_2\text{Cl}_2$ . 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-5H-1,4-benzodiazepin-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  $\text{H}_2$  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  $\text{CH}_2\text{Cl}_2$ . The filtrate was concentrated under reduced pressure to give 5.5 g (86%) 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-3(1H)-one (1x).** Under Ar powdered LAH (8.0 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  $\text{H}_2\text{O}$  (5 mL) in 25 mL

of THF, 3 N NaOH (5 mL), and  $\text{H}_2\text{O}$  (15 mL) after which the mixture was stirred at 0 °C for an additional 2 h. The mixture was then treated with  $\text{MgSO}_4$ , and filtered, and the resulting salts were rinsed with warm  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (50 mL) and added dropwise over 30 min to a 0 °C solution of trichloromethyl chloroformate (2.75 mL, 0.023 mol) in  $\text{CH}_2\text{Cl}_2$  (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: $\text{H}_2\text{O}$  (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  $\text{CH}_2\text{Cl}_2$ , basified with concentrated  $\text{NH}_4\text{OH}$ , and then reextracted three times more with  $\text{CH}_2\text{Cl}_2$ . The latter three  $\text{CH}_2\text{Cl}_2$  extracts were combined, washed with brine, dried over  $\text{MgSO}_4$ , 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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-3(1H)-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: $\text{H}_2\text{O}$  to 85:15  $\text{H}_2\text{O}$ :dioxane.

**4,5,6,7-Tetrahydro-4-phenylimidazo[4,5,1-jk][1,4]benzodiazepin-3(1H)-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: $\text{H}_2\text{O}$  to 85:15  $\text{H}_2\text{O}$ :dioxane.

**4,5,6,7-Tetrahydro-4-methylimidazo[4,5,1-jk][1,4]benzodiazepin-3(1H)-one (1i).** 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 (8 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: $\text{H}_2\text{O}$  to 85:15  $\text{H}_2\text{O}$ :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'-(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  $\text{CH}_3\text{CN}$  and cooled to 0 °C for 14 h. The resulting solid was filtered and the organic phase extracted with saturated aqueous  $\text{NaHCO}_3$  and then brine. The organic phase was then dried over  $\text{Na}_2\text{SO}_4$ , 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  $\text{NaHCO}_3$  which was then continuously extracted with  $\text{CH}_2\text{Cl}_2$  for 16 h. The organic phase was then dried over  $\text{Na}_2\text{SO}_4$ , 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<sub>2</sub>O (11.4 mL), 3 N NaOH (34.2 mL), and H<sub>2</sub>O (11.4 mL). The resulting solid was filtered and rinsed with THF (25 mL). The combined filtrates were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give 11.8 g (92%) of **3a** which was used without further purification.

(S)-N-(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<sub>2</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>. This reaction mixture was filtered, concentrated, and dissolved in CH<sub>2</sub>Cl<sub>2</sub> prior to the aqueous extractions to give an 85% yield of BOC-Ala-NH-CH<sub>2</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>. The TFA BOC removal yielded 49% of H<sub>2</sub>N-Ala-NH-CH<sub>2</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>. 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-5H-1,4-benzodiazepin-5-one (**10a**). Under Ar, **8a** (5.0 g, 0.020 mol) was added to a room temperature suspension of Na<sub>2</sub>CO<sub>3</sub> (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 1:1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The desired fractions were combined, concentrated, and crystallized from CH<sub>2</sub>CN to give 2.93 g (47%) of **10a** as an orange solid, mp 78–80 °C. **10a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>14</sub>H<sub>16</sub>ClN<sub>2</sub>O<sub>2</sub>) C, H, N.

(+)-(S)-7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-(2-methyl-2-propenyl)-9-nitro-5H-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<sub>14</sub>H<sub>16</sub>ClN<sub>2</sub>O<sub>2</sub>) C, H, N.

(-)-(R)-8-Chloro-6-(cyclopropylmethyl)-4,5,6,7-tetrahydro-4-methylimidazo[4,5-*b*][1,4]benzodiazepine-3(1H)-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<sub>2</sub>O (2.0 mL), 3 N NaOH (6 mL), and H<sub>2</sub>O (2 mL). The resulting salts were filtered and rinsed with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The concentrated residue was dissolved in THF (50 mL), combined with 1,1'-thiocarbonyldimidazole (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<sub>2</sub>O (25 mL each). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting crude product was purified as described in Table 2. **1w**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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)-8-Chloro-4,5,6,7-tetrahydro-4-methyl-6-(2-methyl-2-propenyl)imidazo[4,5-*b*][1,4]benzodiazepine-3(1H)-thione (**1v**). The desired product was prepared by following the procedure used for **1w**, except the 1,1'-thiocarbonyldimidazole 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-11H-dibenzo[*bc*][1,4]diazepin-11-one (**11a**). Under N<sub>2</sub>, **8b**<sup>2</sup> (2.61 g, 0.010 mol), 1,2-phenylenediamine (1.06 g, 0.010 mol), and Na<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>O (30 mL), refiltered, and rinsed with an additional portion of H<sub>2</sub>O (30 mL) and then Et<sub>2</sub>O. 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<sub>2</sub>Cl<sub>2</sub>:MeOH, R<sub>f</sub> = 0.4).

*cis*-1,2,3,4-Tetrahydro-2,3-dimethyl-9-nitro-5H-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**<sup>3</sup> in place of **8b**. Also 3 mol excess of Na<sub>2</sub>CO<sub>3</sub> 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<sub>2</sub>Cl<sub>2</sub>, filtered, and reconcentrated under reduced pressure, and triturated with Et<sub>2</sub>O to yield 58% of **11b** which was used without further purification.

*trans*-1,2,3,4-Tetrahydro-2,3-dimethyl-9-nitro-5H-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 **8a** in place of **8b**. Also 3 mol excess of Na<sub>2</sub>CO<sub>3</sub> 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<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, 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<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>) C, H, N.

4-Amino-5,10-dihydro-11H-dibenzo[*bc*][1,4]diazepin-11-one (**12a**). Under N<sub>2</sub>, NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (0.45 mL, 9.2 mmol) was added over 15 min to a refluxing suspension of **11a** (0.38 g, 1.5 mmol) and BaNi (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<sub>2</sub>O (5 mL) to give 0.27 g (80%) of **12a** as a pea green solid, mp 218–219 °C (TLC: 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, R<sub>f</sub> = 0.35). **12a**: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 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(5H)-one (**1ax**). Under N<sub>2</sub>, a mixture of **12a** (0.45 g, 2.0 mmol) and 1,1'-thiocarbonyldimidazole (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**: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 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-5H-dibenzo[*bc*][1,4]diazepine (**13a**). Under Ar, BH<sub>3</sub>·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<sub>2</sub>Cl<sub>2</sub>. The organic phase was then dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>:MeOH. The desired fractions were combined and concentrated to give 1.04 g (40%) of **13a** as a dark, deep purple solid, mp 135–136 °C (TLC: 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, R<sub>f</sub> = 0.8). **13a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>13</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>) C, H, N.

2,3-*trans*-2,3,4,5-Tetrahydro-2,3-dimethyl-9-nitro-1H-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<sub>3</sub>·THF was used, instead of 2 mol equiv as for **13a**, and the reaction mixture was heated

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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  $\text{Na}_2\text{SO}_4$ , 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/ $\text{CH}_2\text{Cl}_2$  containing 0.1% of  $\text{NH}_4\text{OH}$ . 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-*i*,1-*j*][1,4]benzodiazepine-2(1*H*)-thione (1ay).** Under Ar, cyclopropanecarbonyl chloride (0.18 mL, 2 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added over 2 min to a 0 °C solution of 13a (0.48 g, 2 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to yield 0.62 g (100%) of orange solid, mp 158–160 °C (TLC: 20%  $\text{CH}_2\text{Cl}_2$ :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  $\text{H}_2\text{O}$  (0.41 mL), 3 N NaOH (0.41 mL), and  $\text{H}_2\text{O}$  (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  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to yield a purplish oil. This material was combined with 1,1'-thiocarbonyldimidazole (0.33 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  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{MgSO}_4$ , 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:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.05–0.15 (d, 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-*i*,1-*j*][1,4]benzodiazepine-2(1*H*)-thione (1av).** A mixture of 13c (0.34 g, 1.54 mmol), 1-bromo-3-methyl-2-butene (0.13 g, 1.54 mmol),  $\text{Na}_2\text{CO}_3$  (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  $\text{H}_2\text{O}$ . The organic phase was then washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{K}_2\text{CO}_3$ , 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/ $\text{CH}_2\text{Cl}_2$  containing 0.1% of  $\text{NH}_4\text{OH}$ . 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  $\text{H}_2\text{O}$  (100  $\mu\text{L}$ ), 3 N NaOH (800  $\mu\text{L}$ ), and then  $\text{H}_2\text{O}$  (100  $\mu\text{L}$ ). After stirring for 30 min the mixture was filtered. The filtrate was dried over  $\text{Na}_2\text{SO}_4$ , 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'-thiocarbonyldimidazole (0.144 g, 0.81 mmol) in THF (5 mL) and warmed to reflux for 1 h. The reaction mixture was then partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was then washed twice with  $\text{H}_2\text{O}$  and once with brine, dried over  $\text{Na}_2\text{SO}_4$ , 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:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.06–1.15 (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).

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**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, 53.8 mmol) in 1,4-dioxane (30 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  $\text{H}_2\text{O}$  (2 mL), 3 N NaOH (6 mL), and  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was then filtered and the filtrate concentrated under reduced pressure to yield 1.67 g (88%) of 14b as a brown oil which was used without further purification. 14b (crude):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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-*i*,1-*j*][1,4]benzodiazepine-2(1*H*)-thione (1au).** Under Ar, 14c (0.51 g, 2.67 mmol) and 1,1'-thiocarbonyldimidazole (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  $\text{H}_2\text{O}$ . The organic phase was then washed twice with  $\text{H}_2\text{O}$  and once with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to give 0.38 g (61%) of orange solid. A 0.316-g sample (0.921 mmol) of this material was combined with cyclopropanecarboxaldehyde (76  $\mu\text{L}$ , 1.02 mmol), sodium cyanoborohydride (0.116 g, 1.85 mmol), and AcOH (53  $\mu\text{L}$ , 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  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to give a brown oil. This material was purified as described in Table 2. 1au:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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-*i*,1-*j*][1,4]benzodiazepine-2(1*H*)-one (1ed).** 1ed was prepared by reacting 14b with trichloromethyl chloroformate in a similar manner as outlined for the preparation of 5. The crude 1ed was purified by flash chromatography on a silica gel column eluting with 7% MeOH/ $\text{CH}_2\text{Cl}_2$  containing 0.1% of  $\text{NH}_4\text{OH}$ . The desired fractions were combined and concentrated under reduced pressure to yield 44% of 1ed 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-*i*,1-*j*][1,4]benzodiazepine-2(1*H*)-one (1as).** Alkylation of 1ed following method A-3 yielded desired 1as which was purified as described in Table 2.

**4,5-*cis*-3-Chloro-4,5,6,7-tetrahydro-4,5-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5-*i*,1-*j*][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  $\text{CH}_2\text{Cl}_2$  (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<sub>2</sub>O (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  $\text{NaHCO}_3$  solution. The aqueous phase was separated and washed twice with  $\text{CH}_2\text{Cl}_2$ . The organic phases were combined, dried over  $\text{Na}_2\text{SO}_4$ , 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/ $\text{CH}_2\text{Cl}_2$  containing 0.1% of  $\text{NH}_4\text{OH}$ . The desired fractions were combined and concentrated under reduced pressure to yield 0.22 g (51%) of 15b which was used without further purification.

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4,5-cis-4,5,6,7-Tetrahydro-4,5-dimethyl-6-(3-methyl-2-butanyl)imidazo[4,5-f][1,4]benzodiazepine-3(1H)-thione (1a). Compound 1b was treated with thiourea in EtOH following the reaction conditions employed in method A-5. Desired product 1a was purified as described in Table 2. 1a:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 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), 5.8–5.9 (d, 1H), 7.0–7.2 (d, 2H), 9.4–9.5 (br, 1H).

**Typical Procedure: Sequences for Method G.** 1-(3-Bromo-3-nitrophenyl)ethanone (16a). The desired product was prepared following a literature procedure for the closely related 2-chloro-3-nitroacetophenone.<sup>12</sup> 16a was isolated in 71% crude yield and used without further purification (TLC: 1:1 EtOAc/hexane,  $R_f = 0.7$ ). 16a (crude):  $^1\text{H NMR}$  (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.7 (s, 3H), 7.3–7.5 (m, 3H).

1-(2,6-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-(2,6-Dichloro-3-nitrophenyl)-3-methyl-1-butanone (16d). Under Ar, a solution of freshly prepared isopropylmagnesium bromide<sup>13</sup> in THF (164 mL containing 0.136 mol of reagent) was added slowly to a maintained 10 °C solution of monoethyl ester of isopropylmalonic acid (11.4 g, 66 mmol)<sup>14</sup> 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 (1.6 mL), and stirred for an additional 40 min. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between  $\text{Et}_2\text{O}$  and saturated aqueous  $\text{NH}_4\text{Cl}$ . The ether layer was then washed sequentially with  $\text{H}_2\text{O}$ , saturated aqueous  $\text{NaHCO}_3$ , and  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to give 10.2 g of a viscous oil. This oil was combined with a solution of  $\text{H}_2\text{SO}_4$  (1.1 mL, 32 mmol) and AcOH (34 mL) in  $\text{H}_2\text{O}$  (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  $\text{H}_2\text{O}$ , and neutralized with  $\text{NaHCO}_3$ . The resulting aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was then washed sequentially with  $\text{H}_2\text{O}$ , saturated aqueous  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to give 7.6 g (76%) 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  $\text{HNO}_3$  (500 mL) in concentrated  $\text{H}_2\text{SO}_4$  (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  $\text{CH}_2\text{Cl}_2$ . The organic phases were combined, extracted with saturated aqueous  $\text{NaHCO}_3$ , dried over  $\text{K}_2\text{CO}_3$ , 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-1H-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  $\text{NaHCO}_3$  (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  $\text{NaBH}_3\text{CN}$  (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  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried over  $\text{MgSO}_4$ , 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  $\text{CH}_2\text{Cl}_2$ :MeOH,  $R_f = 0.28$ ). 17a:  $^1\text{H NMR}$  (90 MHz,  $\text{CDCl}_3$ )  $\delta$  1.6 (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 (br, 1H), 7.9–8.1 (d, 1H).

2,3,4,5-Tetrahydro-9-nitro-5-phenyl-1H-1,4-benzodiazepine (17b). Under Ar, a mixture of ethylenediamine (3.3 mL, 49 mmol), 16b<sup>15</sup> (15 g, 49 mmol), and  $\text{NaHCO}_3$  (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  $\text{CH}_2\text{Cl}_2$  and water. The organic phase was dried over  $\text{MgSO}_4$ , 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  $\text{NaBH}_3\text{CN}$  (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  $\text{CH}_2\text{Cl}_2$  and water. The organic phase was dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to give 9.6 g (82%) of 17b as a red oil which was used without further purification.

7-Chloro-2,3,4,5-tetrahydro-5-methyl-9-nitro-1H-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-1H-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  $\text{NaBH}_3\text{CN}$  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-1H-1,4-benzodiazepine (17e). Under Ar 16e<sup>16</sup> (5.0 g, 22.7 mmol) and ethylenediamine (1.62 g, 22.7 mmol) were combined in MeOH at room temperature. After 20 min  $\text{NaBH}_3\text{CN}$  (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  $\text{CH}_2\text{Cl}_2$  after which the organic phase was dried over  $\text{K}_2\text{CO}_3$ , filtered, and concentrated under reduced pressure to give 4.95 g of acyclic intermediate. This material was combined with  $\text{Na}_2\text{CO}_3$  (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/ $\text{CH}_2\text{Cl}_2$ . 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-1H-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  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ ; the organic phase was dried over  $\text{K}_2\text{CO}_3$ , filtered, and concentrated. This residue was dissolved in MeOH and treated with  $\text{NaBH}_3\text{CN}$  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/ $\text{CH}_2\text{Cl}_2$ . 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-1H-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  $\text{Na}_2\text{CO}_3$  (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  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ ; the organic phase was dried over  $\text{K}_2\text{CO}_3$ , filtered, and concentrated to give 27.3 g. On the basis of  $^1\text{H NMR}$ , 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:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.4–1.5 (d, 3H), 2.4 (s, 3H), 3.55–3.65 (dd, 1H), 3.35–3.75 (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,  $R_f$  = 0.36). 19a:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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-2,3,4,5-tetrahydro-3,5-dimethyl-9-nitro-1H-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<sup>17</sup> (23.55 g, 0.160 mol) in *n*-BuOH (1.5 L). After stirring for 0.5 h, 18c (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  $\text{CH}_2\text{Cl}_2$  which was sequentially washed with  $\text{H}_2\text{O}$ , 3 N NaOH, and brine. The organic phase was dried over  $\text{K}_2\text{CO}_3$ , 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-2,3,4,5-tetrahydro-3,5-dimethyl-9-nitro-1H-1,4-benzodiazepine (18c). This desired product was prepared following the procedure for 18b after substituting (S)-1,2-diaminopropane dihydrochloride<sup>17</sup> 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-1H-1,4-benzodiazepine (20a). Under Ar at room temperature,  $\text{NaBH}_4\text{CN}$  (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  $\text{NaBH}_4\text{CN}$  (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 4.95 g (30%) of pure 21a as the HCl salt, mp 285–289 °C. Anal. ( $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2\text{HCl}$ ) C, H, N. All of the above filtrates were combined and concentrated under reduced pressure. The residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and aqueous 10%  $\text{K}_2\text{CO}_3$ . The organic phase was dried over  $\text{MgSO}_4$ , 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,  $R_f$  = 0.26). 20a:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  0.98 (d, 3H), 1.42 (d, 3H), 2.07 (b, 1H), 2.58 (dd, 1H), 3.07 (m, 1H), 3.61 (dd, 1H), 3.90 (t, 1H), 6.84 (t, 1H), 7.45 (d, 1H), 7.66 (d, 1H), 7.87 (d, 1H). Anal. ( $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2$ ) C, H, N. Residual 21a eluted in the latter running fractions which were combined and concentrated under reduced pressure to yield an additional 3.86 g (29%) of free base 21a as a viscous red oil (TLC: 1:1 acetone:hexane,  $R_f$  = 0.18). 21a:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  0.98 (d, 3H), 1.56 (d, 3H), 2.33 (b, 1H), 3.23 (m, 2H), 3.42 (dd, 1H), 4.87 (q, 1H), 6.72 (t, 1H), 7.38 (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-1H-1,4-benzodiazepine (21a). The preparation of the desired product is described in the experimental for 20a.

(3R)-*trans*-7-Chloro-2,3,4,5-tetrahydro-3,5-dimethyl-9-nitro-1H-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  $\text{CH}_2\text{Cl}_2$  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  $\text{CH}_2\text{Cl}_2$  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.

(3S)-*trans*-7-Chloro-2,3,4,5-tetrahydro-3,5-dimethyl-9-nitro-1H-1,4-benzodiazepine (21c). Under Ar at room temperature,  $\text{NaBH}_4\text{CN}$  (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  $\text{CH}_2\text{Cl}_2$  and aqueous 3 N NaOH. The organic phase was dried over  $\text{K}_2\text{CO}_3$ , 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-1H-1,4-benzodiazepine (22a). Under Ar at room temperature,  $\text{NaBH}_4\text{CN}$  (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  $\text{CH}_2\text{Cl}_2$  and aqueous 10%  $\text{K}_2\text{CO}_3$ . The organic phase was dried over  $\text{K}_2\text{CO}_3$ , 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 22a eluted in the front running fractions which were combined and concentrated under reduced pressure to yield 0.84 g (14%) of 22a which was used without further purification (TLC: 1:1 acetone:hexane,  $R_f$  = 0.17). 22a:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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-1H-1,4-benzodiazepine (22a). The preparation of the desired product is described in the experimental for 22a.

2,3,4,5-Tetrahydro-5-methyl-9-nitro-4-propyl-1H-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  $\text{Na}_2\text{CO}_3$  (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  $\text{Et}_2\text{O}$  and  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{MgSO}_4$ , 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  $\text{CH}_2\text{Cl}_2$ :MeOH,  $R_f$  = 0.4).

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**2,3,4,5-Tetrahydro-5-methyl-4-(3-methyl-2-butenyl)-9-nitro-1*H*-1,4-benzodiazepine (24b).** Under N<sub>2</sub>, 1-bromo-3-methyl-2-butene (2.89 g, 18 mmol) was added neat over 20 s to a stirring room temperature mixture of 17a (3.75 g, 15 mmol), Na<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic phase was then dried over MgSO<sub>4</sub>, 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 (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<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>7</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) 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<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>Cl<sub>2</sub>. 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 (0.23 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<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>7</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) 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<sub>2</sub>Cl<sub>2</sub>. The desired fractions were combined and concentrated under reduced pressure to give 47% of 24h which was used without further purification.

**(2*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<sub>2</sub>Cl<sub>2</sub>. 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)-9-(3-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<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>, 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<sub>2</sub>O (1.52 mL), 3 N NaOH (1.52 mL), and H<sub>2</sub>O (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<sub>2</sub>Cl<sub>2</sub> (60 mL); dried over MgSO<sub>4</sub>, 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<sub>3</sub>:MeOH, R<sub>f</sub> = 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 workup 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-(3-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-*b*][1,4]benzodiazepin-2(1*H*)-one (1a*g*).** 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-*b*][1,4]benzodiazepin-2(1*H*)-one (1a*h*).** Under Ar, trichloromethyl chloroformate (0.96 mL, 2.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added over 4 min to a 0 °C solution of 25a (0.93 g, 4.25 mmol) and NMN (0.93 mL, 8.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL). After 0.5 h the mixture was extracted with saturated aqueous NaHCO<sub>3</sub>. The organic phase was then dried over MgSO<sub>4</sub>, 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<sub>3</sub>:MeOH, R<sub>f</sub> = 0.75). 1a*h*: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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), 6.8–6.7 (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-jh][1,4]benzodiazepine-2(1H)-one (1af).** 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-jh][1,4]benzodiazepine-2(1H)-one (1ak).** Under Ar, 25h (0.71 g, 1.5 mmol) and 1,1'-carbonyldiimidazole (0.45 g, 2.5 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<sub>2</sub>O twice, dilute aqueous AcOH, H<sub>2</sub>O twice, and brine. The organic phase was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give 0.72 g of crude product which was further purified as described in Table 2.

**(5R)-trans-9-Chloro-4,5,6,7-tetrahydro-5,7-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jh][1,4]benzodiazepine-2(1H)-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.

**(+)-(5S)-trans-9-Chloro-4,5,6,7-tetrahydro-5,7-dimethyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jh][1,4]benzodiazepine-2(1H)-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-jh][1,4]benzodiazepine-2(1H)-one (1ap).** The desired product was prepared in a similar manner as 1al: after substituting 25k in place of 25a. 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<sub>3</sub>, H<sub>2</sub>O, and brine. The organic phase was then dried over Na<sub>2</sub>SO<sub>4</sub>, 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-jh][1,4]benzodiazepine-2(1H)-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-jh][1,4]benzodiazepine-2(1H)-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<sub>2</sub>O (1 mL). CS<sub>2</sub> (0.34 mL, 5.66 mmol) was added to the resulting solution. After stirring for 10 min the reaction mixture was warmed to 80 °C for 1 h under Ar. After cooling to room temperature the reaction mixture was diluted with H<sub>2</sub>O (5.6 mL) and then AcOH (0.47 mL). The reaction mixture was then filtered. The filtered solid was partitioned between dilute NH<sub>4</sub>OH and CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>:MeOH, R<sub>f</sub> = 0.5). 1al: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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-jh][1,4]benzodiazepine-2(1H)-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-jh][1,4]benzodiazepine-2(1H)-thione (1ax).** 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<sub>2</sub>O. The organic phase was then washed twice with H<sub>2</sub>O and once with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was further purified as described in Table 2. 1ax: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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), 3.85–3.92 (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, 1bg, 1bh, 1ar, 1ao, 1be, 1ba, 1an.** The desired products were prepared following the procedure for 1ax, after substituting the respective diamines 25d–j, m in place of 25c, and were purified as described in Table 2. 1ba: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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-jh][1,4]benzodiazepine-2(1H)-thione (1aq).** The desired product was prepared following the procedure for 1ax, 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, 28<sup>14</sup> (44.27 g, 0.238 mol), ethyl 2-bromopropionate (33.92 mL, 0.261 mol), and Na<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>O which was washed three times with H<sub>2</sub>O and then with brine. The organic phase was dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>:MeOH, R<sub>f</sub> = 0.85). 27: <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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-1,2,4,5-tetrahydro-3-methyl-2H-1,4-benzodiazepine-2-one (28).** At room temperature a mixture of 27 (22 g, 0.077 mol) and PtO<sub>2</sub> (2 g) in EtOH (120 mL) was placed under a H<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub>:MeOH, R<sub>f</sub> = 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<sub>2</sub>Cl<sub>2</sub> proved less than promising in separating desired 28 from residual HOBT. Therefore a 6.06-g sample was stirred in saturated aqueous NaHCO<sub>3</sub> (70 mL). After 0.75 h the suspension was filtered and rinsed with a small amount of ice cold H<sub>2</sub>O 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<sub>2</sub>Cl<sub>2</sub> to yield pure 28 as a white solid, mp 186–188 °C (TLC: 5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, R<sub>f</sub> = 0.7). 28: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 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<sub>16</sub>H<sub>11</sub>ClN<sub>2</sub>O) C, H, N.

**7-Chloro-1,2,4,5-tetrahydro-3-methyl-4-propyl-2H-1,4-benzodiazepine-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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic phase was then washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give an off-white solid. This solid was trituated in Et<sub>2</sub>O (20 mL), filtered, and rinsed with Et<sub>2</sub>O (10 mL) to yield 3.07 g (84%) of 29 (TLC > 95%) which was used without further purification. A small sample was

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further purified by an additional trituration in Et<sub>2</sub>O to yield pure 29 as a white solid, mp 137–138 °C (TLC: 5:1 CHCl<sub>3</sub>:MeOH, *R<sub>f</sub>* = 0.85; 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.4). 29: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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), 7.3–7.5 (m, 2H), 7.8–7.9 (s, 1H). Anal. (C<sub>15</sub>H<sub>17</sub>ClN<sub>2</sub>O) C, H, N.

**7-Chloro-1,3,4,5-tetrahydro-3-methyl-9-nitro-4-propyl-2H-1,4-benzodiazepine-2-one (30).** Over 10 min, 29 (2.77 g) was added neat to fuming HNO<sub>3</sub> 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<sub>2</sub>Cl<sub>2</sub> (100 mL each). The organic extracts were combined, dried over MgSO<sub>4</sub>, 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<sub>3</sub>:MeOH, *R<sub>f</sub>* = 0.85; 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.45). 30: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>2</sub>) C, H, N.

**9-Amino-7-chloro-1,3,4,5-tetrahydro-3-methyl-4-propyl-2H-1,4-benzodiazepine-2-one (31).** At room temperature a mixture of 30 (0.53 g, 1.76 mmol) and PtO<sub>2</sub> (0.06 g) in EtOH (12 mL) was placed under a H<sub>2</sub> atmosphere at 35 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 > 15%) 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 137.5–138.5 °C (TLC: 5:1 CHCl<sub>3</sub>:MeOH, *R<sub>f</sub>* = 0.7; 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.25). 31: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>O) C, H, N.

**9-Chloro-2,5,6,7-tetrahydro-5-methyl-6-propyl-2-thioxoimidazo[4,5,1-*b*][1,4]benzodiazepine-4(1H)-one (1aw).** Under N<sub>2</sub>, a solution of triphosgene (0.13 mL, 1.76 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) was added over 5 min to a stirring 0 °C mixture of 31 (0.47 g, 1.76 mmol) and Et<sub>3</sub>N (0.49 mL, 3.52 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The final reaction mixture was stirred an additional 10 min at 0 °C and then extracted with saturated aqueous NaHCO<sub>3</sub>. The organic phase was then dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.4). 1aw: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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-1H-1,4-benzodiazepine-2,5(3H,4H)-dione (32a).** At room temperature a solution of ethyl 2-bromopropionate (12.98 mL, 0.1 mol) and *n*-PrNH<sub>2</sub> (18.44 mL, 0.3 mol) in Et<sub>2</sub>O (70 mL) was stirred for 72 h. The mixture was then filtered, and the resulting salts were rinsed with a small amount of Et<sub>2</sub>O. 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, a conc with Et<sub>3</sub>N (7.56 mL, 54 mmol), in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at 0 °C was treated with a semisuspension of 3a (10.83 g, 54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, 3 N citric acid, and then saturated aqueous NaHCO<sub>3</sub> once again. The organic phase was then dried over MgSO<sub>4</sub>, 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub>:MeOH. The desired fractions were combined and concentrated under reduced pressure to give 4.80 g (34%) of 32a which was used without further purification (TLC: 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.25).

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

**9-Amino-2,5-dihydro-3-methyl-4-propyl-1H-1,4-benzodiazepine-6(4H)-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<sub>2</sub>O (115 mL), 3 N NaOH (1.15 mL), and H<sub>2</sub>O (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<sub>4</sub>, filtered, and concentrated under reduced pressure to give 33 as an oil which was used without further purification (TLC: 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.4).

**4,5-Dihydro-5-methyl-6-propylimidazo[4,5,1-*b*][1,4]benzodiazepine-3,7(1H,6H)-dione (1bf).** The above residual oil 33 was combined with Et<sub>3</sub>N (0.695 mL, 5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), cooled to 0 °C, and treated with a solution of trichloromethyl chloroformate (0.30 mL, 2.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) over 15 min. Five minutes after completion of addition the reaction mixture was washed sequentially with H<sub>2</sub>O, 3 N HCl, and saturated aqueous NaHCO<sub>3</sub>. The organic phase was then dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.3). 1bf: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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-6-methylimidazo[4,5,1-*b*][1,4]benzodiazepine-3(1H)-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. (2R)-cis-7-Chloro-2,3-dihydro-2-hydroxy-1H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10H,11aH)-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<sub>2</sub>O (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<sub>2</sub>O (800 mL) to yield 25.04 g (58%) of 34 as a white solid, mp 137–138 °C (TLC: 5% (10% NH<sub>4</sub>OH/MeOH)/CH<sub>2</sub>Cl<sub>2</sub>, *R<sub>f</sub>* = 0.28). 34: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 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), 5.3 (d, 1H), 7.15–7.2 (d, 1H), 7.6 (d, 1H), 7.75 (s, 1H), 10.7 (s, 1H).

**(+)-(11aS)-7-Chloro-1,3,10,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione (35).** Jones reagent<sup>10</sup> (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<sub>2</sub>O and then filtered. The solid was rinsed with H<sub>2</sub>O 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<sub>3</sub> to yield pure 35 as a white solid, mp 268–270 °C (TLC: 5% (10% NH<sub>4</sub>OH/MeOH)/CH<sub>2</sub>Cl<sub>2</sub>, *R<sub>f</sub>* = 0.57). 35: <sup>1</sup>H

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NMR (DMSO- $d_6$ )  $\delta$  2.35–2.95 (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<sub>15</sub>H<sub>12</sub>ClN<sub>2</sub>O<sub>4</sub>) C, H, N

(+)-(11aS)-7-Chloro-8-nitro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,5,11(10H,10H,11aH)-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<sub>2</sub>O. After drying the resulting solid under high vacuum at 50 °C for 16 h, there remained 11.04 g (83%) of 36 which was used without further purification (TLC: 5% (10% NH<sub>4</sub>OH/MeOH)/CH<sub>2</sub>Cl<sub>2</sub>,  $R_f$  = 0.76). 36: <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  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), 10.6 (s, 1H).

(+)-(11aS)-7-Chloro-2,3-dihydro-2-methylene-8-nitro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (37a). Under Ar, 10% NaH (1.85 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 (300 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<sub>2</sub>O (500 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub>,  $R_f$  = 0.73). 37a: <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  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<sub>15</sub>H<sub>10</sub>ClN<sub>2</sub>O<sub>4</sub>) C, H, N.

[11aS(E + Z)]-7-Chloro-2-ethylidene-2,3-dihydro-8-nitro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-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<sub>2</sub>Cl<sub>2</sub> 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<sub>17</sub>H<sub>12</sub>ClN<sub>2</sub>O<sub>4</sub>) C, H, N. 37b, major isomer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.68 (d, 3H), 1.80–2.67 (m, 1H), 3.42 (d, 1H), 4.20 (d, 1H), 4.31 (s, 2H), 5.59–5.63 (m, 1H), 6.26 (d, 1H), 8.30 (d, 1H), 9.76 (s, 1H).

(11aS)-7-Chloro-2,3,5,10,11,11a-hexahydro-2-methylene-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8-amine (38a). Under Ar, 37a (2.0 g, 6.6 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<sub>2</sub>O, 3 N NaOH, and H<sub>2</sub>O. After stirring for an additional 30 min, the salts were filtered. The combined filtrates were concentrated under reduced pressure, and the residue was partitioned between CHCl<sub>3</sub> and H<sub>2</sub>O. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, 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<sub>3</sub>,  $R_f$  = 0.5E).

[11aS(E + Z)]-7-Chloro-2-ethylidene-2,3,5,10,11,11a-hexahydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8-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.

(10aS)-4-Chloro-6,8,9,10,10a,11-hexahydro-8-methylenetetrahydro[4,5,1-j]pyrrolo[2,1-c][1,4]benzodiazepine-1(2H)-thione (1bk). The desired product was prepared fol-

lowing 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<sub>2</sub>O. The crude product was purified as described in Table 2. 1bk: <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  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).

(+)-(10aS(E + Z))-4-Chloro-9-ethylidene-6,8,9,10,10a,11-hexahydroimidazo[4,5,1-j]pyrrolo[2,1-c][1,4]benzodiazepine-1(2H)-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<sub>2</sub>O. The crude product was purified as described in Table 2.

Procedure Sequence for Method K. 5-Chloro-3-methoxy- $\gamma$ -oxobenzenebutanoic Acid (39a). The desired product was prepared following a previously published procedure.<sup>20</sup> 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<sub>2</sub>Cl<sub>2</sub>. The organic phase was separated and washed with an aqueous NaHCO<sub>3</sub> solution. This aqueous solution was treated slowly with 3 N HCl until acidic. The resulting solid was filtered, rinsed with H<sub>2</sub>O, and air-dried to give 39a in 41% yield.

5-Chloro-3-methoxy-3-oxobenzenebutanoic 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-3-methoxy-3-nitro- $\gamma$ -oxobenzenebutanoic Acid (40a). Under Ar, 39a (14.0 g, 57.85 mmol) was added neat over 2 min to 0 °C fuming HNO<sub>3</sub> (140 mL). After 0.75 h the solution was poured into ice (600 g) with stirring. The resulting solid was filtered, rinsed with a small amount of ice cold H<sub>2</sub>O, 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<sub>2</sub>Cl<sub>2</sub>:MeOH,  $R_f$  = 0.65; 1:1 EtOAc:hexane,  $R_f$  = 0.05). 40a: <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  2.6 (t, 2H), 3.2 (t, 2H), 3.8 (s, 3H), 5.0 (s, 1H), 8.3 (s, 1H).

5-Chloro-3-methoxy-3-nitro-3-oxobenzenebutanoic Acid (40b). Under Ar, 39b (18.36 g, 71.7 mmol) was added neat over 20 min to 0 °C fuming HNO<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub>. The organic phase was separated, dried over MgSO<sub>4</sub>, 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-3-methoxy-3-nitro- $\gamma$ -oxobenzenebutanoate (41a). A mixture of 40a (10 g, 34.84 mmol) and concentrated H<sub>2</sub>SO<sub>4</sub> (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<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic phase was further washed with saturated NaHCO<sub>3</sub> and then brine, dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>:MeOH,  $R_f$  = 0.99; 1:1 EtOAc:hexane,  $R_f$  = 0.8). 41a: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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-3-methoxy-3-nitro-3-oxobenzenebutanoate (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-3H-pyrrolo[1,2-d][1,4]benzodiazepine-3(2H)-one (42a). Under Ar, NaBH<sub>4</sub>-CN (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<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub>, 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 1.27 g (38%) of 43a as an orange-copper-colored solid, mp 166–168 °C (TLC: 5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.75; 80:20:5 CHCl<sub>3</sub>:MeOH:HCOOH, *R<sub>f</sub>* = 0.8). 43a: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>15</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>2</sub>) C, H, N.

**2-Chloro-6,7,10,11,12,13a-hexahydro-4-nitropyrido[1,2-d][1,4]benzodiazepine-9(8H)-one (43b).** The desired product was prepared in a similar manner as 43a 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 43a in that the crude material was flash chromatographed on a silica gel column eluting with 1:35 MeOH:CH<sub>2</sub>Cl<sub>2</sub>. The desired fractions were combined and concentrated under reduced pressure to give 23% of 43b as a copper-colored oil which was used without further purification.

**8-Amino-10-chloro-1,2,3,6,7,11b-hexahydro-5H-pyrrolo[1,2-d][1,4]benzodiazepine (43a).** Under N<sub>2</sub>, 43a (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<sub>2</sub>C (0.46 mL), 3 N NaOH (0.46 mL), and H<sub>2</sub>O (1.35 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<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.1).

**2-Chloro-5,6,7,9,11,12,13a-octahydropyrrolo[1,2-d][1,4]benzodiazepine-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-7,8,10,11,12,13a-hexahydroimidazo[4,5,1-*h*]pyrrolo[1,2-d][1,4]benzodiazepine-5(4H)-thione (1bm).** Under N<sub>2</sub>, 1,1'-thioa-bonyldimidazole (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<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.7). 1bm: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.7–1.9 (m, 3H), 2.65–2.65 (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-7,8,11,12,13a-hexahydro-10H-imidazo[4,5,1-*h*]pyrrolo[1,2-d][1,4]benzodiazepine-5(4H)-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-3H-pyrrolo[1,2-d][1,4]benzodiazepine-9(2H)-one (44a).** The desired product was prepared in 100% yield following the procedure of 25b, after substituting 42a for 24b, and was used after reaction workup without further purification (TLC: 80:20:5 CHCl<sub>3</sub>:MeOH:HCOOH, *R<sub>f</sub>* = 0.55).

**2-Chloro-4,5,7,8,11,12a-hexahydro-5-thiomimidazo[4,5,1-*h*]pyrrolo[1,2-d][1,4]benzodiazepine-10(11H)-one (1bm).** Under Ar, 1,1'-thioa-bonyldimidazole (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 1bm as a tan solid (TLC: 80:20:5 CHCl<sub>3</sub>:MeOH:HCOOH, *R<sub>f</sub>* = 0.7). 1bm: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.9–2.1 (m, 1H), 2.3–2.45 (m, 2H), 2.7–2.3 (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-1H-inden-1-one (45). The desired product was

prepared as previously described<sup>21</sup> 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-1H-inden-1-one (46).** Over 0.33 h under Ar, 45 (41.88 g, 0.209 mol) was added neat to 0 °C fuming HNO<sub>3</sub> (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<sub>2</sub>O (100 mL each). After air-drying the resulting 38.98 g (80%) of off-white 46 was used without further purification (TLC: 1:1 EtOAc:hexane, *R<sub>f</sub>* = 0.8). 46: <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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-1H-inden-1-yl)amino]acetamide (47).** Under Ar, NaBH<sub>4</sub>CN (11.31 g, 0.18 mol) was added to a room temperature solution of 46 (22.05 g, 0.09 mol), glycineamide 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<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, 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<sub>f</sub>* = 0.3; 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, *R<sub>f</sub>* = 0.45). 47: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 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), 8.3 (s, 1H).

**7-Chloro-2,3,4,4a,5,6-hexahydro-9-nitro-1H-indeno[1,7-*ef*][1,4]diazepine (48).** Over 15 min, BH<sub>3</sub>·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 3 N NaOH (60 mL) and the mixture slightly concentrated under reduced pressure. The resulting concentrated aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to yield 4.96 g of oil (TLC: 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, *R<sub>f</sub>* = 0.25). This material was combined with NaOAc (1.19 g, 13.78 mmol) in n-BuOH (50 mL) and warmed to reflux. After 16 h the mixture was concentrated under reduced pressure and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub>. The organic phase was then washed with brine, dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, *R<sub>f</sub>* = 0.5; 20:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.3). 48: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 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-1H-indeno[1,7-*ef*][1,4]diazepine (49).** Under N<sub>2</sub>, 1-bromo-3-methyl-2-butene (0.86 g, 6.45 mmol) was added neat to a stirring, room temperature mixture of 48 (1.38 g, 5.38 mmol), NaHCO<sub>3</sub> (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<sub>2</sub>O and H<sub>2</sub>O. The aqueous phase was reextracted with a second portion of Et<sub>2</sub>O. The organic phases were combined and washed with H<sub>2</sub>O and then brine, dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.4; 5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH, *R<sub>f</sub>* = 0.8).

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

511

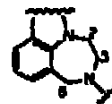
for 42a. The resulting amine THF solution (TLC: 8:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH, *R<sub>f</sub>* = 0.5) was treated with 1 mol equiv of 1,1'-thiocarbonyldiimidazole and warmed to reflux for 3 h. The reaction mixture was then concentrated under reduced pressure and partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to yield crude product which was further purified as described in Table 2 (TLC: 25% EtOAc/hexane, *R<sub>f</sub>* = 0.4). 1bp: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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), 3.35–3.6 (t, 2H), 3.65–3.75 (t, 1H), 4.0–4.1 (m, 1H), 4.7–4.8 (d, 1H), 5.3–5.4 (m, 1H), 7.0 (s, 1H), 8.8–9.0 (bs, 1H).

**Acknowledgment.** We appreciate the assistance of John Mauceri, Gary Caldwell, and William Jones of the R.W. Johnson Pharmaceutical Research Institute for obtaining all mass spectra data and Hilda Azijn of the Rega Institute for technical assistance in the HIV-1 testing. We thank William Lauwers, Danny Verbinen, and James Fortunato of the Janssen Research Foundation for nomenclature assistance for all compounds. We also thank Robert Kavash and Alfons Raeymaekers of the Janssen Research Foundation and Bridget Braslin for advice and discussion.

## References

- (1) Pauwels, R.; Andries, K.; Demmyter, J.; Schols, D.; Kukla, M.; Brudwig, H.; Raeymaekers, A.; Van Gelder, J.; Wautersberghe, R.; Hoogstraete, J.; Schellens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. Patent and selective inhibition of HIV-1 replication in vitro by a novel series of TIRO derivatives. *Nature* 1990, 347, 470–474.
- (2) Kukla, M.; Braslin, H.; Pauwels, R.; Fedda, C.; Miranda, M.; Senti, 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-8-methylimidazo[4,5-f][1,4]benzodiazepine-2(1H)-one (TIRO) Derivatives. *J. Med. Chem.* 1991, 34, 748–751.
- (3) Kukla, M.; Braslin, H.; Diamond, C.; Ormrod, P.; Hu, C. Y.; Miranda, M.; Rodgers, J.; Sherrill, R.; De Clercq, E.; Pauwels, R.; Andries, K.; Moon, T.; Janssen, M. A. C.; Janssen, P. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5-f][1,4]benzodiazepine-2(1H)-one (TIRO) Derivatives. *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), 325–354.
- (5) Molloy, U.; Yank, R.; DuPont, B.; Gazzard, B.; Cawston, B.; Stoff, J.; Davies, S.; De Saint Martin, J.; Janssen, P. Pharmacokinetics of R 52013 in patients with AIDS or AIDS-related complex. *Lancet* 1991, 338, 140–141.
- (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 diastereomeric models while evaluating <sup>1</sup>H NMR NOE difference data and, when applicable, <sup>1</sup>H NMR H–H coupling data. A summary of the key observations follows. The <sup>1</sup>H NMR interaction distinguishing 20a from 21a was the NOE between H-3 and H-5 (see geometric 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 22a and 21a, respectively, were also examined. In 1ba, 1,3-diaxial NOE's between H-3 and H-5 were observed, while for 1az no NOE was observed between H-3 and the C-6 methyl group. Differentiating 22a (cis, axial equatorial,

methyl groups) from 21a (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 21a, the diequatorial 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 22a, a 1,3-diaxial NOE was observed between H-3 and H-5.



- (7) Pauwels, R.; De Clercq, E.; Demmyter, J.; Balzarini, J.; Onghena, P.; Herdewijn, P.; Vankaputle, M. Sensitive and rapid assay on MT-4 cells for detection of antiviral compounds against the AIDS virus. *J. Virol. Methods* 1987, 18, 171–185.
- (8) Pauwels, R.; Balzarini, J.; Baba, M.; Konack, R.; Schols, D.; Herdewijn, P.; Demmyter, 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.; Oroszinger, K.; Gullen, E.; Kapadia, R.; Patel, U.; Pucha, V.; Maubdin, S.; Vamur, J.; Schenke, M.; Klunder, J.; Pal, K.; Skiles, J.; McNeil, D.; Rana, J.; Chow, G.; Skoog, M.; Wu, J.; Schmidt, G.; Knapp, W.; Eberlein, W.; Anbur, T.; Campbell, R.; Rosenthal, A.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridohexans and Dipyridylazapinones. *J. Med. Chem.* 1991, 34, 2281–2291.
- (10) James, C.; Kenner, J.; Stubbings, W. Note on the Preparation of certain Indo-compounds. *J. Chem. Soc.* 1930, 177, 772–773.
- (11) Matsumura, K.; Suzuki, M.; Iwasaki, T.; Miyoshi, M.; Okamura, K. New Convenient Synthesis of alpha-C-Acylamino Acids and alpha-Amino Ketones. *J. Org. Chem.* 1973, 38, 3571–3575.
- (12) Serranton, R.; Cooper, J. Substitution Reactions of Benzothio-phenyl Derivatives. Part III. Nitration of Benzothio-phenyl-2-carboxylic Acid and its 3-Methyl Derivative. *J. Chem. Soc. C* 1971, 2408–2409.
- (13) Ireland, R.; Marshall, J. A. New Synthetic Method For The Preparation Of alpha-substituted beta-ketones. *J. Am. Chem. Soc.* 1959, 81, 2907–2908.
- (14) Reported: Carey, E. The Mechanism of the Decarboxylation of alpha, beta, and gamma, gamma-Unsaturated Malonic Acid Derivatives and the Course of Decarboxylative Condensation Reactions in Pyridine. *J. Am. Chem. Soc.* 1953, 75, 5997–6005. 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-Phenylanthracene and 9-Phenylthioxanthene Sulfone in Electrophilic and Nucleophilic Reactions. I. Nitration. *J. Chem. Pharm. Bull.* 1973, 21 (8), 1272–1281.
- (16) Dornat, A. Methods for the Control of Plant Growth. U.S. Patent 3,823,615, December 14, 1965.
- (17) Miller, D.; Mau, F. L.; Ruffalo, R., Jr.; Pfall, P. Stereochemical Studies of Adrenergic Drugs. Optically Active Derivatives of Imidazoline. *J. Med. Chem.* 1976, 19, 1382–1384.
- (18) Chmuk, R.; Jankowska, Z. Synthesis and properties of some 2-nitrobenzylamine derivatives. *Fol. J. Chem.* 1978, 82 (5), 947–951.
- (19) Dymov, C.; Engle, R. R.; Bowser, A. The Direct Conversion of Steroidal 4'-3'-Alcohols to 4' and 3'-Ketones. *J. Org. Chem.* 1966, 31, 1547–1548.
- (20) Hoffman, J. A. New Synthetic Route to Methoxytryptamines. *J. Org. Chem.* 1969, 34, 1758–1763.
- (21) Murechal, E.; Nivier, M. Etude de monomeres halogenes et de leur polymerisation cationique. IV-Preparation, homopolymerisation et copolymerisation cationique du (dichloro-4,7 indanol). (Study of halogenated monomers and their cationic polymerization. IV. Preparation, homopolymerization and cationic copolymerization of (dichloro-4,7 indanol).) *Bull. Soc. Chim. Fr.* 1974, 694–700.

JM0405710

XP-002162228

STN CA Caesar accession number: 1172

AN - 1978:182987 CAPLUS

DN - 88:182987

TI - Studies on the imidazo[4,5,1-jk][1,4]benzodiazepine and imidazo[1,5,4-ef][1,5]benzodiazepine series

IN - Geneste, P.; Kamenka, J. M.; Vidal, Y.; Fauquet, J. P.; Morel, E.; Muller, P.; Warolin, C.

CS - Lab. Chim. Org. Phys. Appl., Ec. Natl. Super. Chim., Montpellier, Fr.

SO - Eur. J. Med. Chem. - Chim. Ther. (1978), 13(1), 53-9

CODEN: EJMCA5

DT - Journal

LA - French

AB - Of the 7 title compds. (I and II, R = Me or PhCH<sub>2</sub>; X = O; Y = H, Cl, or NO<sub>2</sub>) prepd., none showed tranquilizing activity in pentetrazole-induced convulsions or mouse motor activity. The prepn. of I and II from imidazoquinolinones (III) is also described.

IT - ---66596-64-3P---

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation) (prepn. and reaction with triethyloxonium fluoroborate)

RN - 66596-64-3 CAPLUS

CN - Imidazo[4,5,1-jk][1,4]benzodiazepin-7(4H)-one, 5,6-dihydro-2-methyl- (9CI) (CA INDEX NAME)

IT \*\*\*66596-57-4P\*\*\* \*\*\*66596-59-6P\*\*\*

RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. and tranquilizing activity of)

RN 66596-57-4 CAPLUS

CN Imidazo[4,5,1-jk][1,4]benzodiazepin-7(4H)-one, 9-chloro-5,6-dihydro-2-methyl- (9CI) (CA INDEX NAME)

RN 66596-59-6 CAPLUS

CN Imidazo[4,5,1-jk][1,4]benzodiazepin-7(4H)-one, 9-chloro-5,6-dihydro-2-(phenylmethyl)- (9CI) (CA INDEX NAME)

ANEXO C

XP-002162229

STN CA Caesar accession number : 1173

AN - 1976:432967 CAPLUS

DN - 85:32967

TI - Schmidt reaction of tetrahydroquinolone derivatives

IN - Haerter, H. P.; Stauss, U.; Osiecki, J. H.; Schindler, O.

CS - Forschungsinst., Wander A.-G., Bern, Switz.

SO - Chimia (1976), 30(2), 50-2

CODEN: CHIMAD

DT - Journal

LA - German

AB - Diazepinones I [Z = O; R = H, R1 = H, Et, R2 = Me, R1R2 = (CH)<sub>4</sub>, CH:CHCCl:CH, (CH<sub>2</sub>)<sub>4</sub>; R = Cl, R1 = R2 = Me, R1R2 = (CH)<sub>2</sub>CH<sub>2</sub>] were obtained by Schmidt reaction of the tetrahydroquinolones II. Structure of I (Z = O) was confirmed by redn. to I (Z = H<sub>2</sub>). II were prepd. by treating III (R3 = H) with CH<sub>2</sub>:CHCN, ethanolysis of III (R3 = CH<sub>2</sub>CH<sub>2</sub>CN), hydrolysis of III (R3 = CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Et), and cyclization of III (R3 = CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H). Schmidt reaction of IV, similarly prepd. from phenanthridone, gave isomeric diazepinones V and VI.

IT - 59705-04-3P--

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation) (prepn. and redn. of)

RN - 59705-04-3 CAPLUS

CN - Pyrrolo[3,2,1-k][1,4]benzodiazepin-1(2H)-one, 6-ethyl-3,4-dihydro-7-methyl- (9CI) (CA INDEX NAME)

IT - 59705-05-4P--

RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. of)

RN - 59705-05-4 CAPLUS

CN - Pyrrolo[3,2,1-k][1,4]benzodiazepin-1(2H)-one, 9-chloro-3,4-dihydro-6,7-dimethyl- (9CI) (CA INDEX NAME)

ANEXO D

no. of  
documents  
complete

XP-002162226

CHIMIE THÉRAPEUTIQUE, JUILLET-AOÛT 1973, N° 4, p. 455 à 458

Sur quelques dérivés  
de la phényl-1 méthyl-2 dihydro-4,5 6H-pyrrolo-  
(3,2,1-ij)-quinoléine-6 (1<sup>er</sup> Mémoire)

FRANCO GATTA, Rodolfo LANDI VITTORY, Mario TOMASETTI (\*)

avec la collaboration technique de Luciano SERECA

Laboratoires de Chimie Thérapeutique, Institut Supérieur de la Santé,  
299 Viale Regina Elena, 00161 Rome.

(Manuscrit reçu le 24 décembre 1972).

Les auteurs décrivent la synthèse de quelques pyrrolo-(3,2,1-ij)-quinoléines, pyrrolo-(3,2,1-jk)- et pyrrolo-(3,2,1-jl)-benzodiazépines-1,4, préparées par aldolisation, par la réaction de CLAUSEN et par action de l'acide hydrazotique à partir de la phényl-1 méthyl-2 dihydro-4,5 6H-pyrrolo-(3,2,1-ij)-quinoléine-6.

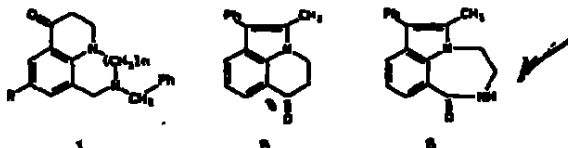
Dans un précédent travail (1), nous avons décrit une série de dérivés tricycliques azotés dans lesquels le système hétérocyclique de la quinazoline, de la benzodiazépine-1,4 et de la benzodiazépine-1,5 est agrandi par l'introduction d'un noyau de la pyridine 1.

Il nous a paru intéressant de poursuivre les recherches dans ce domaine et d'étudier la synthèse et les propriétés de nouveaux dérivés formés par condensation d'un noyau pyrroloïque avec la quinazoline 5 ou la benzodiazépine 6 (schéma 1). La littérature a récemment mentionné des données très intéressantes sur les propriétés pharmacologiques au niveau du système nerveux central de quelques composés semblables (2).

hydroquinoléine et par HASTEN et coll. (2) par déshydrogénation des pyrrolo-tétrahydro-(3,2,1-ij)-quinoléines.

La cétone 5 par l'azoture de sodium en milieu sulfurique concentré donne un mélange (8 : 1) des deux benzodiazépines isomères 6 et 7, aisément séparables par chromatographie sur colonne de silicagel. Ces produits peuvent aussi être préparés, avec un rendement inférieur, par la transposition de BECKMANN, à partir de l'oxime de la cétone 5.

La phényl-1 méthyl-2 trihydro-4,5,6 7H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 one-7 6, par action de l'hydruide d'aluminium lithium, donne la phényl-1 méthyl-2 trihydro-4,5,6 7H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 8, tandis que par traitement avec



R = 1, 2, 3.

Schéma 1.

Le produit de départ, pour nos synthèses schématisées dans le tableau I, est la phényl-1 méthyl-2 dihydro-4,5 6H-pyrrolo-(3,2,1-ij)-quinoléine-6 5, qui n'a jamais été décrite.

Ce composé a été obtenu avec un très bon rendement en modifiant la méthode de ALMOND et MASON (3) pour la synthèse de l'analogue diméthylé en 1 et 2. D'autres pyrrolo-(3,2,1-ij)-quinoléines ont été obtenues par KOET et YUDIN (4, 5, 6) par la réaction de FISCHER à partir de l'amino-1-tétra-

l'iodure de méthyle, elle donne le dérivé méthylé 9. Celui-ci est réduit par l'hydruide d'aluminium lithium en phényl-1 diméthyl-2,6 dihydro-4,5 7H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 10, qui peut aussi être obtenue par méthylation de 8 par le formaldéhyde et l'acide formique.

Par dégradation oxydative du noyau pyrroloïque de 6 par l'anhydride chromique en milieu acétique, on obtient l'acétyl-1 benzoyl-9 tétrahydro-1,2,3,4 5H-benzodiazépine-1,4 one-5 11, qui, en présence de méthylate de sodium se cyclise en phényl-8 trihydro-2,3,4 5,6H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 dione-3,6 12.

(\*) Reçu aux Laboratoires de Chimie Thérapeutique de l'Institut Supérieur de la Santé, Rome.

STUD. THERAPEUT. JULY-AUG. 1973, N° 4

The diagram illustrates the synthesis of various phthalazine derivatives starting from compound 12. The reactions are as follows:

- Compound 12** reacts with  $\text{CH}_3\text{COOH}$  to form **Compound 11**.
- Compound 11** reacts with  $\text{NH}_3$  to form **Compound 7**.
- Compound 11** reacts with  $\text{LiO}_2$  to form **Compound 6**.
- Compound 6** reacts with  $\text{H}_2\text{LiAl}$  to form **Compound 8**.
- Compound 6** reacts with  $\text{Na(CH}_3)_2$  to form **Compound 9**.
- Compound 8** reacts with  $\text{CH}_3\text{O}/\text{HClO}_4$  to form **Compound 10**.
- Compound 11** reacts with  $\text{Ph-NH}_2$  to form **Compound 5**.
- Compound 5** reacts with  $\text{Ph-NH}_2$  to form **Compound 13**.
- Compound 5** reacts with  $\text{Na/mC(HC}_6\text{H}_5)_3$  to form **Compound 14**.
- Compound 14** reacts with  $\text{NH}_2\text{-R}$  to form **Compound 17**.
- Compound 14** reacts with  $\text{NH}_2\text{-OH}$  to form **Compound 16**.
- Compound 16** reacts with  $\text{NH}_2\text{-R}$  to form **Compound 15**.

Les résultats analytiques (C, H, N), conformes aux données traditionnelles exigées, ne sont pas publiés dans le présent mémoire. Les points de fusion ont été déterminés au bain de Kofler et ne sont pas corrigés. Les spectres R. M. ont été enregistrés avec un spectromètre Varian T-60, utilisant le TMS comme référence interne. Les déplacements chimiques sont exprimés en ppm (δ). Les séparations chromatographiques ont été effectuées sur colonne de silicagel (60-80, 2).

GATTA, LANUI VITURV, TOMASSETTI

R. M. N. :  $CDCl_3$ ,  $\delta$  7,80 (H<sub>1</sub>),  $\delta$  4,26 (H<sub>2</sub>),  $\delta$  3,03 (H<sub>3</sub>);  $\delta$  2,46 (-CH<sub>3</sub>).

*Phényl-1 méthyl-2 trihydro-4,5,6 7H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 une 7 b.*

*Phényl-1 méthyl-2 trihydro-4,5,7 6H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 une 6 7.*

a) A 1 g de la cétone 5 dans 10 cm<sup>3</sup> de chloroforme, on ajoute 1 cm<sup>3</sup> d'acide sulfurique concentré et après refroidissement, on agite, 1 g d'azote de sodium par petites quantités, pendant 1/2 h. La réaction est achevée après 1 h environ; on alcalinise par une solution de carbonate de potassium et on extrait au chloroforme. Le mélange de deux homères est séparé par chromatographie sur colonne et élué avec de l'acétate d'éthyle.  
6 F : 238-239° éthanol; 0,79 g; Rdt : 75 %.  
7 F : 233-234° acétate d'éthyle; 0,10 g; Rdt : 9 %.

b) 1 g de l'amine de la cétone 5 est chauffée à 120° en agitant pendant 3 h, avec 10 g d'acide polyphosphorique. On verse dans un mélange eau-glace et on extrait au chloroforme. Les rendements atteignent 0,10 g (10 %) pour le 6 et 0,05 g (5 %) pour le 7.  
R. M. N. : DMSO  
6  $\delta$  8,22 (NH);  $\delta$  4,26 (H<sub>1</sub>);  $\delta$  3,60 (H<sub>2</sub>);  $\delta$  2,40 (-CH<sub>3</sub>).  
7  $\delta$  10,81 (NH);  $\delta$  4,30 (H<sub>1</sub>);  $\delta$  2,97 (H<sub>2</sub>);  $\delta$  2,40 (-CH<sub>3</sub>).

*Phényl-1 méthyl-2 trihydro-4,5,6 7H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 8.*

On prépare selon la technique habituelle par réduction avec l'hydruure d'aluminium lithium dans l'éther, en chauffant pendant 20 h, à partir de l'amide 6.  
F : 121-122° cyclohexane; Rdt : 74 %.  
R. M. N. :  $CDCl_3$ ,  $\delta$  4,20 (H<sub>1</sub>);  $\delta$  3,91 (H<sub>2</sub>);  $\delta$  3,06 (H<sub>3</sub>);  $\delta$  2,40 (-CH<sub>3</sub>);  $\delta$  1,80 (-NH-).

*Phényl-1 diméthyl-2,6 dihydro-4,5 7H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 une 7 9.*

Dans une suspension de 0,6 g (0,012 mole) d'hydruure de sodium (50 % dans l'huile), on ajoute, en agitant, 2,4 g (0,01 mole) de l'amide 6 et, après 1 h, goutte à goutte, 2,9 g (0,01 mole) d'iodure de méthyle. On agit pendant 3 h encore. Après addition d'eau, il se forme un précipité.  
F : 212-213° éthanol; 2,6 g; Rdt : 90 %.  
R. M. N. : DMSO  $\delta$  4,31 (H<sub>1</sub>);  $\delta$  3,86 (H<sub>2</sub>);  $\delta$  1,26 (N-CH<sub>3</sub>);  $\delta$  2,41 (-CH<sub>3</sub>).

*Phényl-1 diméthyl-2,6 dihydro-4,5 7H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 10.*

a) A une solution de 2,6 g (0,01 mole) de 8 dans 2,5 g d'acide formique 90 %, chauffée à 60°, on ajoute 1,6 g de formaldéhyde à 35 %. On chauffe pendant 3 h à 90° encore. Le milieu réactionnel est dilué dans l'eau, alcalinisé par la soude 10 % et extrait à l'acétate d'éthyle.  
Lib.  $\delta$  140-145°; 1,5 g; Rdt : 72 %.

b) Le même produit peut être obtenu, avec un rendement de 64 %, par réduction de l'amide 9 par l'hydruure d'aluminium lithium dans l'éther, selon la méthode habituelle.

*Acétyl-1 benzyl-9 tétrahydro-1,2,3,4 5H-benzodiazépine-1,4 une 11.*

A 1 g de l'amide 6 dans 20 cm<sup>3</sup> d'acide acétique, on ajoute goutte à goutte et en agitant, une solution d'acétylure chromique (1 g) dans 1 cm<sup>3</sup> d'eau. On laisse l'agitation pendant 1 h à température ambiante, puis on

dilue par l'eau et on extrait au chloroforme. Le produit obtenu est purifié par chromatographie sur colonne en éluant par de l'acétate d'éthyle, contenant 5 % de méthanol.

F : 180-181° éthanol; 0,8 g; Rdt : 71 %.

*Phényl-8 trihydro-2,3,4,5 6H-pyrrolo-(3,2,1-jk)-benzodiazépine-1,4 diène-3,6 12.*

A une solution de 0,3 g (0,02 mole) de sodium dans 100 cm<sup>3</sup> de méthanol anhydre, on ajoute 3,1 g (0,01 mole) de 11. On chauffe à l'ébullition, au reflux, pendant 2 h, puis évapore le méthanol, dilue à l'eau et extrait au chloroforme.

F : 195-196° éthanol; 2,4 g; Rdt : 82 %.

R. M. N. :  $CDCl_3$ ,  $\delta$  8,30 (H<sub>1</sub>);  $\delta$  7,70 (H<sub>2</sub>);  $\delta$  6,63 (H<sub>3</sub>);  $\delta$  4,70 (H<sub>4</sub>);  $\delta$  3,70 (H<sub>5</sub>);  $\delta$  2,17 (-NH-).

*Phényl-1 méthyl-2 benzylidène-5 dihydro-4,5 6H-pyrrolo-(3,2,1-jk)-quinolénone-6 13.*

1,2 g (0,022 mole) de méthylate de sodium est ajouté sous agitation, à une solution de 2,6 g (0,01 mole) de cétone 5 et de 2,1 g (0,02 mole) de benzaldéhyde dans 40 cm<sup>3</sup> de benzène anhydre. Après 2 h on concentre sous pression réduite, on ajoute de l'eau et on extrait au chloroforme.  
F : 198-200° acétate d'éthyle; 2 g; Rdt : 66 %.

*Phényl-1 méthyl-2 hydroxyméthylène-3 dihydro-4,5 6H-pyrrolo-(3,2,1-jk)-quinolénone-6 14.*

Une solution de 2,6 g (0,01 mole) de la cétone 5 dans 50 cm<sup>3</sup> de benzène anhydre est ajoutée, goutte à goutte en agitant, à un mélange de 0,8 g (0,015 mole) de méthylate de sodium et de 1,5 g (0,02 mole) de formiate d'éthyle dans 100 cm<sup>3</sup> de benzène anhydre. Après 12 h d'agitation, on dilue par l'eau et on sépare la couche benzénique qui contient encore 1,6 g de 5 qui n'a pas réagi. On extrait enfin à l'acétate d'éthyle la solution aqueuse acidifiée par l'acide chlorhydrique.

F : 152-154° méthanol; 1 g; Rdt : 90 %.

R. M. N. :  $CDCl_3$ ,  $\delta$  8,10 (-OH);  $\delta$  7,73 (H<sub>1</sub>);  $\delta$  4,33 (H<sub>2</sub>);  $\delta$  2,43 (-CH<sub>3</sub>).

*Phényl-1 méthyl-2 pyrrolidinométhylène-5 dihydro-4,5 6H-pyrrolo-(3,2,1-jk)-quinolénone-6 15 a.*

*Phényl-1 méthyl-2 piperidinométhylène-1 dihydro-4,5 6H-pyrrolo-(3,2,1-jk)-quinolénone-6 15 b.*

*Phényl-1 méthyl-2 morpholinométhylène-1 dihydro-4,5 6H-pyrrolo-(3,2,1-jk)-quinolénone-6 15 c.*

On laisse 20 h à température ambiante une solution de 2,9 g (0,01 mole) de 14 et 0,012 mole de l'amine cyclique respective dans 50 cm<sup>3</sup> de benzène anhydre. Après évaporation du solvant, le produit est cristallisé.

15 a F : 230-232° benzène; 2,5 g; Rdt : 72 %.

15 b F : 210-211° benzène; 2,3 g; Rdt : 65 %.

15 c F : 230-232° acétate d'éthyle; 2,8 g; Rdt : 79 %.

*Phényl-1 méthyl-2 hydro-4 imazolo-(4,1-c)-pyrrolo-(3,2,1-jk)-quinoléline 16.*

2,9 g (0,01 mole) de 15, 2,2 g (0,01 mole) de chlorhydrate d'hydronylamine et 50 cm<sup>3</sup> d'éthanol sont chauffés à reflux pendant 2 h. On chasse sous vide le solvant et on cristallise.

F : 190-192° acétate d'éthyle; 1,8 g; Rdt : 63 %.

*Phényl-1 méthyl-2 hydro-4 6H-pyrrolo-(4,1-c)-pyrrolo-(3,2,1-jk)-quinoléline 17.*

Le mode opératoire est le même que pour 16, mais il

5253  
518

458

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(aut employer 0,4 g (0,015 mole) d'hydrate d'hydrazine 91 %

F : 222-224° acetate d'éthyle; 2 g; Rdt : 70 %.

Nous remercions le Dr. J. ZAVATTARO pour les micro-analyses.

## SUMMARY

Synthesis of pyrrolo-(3,2,1-g) quinolines, pyrrolo-(3,2,1-g) and pyrido-(3,2,1-g) 1,4 benzodiazepines, by aldol condensation, Claisen reaction and hydrazine acid action, on 1-phenyl 2-methyl 4,5-dihydro 6H-pyrrolo-(3,2,1-g) 6-quinolinone.

## ZUSAMMENFASSUNG

Die Autoren beschreiben die Synthese einiger Pyrrolo-(1,2,1-g)-chinoline, Pyrrolo-(3,2,1-g)- und Pyrido-(1,2,1-g)-benzodiazepine-1,4, die durch Aldolkondensation, Claisenreaktion und Einwirkung von Stickstoffwasserstoffsäure ausgehend von 1-Phenyl-2-methyl-4,5-dihydro-6H-pyrrolo-(3,2,1-g)-chinolinon-6 dargestellt wurden.

## BIBLIOGRAPHIE

- (1) F. GIATTA, R. LANDI VITTI, M. TOMASETTI et G. NUNZI BARRICK, *Chim. Ind.*, 1972, 7 (6), 400.
- (2) J. B. HESTER, A. D. RUDZIN et W. VEDJAKAR, *J. Med. Chem.*, 1970, 13, 827.
- (3) C. V. ALMOND et R. G. MANN, *J. chem. Soc.*, 1952, 1870.
- (4) A. N. KOST et I. G. YUDIN, *Khim. zashch i priro.*, 1957, 2, 300; *Chem. Abstr.*, 52, 11871 d.
- (5) I. G. YUDIN, V. A. RUDYLYN et A. N. KOST, *Metody polucheniya khim. reaktivov i preparatov*, 1964, 12, 63; *Chem. Abstr.*, 64, 19551 f.
- (6) I. G. YUDIN, V. A. RUDYLYN et A. N. KOST, *Khimi. Geterotsikl. Soedin.*, 1967, 704; *Chem. Abstr.*, 68, 114151 z.
- (7) P. SCHINDLER, I. MERTI, et G. BERNARDI, *Farmaco. Ed. Sci.*, 1971, 26, 837, et ref. cit.
- (8) N. P. BUTY-LIC, P. JACQUIGNON et O. PYRIN-ROBERT, *Bull. Soc. chim.*, 1965, 2849.
- (9) HELL, MALCOLM RIE, *Ger. Offen.*, 1, 906, 54; *Chem. Abstr.*, 72, 66807 m.