Regioselectivity in Intramolecular Nucleophilic Aromatic Substitution. Synthesis of the Potent Anti HIV-1 8-Halo TIBO Analogues

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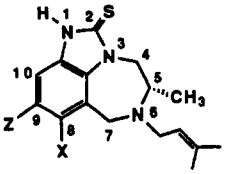
Regioselective intramolecular nucleophilic substitution of 2,6-dihalo-3-nitrobenzyl diamines **2b** and **2c** gave benzodiazepines **3**. These intermediates are useful in the preparation of the 8-halo TIBO derivatives **1**, inhibitors of HIV-I replication in cell culture.

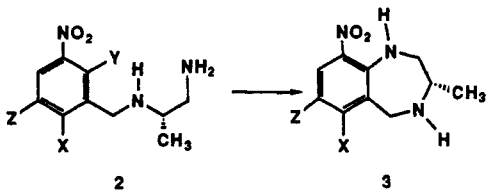
In a recent communication,[1] we described the synthesis of TIBO R82150 (**1a**), an inhibitor of HIV-1 replication,[2] by a four-step sequence. A key transformation in that four-step preparation was the conversion of intermediate **2a** to bicyclic **3a** by intramolecular nucleophilic aromatic substitution.[3]



1a X, Z = H
b X = Cl, Z = H
c X = F, Z = H
d X = H, Z = Cl

We now report the preparation of the 8-chloro and 8-fluoro TIBO's **1b** and **1c** and the 9-chloro TIBO, R82913 (**1d**). The preparation of TIBO **1d**,[2] according to our four-step protocol, is straightforward and is described without further comment in the Experimental Section.

The expansion of our synthetic approach to the efficient synthesis of the 8-halo compounds requires regioselectivity in the cyclizations of amines **2b** and **2c**. The desired regioselectivity, leading to benzodiazepines **3b** and **3c**, was observed, and elaboration afforded TIBO's **1b** and **1c**. These compounds, like the parent TIBO **1a** and the 9-chloro derivative **1d**, proved to be potent inhibitors of HIV-1 replication in vitro with low toxicity to cells.

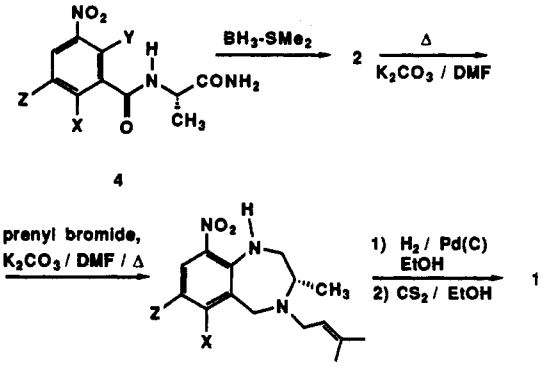


2 **3**

a X, Z = H; Y = Cl
b X, Y = Cl; Z = H
c X, Y = F; Z = H
d X = H; Y, Z = Cl

A test of the key cyclization in the context of the synthesis of TIBO **1b** requires dichloro diamine **2b**. Diamine **2b** was prepared from *N*-(2,6-dichloro-3-nitrobenzoyl)-L-alaninamide (**4b**, from commercially available 2,6-dichloro-3-nitrobenzoic acid; see Experimental Section) by borane–methyl sulfide reduction. The crude diamine (isolated in 58% yield) was subjected to heating with potassium carbonate in DMF to effect cyclization.

Scheme I. Synthesis of 8-Halo (and 9-Chloro) TIBO's



4 **5**

b X, Y = Cl; Z = H
c X, Y = F; Z = H
d X = H; Y, Z = Cl

A crude cyclization product was obtained in 93% yield. The ^1H and ^{13}C spectra of this material each contained *a single set* of signals; in the ^1H spectrum, the broad singlet at 8.22 ppm was correlated with an N–H proton, strongly hydrogen-bonded to the nitro group and indicating exclusive formation of benzodiazepine **3b**. Thus, intramolecular nucleophilic aromatic substitution occurred regiospecifically and ortho to the nitro group.

By analogy to our previous work, completion of the synthesis was straightforward. Alkylation of benzodiazepine **3b** afforded the desired *N*-alkylated cyclized diamine, TIBO precursor **5b** in 65% yield. Reduction of the nitro benzodiazepine **5b** and capping of the intermediate triamine gave the 8-chloro TIBO **1b** in 36% yield.

Preparation of 8-fluoro TIBO was accomplished by a parallel route. Treatment of *N*-(2,6-difluoro-3-nitrobenzoyl)-L-alaninamide (**4c**, two steps from commercially available 2,6-difluorobenzoic acid; see Experimental Section) with borane–methyl sulfide (2 mol equiv) gave a mixture which appeared to contain the expected difluoro diamine **2c** and cyclized material. An attempt to separate the two components of this mixture by preparative TLC led to the isolation of benzodiazepine **3c** only; thus, the cyclization of diamine **2c** is extremely facile and, like the cyclization of diamine **2b**, it is regiospecific. The yield for the diborane reduction and concomitant cyclization was 67%.

Alkylation of crude cyclic diamine **3c** (62% yield) completed the preparation of TIBO precursor **5c**. When

(1) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1991**, *56*, 4600.
(2) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M.; Breslin, H.; Raeymaekers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M. A.; De Clercq, E.; Janssen, P. *Nature* **1990**, *343*, 470.
(3) Previous examples of intramolecular nucleophilic aromatic substitution had been limited. (a) Several annelations had been reported by: Meyers, A. I.; Reuman, M.; Gabel, R. A. *J. Org. Chem.* **1981**, *46*, 783. In these, a methoxyl substituent, positioned ortho to the activating group of an aryloxazoline, was displaced. (b) Intramolecular "vicarious" nucleophilic aromatic substitutions have also been achieved. See: Ahmed, Z.; Cava, M. P. *Tetrahedron Lett.* **1981**, *22*, 5239. Murphy, R. A., Jr.; Cava, M. P. *Tetrahedron Lett.* **1984**, *25*, 803.

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Table I. Activity of TIBO Compounds[a]

structure	IC_{50}[b] (M)	CC50[c] (M)	TI[d]
1a (R82150)[e]	2.04×10^{-8}	$>1.74 \times 10^{-4}$	>8529
R82913[f,g] (9-chloro)	$<1.00 \times 10^{-9}$	2.84×10^{-5}	>28400
1b	$<1.85 \times 10^{-9}$	$>5.85 \times 10^{-6}$	>3162
1c	3.65×10^{-8}	$>8.19 \times 10^{-5}$	>2244

[a] The anti-HIV-1 activities reported here were determined in CEM cells as part of the NCI In Vitro Anti-AIDS Drug Discovery Program. [b] 50% inhibitory concentration. [c] 50% cytotoxic concentration. [d] Therapeutic index (TI = CC_{50}/IC_{50}). [e] Data reported for MT-4 cells: IC_{50} (M) 2.8×10^{-8}; CC_{50} (M) 8.7×10^{-4}; TI > 31071 (ref 2). [f] R82913, the 9-chloro TIBO sample used in this screen, was prepared by our four-step synthesis; see Experimental Section. [g] Data reported for MT-4 cells: IC_{50} (M) 1.5×10^{-9}; CC_{50} (M) $>3.1 \times 10^{-5}$; TI = 20667 (ref 2).

subjected to our standard capping procedure, benzodiazepine **5c** was converted to the desired 8-fluoro TIBO **1c** in 48% yield.

Regioselectivity in *inter*molecular nucleophilic aromatic substitution has been the subject of a number of studies. In general, substitution occurs more rapidly para to the activating group, but in the case of the reaction of halo nitrobenzenes with amine nucleophiles, substitution is faster in the ortho position. For 2,4-dihalo nitrobenzenes, substitution occurs exclusively or almost exclusively at the ortho position. These effects have been attributed to steric effects, dipole effects, and hydrogen bonding.[4]

*Intra*molecular nucleophilic aromatic substitution as an approach to benzo-fused ring systems has been examined only recently.[3a] Examples of intramolecular substitutions in which regiochemistry is an issue are limited to the special cases of annelations of anthraquinone systems employed by Cava in his approach to aklavinones.[3b]

In the cyclizations of amines **2b** and **2c**, closure ortho to the nitro group is consistent with the pattern derived for intermolecular nucleophilic aromatic substitutions of 2,4-dihalonitrobenzenes. This transformation is noteworthy as, in each case, it leads to a single, functionalized benzodiazepine.

The 8-chloro and 8-fluoro TIBO's (**1b** and **1c**) were tested for anti-HIV-1 activity in T-4 lymphocyte culture in the NIH screen.[5] Structure–activity data for these new compounds and for the two known TIBO compounds **1a** and **1d** are shown in Table I. All four compounds demonstrated anti HIV-1 activity at low concentrations and were relatively nontoxic to cells in this screen.

Experimental Section[6]

***N*-(2,6-Dichloro-3-nitrobenzoyl)-L-alaninamide (4b).** To a stirred slurry containing 2.36 g (10.0 mmol) of 2,6-dichloro-3-nitrobenzoic acid (Aldrich) in 7 mL of toluene and 0.05 mL of DMF was added 0.92 mL (1.33 g, 10.5 mmol) of oxaloyl chloride. The mixture was heated to 70 °C for 30 min, and the solvent was evaporated. The resulting acid chloride was added to a 0 °C mixture of 1.5 g (12.0 mmol) of L-alaninamide hydrochloride (Sigma) and 3.45 g (25.0 mmol) of K_2CO_3 in 10 mL of H_2O and 5 mL of toluene. After being stirred at 0 °C for 11 h, the precipitate was filtered and recrystallized (acetone/EtOH) to leave 2.56 g (84%) of a white solid, mp 237 °C dec: ^1H NMR (DMSO-d_6) δ 9.05 (d, J = 7.2 Hz, 1 H), 8.10 (d, J = 8.7 Hz, 1 H), 7.76 (d, J = 8.7 Hz, 1 H), 7.43 (bs, 1 H), 7.11 (bs, 1 H), 4.49 (t, J = 7.0 Hz, 1 H), 1.30 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 173.2, 161.7, 146.9, 138.5, 135.1, 129.4, 126.1, 123.7, 48.4, 18.5; IR (KBr) 3429, 3177, 1668, 1574, 1523, 1339, 1290 cm^{-1}. Anal. Calcd for $C_{10}H_9Cl_2N_3O_4$: C, 39.22; H, 2.94; N, 13.72; Cl, 23.20. Found: C, 39.29; H, 3.07; N, 13.59; Cl, 23.92.

(+)-(*S*)-*N*-(2,6-Dichloro-3-nitrobenzyl)-1,2-propanediamine (2b). A slurry of 1.75 g (5.71 mmol) of diamine **4b** in 50 mL of THF and 5.7 mL (57 mmol, 10 equiv) of BMS was heated at reflux for 12h. The solution was then cooled and quenched with 5% HCl. The aqueous phase was extracted with ether (3 × 15 mL). The acidic extracts were made basic (pH 12) with solid NaOH, then extracted with ether (5 × 20 mL) and dried (Na_2SO_4). Evaporation of the solvent and column chromatography left 933 mg (58%) of a yellow oil: ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 8.7 Hz, 1 H), 7.46 (d, J = 8.7 Hz, 1 H), 4.22 (d, J = 12.5 Hz, 1 H), 4.07 (d, J = 12.5 Hz, 1 H), 2.85–2.50 (m, 5 H), 1.22 (d, J = 7 Hz, 3 H); IR (neat) 3359, 1608, 1526, 1348, 1131 cm^{-1}.

(+)-(*S*)-6-Chloro-3-methyl-9-nitro-2,3,4,5-tetrahydro-1*H*-[1,4]benzodiazepine (3b). A solution of 100 mg (0.36 mmol) of **2b** and 74.5 mg (0.54 mmol) of K_2CO_3 in 2 mL of dry DMF was stirred at 135 °C for 4 h. The resulting dark brown reaction mixture was cooled and poured into 10 mL of $CHCl_3$. Extraction with H_2O (10 × 2 mL), drying ($MgSO_4$), and removal of the solvent afforded 80.7 mg (93%) of an orange oil: ^1H NMR ($CDCl_3$) δ 8.22 (bs, 1 H), 7.96 (d, J = 9.2 Hz, 1 H), 6.75 (d, J = 9.1 Hz, 1 H), 4.44 (d, J = 16.6 Hz, 1 H), 4.06 (d, J = 16.6 Hz, 1 H), 3.65 (m, 1 H), 3.42 (m, 1 H), 3.20 (m, 1 H), 1.17 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 148.9, 141.2, 133.6, 128.5, 125.4, 118.8, 52.9, 51.8, 46.7, 19.6; IR (neat) 3361, 1588, 1480, 1327, 1239 cm^{-1}; HRMS calcd 241.0614, found 241.0610.

(+)-(*S*)-6-Chloro-3-methyl-4-(3-methyl-2-butenyl)-9-nitro-2,3,4,5-tetrahydro-1*H*-[1,4]benzodiazepine (5b). To a solution of 24 mg (0.10 mmol) of diazepine **3b** in 1 mL of DMF containing 21 mg (0.15 mmol) of K_2CO_3 was added 19.5 mg (0.13 mmol) of prenyl bromide. The reaction mixture was stirred at 23 °C for 24 h. Water (1 mL) was added, the phases were separated, and then the water layer was extracted with ether (3 × 1 mL). The combined organic solution was washed well with water (7 × 0.5 mL) and with brine (2 × 0.5 mL) and dried over Na_2SO_4. Column chromatography (1:1 EtOAc/Hex) gave 16 mg (65%) of an orange oil; ^1H NMR ($CDCl_3$) δ 8.48 (bs, 1 H), 7.95 (d, J = 9.2 Hz, 1 H), 6.67 (d, J = 9.2 Hz, 1 H), 5.25 (t, J = 7.3 Hz, 1 H), 4.31 (d, J = 16.5 Hz, 1 H), 4.15 (d, J = 16.5 Hz, 1 H), 3.53 (t, J = 5.7 Hz, 2 H), 3.25 (m, 2 H), 3.10 (m, 1 H), 1.72 (s, 3 H), 1.54 (s, 3 H), 1.14 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.5, 148.6, 142.2, 135.5, 125.8, 121.8, 118.2, 114.1, 57.7, 51.7, 50.6, 48.8, 25.9, 18.0, 17.9; IR (CCl_4) 3361, 2970, 2926, 1592, 1527, 1486, 1332, 1236, 1142, 922, 756 cm^{-1}; HRMS calcd 309.1240, found 309.1237.

(+)-(*S*)-4,5,6,7-Tetrahydro-8-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2-(1*H*)-thione (1b). To a stirred solution of 40 mg (0.13 mmol) of benzodiazepine **5b** in 3 mL of methanol under an atmosphere of H_2 was added 10 mg of 5% Pd(C), and the orange mixture was stirred at 23 °C for 20 min. The colorless solution was filtered through Celite, and the volume was reduced to 1.5 mL. Carbon disulfide (40 mg, 0.51 mmol) was added, and the solution was stirred under argon for 6.5 h. Removal of the solvent and chromatography (1:1 EtOAc/Hex) left 15.0 mg (36%) of a white solid: ^1H NMR ($CDCl_3$) δ 10.0 (bs, 1 H), 7.18 (d, J = 8.5 Hz, 1 H), 7.00 (d, J = 8.5 Hz, 1 H), 5.22 (t, J = 7.0 Hz, 1 H), 4.56 (dd, J = 3.6, 14.5 Hz, 1 H), 4.91 (d, J = 17.5 Hz, 1 H), 4.24 (m, 2 H), 3.53 (m, 1 H), 3.18 (m, 2 H), 1.74 (s, 3 H), 1.47 (s, 3 H), 1.30 (d, J = 6.7 Hz, 3 H); IR (CCl_4) 3144, 2972, 2922, 1616, 1506, 1470, 1328 cm^{-1}; HRMS calcd 321.1063, found 321.1071.

***N*-(2,6-Difluoro-3-nitrobenzoyl)-L-alaninamide (4c).** To a stirred solution of 1.83 g (9.03 mmol) of 2,6-difluoro-3-nitro-

(4) (a) Bunnett, J. F.; Morath, R. J.; Okamoto, T. *J. Am. Chem. Soc.* **1955**, *77*, 5051 and references cited therein. (b) Greizerstein, W.; Brieux, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 1032.

(5) Weislow, O. W.; Kiser, R.; Fine, D.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 577.

(6) Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 Series FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Bruker 250 or Bruker 400 spectrometer and are reported in parts per million. Proton nuclear magnetic resonance spectra were taken in deuteriochloroform using tetramethylsilane (0.00 ppm) as the internal standard. Values of the coupling constant, J, are given in hertz (Hz). For complex multiplets, the chemical shift is in the center of the multiplet. Carbon nuclear magnetic resonance spectra were taken in deuteriochloroform using the central peak of chloroform (77.0 ppm) as the internal standard. High-resolution mass spectra were recorded with a Kratos MS-80 spectrometer under e.i. or c.i. conditions. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee.

benzoic acid[7] in 3 mL of dry toluene and 0.1 mL of DMF was added 0.87 mL (9.9 mmol) of oxaloyl chloride and the solution was heated at 55 °C for 30 min. The reaction mixture was cooled and added portionwise to a 0 °C solution of 1.36 g (10.9 mmol) of L-alaninamide hydrochloride and 3.13 g (22.7 mmol) of K_2CO_3 in 10 mL of H_2O and 5 mL of toluene. After 95 min the precipitate was isolated by filtration, air dried, and recrystallized (H_2O), affording 2.46 g (100%) of a yellow powder, mp 191–192 °C: ^1H NMR (DMSO-d_6) δ 9.15 (bs, 1 H), 8.31 (m, 1 H), 7.52 (bs, 1 H), 7.43 (m, 1 H), 7.11 (bs, 1 H), 4.46 (t, J = 7.0 Hz, 1 H), 1.30 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 173.1, 162.8, 160.1, 157.2, 153.9, 151.2, 128.3, 112.9, 48.6, 18.4; IR (KBr) 3381, 3308, 3193, 1627, 1538, 1475, 1345, 1287, 1048 cm^{-1}. Anal. Calcd for $C_{10}H_9F_2N_3O_4$: C, 43.96; H, 3.30; N, 15.38. Found: C, 43.93; H, 3.39; N, 15.29.

(+)-(*S*)-6-Fluoro-3-methyl-9-nitro-2,3,4,5-tetrahydro-1*H*-[1,4]benzodiazepine (3c). To a solution of 78 mg (0.30 mmol) of diamide **4c** in 3 mL of dry THF was added 0.06 mL (0.6 mmol) of BH_3·SMe_2. The solution was stirred at reflux for 16 h and then cooled. Excess borane was quenched by slow addition of 5% HCl. The aqueous phase was extracted with ether (3 × 3 mL) and then made basic (pH 11) with solid NaOH pellets. The resulting aqueous solution was extracted with ether, dried (Na_2SO_4), and concentrated. Subjection of the residue to column chromatography (silica gel/EtOAc) gave 45 mg (67%) of an orange oil: ^1H NMR ($CDCl_3$) δ 8.18 (bs, 1 H), 8.08 (dd, J = 6.0, 9.5 Hz, 1 H), 6.46 (dd, J = 8.7, 9.5 Hz, 1 H), 4.32 (d, J = 16.4 Hz, 1 H), 3.94 (d, J = 16.3 Hz, 1 H), 3.68 (m, 1 H), 3.39 (m, 1 H), 3.22 (m, 1 H), 2.40 (bs, 1 H), 1.20 (d, J = 6.5 Hz, 3 H); IR (neat) 3364, 1616, 1493, 1247, 906, 731 cm^{-1}; HRMS calcd 225.2474, found 225.2447.

(+)-(*S*)-6-Fluoro-3-methyl-4-(3-methyl-2-butenyl)-9-nitro-2,3,4,5-tetrahydro-1*H*-[1,4]benzodiazepine (5c). To a solution of 18.4 mg (0.082 mmol) of diazepine **3c** in 0.5 mL of DMF containing 11 mg of K_2CO_3 was added 12.2 mg (0.082 mmol) of prenyl bromide. The mixture was stirred at rt for 24 h before it was diluted with water (1 mL) and extracted with ether (3 × 1 mL). The combined organic solution was washed with water (7 × 0.5 mL) and brine (0.5 mL) and dried over $MgSO_4$. Column chromatography (1:1 EtOAc/Hex) afforded 14.9 mg (62%) of an orange oil: ^1H NMR ($CDCl_3$) δ 8.50 (bs, 1 H), 8.06 (dd, J = 6.0, 9.5 Hz, 1 H), 6.39 (dd, J = 8.4, 9.5 Hz, 1 H), 5.22 (m, 1 H), 4.20 (d, J = 16.3 Hz, 1 H), 3.98 (d, J = 16.3 Hz, 1 H), 3.54 (m, 2 H), 3.16 (m, 3 H), 1.73 (s, 3 H), 1.57 (s, 3 H), 1.17 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.2, 163.7, 149.5, 135.4, 127.6, 121.4, 113.6, 105.3, 58.3, 51.4, 50.2, 43.4, 25.8, 18.5, 17.9; IR (neat) 3361, 2971, 2927, 1616, 1506, 1456, 1247 cm^{-1}; HRMS calcd 293.1535, found 293.1503.

(+)-(*S*)-4,5,6,7-Tetrahydro-8-fluoro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2-(1*H*)-thione (1c). A solution of 40.0 mg (0.137 mmol) of **5c** in 5 mL of CH_3OH was hydrogenated in the presence of 50 mg of 10% Pd(C) as the catalyst for 95 min. The colorless solution was filtered through Celite, CS_2 (17.5 mg, 0.23 mmol) was added, and the reaction mixture was stirred under argon for 24 h. Volatile materials were removed in vacuo, and the residue was chromatographed (3:1 EtOAc/Hex) to leave 20.0 mg (48%) of a white powder: ^1H NMR ($CDCl_3$) δ 11.23 (bs, 1 H), 7.05 (dd, J = 4.4, 8.7 Hz, 1 H), 6.90 (dd, J = 8.7, 10.2 Hz, 1 H), 5.23 (t, J = 7.3 Hz, 1 H), 4.48 (dd, J = 3.3, 14.5 Hz, 1 H), 4.33 (d, J = 15.8 Hz, 1 H), 4.24 (m, 1 H), 4.12 (d, J = 17.6 Hz, 1 H), 3.56 (m, 1 H), 3.19 (m, 2 H), 1.74 (s, 3 H), 1.48 (s, 3 H), 1.30 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.3, 157.9, 155.6, 136.2, 126.4, 121.4, 112.1, 110.4, 107.9, 55.4, 53.1, 47.7, 46.6, 25.9, 17.7, 16.9; IR (CCl_4) 3149, 3062, 2931, 1542, 1505, 1462, 1364, 1209, 1154, 1016 cm^{-1}; HRMS calcd 305.1358, found 305.1349.

***N*-(2,5-Dichloro-3-nitrobenzoyl)-L-alaninamide (4d).** To a stirred slurry of 3.42 g (14.5 mmol) of 2,5-dichloro-3-nitrobenzoic acid (Lancaster Synthesis) in 10 mL of toluene containing 0.1 mL of DMF was added 1.33 mL (15.2 mmol) of oxaloyl chloride. The mixture was heated to 50 °C for 30 min then cooled and added to a solution of 5.0 g (36.2 mmol) of K_2CO_3 and 2.17 g (17.4 mmol) of L-alaninamide hydrochloride in 15 mL of H_2O and 5 mL of toluene. After stirring for 11 h at this temperature, H_2O (20 mL) was added. The precipitate was isolated by filtration, affording 4.39 g (99%) of a white powder mp 218–219 °C: ^1H NMR ($CDCl_3$/5% DMSO) δ 8.78 (d, J = 7.5 Hz, 1 H), 8.06 (d, J = 2.4 Hz, 1 H), 7.84 (d, J = 2.4 Hz, 1 H), 7.37 (bs, 1 H), 6.92 (bs, 1 H), 4.51 (t, J = 7.2 Hz, 1 H), 1.39 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 173.4, 163.1, 149.0, 140.0, 132.4, 131.9, 125.1, 120.7, 48.8, 18.0; IR (CCl_4) 3361, 3285, 1644, 1537 cm^{-1}. Anal. Calcd for $C_{10}H_9Cl_2N_3O_4$: C, 39.22; H, 2.94; N, 13.72; Cl, 23.20. Found: C, 39.36; H, 3.02; N, 13.72; Cl, 23.36.

(+)-(*S*)-*N*-(2,5-Dichloro-3-nitrobenzyl)-1,2-propanediamine (2d). To a stirred slurry of 3.06 g (10.0 mmol) of diamide **4d** in 100 mL of dry THF under argon was added 10.0 mL (100 mmol) of BMS (10.0 M in BH_3), and the reaction mixture was stirred at reflux for 10.5 h. After being cooled to 0 °C it was carefully quenched with 5% HCl (pH 1) and then extracted with ether (2 × 30 mL). The aqueous phase was made basic by the addition of solid NaOH (pH 8) and then extracted with ether (2 × 50 mL), CH_2Cl_2 (2 × 20 mL), and EtOAc (2 × 50 mL). The combined organic phases were dried ($NaSO_4$) and concentrated to leave 1.8 g (66%) of a yellow oil which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 2.0 Hz, 1 H), 7.67 (d, J = 2.2 Hz, 1 H), 4.00 (m, 2 H), 2.66 (m, 3 H), 1.10 (d, J = 6.1 Hz, 3 H).

(+)-(*S*)-7-Chloro-3-methyl-4-(3-methyl-2-butenyl)-9-nitro-2,3,4,5-tetrahydro-1*H*-[1,4]benzodiazepine (5d). To a solution of 1.8 g (6.5 mmol) of **2d** in 50 mL of DMF was added 2.3 g (16.7 mmol) of K_2CO_3. The mixture was stirred at 125 °C for 7 h. Then additional K_2CO_3 (2.0 g, 14.5 mmol) was added, followed by 1.20 g (8.0 mmol) of prenyl bromide. The resulting reaction mixture was stirred at reflux for 12 h. Water (50 mL) was added, and the brown solution was extracted with ether (5 × 50 mL). The combined organic extracts were washed free of DMF with H_2O (4 × 50 mL) then washed with brine (2 × 50 mL). Column chromatography (3:1 EtOAc/Hex) left 820 mg (41%) of an orange oil: ^1H NMR ($CDCl_3$) δ 8.24 (bs, 1 H), 8.01 (d, J = 2.5 Hz, 1 H), 7.05 (d, J = 2.5 Hz, 1 H), 5.22 (m, 1 H), 4.36 (d, J = 15.8 Hz, 1 H), 3.69 (d, J = 15.8 Hz, 1 H), 3.62 (m, 2 H), 3.44 (m, 1 H), 3.14 (m, 3 H), 1.76 (s, 3 H), 1.56 (s, 3 H), 1.14 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.9, 137.1, 135.4, 133.1, 130.6, 124.5, 121.7, 120.2, 58.3, 52.5, 50.7, 50.1, 25.9, 18.8, 18.1; IR (neat) 3368, 1611, 1503 cm^{-1}; HRMS calcd 309.1240, found 309.1230.

(+)-(*S*)-4,5,6,7-Tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2-(1*H*)-thione (1d). To a solution of 800 mg (0.26 mmol) of **5d** in 14 mL of CH_3OH was added 5.0 mg of 10% Pd on carbon. The reaction mixture was stirred under an atmosphere of H_2 for 3h. The catalyst was removed by filtration (Celite), and the solvent was removed in vacuo. The residue was dissolved in absolute EtOH containing 23 mg (0.30 mmol) of CS_2, and the reaction mixture was stirred at room temperature for 7 days. Column chromatography (1:1 EtOAc/Hex) and recrystallization (acetone) left 50 mg (60%) of a white solid, mp 179–181 °C (lit.[2] mp 180.3 °C); ^1H NMR ($CDCl_3$) δ 10.36 (bs, 1 H), 7.09 (d, J = 1.7 Hz, 1 H), 6.88 (d, J = 1.7 Hz, 1 H), 5.20 (m, 1 H), 4.52 (dd, J = 3.3, 14.6 Hz, 1 H), 4.25 (d, J = 17.6 Hz, 1 H), 4.16 (m, 1 H), 4.04 (d, J = 16.6 Hz, 1 H), 3.54 (m, 1 H), 3.16 (m, 2 H), 1.74 (s, 3 H), 1.46 (s, 3 H), 1.30 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.1 135.9, 130.9, 130.7, 128.9, 125.7, 122.1, 121.2, 107.9, 55.7, 53.3, 52.4, 46.6, 25.8, 17.8, 17.5; IR ($CDCl_3$) 3144, 3099, 2972, 2922, 1616, 1558, 1507, 1471, 1458, 1377, 1328, 1240, 1201, 1152 cm^{-1}; HRMS calcd 321.1063, found 321.1051.

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Registry No. 1b, 137332-54-8; **1c**, 137332-55-9; **1d**, 126347-69-1; **2b**, 137332-56-0; **2d**, 137332-57-1; **3b**, 137332-58-2; **3c**, 137332-59-3; **4b**, 137332-60-6; **4c**, 137332-61-7; **4d**, 137332-62-8; **5b**, 137332-63-9;

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5c, 137332-64-0; 5d, 137332-65-1; L-alaninamide hydrochloride, 33208-99-0; 2,6-dichloro-3-nitrobenzoic acid, 55775-97-8; 2,6-difluoro-3-nitrobenzoic acid, 83141-10-0; 2,5-dichloro-3-nitrobenzoic acid, 88-86-8; prenyl bromide, 870-63-3.

Supplementary Material Available: ^1H spectra for compounds 1b, 3b–5b, 1c, 3c–5c, 1d, and 5d; ^{13}C spectra for 3b–5b, 1c, 4c, 5c, 1d, and 5d (20 pages). Ordering information is given on any current masthead page.

Vinylcyclopentane Synthesis via Phenylthio Radical Catalyzed Alkenylation of Vinylcyclopropanes: Preparative and Mechanistic Studies

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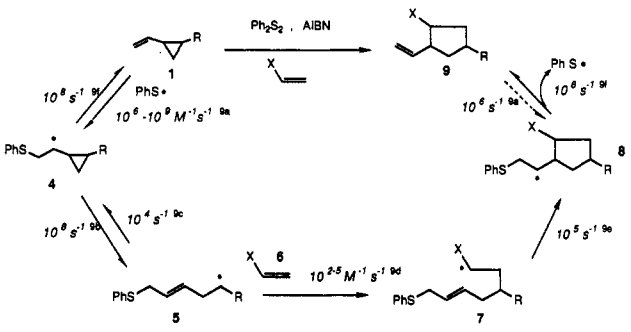
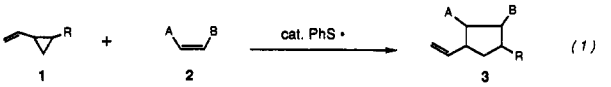
1-Vinylcyclopropanes bearing ether or ester substituents at C(2) of the cyclopropyl ring or alkyl groups at other ring (or alkenyl) positions were subjected to PhS• catalyzed olefination with ester- or oxygen-functionalized alkenes. In some instances, variations in reaction conditions (low temperature, Lewis acids) led to levels of stereoselectivity unprecedented in such simple, unbiased substrates. In general, the stereochemical outcome of these transformations can be rationalized by citing existing models for selectivity upon cyclization of substituted 5-hexenyl radicals. However, in a few specific instances, results obtained with alkylated vinylcyclopropyl substrates are not consistent with some of the predictions of these models.

The development of methodology for the regio- and stereocontrolled synthesis of highly functionalized five-membered carbocycles has enabled efficient construction of a host of cyclopentanoid target molecules. Two distinct approaches, acyclic closure of five carbon chains and [3 + 2] addition, have emerged as the most versatile strategies in this regard. The roster of addition reactions which utilize a [3 + 2] bond construction strategy includes the combination of alkenes or alkynes with three-atom synthons such as trimethylene methane equivalents,[1] substituted allyl or allenyl fragments,[2] and functionalized cyclopropanes.[3] Each approach has characteristic strengths and weakness, typically involving issues of functional group compatibility, stereoselectivity, and/or regioselectivity.

We[4] and others[5] have recognized that [3 + 2] strategies for cyclopentanoid synthesis which are based on free radical transformations have the decided advantages of functional group tolerance and regiochemical predictability relative to many dipolar approaches. However, often modest stereoselectivity accompanies these radical reactions. Our approach to free radical based cyclopentanoid synthesis relies on the phenylthio radical catalyzed combination of substituted vinylcyclopropanes 1 with functionalized alkenes 2 to afford the vinylcyclopentane derivatives 3 eq 1. Although this reaction proceeds through

Scheme I





(1)

a complex multistep mechanism, product stereochemistry is set in a single step—the cyclization of a substituted 5-hexenyl radical (vide infra, Scheme I, 7 → 8). Substituent/stereoselectivity relationships have been documented for a variety of 5-hexenyl radical cyclizations, and general guidelines with predictive value have emerged.[6] Nevertheless, some subtle issues remain unresolved, including (1) ranking the relative importance of specific steric interactions in cyclization transition states and (2) identifying which of two possible transition states precedes a

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