NOVEL BICYCLIC PHOSPHORDIAMIDATE HIV PROTEASE INHIBITORS

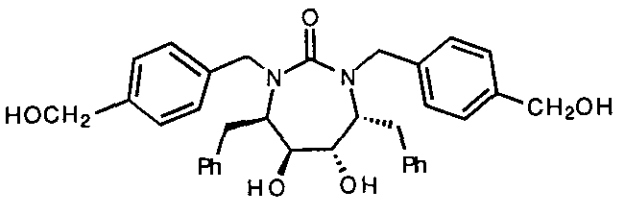
Joanne M. Smallheer* and Steven P. Seitz

The DuPont Merck Pharmaceutical Co., Inc.
Wilmington, DE 19808, U.S.A.

Abstract- Several substituted (3-endo,4-endo,6-exo)-8-oxa-7-diaza-1-phosphabicyclo[3.2.1]octanols were prepared and evaluated as inhibitors of HIV protease. This new bicyclic ring system is the product of an unexpected intramolecular cyclization observed upon base treatment of a 4,5,6,7-hexahydro-5,6-bishydroxy-2-phenoxy-1*H*-1,3,2-diazaphosphepine -2-oxide. An example of this new class of compounds had subnanomolar activity vs. HIV protease and antiviral activity in a cell-based assay.

Clinical data suggest that an inhibitor of HIV protease, either alone or in combination with retroviral transcriptase inhibitors, will have therapeutic value in the treatment of AIDS in humans.[1] Many potent and selective inhibitors of HIV protease have now been described, and the mechanism by which these compounds inhibit the virus is well understood.[2] Unfortunately, the clinical experience to date also indicates that viral resistance will be an ongoing concern so that new classes of inhibitors are still being sought.

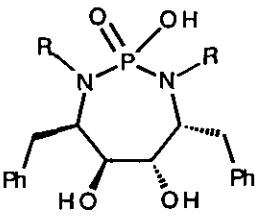
A series of cyclic ureas were designed to displace a structural water that bridged peptidic inhibitors and the flap region of the protease.[3] The use of this scaffold permitted the preparation of potent inhibitors that occupied only four side chain binding pockets (S1, S1', S2, S2'). An early example from this series that progressed to clinical trials is DMP323.



DMP 323

The X-ray crystal analyses of cyclic urea inhibitors bound to HIV protease confirmed that the urea carbonyl in these molecules displaces the structural water molecule from the active site.

These structures suggest that the carbonyl oxygen interacts with the backbone amide NH of the Ile 50/50' residues in the "flap" region of the enzyme; however, at 3.18 and 3.35 Å respectively, these hydrogen bond distances are somewhat longer than optimal. Introduction of surrogates for the urea carbonyl which would have potential for stronger interaction with the enzyme provide attractive targets for second generation compounds. We therefore undertook the introduction of a phosphordiamidate group into an analogous seven-membered ring system (**1**).



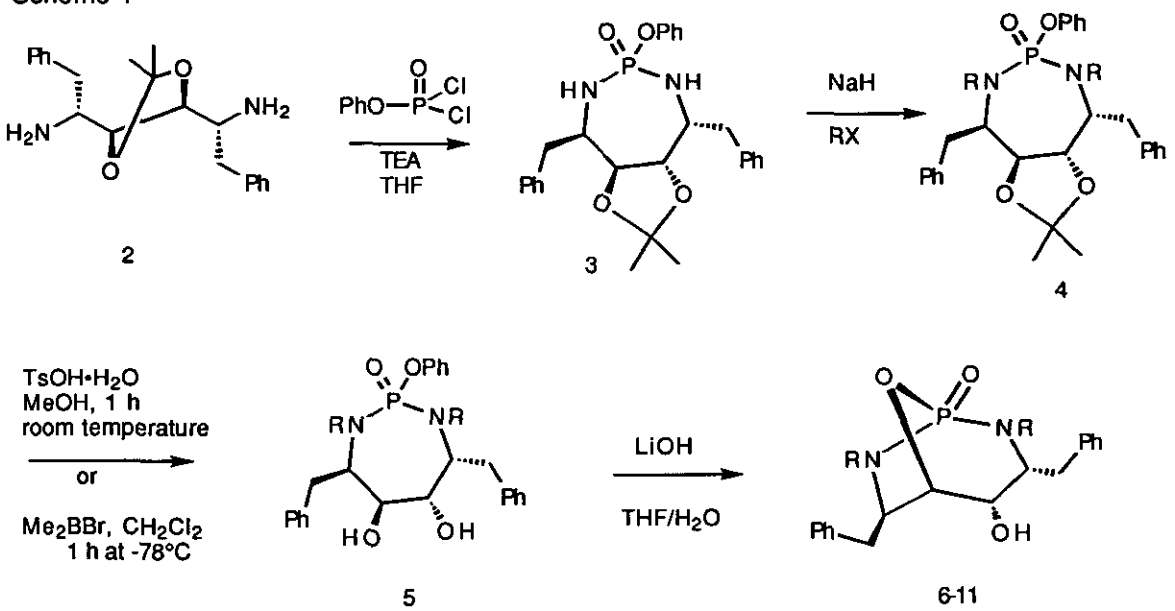
1

The replacement of carbon by a pentavalent phosphorus would result in a slightly larger seven-membered ring due to the longer phosphorus-nitrogen bond lengths. This should effectively increase the distance between the diol at the bottom of the ring and the oxygens of phosphorous, and in combination with the tetrahedral geometry around the phosphorus atom will place the oxygens on phosphorus closer to the enzyme flap than can be achieved in a seven-membered cyclic urea, thus shortening the hydrogen-bonding distance to the Ile residues.

The synthesis of the target compounds proceeds as outlined in Scheme 1. Treatment of the acetonide diamine (**2**) with commercially available phenyl dichlorophosphate under conditions described for the cyclization of ethylenediamine analogs to five-membered ring phosphordiamidates[4] yields the desired monocyclic phosphordiamidate ester (**3**). This unsubstituted ring system was not very robust, however, alkylation of crude **3** with a variety of alkyl bromides in the presence of excess sodium hydride readily provided the stable bisalkylated products (**4**). The acetonide protecting group could subsequently be removed from **4** under mildly acidic conditions (p-toluenesulfonic acid in methanol or anhydrous dimethylboron bromide) to provide the diol (**5**).

Attempts to cleave the phenyl ester by acid hydrolysis were unsuccessful and led to decomposition of the cyclic system. Removal of the phenyl esters by hydrogenolysis was also ineffective.[5] Upon hydrolysis of **5** with base, a white solid, which had a molecular weight corresponding to loss of phenol from the desired product, was obtained. In addition to the absence of the phenyl protons, the ^{1}H nmr of this product showed only one of the diol protons. A downfield shift was observed in the ^{31}P nmr spectrum of **5** (R = 2-naphthylmethyl) from δ 12.50 to δ 22.19 ppm.

Scheme 1



Based on the above data, structure (**6**) was assigned to this product. This bicyclic structure arises from an intramolecular cyclization, wherein one hydroxyl of the diol attacks at phosphorus, resulting in loss of phenol and formation of the novel [3.2.1] bicyclic ring system, containing phosphorus as a bridgehead atom. The observed intramolecular cyclization is very facile and occurs readily under relatively mild alkaline conditions.

Compound (**6**) was crystallized from methylene chloride/hexane, and a single crystal X-ray analysis was carried out. The resulting X-ray crystal structure shown in Figure 1 confirmed the above structural assignment for this new ring system. The phosphorus-oxygen double bond length, as measured from the X-ray structure of **6**, is 1.49 angstroms as compared with 1.22 angstroms for the carbon-oxygen distance in the urea carbonyl of DMP323.

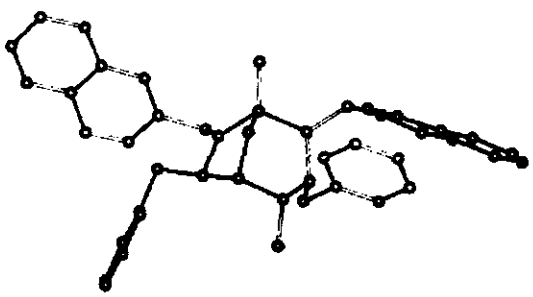


Figure 1

***X-ray Crystal Structure of Compound* (6)**

A series of bicyclic analogs, compounds (**6-11**), were prepared and tested for inhibitory activity vs. HIV protease[6] and in vitro antiviral potency.[7] Although, most of the bicyclic phosphordiamidates were less active than their corresponding cyclic urea analogs, compound (**10**), which bears the same P2/P2' groups as DMP323 (R=4-hydroxymethylbenzyl) showed a comparable activity profile. (Table 1)

Table 1

Biological Activity of Bicyclic Compounds

Compound	R	K_i(nM)	IC_{90}(nM)
6	2-naphthylmethyl	660	>80,000
7	cyclopropylmethyl	230	~110,500
8	n-butyl	350	>109,500
9	benzyl	44	>95,300
10	4-hydroxymethylbenzyl	0.6	154
11	4-hydroxybenzyl	4.9	1,258
DMP323		0.34	136[a]

[a]IC_{90} for DMP323 represents an n of 181, standard deviation ±55.

A side-by-side comparison of compound (**10**), modeled from the X-ray structure of **6**, with the bound conformation of DMP323, shows that **10** can assume a similar but not exact spatial orientation (Figure 2). A distinct difference can be seen in the orientation of the P1' groups and to a lesser extent the P2' groups on the two molecules. Hence additional modification of this prototype molecule (i.e. **10**) could conceivably lead to more active inhibitors.

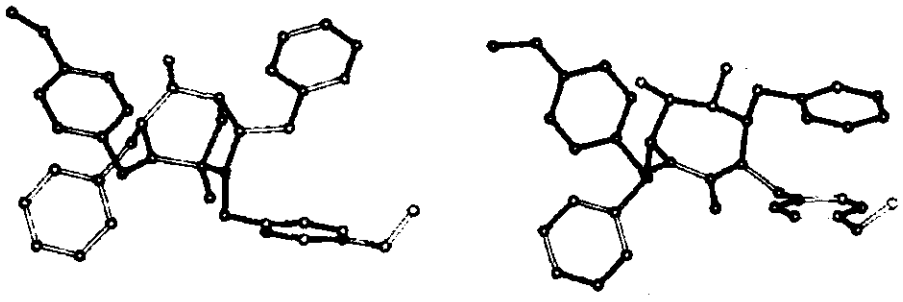
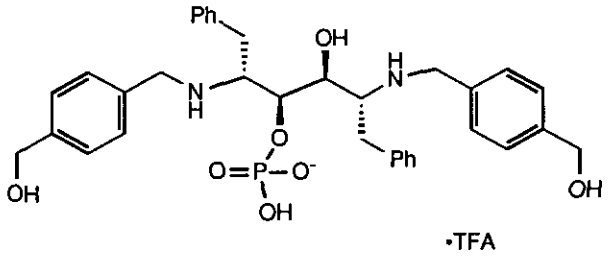


Figure 2

Side-by-Side Comparison of Compound (10) with DMP323 (shown on the right)

Compound (**10**) is completely stable in base but can be hydrolyzed in aqueous trifluoroacetic acid to give a highly insoluble white solid product. The hydrolysis product was identified as acyclic diaminophosphate ester (**12**), which arises from selective cleavage of the phosphorus-nitrogen bonds in **10**.



(12)

Compound (**12**) was tested for inhibitory activity vs. HIV protease and was found to have a K_i of 730 nM demonstrating that this hydrolysis product is not responsible for the activity observed with compound (**10**).

The bicyclic phosphordiamidate system present in **10** represents a previously unreported heterocycle as well as a new structural scaffold on which to build potent inhibitors of HIV protease.

ACKNOWLEDGMENTS

We would like to thank Beverly Cordova, Marlene Rayner and Ronald Klabe for the biological assays, Joseph Calabrese of *DuPont CR&D for the X-ray structure of* **10**, *and Peter Crawford* for nmr spectra.

EXPERIMENTAL

Nmr spectra were obtained on Varian VXR or Unity 300 or 400 MHz instruments; chemical shifts are expressed in ppm (δ) downfield from TMS as an internal standard. Mass spectra were measured by NH_3 chemical ionization method using either a Finnegan MAT8230 or HP5988A spectrometer. Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Elemental analyses were determined by Quantitative Technologies, Inc., Bound Brook, NJ. Flash chromatography was carried out on EM Science silica gel (230-400 mesh) using the indicated solvents. All solvents and reagents were used without purification unless otherwise noted.

(2R,3S,4S,5R)-2,5-Diamino-1,6-diphenyl-3,4-(1-methylethylidene)bis(oxy)hexane (2).

A *suspension of* (2*R*,3*S*,4*S*,5*R*)-2,5-*bis*-(*N*-*Cbz-amino*)-3,4-dihydroxy-1,6-diphenylhexane[8] (10 g, 0.018 mol) in methylene chloride (200 ml) was treated with 2,2-dimethyoxypropane (10.8

ml, 0.088 mol) and camphor sulfonic acid (0.41 g, 1.8 mmol), and the whole was stirred at room temperature for 48 h. The resulting solution was washed with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated. Crystallization of the residue from ether/hexane gave 6.6 g (60%) of white needles, mp 76-77°C; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 1.51 (6H, s), 2.81 (4H, m), 3.71 (2H, m), 3.92 (1H, m), 4.08 (1H, dd, J = 3.3 and 7.5 Hz), 4.73 (1H, m), 4.85 (1H, m), 4.90 (1H, dd, J = 4.8 and 18 Hz), 7.03-7.40 (10H, m). The resulting crystals were dissolved in 100 ml of a 1:1 mixture of tetrahydrofuran/ethanol and 10% Pd/C (0.7 g) added. The mixture was stirred vigorously under 1 atm hydrogen gas for 18 h. Catalyst was removed by filtration and was washed with tetrahydrofuran. Filtrate was evaporated to give 3.6 g (100%) of diamine **(2)** as a colorless oil, which was used without further purification in subsequent reactions, ir (film) 3382, 1246, 1216, 1054 cm^{-1}; $[\alpha]_D$ -35.94° (MeOH, c 0.13 g/dl); ^{1}H nmr (300 MHz, $CDCl_3$) δ: 1.18 (4H, br s), 1.46 (6H, s),2.58 (2H, dd, J = 3.6 and 16.5 Hz),2.83 (2H, dd, J = 2.4 and 16.5 Hz), 2.98 (2H, m), 4.03 (2H, app. s), 7.13-7.35 (10H, m); ms m/z 341 $(M+H)^+$. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.30; N, 8.24. Found: C, 73.85; H, 8.10; N, 8.21.

(4α,5α,6β,7β)-Hexahydro-5,6-(1-methylethylidene)bisoxy-2-phenoxy-4,7-bisbenzyl-1H-1,3,2-diazaphosphepine 2-oxide (3). A well-stirred solution of **2** (2 g, 5.87 mmol) and triethylamine (1.8 ml, 12.9 mmol) in 15 ml of anhydrous tetrahydrofuran, was cooled to 0-10° C under nitrogen and a solution of phenyl dichlorophosphate (0.9 ml, 5.87 mmol) in 4 ml of tetrahydrofuran was added dropwise. The resulting mixture was stirred for 16 h at room temperature. Triethylamine hydrochloride was removed by filtration and washed with tetrahydrofuran. The combined filtrate and washings were concentrated in vacuo, and the residue was taken up in methylene chloride/ether (1/1 v/v), and washed successively with water (2X) and saturated sodium chloride solution (1X); then dried over anhydrous magnesium sulfate, filtered and evaporated. Quick filtration through silica gel [hexane/ethyl acetate (1/1 v/v)] gave 1.8 g (64%) of **3** as a sticky white foam which was used immediately without further purification to avoid decomposition,^{1}H nmr (300 MHz, $CDCl_3$) δ: 1.53 (6H, s), 2.66 (1H, dd, J = 4.5 and 6.0 Hz), 2.98 (1H, m), 3.00 (1H, m), 3.23 (2H, m), 3.32 (1H, t, J = 2.4 Hz), 3.60-3.89 (2H, m), 4.53 (2H, m), 7.04 (2H, d, J = 3.0 Hz), 7.12 (1H, t, J = 3.0 Hz), 7.17-7.34 (13H, m); ms m/z 479 $(M+H)^+$.

1,3-Bis(2-naphthylmethyl)-(4α,5α,6β,7β)-hexahydro-5,6-(1-methylethylidene)bis(oxy)-2-phenoxy-4,7-bisbenzyl-1H-1,3,2-diazaphosphepine-2-oxide (4, R = 2-naphthyl-methyl). A solution of **3** (0.1 g, 0.21 mmol) in 3 ml of anhydrous *N,N*-dimethylformamide, was treated under nitrogen at room temperature with NaH (35 mg, 60% by weight, dispersed in oil, 0.88 mmol). The mixture was stirred for 10-15 min followed by addition of 2-bromomethyl-naphthalene (0.37 g, 1.6 mmol). The mixture was stirred for 72 h at room temperature, then

quenched by addition of water. The product was extracted with ethyl acetate (3X). The combined extracts were washed successively with water (2X) and saturated sodium chloride solution (1X), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified using rotary preparative tlc [hexane/ethyl acetate (4/1 v/v)] to give 80 mg (50%) of **4** as a white foam, ir (KBr) 1492, 1236, 1086 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.15 (3H, s) ,1.24 (3H, s), 3.06 (2H, d, J = 3.0 Hz), 3.31 (2H, m), 3.60-4.13 (5H, m), 4.50 (1H, dd, J = 3.9 and 6.0 Hz), 4.64 (1H, dd, J = 3.6 and 6.0 Hz), 4.90 (1H, dd, J = 3.0 and 6.0 Hz), 6.88-7.85 (29H, aromatics); ms m/z 759 $(M+H)^+$. Anal. Calcd for $C_{49}H_{48}N_2O_4P$: C, 77.55; H, 6.24; N, 3.69; P, 4.08. Found: C, 77.41; H, 6.34; N, 3.61; P, 4.11.

5,6-Bishydroxy-1,3-bis(2-naphthylmethyl)-(4α,5α,6β,7β)-hexahydro-2-phenoxy-4,7-bisbenzyl-1H-1,3,2-diazaphosphepine 2-oxide (5, R = 2-naphthylmethyl). To a solution of **4** (80 mg, 0.105 mmol) in 2 ml of dry methylene chloride, maintained under an argon atmosphere at -78°C, was added dropwise over 10-15 min, a solution of dimethylboron bromide in methylene chloride (0.32 ml of a 2.0 M solution, 0.63 mmol). Stirring was continued for 1 h at -78°C. The mixture was then transferred *via* syringe to a rapidly stirring mixture of 1 ml tetrahydrofuran and 0.5 ml aqueous saturated sodium hydrogen carbonate solution. After stirring for 5 min, the mixture was extracted with ethyl acetate (3X). The combined extracts were washed successively with 10% aqueous potassium hydrogen sulfate solution and saturated sodium chloride solution then dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo. The residue was purified by preparative TLC [silica gel, hexane/ethyl acetate (4/1 v/v)] to give 50 mg (66%) of **5** as an amorphous white solid, ^1H nmr (400 MHz, $CDCl_3$) δ: 1.90 (1H, d, J= 2.0 Hz), 2.18 (1H, d, J = 2.0 Hz), 2.95 (1H, m), 3.17 (1H, dd, J = 2.0 and 4.0 Hz), 3.28 (2H, m), 3.61 (1H, m), 3.78 (1H, m), 4.60 (1H, m), 4.77 (1H, m), 7.03-7.85 (29 H, aromatics); ^{31}P nmr δ: 12.50; ms m/z 736 $(M+NH_4)^+$; High Resolution ms: Calcd for $C_{46}H_{44}N_2O_4P$: 719.303872. Found: 719.304816. Anal. Calcd for $C_{46}H_{43}N_2O_4P \cdot 0.5\ H_2O$: C, 75.91; H, 6.049 N, 3.85. Found: C, 75.96 H, 6.03 N, 3.72.

(3-endo,4-endo,6-exo)-2,7-Bis(2-naphthylmethyl)-3,6-bisbenzyl-8-oxa-2,7-diaza-1-phosphabicyclo[3.2.1]octan-4-ol-1-oxide (6, R = 2-naphthylmethyl). To a solution of **5** (30 mg, 0.042 mmol) in 1.0 ml of tetrahydrofuran/water (3/1 v/v) was added 1 M aqueous lithium hydroxide (0.09 ml, 0.22 mmol). The mixture was heated for 2 h with stirring in a 65-70°C oil bath under a nitrogen atmosphere. After cooling to room temperature, the mixture was extracted with ether (3X). The combined ether extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated in vacuo. Purification of the residue using preparative tlc [hexane/ethyl acetate (65/35 v/v)] followed by crystallization from methylene chloride/hexane gave 15 mg (60%) of **6** as colorless needles, mp 131-132°C; ir (KBr) 3346, 1240, 1152 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 1.43 (1H, d, J = 2.0 Hz), 2.54 (1H, dd, J = 4.0 and 5.6 Hz), 2.72 (2H, m), 3.24 (2H, m), 3.54 (1H, m),

3.78 (2H, m), 4.15 (1H, dd, J = 2.4 and 8.0 Hz), 4.38 (1H, dd, J = 4.0 and 6.0 Hz), 4.74 (1H, dd, J = 3.3 and 6.0 Hz), 5.03 (1H, dd, J = 4.0 and 6.0 Hz), 7.00 (2H, d, J = 3.3 Hz), 7.10 (1H, t, J = 3.3 Hz), 7.18 (2H, t, J = 3.3 Hz), 7.30 (6H, m), 7,39 (1H, s), 7.46 (5H, m), 7.77 (3H, m), 7.88 (3H, m), 8.00 (1H, s); ^{31}P nmr δ: 22.19; ms m/z 642 $(M+NH_4)^+$. Anal. Calcd for $C_{40}H_{37}N_2O_3P$: C, 76.90; H, 5.97; N, 4.48; P, 4.97. Found: C, 76.90; H, 6.05; N, 4.45; P, 4.81.

Similarly prepared from **3** using indicated alkylating agent (yields are over three steps) were the following:

(3-endo,4-endo,6-exo)-2,7-Bis(cyclopropylmethyl)-3,6-bisbenzyl-8-oxa-2,7-diaza-1-phosphabicyclo[3.2.1]octan-4-ol-1-oxide (7, R = cyclopropylmethyl). (Bromomethylcyclopropane, 42.5%), white solid, mp 167-169°C; ir (KBr) 3314, 1246 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.00 (1H, m), 0.10 (1H, m), 0.34 (4H, m), 0.65 (2H, d, J = 3.3 Hz), 0.76 (1H, m), 1.19 (1H, m), 2.07 (1H, m), 2.48 (1H, br s), 2.66 (1H, dd, J = 3.3 and 5.4 Hz), 2.83 (1H, dd, J = 4.5 and 6.0 Hz), 3.01 (2H, m), 3.22 (2H, m), 3.41 (1H, dd, J = 1.5 and 6.0 Hz), 3.72 (2H, m), 4.26 (1H, dd, J = 1.5 and 6.0 Hz), 4.29 (1H, m), 7.16-7.37 (10H, m); ms m/z 453 $(M+H)^+$. Anal. Calcd for $C_{26}H_{33}N_2O_3P$•0.1 H_2O: C, 68.73; H, 7.37; N, 6.17; P, 6.82. Found: C, 68.68; H, 7.15; N, 6.08; P, 6.71.

(3-endo,4-endo,6-exo)-2,7-Bisbutyl-3,6-bisbenzyl-8-oxa-2,7-diaza-1-phosphabicyclo[3.2.1]octan-4-ol-1-oxide (8, R = n-butyl). (n-Butylbromide, 30%) prisms, mp 219-220°C (methylene chloride/hexane); ir (KBr) 3304, 1244 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.79 (3H, t, J = 3.0 Hz), 0.98 (3H, t, J = 3.0 Hz), 1.05-1.48 (6H, m), 1.64 (1H, d, J = 2.5 Hz), 1.83 (2H, m), 2.16 (1H, m), 2.65 (1H, dd, J = 3.6 and 6.0 Hz), 2.82 (1H, dd, J = 4.5 and 6.0 Hz), 3.00-3.35 (5H, m), 3.50 (1H, m), 3.64 (1H, m), 4.19 (2H, m), 7.26 (10H, m); ms m/z 457 $(M+H)^+$. Anal. Calcd for $C_{26}H_{37}N_2O_3P$•0.25 H_2O: C, 67.73; H, 8.20; N, 6.08. Found: C, 67.72; H, 8.00; N, 6.07.

(3-endo,4-endo,6-exo)-2,3,6,7-Tetrakis(benzyl)-8-oxa-2,7-diaza-1-phosphabicyclo-[3.2.1]octan-4-ol-1-oxide (9, R = benzyl). (Benzylbromide, 23%) white solid, mp 82-83°C, ir (KBr) 3338, 1250 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 1.44 (1H, d, J = 2.5 Hz), 2.49-3.78 (3H, m), 3.04 (1H, m), 3.19 (1H, dd, J = 2.5 and 6.0 Hz), 3.46 (1H, m), 3.78 (2H, m), 4.17 (2H, m), 4.57 (1H, dd, J = 3.0 and 6.0 Hz), 4.84 (1H, dd, J = 3.6 and 6.0 Hz), 7.05 (2H, d, J = 3.0 Hz), 7.24 (6H, m), 7.40 (2H, t, J = 3.0 Hz), 7.64 (2H, d, J = 3.0 Hz); ms m/z 525 $(M+H)^+$. Anal. Calcd for $C_{32}H_{33}N_2O_3P$•0.75 H_2O: C, 71.43; H, 6.46; N, 5.21. Found: C, 71.21; H, 6.17; N, 5.04.

(3-endo,4-endo,6-exo)-2,7-Bis(4-(hydroxymethyl)benzyl)-3,6-bisbenzyl-8-oxa-2,7-diaza-1-phosphabicyclo[3.2.1]octan-4-ol-1-oxide (10, R = 4-hydroxymethylbenzyl). A solution of **3**

(1.5 g, 0.003 mol) in 25 ml DMF was stirred at room temperature under nitrogen and treated with sodium hydride(0.5 g, 0.012 mol, 60% by weight, dispersed in oil). The resulting mixture was stirred for 10-15 min followed by addition of 4-(tetrahydropyranyloxymethyl)benzyl chloride (6.0 g, 0.024 mol) and a catalytic amount of tetrabutylammonium iodide. The whole was stirred at room temperature for 36 h. The reaction mixture was quenched by addition of water and extracted with ethyl acetate (3X). Combined extracts were worked up as described above and residue chromatographed on silica gel [hexane/ethyl acetate (4/1 v/v)] to provide 1.89 g (71%) of the bisalkylated intermediate . This intermediate (1.89 g, 0.0021 mol) was dissolved in 25 ml of methanol and p-toluenesulfonic acid monohydrate (0.1 g, 0.5 mmol) was added. The solution was stirred for 1 h at room temperature. Methanol was evaporated on a rotary evaporator and the residue was taken up in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Chromatography on silica gel [methylene chloride/ethyl acetate/ethanol 10:10:0.5] gave 0.63 g (44%) of deprotected tetraol. The tetraol (0.63 g, 0.93 mmol) thus obtained was dissolved in 15 ml of tetrahydrofuran and 5 ml of water and 1.95 ml (1.95 mmol) of 1M lithium hydroxide solution were added, and the whole was stirred for 1 h at room temperature. The reaction was diluted with water and extracted with ether (3X). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated. Chromatography on silica gel gave 0.42 g (77%) of **10,** mp 107-110°C; ir (KBr) 3346, 1252 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6) δ: 2.37 (1H, dd, J = 4.0 and 6.0 Hz), 2.59 (2H, m), 2.80 (1H, t, J = 6.0 Hz), 3.21 (2H, m), 3.58 (1H, m), 3.76 (1H, m), 4.04 (1H, dd, J = 2.0 and 8.0 Hz), 4.29 (1H, dd, J = 3.2 and 6.0 Hz), 4.47 (5H, m), 4.61 (1H, dd, J = 4.0 and 6.0 Hz), 5.11 (2H, m), 5.35 (1H, d, J = 3/2 Hz), 6.96 (2H, d, J = 4.0 Hz), 7.11-7.39 (14H, m), 7.62 (2H, d, J = 3.6 Hz); ms m/z 585 $(M+H)^+$. Anal. Calcd for $C_{34}H_{37}N_2O_5P$: C, 69.85; H, 6.39; N, 4.79; P, 5.31. Found: C, 69.59; H, 6.47; N, 4.57; P, 5.33.

(3-endo,4-endo,6-exo)-2,7-Bis(4-hydroxybenzyl)-3,6-bisbenzyl-8-oxa-2,7-diaza-1-phosphabicyclo[3.2.1]octan-4-ol-1-oxide (11), (R = 4-hydroxybenzyl). Obtained in a similar manner in 13.6% yield over four steps from **3**, mp 134-135°C; ir)KBr) 3352, 1614, 1514, 1232 cm^{-1}; ^1H nmr (300 MHz, acetone-d_6) δ: 2.44 (1H, dd, J = 4.0 and 6.0 Hz), 2.70 (1H, dd, J = 4.0 and 6.0 Hz), 2.80 (1H, m), 3.34 (1H, m), 3.47 (1H, m), 3.75 (1H, m), 3.87 (1H, m), 4.15 (1H, dd, J = 2.0 and 8.0 Hz), 4.30-4.48 (3H, m), 4.71 (1H, dd, J = 4.0 and 6.0 Hz), 6.74 (2H, d, J = 4.0 Hz), 6.88 (2H, d, J = 4.0 Hz), 6.95 (2H, d, J = 3.0 Hz), 7.15 (3H, m), 7.24 (3H, m), 7.38 (4H, d, J = 2.0 Hz), 7.59 (2H, d, J = 4.0 Hz), 8.29 (1H, s), 8.33 (1H, s); ms m/z 557 $(M+H)^+$. Anal. Calcd for $C_{32}H_{33}N_2O_5P \cdot 0.33\ H_2O$: C, 68.32; H, 6.03; N, 4.98; P, 5.51. Found: C, 68.37; H, 6.02; N, 4.86; P, 5.26.

Hydrolysis product (12) A solution of **10** (0.13 g, 0.222 mmol) in water/DMSO (10/1, 5.5 ml) was treated with trifluoroacetic acid (0.5 ml, 6.5 mmol). Tetrahydrofuran was added to

maintain a homogeneous solution and the mixture was stirred for 72 h at room temperature. Reaction was evaporated to dryness and treated with water to give a gummy precipitate. This was decanted and washed with water (3X). Residue was taken up in ethyl acetate and washed with water (2X) and brine (1X) then dried over anhydrous magnesium sulfate, filtered and evaporated to provide **12** as a white solid (0.09 g, 55%), mp 190-195°C; ^{1}H nmr (400 MHz, DMSO-d_6) δ: 2.82 (1H, dd, J = 4.0 and 6.0 Hz), 3.02 (1H, m), 3.09 (1H, dd, J = 2.0 and 6.0 Hz), 3.34 (2H, m), 3.59 (2H, m), 3.93 (2H, m), 4.13 (1H, d, J = 6.0 Hz), 4.24 (1H, d, J = 6.0 Hz), 4.28 (2H, m), 4.50 (4H, d, J = 6.0 Hz), 4.78 (1H, d, J = 6.0 Hz), 5.44 (1H, d, J = 6.0 Hz), 7.14 (2H, d, J = 3.6 Hz), 7.24-7.39 (16H, m), 7.49 (1H, d, J = 4.0 Hz); ^{31}P nmr (DMSO) δ: 4.803; ms m/z 621 $(M+H)^+$.

REFERENCES AND NOTES

1. Several recent publications have reported promising human clinical data for HIV protease inhibitors as effective therapeutic agents for HIV infection, i.e., *Chemical and Engineering News*, February 6, 1995, 7; F. Stewart, P. E. O. Williams, J. F. Delfraissy and D. Sereni, *Clinical Pharmacol. and Therapeutics*, 1994, **55**, 145; K. E. Squires, M. S. Saag, H. Teppler, R. Pomerantz, S. Waldman, T. Bjornsson, E. Woolf, K. Yeh, E. Emini, and P. Deutsch, *Clinical Res.*, 1994, **42**, 280A; Bassett and Schoenfeld Report on ACTG 229: Antiviral Trial of Combination Therapy presented at the Tenth Intl. Conf. on AIDS 8/94 in Yokohama, Japan; *Pharma Japan*, 1994, **1415**, 16; X. Wei, S. K. Ghosh, M. E. Taylor, V. A. Johnson, E. A. Emini, P. Deutsch, J. D. Lifson, S. Bonhoeffer, M. A. Nowak, B. H. Hahn, M. S. Saag and G. M. Shaw, *Nature*, 1995, **373**, 117; D. D. Ho, A. U. Neumann, A. S. Perelson, W. Chen, J. M. Leonard and M. Markowitz, *Nature*, 1995, **373**, 123; K. T. Chong, *Exp. Opin. Invest. Drugs*, 1996, **5**, 115.
2. P. Darke and J. Huff, *Adv. Pharmacol.*, 1994, **25**, 399.
3. P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, N. Y. Wong, C. H. Chang, P. C. Weber, D. A. Jackson, T. R. Sharpe and S. Erickson-Viitanen, *Science, 1994*, **263**, 380.
4. C. Patois and P. Savignac. *Heteroatom Chemistry, 1990*, **1**, 369.
5. S. J. Hays, T. C. Malone and G. Johnson, *J. Org. Chem.*, 1991, **56**, 4084.
6. S. Erickson-Viitanen, R. M. Klabe, P. G. Cawood, P. L. O'Neal and J. L. Meek, *Antimicro. Agents Chemo.*, 1994, **38**, 1628.
7. L. T. Bacheler, M. Paul, P. K. Jadhav, M. Otto, B. Stone and J. Miller, *Antiviral Chemistry and Chemotherapy*, 1994, **5**, 111.
8. Prepared by pinacol coupling of N-Cbz-D-phenylalanal by the method described by A. W. Konradi and S. F. Pederson, *J. Org. Chem., 1992*, **57**, 28.

Received, 20th May, 1996