Articles

Stereoselective Synthesis of HIV-1 Protease Inhibitor, DMP 323

Michael E. Pierce,* Gregory D. Harris, Qamrul Islam, Lilian A. Radesca, Louis Storace, Robert E. Waltermire, Ed Wat, Prabhakar K. Jadhav, and George C. Emmett

Chemical Proces R&D Department, Process Research Facility, The DuPont Merck Pharmaceutical Company, Deepwater, New Jersey 08023-0999, and Chemical & Physical Sciences Department, The DuPont Merck Pharmaceutical Company, Experimental Station, Wilmington, Delaware 19880-0500

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DMP 323, a potent HIV-1 protease inhibitor, has been synthesized by an efficient stereoselective process, amenable to large scale preparations. The core C_2 symmetric diol was synthesized by a stereoselective pinacol coupling of CBZ protected D-phenylalanine. Judicious selection of protecting groups allowed cyclic urea formation under mild conditions, enhanced the ease of bis-alkylation, and led to intermediates which were easily purified without chromatography. Additionally, a one-pot, high yield process was developed to prepare the alkylating agent, 4-[(triphenylmethoxy)methyl]-benzyl chloride from 1,4-benzenedimethanol.

Introduction

Inhibition of HIV-1 (human immunodeficiency virus type 1) protease, an essential enzyme for the maturation of the fully infectious virion, is an attractive therapeutic target. On the basis of X-ray crystal data which shows that HIV protease exists as a C_2-symmetric dimer, a number of C_2-symmetric peptidic and non-peptidic HIV protease inhibitors have been investigated. Optimization from molecular modeling, followed by *in vivo* binding affinity studies, led to development of the novel cyclic urea DMP 323, **1**.[1,2]

A major attribute of DMP 323 is the C_2 symmetry which greatly simplifies any chiral synthetic approach. Our immediate goal was to implement any route suitable for production of kilogram quantities of material for clinical use. Retrosynthetic analysis of DMP 323, based on a C_2-symmetric amino diol **2** (or a suitably protected equivalent) as the key intermediate is shown in Scheme 1. Review of the literature suggested four likely precursors to **2**. Although the mannitol approach had been demonstrated on a small scale, it suffered in that the natural D-isomer produces the wrong (*SRRS*) enantiomer. Another drawback was the formation of an elimination byproduct during the Mitsunobu reaction.[3] An approach based on 2,3-isopropylidene-D-threitol has recently been reported, but it suffers from the high cost of D-threitol.[4] Additionally, the extensive stereocontrolled refunctionalization required to transform a threitol derivative to **2** made this route appear unlikely for rapid introduction into pilot plant scale production. Natural L-tartartic acid was appealing due to the low cost of raw material; however, it too required what we percieved as difficult chemistry for rapid scale-up. We have since continued research on tartrate routes, which is reported elsewhere.[5,6]

The most appealing method for the initial large scale synthesis of **2** and ultimately DMP 323 was based on pinacol homocoupling of a protected D-phenylalaninal as described by Pedersen[7,8] and applied by the Abbott group to make the mirror image isomer of **2** from L-phenylalanine.[9,10] A major attribute to this method is that the dimerization gives simultaneous and reasonably good control over all four chiral centers. The ultimate starting material, D-phenylalanine, though moderately expensive, was readily available in bulk. Additionally, its preparation by the DuPHOS-mediated chiral reduction of readily available methyl α-acetamidocinnamate is a potential long term source.[11,12]

Synthesis of Dihydroxy Diazapinone 3

We quickly found, as depicted in Scheme 2, that the unprotected intermediate **2** was not suitable for conversion to the corresponding cyclic urea **3**. Attempts to convert **2** to **3** with either phosgene or 1,1′-carbonyldiimidazole (CDI) gave the bis-oxazolidinone **4**. This was not entirely surprising as the (*SRRS*) bis-N-BOC diol had previously been shown to give the bis-oxazolidinone upon treatment with sodium hydride.[9] Attempts to protect the diol as the acetonide **6** gave the bis-oxazole **5** as the major product. Although the bis-MEM ether **7** did readily react

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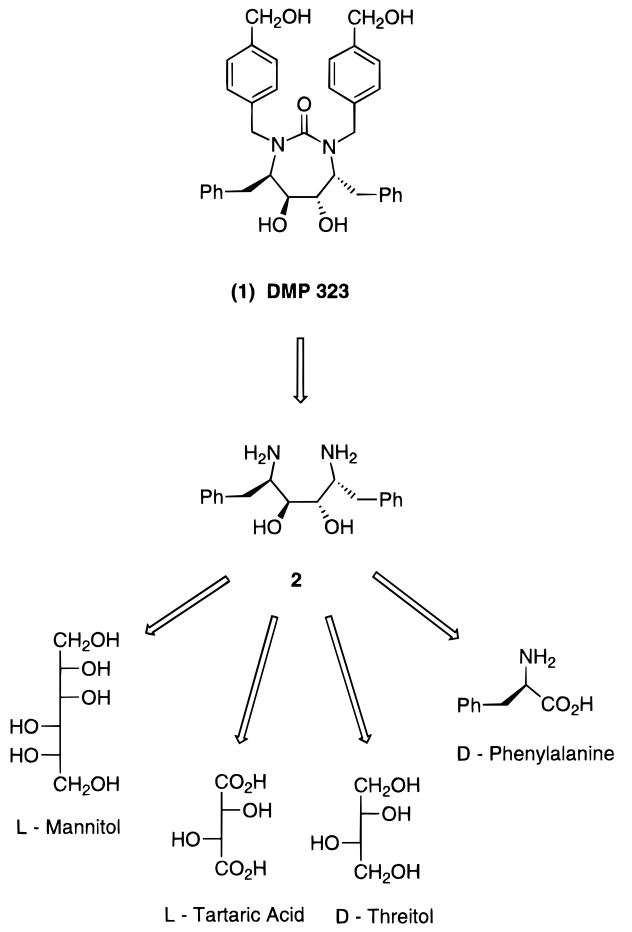
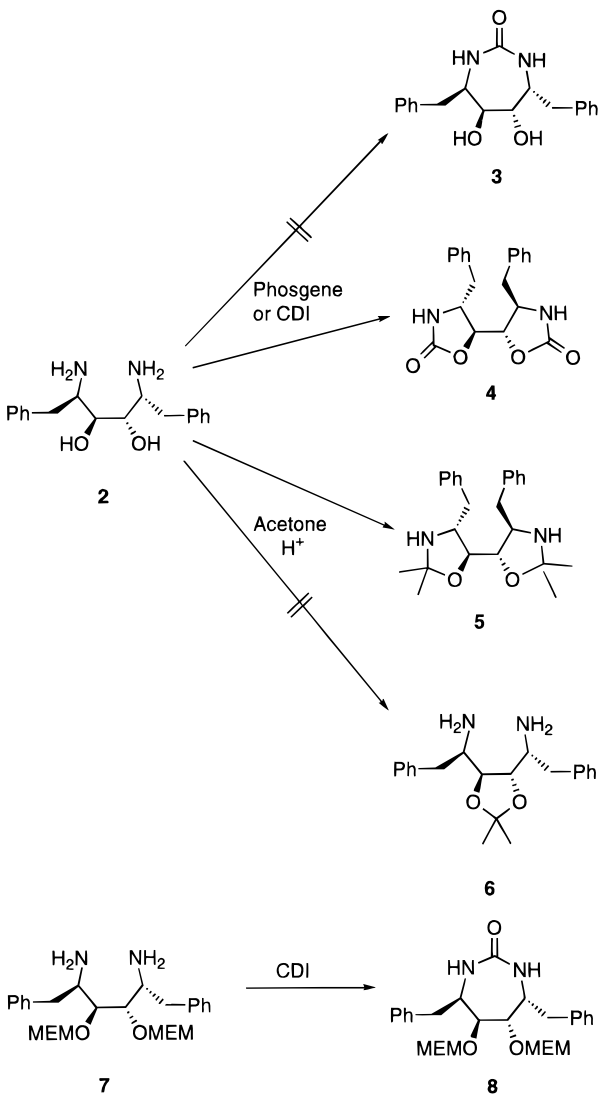
Scheme 1



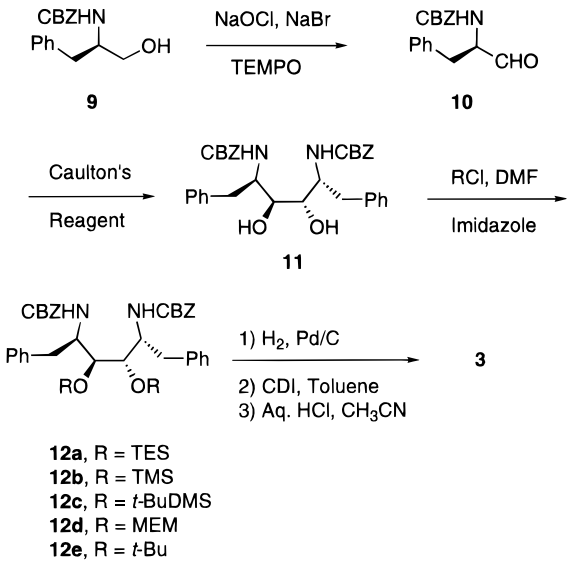
with CDI to give the cyclic urea **8**, this intermediate was not desirable for large scale synthesis because we were unable to find alkylation conditions to give complete conversion to the bis alkylated urea, and the precursors to the final product were not crystalline. Only a tedious chromatography gave pure DMP 323. Additionally, the use of MEM chloride was not desireable since it contains chloromethyl methyl ether, an OSHA listed carcinogen.

We ultimately designed the route shown in Scheme 3, which takes advantage of exchanging the diol protecting groups. Our preparation of CBZ-D-phenylalaninal **10** from the alcohol **9**[13] was based on a modification of the literature synthesis, employing 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) catalyzed oxidation to the L-isomer.[9,14] The preferred conditions from the published procedure failed dramatically on large scale with yields as low as 30%. To a large extent this was due to the requirement of extremely good mixing to avoid overoxidation. We had problems with emulsions, giving long separation times where localized bromine/low pH (4−5) led to polymerization and other degradation products. Also, the removal of ethyl acetate and toluene by vacuum distillation was very slow and difficult at 20 °C, the pot temperature chosen to minimize product degradation. We found these problems to be eliminated by using a high concentration of bleach (12.5%) and CH_2Cl_2 as solvent. At the completion of the reaction we quenched the excess oxidant with thiosulfate. Under these conditions the reaction did not need high agitation, no emulsions formed, and the reaction mixture was easily concentrated at low temperatures, producing aldehyde **10** in reproducibly high yield.

Scheme 2



Scheme 3



12a, R = TES
12b, R = TMS
12c, R = *t*-BuDMS
12d, R = MEM
12e, R = *t*-Bu

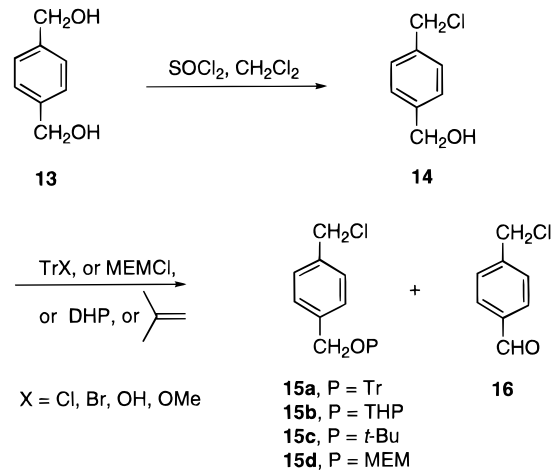
(13) CBZ-D-phenylalaninol was purchased from Synthetech, Inc. Albany, OR.

(14) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.

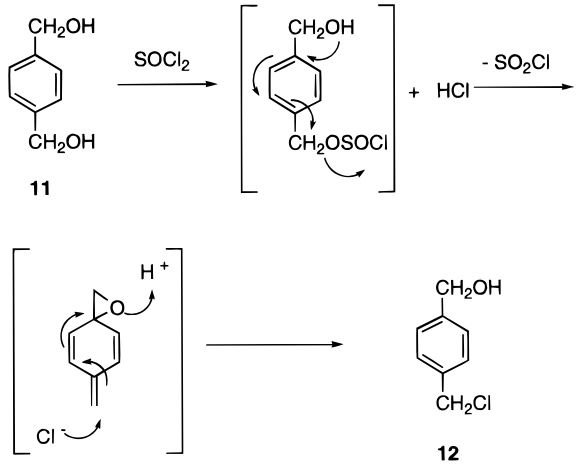
The pinacol coupling with Caulton's reagent[15] was based on the literature procedure,[9] except we used **10** as a solution from the previous step and simplified the purification procedure. The use of **10** as its initially formed solution is advantageous not only because it eliminates losses during isolation, but because the aldehyde is unstable upon storage.[16] Over time, at low pH, or with high temperature, the aldehyde forms an insoluble polymeric material. This material, which may be a poly-hemiaminal liberates racemized aldehyde by treatment with methanol. As expected, the homopinacol coupling gave a mixture of diastereomers, of which the desired (*RSSR*)-isomer comprised ~73% as determined by HPLC. We isolated the crude diol by adding dilute aqueous HCl followed by solvent exchange to remove CH_2Cl_2 and then recrystallized the wet cake from methyl ethyl ketone (MEK) and water. The overall yield of chirally pure **11** was comparable (53%) whether the aldehyde was used *in situ* or isolated. Although others have demonstrated the pinacol coupling on a kilogram scale without the use of a chlorinated solvent,[17] our procedure lends itself to combining *in situ* aldehyde preparation and the pinacol coupling reaction.

In order to avoid oxazolidinone formation it was necessary to protect the diol functionality prior to removal of the CBZ groups and subsequent cyclization to the cyclic urea. A number of groups were screened for this purpose including acetonide, MEM, TMS, triethylsilyl, *tert*-butyldimethylsilyl, trityl, *tert*-butyl, benzoyl, and THP. The acetonide protecting group proved not to be useful at this point of the synthesis. This group forms a five-membered ring with the diol which imposes such strain on the corresponding intermediate that cyclization to the seven-membered ring cyclic urea is very difficult.[18] The problems with using the MEM group have already been noted. The TMS group proved unstable to CBZ removal conditions, and we had difficulty putting the bulky *tert*-butyldimethylsilyl or trityl groups on both alcohols. The bis *tert*-butyl-protected diol proved difficult to cleanly deprotect. The preferred protecting group for the diol was triethylsilyl (TES), giving clean protection of both hydroxyl groups.[19] The product **12a** was not crystalline; however, the series of reactions for conversion of bis-CBZ diol **11** to urea diol **3** were so clean that we telescoped the process without any isolation of the intermediates. We found that preparation of the bis-TES derivative to be the cleanest with DMF/imidazole. After an aqueous quench, the reaction product was extracted into toluene. This solution was subjected to catalytic hydrogenation at 45 °C to remove the CBZ groups and then immediately reacted with CDI to avoid decomposition of the somewhat unstable diamine intermediate. Prior to deprotection, toluene was azeotropically solvent exchanged to acetonitrile, a solvent from which product **3** crystallized out as it was formed. The overall yield for the four-step procedure was 78%.

Scheme 4



Scheme 5



Synthesis of Alkoxymethyl Benzyl Chlorides 15a−c

To complete the synthesis of DMP 323, we needed an alkylating agent **15.** The preparation of unsymmetrically protected agents from 1,4-benzenedimethanol, **13** is shown in Scheme 4. Although (hydroxymethyl)aryl halides have been prepared from the corresponding arenedimethanols by treatment with hydrogen halides, the yields are generally low.[20,21] The notable exception is the reaction of 1,4-bis(hydroxymethyl)-2,3,4,5-tetrafluorobenzene with hydrobromic acid, where the monohalogenated product precipitates from the reaction medium, thereby minimzing dibromination.[22] Remarkably, we obtained high selectivity for monochlorination of **13** with thionyl chloride, when the reaction was run in chloroform or methylene chloride, even though the product remains in solution. Under optimal conditions, approximately 80% of the monochloro product was formed along with about 10% each of the diol and dichloro products. The high selectivity may be due to formation of the xylidene oxide product as shown in Scheme 5. Although the product **14** could be isolated in 75% yield by chromatography, isolation of >98% pure material by direct crystallization on a large scale gave unsatisfactorily low and variable yields of 25−50%.

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(16) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
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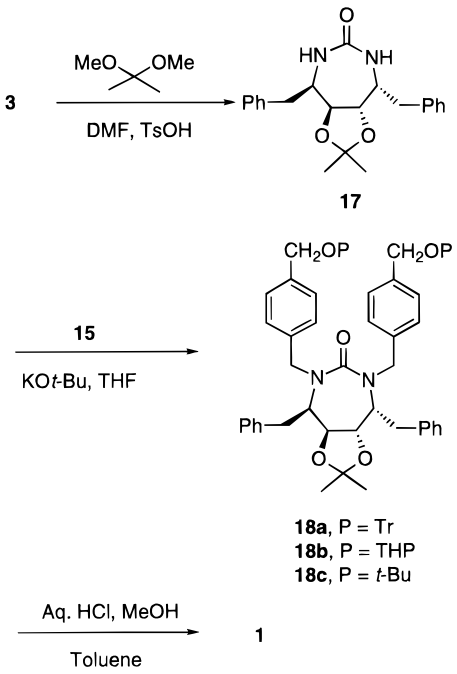
Protection of the alcohol function of **14** is complicated by the presence of the internal alkylating agent. Although the trityl, MEM, or silyl moieties could be incorporated under standard basic conditions,[23] considerable quaternization byproducts competed and isolated yields were generally low. Under optimum conditions, the trityl derivative **15a** could be obtained in 73% yield. Other protecting groups such as THP and *tert*-butyl could readily be attached under acidic conditions, avoiding the quaternization byproducts; however, we found their alkylation of **8** or **17** gave impure, noncrystalline intermediates. We then investigated the preparation of **15a** by acid catalysis. There are few examples of this type of tritylation in the chemical literature,[24,25] though the method has been used to prepare tritylone ethers in high yield.[26] Under a variety of conditions, the acid catalyzed preparation of **15a** worked quite well. The leaving group on the trityl moiety can be Cl, OH, OMe or a mixture thereof. To drive the reaction, OMe or OH are preferable to Cl since methanol or water are easily removed azeotropically. Not only are quaternization products avoided, but this procedure allows the trityl alcohol or trityl methyl ether to be recycled, which are generated after deprotection of **18a**.

Due to the difficulty in isolating **14**, we investigated combining the chlorination and tritylation steps into a "one-pot" process. For this purpose we found it preferable to perform the chlorination in CH_2Cl_2. Afterwards, trityl alcohol was added, the solvent was exchanged to heptane or cyclohexane, and **15a** was isolated by vacuum filtration. On scale-up (prolonged distillation time) or with stronger acids such as TsOH or H_2SO_4, we observed some degradation to aldehyde **16**. The conversion of trityl ethers to aldehydes and triphenylmethane under forcing conditions is well known.[27−30] A simple solution was to distill part of the CH_2Cl_2 and HCl prior to addition of trityl alcohol and cyclohexane. This procedure gave 99% pure material in an overall yield of 55% from **13** to **15a**.

Synthesis of DMP 323 (1)

The selection of acetonide **17** as the preferred diol protecting group was critical in that it gave a highly pure cyclic urea intermediate that facilitated bis-alkylation of the cyclic urea and ultimately the synthesis of highly pure DMP 323 as shown in Scheme 6. The acetonide protecting group was found to be more effective for the above purposes than other similar groups such as the benzylidene or cyclohexylidene. The process for preparing this intermediate using DMF and a cyclohexane azeotrope[31] gave high conversion to product, and the removal of methanol and water from the reaction was superior to the use of molecular sieves, ethyl acetate, acetone, or toluene. The final crystallization from a mixture of DMF and ethyl acetate provided product in 75−95% yield, depending largely on the purity of **3**.

Scheme 6



Our original synthesis of DMP 323 was based on the alkylation of **8** with **15b** using NaH as base in DMF or DMPU. After switching to the acetonide **17**, we reinvestigated alkylation conditions. To study the suitability of alternate bases, model alkylations on **17** with 4-bromobenzyl bromide were run in THF, THF/toluene, or DMSO. We found that the cleanest reactions were in THF and the order of preference for base was KO*t*-Bu > KHMDS > NaHMDS > LiHMDS > LDA, based on conversion. With LDA in particular, it was not possible to drive the reaction to complete bis-alkyation. This may be worth further investigation for the preparation of unsymmetrically alkylated analogues of DMP 323. Using the KO*t*-Bu/THF conditions with **15a**, **15b**, or **15c** as alkylating agents gave clean conversion to **18** at room temperature. At higher temperatures or with a large excess of base, the attack of *tert*-butoxide on **15** became competitive. All three agents gave clean alkylation, but **15a** was preferred, not only because it is a stable recystallizable solid, but more importantly because only **18a** was found to be a crystalline solid. Its crystallization conditions, though quite stringent, are very reproducible, taking place at 20−30 °C with a 1/1 ratio of MeOH to THF. Other conditions lead to oiling out or total dissolution of product. After the product has largely crystallized, further dilution with MeOH and cooling to 5−10 °C could be used to obtain 85−95% yields of 96−99% pure product. The major impurity in **15a** was the bis-trityl ether of **13**; however, it did not interfere in the alkylation reaction and was readily removed in the crystallization of **18a**.

The final step in the preparation of DMP 323 was to remove both protecting groups. The key to success was to largely remove the trityl groups from the mixture prior to crystallization of DMP 323 to avoid cocrystallization of the mono-trityl ether of DMP 323. The best procedure was to use a mixture of toluene/methanol/concd HCl. The two-phase mixture became homogeneous as the reaction proceeded; giving trityl methyl ether, which was removed

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by extraction into heptane (and saved for recycle). Crude DMP 323 was isolated by diluting the methanolic phase with additional water. The impurities from the deprotection step (trityl alcohol, trityl chloride, trityl methyl ether, 2,2-dimethoxypropane, and acetone) were easily removed by recrystallization of DMP 323. Although toluene is an excellent solvent for this recrystallization, DMP 323 is so insoluble, we initially dissolved DMP 323 in a mixture of MeOH and toluene and then azeotropically removed the MeOH. DMP 323 was then given a final clarification and recrystallization from EtOH/water. The overall yield for deprotection and purification was 90−95%.

We briefly investigated alkylation of the cyclic oxydimethylene analogue of **17**.[5] This material was found to be less crystalline than **17** and slower to alkylate than the acetonide by about a factor of 3. This led to increased O-alkylation of **15a** by *tert*-butoxide. Although the alkylated product was crystalline, the deprotection was not clean and it lead to DMP 323 that could not be fully purified by simple crystallization.

Conclusion

A process has been developed and demonstrated that is suitable for production of multi-kilogram quantities of DMP 323. The overall yield from CBZ-D-phenylalaninol is 24%. Further clinical development of DMP 323 is on hold due to highly variable bioavailability as well as a short half-life in humans.[32] Several structurally related compounds are under development, some of which may use portions of the chemistry reported here. Additionally, a method for unsymmetric protected benzenedimethanol alkylating agents has been developed which may find use elsewhere.

Experimental Section

General Methods. Melting points are uncorrected. Analytical HPLC were run with Zorbax RX-C18 columns using 254 nm detection. All reactions were run under nitrogen and all reagents were reagent grade unless otherwise noted. Combustion analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ.

***N*-CBZ-D-Phenylalaninal (10). Method A.** To a solution of **9** (100 g, 350 mmol) in CH_2Cl_2 (1.8 L) was added a solution of NaBr (18 g, 175 mmol) in water (250 mL). The resulting two-phase mixture was stirred and cooled to 0−5 °C. 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical (0.055 g, 2.5 mmol) was added. A solution of buffered sodium hypochlorite, freshly prepared by dissolving $NaHCO_3$ (10 g, 0.12 mol) and commercial sodium hypochlorite solution (12.5% w/w, 250 g, 0.42 mol) in water (250 g), was added over 1 h with high agitation, maintaining the temperature below 5 °C. Sodium thiosulfate pentahydrate (21.8 g, 88 mmol) in water (64 mL) was immediately added and the reaction mixture stirred until excess oxidants were quenched as demonstrated by starch/iodide test. The phases were separated, and the organic phase was washed with aqueous $NaHCO_3$ (3% w/w, 500 mL), followed by 500 mL 3% brine. The organic phase was concentrated *in vacuo* to ~300 mL while maintaining the temperature below 20 °C. Heptane (750 mL) was added and the distillation continued until the ratio of heptane/CH_2Cl_2 was >95/5 w/w. The product was filtered, washed with heptane, and dried *in vacuo* to give 90 g (90%) of **10**: mp 99−102 °C; $[\alpha]^{25}_D$ +61.58° (*c* 0.406, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.4−7.0 (complex, 10H), 5.3 (brs, 1H), 5.12 (s, 2H), 4.50 (q, 1H, J = 7 Hz), 3.13 (d, 2H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 157.8, 142.1, 135.4, 129.0, 128.7, 128.5, 128.3, 128.2, 128.0, 127.2, 67.0, 61.2, 35.5; HRMS calcd for $C_{17}H_{18}NO_3$ (M + H) 284.1287, found 284.1302.

Method B. The same procedure as method A was followed on a 105 mmol scale except, after the aqueous extractions, the organic solution was concentrated to ~180 mL and used directly in the next step.

(1*R*,2*S*,3*S*,4*R*)-Bis(phenylmethyl) [1,4-Bis(phenylmethyl)-2,3-dihydroxy-1,4-butanediyl]bis(carbamate) (11). Preparation of Caulton's Reagent. To a solution of 2 mL of 12 N HCl in degassed THF (5.25 L) was added VCl_3 (437 g). The resulting slurry was refluxed for 1.5 h and then cooled to rt. Most of the supernatent liquid was removed, and then the complex was dissolved in 4.52 L degassed CH_2Cl_2. Zn dust (77 g) was added portionwise, keeping the temperature between 20−25 °C to give a characteristic green solution of Caulton's Reagent.

Pinacol Coupling Reaction. Method A. A degassed solution of *N*-CBZ-D-phenylalaninal (505 g) in CH_2Cl_2 (3.2 L) was charged to Caulton's reagent solution at rt and then stirred for 12 h. HCL (1 N) (9.23 L) was added over 2 h while azeotropically distilling CH_2Cl_2 at 200−300 mm vacuum. The resulting slurry was filtered, washed successively with 7.5 L portions of water, 1 N HCl, and then with water until the wash pH was 5. The wet cake was recrystallized from a mixture of MEK (1.5 L) and water (1.5 L), filtered, washed with MEK, and dried *in vacuo* at 50 °C to give 275.3 g (53%) of **11**. HPLC assay showed 98.3% *RSSR* diol: mp 215−217 °C; $[\alpha]^{25}_D$ +12.50° (*c* 0.042, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.0−7.35 (complex, 20H), 6.82 (d, 2H, J = 9 Hz), 4.93 (m, 4H), 4.55 (brs, 2H), 4.2 (m, 2H), 3.25 (brs, 2H), 2.74 (dd, 2H, J = 13, 9 Hz), 2.60 (dd, 2H, J = 16, 6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.3, 139.8, 138.0, 129.7, 128.7, 128.3, 128.0, 127.7, 126.2, 73.1, 65.3, 53.5, 38.8; HRMS calcd for $C_{34}H_{37}N_2O_6$ (M + H) 569.2652, found 569.2664. Anal. Calcd for $C_{34}H_{36}N_2O_6$: C, 71.87; H, 6.39; N, 4.93. Found: C, 71.66; H, 6.36; N, 4.76.

Method B. The CH_2Cl_2 solution of **9**, prepared in method B was charged over 30 min to Caulton's reagent, prepared from 25.1 g of VCl_3. After stirring for 12 h at rt, the reaction was poured into a solution of 10.7 mL of H_2SO_4 in 175 mL of water. CH_2Cl_2 was removed *in vacuo* and the product isolated by filtration and washed with water. The wet cake was recrystallized from MEK/water to give 14.8 g (50%) of **11**. HPLC assay showed 99.4% (*RSSR*) diol. Other physical properties were identical with product produced by method A.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazapin-2-one (3). Imidazole (11 kg, 161.6 mol) was dissolved in DMF (45.4 L). Triethylchlorosilane (20.4 kg, 135.4 mol), followed by diol **11** (30 kg, 52.8 mol), was added at such a rate as to keep the temperature below 15 °C. The reaction mixture was heated to 35 °C for 12 h. Toluene (45 L) and Celite (3.1 kg) were added, and the mixture was filtered through a 0.5 μm filter. The layers were separated, and the organic layer was washed with water (2 × 45 L). The resulting organic layer was dried by vacuum distillation of 18 L of the toluene−water azeotrope. Toluene (18 L) was added, and the solution was divided into two fractions for subsequent hydrogenation. Palladium hydroxide on wet carbon (0.75 kg) was slurried into the toluene solution. Hydrogen (5 psig) was applied, and the mixture was heated to 45 °C. Every 15 min, the system was purged with N_2 to eliminate CO_2 gas from the solution. After 8 h the system was cooled to 20 °C. CDI (4.5 kg) was added and the mixture stirred for 30 min. HCl (1 N) (34 kg) was added, the mixture was clarified, the layers were separated, and the organic layer was washed with water (25 L). The combined organic layers of two hydrogenation reactions were combined, and toluene (60 L) was distilled *in vacuo* at 30−45 °C. Acetonitrile (125 L) was added in five portions while continuing the distillation at 28−30 °C. The reaction mixture was cooled to 20 °C, and 1.5 L of 30% HCl was added. After 16 h the product was filtered, washed with toluene, and dried at 50 °C *in vacuo* to give 14.6 kg (78%) of **3**: mp 224.0−225.5 °C; $[\alpha]^{25}_D$ +31.75° (*c* 0.400, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35−7.15

(32) Mayner, M. M.; Cordova, B. C.; Meade, R. P.; Lam, P. Y.; Erickson-Viitanen, S. 1st International Conference on Human Retroviruses, Washington, D.C., Dec. 12−16, 1993, Abst 264.

(complex, 10H), 5.0 (brs, 2H), 4.68 (d, 2H, J = 8 Hz), 3.64 (t, 2H, J = 8 Hz), 3.25 (d, 2H, J = 7 Hz), 2.78 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.8, 139.4, 129.8, 128.8, 126.5, 70.5, 52.7, 38.0; HRMS calcd for $C_{19}H_{23}N_2O_3$ (M + H) 327.1709, found 327.1715. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.97; H, 6.80; N, 8.59. Found: C, 69.97; H, 6.76; N, 8.53.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-*O*-isopropylidene-4,7-bis-(phenylmethyl)-2*H*-1,3-diazapin-2-one (17). A slurry of **3** (14.5 kg, 39.8 mol) and TsOH·H_2O (0.30 kg, 1.6 mol) in DMF (30.6 kg) and 2,2-dimethoxypropane (25.5 kg, 245 mol) was heated at 65 °C for 2 h. Cyclohexane (24.1 kg) was added, and the reaction mass was distilled to 95 °C pot temperature. The reaction was cooled to 65 °C, fresh 2,2-dimethoxypropane (12.7 kg, 122 mol) was added, and the reaction was maintained at 65 °C for 1 h. Cyclohexane (11.8 kg) was added, and the reaction mass was distilled to 95 °C pot temperature. After repeating the addition/distillation procedure, the mixture was cooled to 60 °C. NaOH (10 N) (0.095 kg, 2.4 mol) was added, and the reaction mass was concentrated at 75 mmHg to remove residual cyclohexane and 2,2-dimethoxypropane. Water (60 L) and EtOAc (88 kg) were added, the reaction mass was heated to 65 °C, and then the aqueous phase was removed. The organic phase was concentrated to half of the original volume at 70−80 °C. Fresh EtOAc was added, and the distillation was continued to a final volume of approximately 45 L. The reaction mass was cooled to 0−5 °C and filtered. The solids were washed with a cold mixture of heptane (62.6 kg) and EtOAc (27.7 kg). The product was dried *in vacuo* to provide 11.2 kg (76.0%) of **17**: mp 236−238 °C; $[\alpha]^{25}_D$ +161.46° (*c* 0.410, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (complex, 10H), 6.3 (d, 2H, J = 8 Hz), 4.14 (brs, 2H), 3.47 (brt, 2H), 3.30, 2.82 (2d, 1H, J = 8 Hz), 2.95−2.75 (m, 3H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 139.9, 129.9, 129.0, 109.7, 76.0, 53.9, 34.5, 27.2; HRMS calcd for $C_{22}H_{27}N_2O_3$ (M + H) 367.2022, found 367.2016. Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.16; H, 7.16; N, 7.65. Found: C, 72.12; H, 7.11; N, 7.62.

4-(Hydroxymethyl)benzyl Chloride (14). 1,4-Benzenedimethanol (13.8 g, 0.10 mol) was dispersed in chloroform (100 mL) and the mixture cooled to 0 °C in an ice bath. Thionyl chloride (13.1g, 0.11 mol) dissolved in chloroform (10 mL) was added over 10 min with rapid stirring to the cooled mixture. As the addition proceeded, the mixture largely cleared. During the addition step, and for 1 h thereafter, the reaction flask was swept with N_2 which was then passed through the scrubber. The mixture was allowed to come to rt and stirred for 20 h. $NaHCO_3$ was added to neutralize any residual HCl. The mixture was filtered and the solvent removed under reduced pressure at 35 °C. The residue was chromatographed on silica gel (200 g) with EtOAc:hexane (2:3) to give 11.64 g (75%) of **14**. mp: 58−60 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 4H), 4.70 (s, 2H), 4.59 (s, 2H), 1.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.37, 135.10, 128.88, 127.37, 64.93, 46.12.

4-[(Triphenylmethoxy)methyl]benzyl Chloride (15a). Method A. Trityl chloride (578 g, 2.07 mol) and 4-(chloromethyl)benzyl alcohol (300 g, 1.92 mol) were slurried in DMAc (900 mL) and heated to 30 °C. To the mixture was added DMAP (15.6 g, 128 mmol) followed by *N*,*N*-diisopropylethylamine (270 g, 2.09 mol) over 1 h. The solution was heated at 40 °C for 24 h, cooled to rt and diluted with water (165 mL). The resulting slurry was stirred for 12 h and then filtered. The solids were washed with cold 70/30 water/DMAc (100 mL) followed by 200 mL of water. The product was dried *in vacuo* at 50 °C to give 774 g of crude product. The crude product was recrystallized from 1.0 L of acetonitrile and dried *in vacuo* at 45 °C to give 563 g (73%) of **15a**: HPLC 99.3 area %; mp 127−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.6 (complex, 19H), 4.60 (s, 2H), 4.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 139.5, 136.2, 129.0, 128.8, 128.0, 127.3, 127.1, 65.4, 46.2; HRMS calcd for $C_{27}H_{23}ClO$ 398.1437, found 398.1421. Anal. Calcd for $C_{27}H_{23}ClO$: C, 81.29; H, 5.81. Found: C, 80.94; H, 5.85.

Method B. Triphenylmethyl methyl ether (2.74 g, 10 mmol), trityl chloride (2.79 g, 10 mmol), 4-(chloromethyl)benzyl alcohol (3.13 g, 20 mmol), toluene (12 mL), heptane (12 mL), and 32% HCl (2 drops) were combined and refluxed while 12 mL of solvent was distilled over 2 h. The solution was cooled to rt and the resulting slurry diluted with 12 mL of heptane. After cooling in an ice bath, the product was filtered and dried *in vacuo* at 40 °C to give 6.27 g crude product. The crude product was recrystallized from 20 mL of acetonitrile to give 5.46 g (70%) of **15a**. HPLC: 97.8 area %. Physical properties were identical with product produced by method A.

Method C. To a slurry of 1,4-benzenedimethanol (69 g, 500 mmol) in CH_2Cl_2 (550 mL) was added $SOCl_2$ (59.5 g, 500 mmol) over 2 h, keeping the temperature below 10 °C. The mixture was allowed to warm to rt and stir 4 h. Approximately half the CH_2Cl_2 was then removed by atmospheric distillation. Cyclohexane (250 mL) followed by trityl alcohol (100.3 g, 385 mmol) was added, and 250 mL solvent was distilled followed by the addition of 250 mL cyclohexane. This distillation procedure was repeated four times. The final pot temperature was 74 °C. Cyclohexane (350 mL) was added and the mixture cooled to 15−18 °C and held for 3 h. The product was filtered, washed with cold cyclohexane (50 mL), and dried *in vacuo* at 50 °C to give 130 g crude product. HPLC: 86.7 area %. A 100 g portion of the crude product was recrystallized from 200 mL of CH_3CN to give 85 g (55%) of **15a**. HPLC: 99.0 area %. Physical properties were identical with product produced by method A.

4-[(Tetrahydropyranyloxy)methyl]benzyl Chloride (15b). 3,4-Dihydro-2*H*-pyran (925 g, 1.1 mol) and *p*-(hydroxymethyl)benzyl chloride (1.33 kg, 1 mol) were dissolved in CH_2Cl_2 (6 L) and cooled to 5 °C. Pyridinium *p*-toluenesulfonate (1.25 g, 5 mmol) was added as a catalyst. The contents were allowed to warm to rt and stirred 24 h. The solution was washed with water followed by a $NaHCO_3$ solution and then dried over $MgSO_4$. The residue, after removal of solvent, was kept under high vacuum (1−2 mmHg) for 24 h to give 2.28 kg (95%) of **15b** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (s, 4H), 4.75 (t, 1H), 4.65 (AB quartet, 2H, J = 13 Hz), 4.6 (s, 2H), 3.85 (m, 1H), 3.55 (m, 1H), 1.5−1.95 (m, 6H).

4-(*tert*-Butyloxymethyl)benzyl Chloride (15c). A 5-gal stirred pressure reactor was charged with *p*-(hydroxymethyl)-benzyl chloride (600 g, 3.83 mol) in 6 L CH_2Cl_2 and H_2SO_4 (60 mL). Isobutylene gas was charged to the stirred solution for 2 h at 10 psi. At the end of 24 h the reaction was about 85% complete. The reaction mixture was diluted with water and neutralized to pH 7 with 25% aqueous NaOH. The CH_2Cl_2 extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo* and then fractionally distilled through a 24 cm Vigreux column to provide 312 g (45%) of **15c** as an oil: bp 115−125 °C (2−3 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (s, 4H), 4.58 (s, 2H), 4.45 (s, 2H), 1.3 (s, 9H).

4-[[(Methoxyethoxy)methoxy]methyl]benzyl Chloride (15d). To a slurry of *p*-(hydroxymethyl)benzyl chloride (255 g, 1.91 mol) in 2 L CH_2Cl_2 was charged (2-methoxyethoxy)-methyl chloride (300 g, 2.41 mol) followed by *N*,*N*-diisopropylethylamine (500 mL, 2.86 mol) at 20−25 °C. The resulting exotherm caused the solvent to reflux vigorously for 20 min. After stirring at rt for 24 h, the solution was washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*, and then the residue was passed through a plug of silica gel to provide 310 g (67%) of **15d** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 4H), 4.80 (s, 2H), 4.62 (s, 2H), 4.58 (s, 2H), 3.72 (m, 2H), 3.58 (m, 2H), 3.4 (s, 3H).

4-(Chloromethyl)benzaldehyde (16). Benzyl chloride **15a** (3.2 g, 8.0 mmol) and TsOH·H_2O (0.1 g, 0.5 mmol) were dissolved in cyclohexane (20 mL) at reflux for 5 h. The solution was cooled to rt, and the solids were isolated, washed with cyclohexane (5 mL), and dried *in vacuo* to give 0.53 g (43%) as a white crystalline solid: mp 70−72 °C (lit.[33] mp 70−71 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.86 (d, 2H, J = 8 Hz), 7.56 (d, 2H, J = 8 Hz), 4.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 143.4, 136.4, 130.2, 129.0, 45.2.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-*O*-isopropylidene-4,7-bis-(phenylmethyl)-1,3-bis[[4-[[(triphenylmethyl)oxy]methyl]phenyl]methyl]-2*H*-1,3-diazapin-2-one (18a). Cyclic urea

(33) Arcus, C. L.; Salomons, N. S. *J. Chem. Soc.* **1962**, *117*, 1515.

17 (975 g, 2.66 mol) and benzyl chloride **15a** (2.28 kg, 5.73 mol) were slurried in THF (2.83 L) at rt. A solution of 1.5 N potassium *tert*-butoxide in THF (3.96 L, 6.3 mol) was added over 2 h while maintaining the temperature at 20−35 °C. The resulting solution was stirred at 30 °C for 4 h and then at rt overnight. Water (527 mL) was added, followed by Celite 545 (135 g). The slurry was stirred 15 min and then clarified by vacuum filtration. The filtrate, along with a 0.53 L THF rinse of the filter cake was stirred vigorously and diluted with MeOH (6.83 L). The solution was seeded and then diluted over 30 min with MeOH (3.41 L). The slurry was cooled to 6 °C over 6 h and filtered, washed with a mixture of MeOH (0.8 L) and THF (0.27 L) and then twice with MeOH (1.07 L), and dried *in vacuo* at 60 °C to give 2.66 kg (91%) of **18a**: mp 204.2−206.6 °C; $[\alpha]^{25}_{D}$ +51.15° (*c* 0.260, THF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1−7.5 (complex, 48 H), 4.96 (d, 2H, J = 14 Hz), 4.15 (s, 4H), 3.82 (m, 4H), 3.07 (d, 2H, J = 14 Hz), 2.95 (d, 4H, J = 7 Hz), 1.33 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 161.8. 144.2, 139.0, 138.4, 137.3, 129.5, 129.1, 128.7, 128.0, 127.2, 127.0, 126.5, 110.3, 87.0, 75.5, 65.6, 60.5, 56.1, 33.7, 26.6; HRMS calcd for $C_{76}H_{71}N_2O_5$ (M + H) 1091.5363, found 1091.5364. Anal. Calcd for $C_{76}H_{70}N_2O_5$: C, 83.64; H, 6.46; N, 2.57. Found: C, 83.79; H, 6.44; N, 2.45.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-1,3-bis[[4-(hydoxymethyl)phenyl]methyl]-2*H*-1,3-diazapin-2-one (1). Toluene (4.4 L), MeOH (11.0 L), **18a** (2.20 kg), and 32% HCl (181 mL) were stirred vigorously for 3 h. Heptanes (4.4 L), 30% NaOH (190 mL), and water (4.4 L) were added and the phases allowed to separate. The aqueous phase was reextracted with a mixture of heptanes (2.9 L) and toluene (2.9 L) and then finally with 5.9 L of heptanes. The aqueous phase was stirred vigorously and 60 mL of 32% HCl, followed by 1.1 L of water was added. After solids began to crystallize, 4.7 L of additional water was added over 30 min. The slurry was stirred at rt overnight, cooled to 7 °C, and filtered. The product was washed three times with 1.5 L water and dried *in vacuo* to give 1.12 kg crude product. This material was dissolved in a mixture of toluene (11.0 L) and MeOH (2.2 L) at reflux and then partially concentrated (2.2 L distilled). The resulting slurry was cooled to 10 °C and filtered. The solids were washed with 1.1 L toluene and then redissolved in 95% EtOH (6.6 L). The solution was clarified and partially concentrated by atmospheric distillation. Water (6.6 L) was added, and the solution was cooled to rt overnight. The resulting slurry was chilled to 7 °C and the product filtered, washed with 2.0 L water, and dried to a constant weight *in vacuo* to give 1.03 kg (92%) of **1**: HPLC 100 area %, 99.2 weight %; mp 202.3−203.5 °C; $[\alpha]^{25}_{D}$ +104.88° (*c* 0.410, MeOH); ^{1}H NMR (CD_3OD) δ 7.2−7.4 (complex, 10 H), 7.05−7.2 (complex, 8H), 4.9 (s, 4H), 4.75 (d, 2H, J = 14 Hz), 4.57 (s, 4H), 3.6 (m, 2H), 3.5 (brs, 1H), 2.8−3.1 (complex, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.40, 141.51, 140.18, 136.50, 129.21, 128.59, 128.18, 126.44, 126.01, 70.35, 64.79, 62.53, 54.70, 32.03; HRMS calcd for $C_{35}H_{39}N_2O_5$ (M + H) 567.2859, found 567.2874. Anal. Calcd for $C_{35}H_{38}N_2O_5$: C, 74.11; H, 6.75; N, 4.94. Found: 74.35; H, 6.62; N, 4.84.

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