Vanadium(II)- and Niobium(III)-Induced, Diastereoselective Pinacol Coupling of Peptide Aldehydes to Give a C_2-Symmetrical HIV Protease Inhibitor

Bernhard Kammermeier,* Gerhard Beck, Wolfgang Holla, Detlev Jacobi, Bernd Napierski and Heiner Jendralla*

Dedicated to Professor Richard Neidlein on the occasion of his 65th birthday

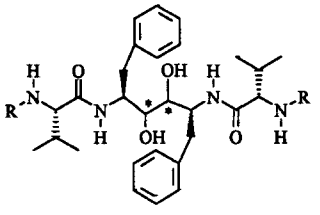
Abstract: Peptide aldehydes **15a–c** are prepared without epimerization from enantiomerically pure (*S*)-α-amino acids (Scheme 3). Reductive pinacol homocoupling of **15a–c**, induced by vanadium complex **11** or niobium complex **16** in refluxing THF, yields C_2-symmetrical (*S,R,R,S*)-configurated **6a**, **6b** and **2**, respectively, with moderate to high stereoselectivity (Scheme 4). In a novel protocol for the preparation and utilization of THF solutions of **11**, the isolation of air-sensitive intermediates can be avoided and the potent HIV protease inhibitor **2** prepared in enantio- and diastereomerically pure form on a kilogram scale without chromatographic purification. The (*S,R,R,S*) selectivity of the pinacol homocouplings is confirmed by means of an independent, stereochemically unequivocal synthesis of **6a** and **2** from D-mannitol **4** (Scheme 1).

Keywords
enzyme inhibitors · niobium complexes · peptide aldehydes · pinacol coupling · vanadium complexes

Introduction

The design of HIV protease inhibitors that could serve as specific antiviral agents and arrest the progression of HIV infection in patients with AIDS has been the subject of intense efforts.[1] At least three HIV protease inhibitors have entered phase III clinical trials;[2, 3a, 3e] others are in advanced preclinical development.[3] The active form of HIV-1 protease is a C_2-symmetric homodimer.[4] It was therefore predicted that the axes of symmetry of an inhibitor with a (pseudo)-C_2-symmetric diaminodiol core unit **1** would coalign with the C_2 axes of the enzyme and thus lead to particularly potent and specific inhibition.[5] Indeed, several peptidomimetic transition-state analogues of structure **1** have been identified as extremely potent, subnanomolar inhibitors in vitro,[5–8] for example, HBY 793 (**2**) ($IC_{50} = 3.0 \times 10^{-10}$ M).[6] Unfortunately, these compounds show very low aqueous solubility and poor oral bioavailability;[3, 6, 7] one such compound is nevertheless in intravenous clinical trial.[7, 8] Nonpeptide cyclic urea **3** ($K_i = 2.7 \times 10^{-10}$ M),[3d] which also contains a C_2-symmetric diaminodiol unit, shows significant oral bioavailability in both rat and dog;[3d] however, it was withdrawn from development due to rapid metabolism and irreproducible blood levels in humans.[3c]

The absolute configurations at the stereocentres of the diol core unit of inhibitors **1** have significant influence on the potency of enzyme inhibition[3d, 6–9] and on the aqueous solubility, which is usually highest for the (*R,R*)-diol.[7] X-ray crystallographic studies on inhibitors **1** cocrystallized with HIV protease indicate that the pseudo-C_2-symmetric (*R,S*)-diol and the C_2-



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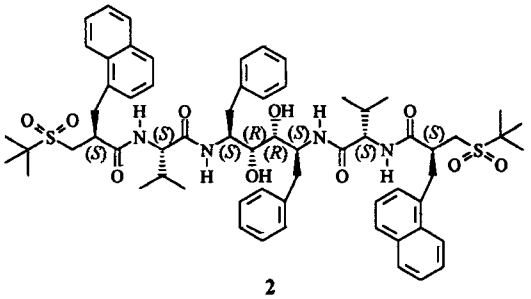

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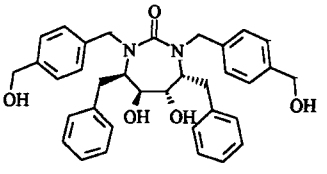

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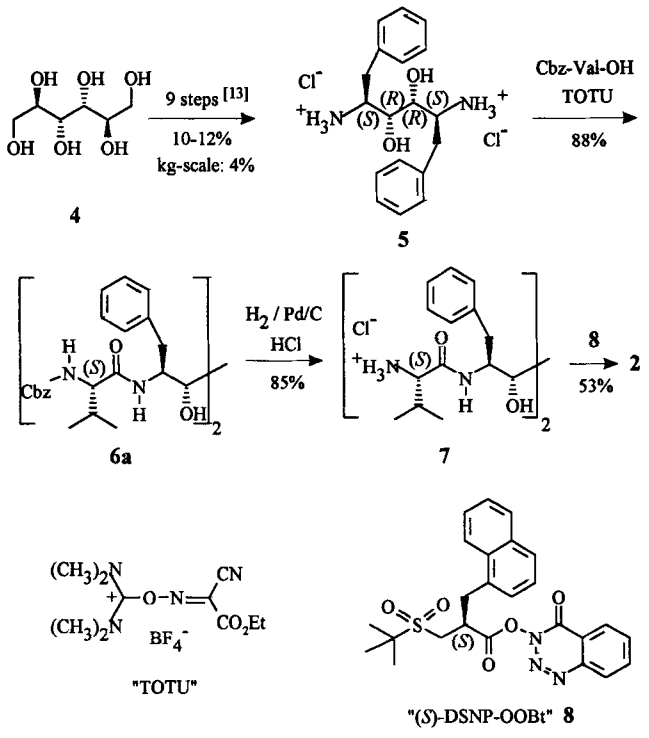
symmetric (*R,R*)-diol have an asymmetric binding mode with the enzyme,[8] and the C_2-symmetric (*S,S*)-diol has a symmetric binding mode,[8] as originally predicted.[5] New efficient methods for the diastereo- and enantioselective synthesis of C_2-symmetric 1,3-diamino-2-ols and (pseudo)-C_2-symmetric 1,4-diamino-2,3-diols are thus of particular interest.[10-12]

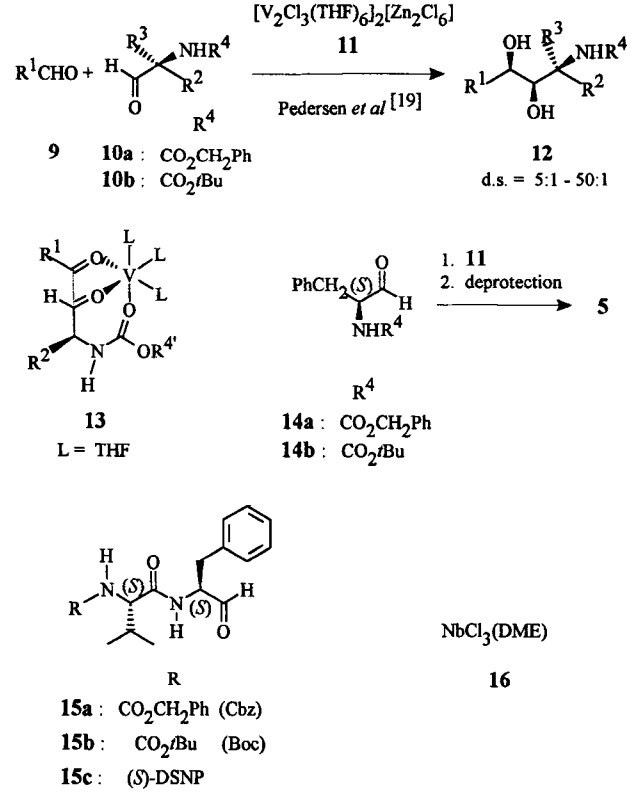
Results and Discussion

1. Original chiral-pool synthesis of HBY 793 (2): By 1991 we had prepared inhibitor **2** from D-mannitol **4** as outlined in Scheme 1.[6] The synthesis of (*S,R,R,S*)-diaminodiol **5** with minor modifications has been reported by other research groups.[13] Core unit **5** was coupled with *N*-benzyloxycarbonyl-L-valine (Cbz-L-Val-OH) with *O*-[cyano(ethoxycarbonyl)-methylenamino]-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TOTU)[14] as coupling reagent to give **6a**. Hydrogenolysis of the Cbz protecting groups liberated the terminal amino groups, which could be coupled with (2*S*)-(1,1-dimethylethylsulfonylmethyl)-3-(1-naphthyl)propionic acid (DSNP-OH)[15] after activation as 4-oxo-3,4-dihydro-1,2,3-benzotriazine-3-oate (OOBt ester)[16] **8**. This synthesis was unsuitable for the preparation of inhibitor **2** on a kg scale. The nine steps from mannitol **4** to the core unit **5** proceed with an overall yield of 10–12% on a laboratory scale; however, only 4% could be attained on a kg scale. Large-scale handling of a diazide (intermediate in the preparation of **5**) was an unacceptable hazard.



Scheme 1. Original chiral pool synthesis of **2**.

2. Development of approaches based on reductive pinacol coupling: It was to be expected that the dimerization of the "molecular halves" would be a more efficient route to a C_2-symmetric compound such as **2**. However, this simple approach is complicated by the fact that the relative configurations of four vicinal stereocentres have to be controlled around the central bond to be formed. A conventional method for the preparation of C_2-symmetrical diols is the reductive pinacol dimerization of the respective aldehydes.[17] The customary conditions are not useful in this case: both titanium(0)-catalysed McMurry couplings (diastereoselectivity d.s. with **14b**: (*S,R,R,S*):(*S,R,S,S*):(*S,S,S,S*) = 2:1:1)[5b,11] and samarium diiodide-induced dimerizations (d.s. with **14b**: 1.6:0.7:1.0)[6] yield only diastereomeric mixtures that are difficult to separate. A report of Pedersen et al. in 1990 gave a hint of how to attain the required diastereoselectivity: dinuclear vanadium(II) complex **11**[18] was found to promote highly *syn,syn*-selective cross-coupling of nonchelating aldehydes **9** with chelating *N*-Cbz- or *N*-Boc-α-amino aldehydes **10** (Scheme 2). Pedersen rationalized the stereochemical preference in terms of intermediate **13**.[19]



Scheme 2. Approaches based on reductive pinacol coupling (DME = 1,2-dimethoxyethane).

Abstract in German: *Die Peptidaldehyde **15a–c** werden epimerisierungsfrei aus enantiomerenreinen (S)-α-Aminosäuren hergestellt (Schema 3). Durch reduktive Pinakol-Homokupplungen, induziert durch den Vanadium-Komplex **11** oder den Niob-Komplex **16** in siedendem THF, entstehen die C_2-symmetrischen (S,R,R,S)-1,4-Diamino-2,3-diole **6a**, **6b** und **2** mit mittlerer bis hoher Stereoselektivität (Schema 4). Bei einer neuen Methode zur Herstellung und Verwendung von THF-Lösungen des Vanadium-Komplexes **11** kann auf die Isolierung luftempfindlicher Zwischenstufen verzichtet werden. Nach dieser Methode gelingt die Synthese des enantio- und diastereomerenreinen, hochwirksamen HIV-Protease Inhibitors **2** im kg-Maßstab ohne chromatographische Reinigungsschritte. Die (S,R,R,S)-Selektivität der Pinakol-Homokupplungen wird durch die stereochemisch eindeutig verlaufende Synthese von **6a** und **2** aus D-Mannit bewiesen (Schema 1).*

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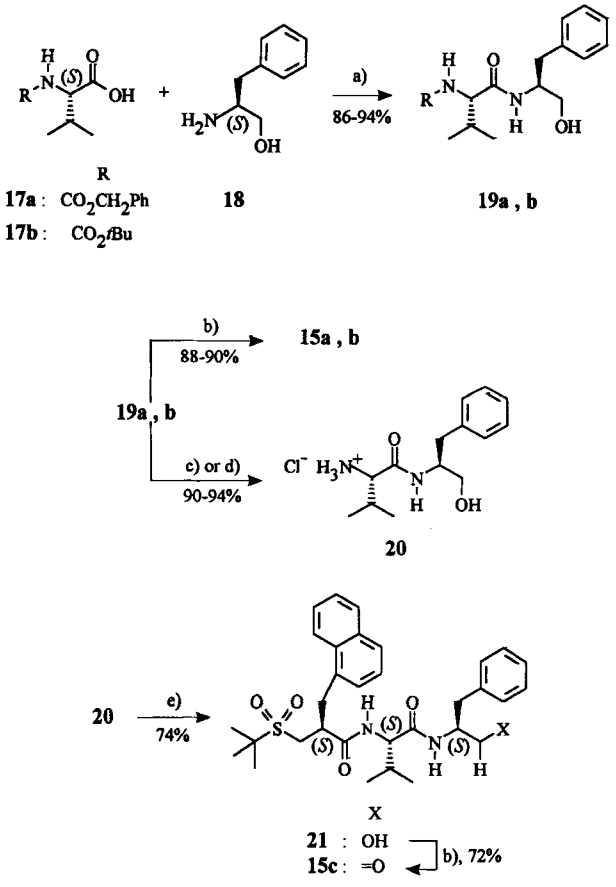
Based on this model we expected that reductive dimerization of *N*-Cbz- (or *N*-Boc)-protected phenylalaninals **14**, promoted by **11**, would give the required (*S,R,R,S*) core unit **5** after deprotection. We also envisioned that the peptidic carbonyl group might endow a peptide aldehyde with chelating abilities similar to protected α-amino aldehyde **10**. This would allow the preparation of **2** by pinacol coupling of protected dipeptide aldehyde **15a** or **15b** and even the synthesis of the entire inhibitor **2** in a single step from DSNP-Val-Phe aldehyde **15c**. All three approaches to **2** were quickly put into practice; the work was concluded and submitted for patent in march 1991.[20] Shortly thereafter we also succeeded in inducing the respective stereoselective couplings with niobium(III) complex **16**,[21] which had been reported by Pederson et al.[22] for the reductive coupling of imines with aldehydes. In the meantime, homocoupling of **14a** promoted by vanadium complex **11** has been reported,[10,11] as well as several similar applications of **11**[23] and **16**.[24] In the following we report the details of the preparation of enantiomerically pure peptide aldehydes **15a–c**, and their diastereoselective pinacol couplings, promoted by vanadium complex **11** and niobium complex **16** to give HIV protease inhibitor HBY 793.[25]

3. Preparation of peptide aldehydes 15a–c: Amazingly, little is known about synthesis and chemistry of terminal peptide aldehydes.[26] Condensation of *N*-Cbz- or *N*-Boc-protected L-valine **17a** or **17b** with L-phenylalaninal **18**, in the presence of *n*-propyl phosphonic anhydride and triethylamine, provided protected Val-Phe alcohols **19a** or **19b** in 86 and 94% yield, respectively (Scheme 3). Oxidation under Swern conditions[26] furnished the corresponding crystalline protected dipeptide aldehydes **15a** and **15b** without epimerization in 88–90% yield. The Cbz group of **19a** or the Boc group of **19b** could be cleaved by hydrogenolysis or protonolysis, respectively, to give the crystalline dipeptide alcohol **20** as a pure diastereomer in 90–94% yield. Coupling with the sulfone carboxylic acid (*S*)-DSNP-OH[15] induced by dicyclohexylcarbodiimide furnished the crystalline pseudo-tripeptide alcohol **21** as a pure diastereomer in 74% yield after purification by recrystallization. Oxidation under Swern conditions provided the crystalline pseudo-tripeptide aldehyde **15c** in 72% yield on a kg scale (78–85% on laboratory scale).



Scheme 3. Preparation of peptide aldehydes **15a–c**: a) *n*-propyl phosphonic anhydride, NEt_3, EtOAc, 20 °C; b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −70 °C; c) MeOH/HCl (pH = 6), H_2, Pd/C, 20 °C; d) HCl (gas), MeOH, 20–35 °C; e) dicyclohexylcarbodiimide, (*S*)-DSNP-OH, EtOAc, 20–45 °C.

Peptide aldehydes are prone to epimerize in the α position to the aldehyde group,[26] notably in the presence of base. Protected dipeptide aldehyde Cbz-L-Ala-L-Leu aldehyde has been reported to epimerize slowly only 1 h after dissolution in $CDCl_3$ at ambient temperature, whereas its more sensitive D,L-isomer was already 10–15% epimerized after 1 h.[26] We noticed that several precautions are necessary to obtain diastereomerically pure peptide aldehydes **15a–c**. The Swern oxidation must be conducted at −60 to −70 °C. Attempts to increase the reaction temperature above −40 °C led to significant epimerization. The workup must start with the addition of excess acid at low temperature, and it should be checked that the reaction medium is really slightly acidic before it is allowed to warm up. In the case of **15a** and **15b** the addition of excess glacial acetic acid and aqueous citric acid gives good results. However, these acids crystallize quickly at the low temperatures used, and the more sensitive aldehyde **15c** epimerized partially as the reaction warmed up, despite of the addition of these acids. This problem was overcome by the use of the low-melting chlorosulfonic acid. Workup must be conducted without interruption until the aldehydes **15a–c** have been precipitated, filtered and dried. The dry, crystalline aldehydes can be stored for several months at ambient temperature without significant loss of quality. In contrast, crude solid aldehydes containing mother liquor and especially crude *oily* aldehydes epimerize partially within several hours. Solutions of the aldehyde in the presence of base epimerize quickly within a few minutes. Only crystalline peptide aldehydes should be used in the vanadium(II)- or niobium(III)-induced pinacol couplings. Their diastereomeric purity must be verified by high field ^1H NMR and (or) HPLC prior to use. The presence of epimers in the peptide aldehyde gives rise to the formation of additional diastereomers in the crude coupling product, and the (*S,R,R,S*) isomer crystallizes in significantly reduced yield or not at all. Provided that these precautions are taken, even the most sensitive aldehyde **15c** can be prepared conveniently on a kg scale (see Experimental Procedure).

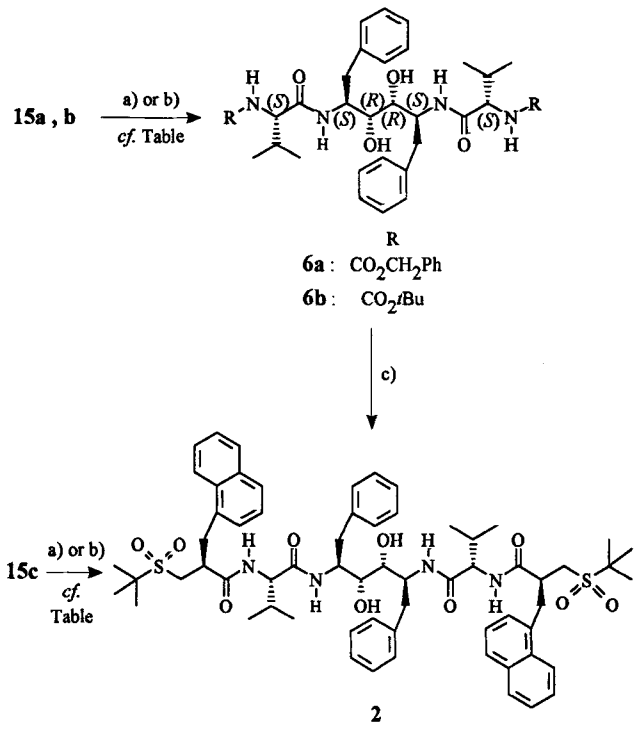
4. Diastereoselective pinacol coupling of peptide aldehydes: *All* reported applications of vanadium(II) complex **11** for reductive pinacol couplings[10,11,23,27] require the isolation of the very air-sentitive $VCl_3(THF)_3$[28] from THF solution by dry-box or Schlenk-tube techniques,[27,28] its subsequent reduction with zinc dust in dichloromethane to give a solution of complex **11**,[29] followed by the addition of a dichloromethane solution of the aldehyde(s) to be coupled at ambient temperature (procedure A). Obviously, this protocol is not practical on pilot-plant scale. We developed a new procedure that allows complex **11** to be formed and used in THF solution and avoids the isolation of intermediates: VCl_3 was refluxed in THF for 5 h, and zinc dust added at 20 °C; after 30 min the mixture was reheated to reflux, 1,3-dimethylimidazolidin-2-one (DMI) added, followed by a THF solution of the aldehyde, and the mixture refluxed for 1 h (procedure B, for details see Experimental Procedure). Initial

experiments with Cbz- and Boc-protected L-phenylalaninal **14a** and **14b**, respectively, served to ascertain that procedures A and B are comparable as regards the yield and diastereoselectivity of the homocouplings (Table 1, entries 1–7). While the total yield of diol products is very similar for **14a** and **14b**, the diastereoselectivity is significantly better for **14a**, irrespective of the coupling protocol (compare entries 1–3 with entries 4–7). In the relatively unselective homocouplings of **14b**, the diastereoselectivity attained in refluxing solvents is better than that at ambient temperature, with both the Pedersen protocol (procedure A) and our new protocol (procedure B) (compare entry 4 with 5 and entry 6 with 7). There are two possible explanations for this observation. In contrast to the configurationally rather stable[26, 30] Cbz-protected α-amino aldehydes, Boc-protected α-amino aldehydes are prone to racemize.[26, 30, 31] Racemization concomitant with the pinacol coupling will manifest itself in a decreased diastereoselectivity and in a diminished enantiomeric purity of the (*S,R,R,S*) isomer. Reaction times for quantitative pinacol coupling are considerably shorter in refluxing solvents. The ratio of reaction rates $k_{coupling}/k_{racem.}$ probably increases with temperature within the range examined. In addition, entry 3 points to an intrinsically improved diastereoselectivity of the homocoupling in refluxing THF; however, the limited data available are clearly not sufficient to establish this effect.

Table 1. Diastereoselective pinacol homocoupling of protected L-phenylalaninal and of peptide aldehydes with *C*-terminal L-phenylalaninal moieties.

Entry	Substr.	Reagent, procedure [a]	Yield (%)	d.s.(*S,R,R,S*) (%) [b]	Ref.
1	**14a**	**11**, A	76 [c,d] (≥85) [e]	≈90	[10]
2	**14a**	**11**, A	70 [c,f] (≥88) [e]	80	[11]
3	**14a**	**11**, B	74 [c,d]	91	this work
4	**14b**	**11**, A	82 [e]	60	this work
5	**14b**	**11**, A [i]	85 [e]	70	this work
6	**14b**	**11**, B [j]	80 [e]	64	this work
7	**14b**	**11**, B	70 [e]	66	this work
8	**15a**	**11**, B	64 [e]	70 [h]	this work
9	**15b**	**11**, B	72 [c,k] (≥83) [e]	87	this work
10	**15c**	**11**, B	70 [c,d] (≥89) [e]	79	this work
11	**15b**	**16**	52 [c,k]	85	this work
12	**15c**	**16**	35 [c,k]	80	this work

[a] For definition of procedures see text and Experimental Procedure. [b] Other diastereomers predominantly (*S,R,S,S*) and (*S,S,S,S*) configuration. [c] Isolated yield of (*S,R,R,S*) product. [d] Isolated by recrystallization of crude product. [e] Total yield of diol products. [f] Isolated by derivatization of crude product. [g] Isolated by trituration of crude product. [h] Diastereomeric composition of isolated product. [i] Refluxing CH_2Cl_2. [j] Reaction in THF at 20 °C. [k] Isolated by chromatography.



Scheme 4. Diastereoselective pinacol homocouplings of peptide aldehydes **15a–c**. a) VCl_3, Zn, 1,3-dimethyl-2-imidazolidinone (DMI), THF, reflux; b) [$NbCl_3$(DME)], THF, reflux; c) see Scheme 1.

Peptide aldehydes **15a–c** were homocoupled according to procedure B in refluxing THF (Scheme 4). The desired (*S,R,R,S*) diols **6a**, **6b** and **2** accounted for 70%, 87%, and 79%, respectively, of all diol products formed (Table 1, entries 8–10). Diol **6a** obtained in entry 8 and diol **2** obtained in entry 10 had the same physical constants, spectra and specific rotations, after recrystallization, as products **6a** and **2** prepared in a stereochemically unambiguous manner from D-mannitol according to Scheme 1. Products **6a** (entry 8) and **6b** (entry 9) were converted to **2** according to the protocol outlined in Scheme 1. The resulting **2** was, after recrystallization, identical in all respects to **2** produced in entry 10. Stereoisomers of **6a**, **6b** and **2** with unambiguously definded configurations were available as reference compounds from former work of Budt et al.[6] Using these reference samples, HPLC analysis of the crude products produced in entries 8–10 indicated the main product to have (*S,R,R,S*) configuration in each case. Additionally, (*S,R,S,S*) and (*S,S,S,S*) isomers could be assigned in most cases (see Experimental Procedure). The efficient and high yielding homocoupling of **15c** (entry 10) indicates that complex **11** in refluxing THF is a highly chemoselective reducing reagent. There is no significant reduction of the sulfone group, in line with the reaction of **11** with β-sulfone aldehydes in dichloromethane at ambient temperature.[23f] In contrast, niobium(III) complex **16** in refluxing THF is a less selective agent. Although its diastereoselectivity is virtually the same as that of vanadium complex **11** (compare entry 9 with 11 and entry 10 with 12), the isolated yields of products **15b** and **15c** are much lower. HPLC analyses of crude reaction products indicate considerable (non-diastereomeric) impurities. The peptide alcohols **19b** and **21**, respectively, are prominent by-products. Very recently it has been reported that acetals, resulting from reaction of the *vic*-diols with the aldehydes, are important products in this type of reaction.[24]

In the case of pinacol homocoupling of peptide aldehydes **15b** and **15c** induced by vanadium(II), the diastereoselectivities and the isolated yields of pure (*S,R,R,S*) isomer are comparable with those of the reported homocoupling of Cbz-L-phenylalaninal (compare entries 1, 2 with entries 9 and 10). The steric conditions proximal to the reaction centre are very similar for these three substrates, since they all have a *C*-terminal L-phenylalaninal unit. The results indicate that, under suitable conditions, the chelating abilities of peptide aldehydes towards vanadium complex **11** are comparable to those of Cbz-protected α-amino aldehydes. However, diastereoselectivity and yield for the coupling of Cbz-protected dipeptide aldehyde **15a** are significantly lower. At this time we do not know why Cbz-protection gives better stereoselectivity than Boc-protection with phenylalaninal, but worse results with valinylphenylalaninal.

In all examined cases 70–90% of all diol products have the required (*S,R,R,S*) configuration under optimal conditions (re-

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fluxing solvents). As expected, the configuration of the diol centres is predominantly controlled by the neighbouring stereocentre of the phenylalaninal unit (1,2-asymmetric induction). The influence of remote stereocentres (1,5- and 1,8-asymmetric induction)[26] is minor. The good yield and diastereoselectivity attained in the coupling of **15c** induced by **11** (Table 1, entry 10) indicates that the method is not impaired by a growing chain length of the peptide aldehyde, nor by the presence of very bulky substituents. It should therefore give useful diastereoselectivities with a large number of different peptide aldehydes.

Conclusion

We have reported the preparation and (*S,R,R,S*)-diastereoselective homocoupling of peptide aldehydes **15a–c**. A novel protocol for preparation and utilization of vanadium(II) complex **11** has been developed, avoiding any isolation of air-sensitive intermediates and rendering the method practical on pilot-plant scale. The homocoupling of pseudo-tripeptide aldehyde **15c** was applied on a kg scale to furnish enantiomerically and diastereomerically pure HIV-protease inhibitor **2** by simple recrystallization. The method should be useful with a large number of peptide aldehydes.

Experimental Procedure

Reagents, instrumentation and general methods: Cbz-L-Val-OH (**17a**) and Boc-L-Val-OH Nova Biochem, >99%), L-phenylalaninol (**18**) (Hoechst, >98%), DMI (Janssen, 98%, 0.13% H_2O), HOOBt (22.5% on ®Dicalite, Hoechst), *n*-propylphosphonic anhydride [Hoechst, 92% (^{31}P NMR), 6% terminal P, 2% *i*Pr terminal P], TOTU (Hoechst) and VCl_3 (Fluka purum, 99.5% argentometric) were used as purchased. All g-scale reactions were run in a dry-glass apparatus under a nitrogen or argon atmosphere. All kg-scale reactions were run in enamel-coated stainless steel reactors under a nitrogen atmosphere. Melting points (M.p.) were determined on a Büchi capillary melting point apparatus and are uncorrected. TLC: 5 × 10 cm glass plates precoated with silicagel 60 F-254 (E. Merck). HPLC: Kontron 420 or Beckman System Gold; peak areas were not corrected. ^1H NMR: Varian Gemini 200 (200 MHz), Bruker AM 270 (270 MHz), and Bruker AM 400 (400 MHz). δ and J values correspond to the common "first order analysis" of the spectra. ^{13}C NMR: Bruker AM 300 (75.429 MHz), multiplicity determined by DEPT 135°. MS: a) fast atom bombardment positive ionization (FAB): VG ZAB SEQ, with *p*-nitrobenzylalcohol (NBA); b) dissociation chemical ionization (DCI): Kratos MS 80. Optical rotations were determined on a Perkin-Elmer 241 polarimeter in a 10 cm long microcuvette.

***N,N'*-Bis{[(*S*)-2-(*tert*-butylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-(*S*)-valinyl-diamide}-(2*S*,5*S*)-diamino-1,6-diphenylhexane-(3*R*,4*R*)-diol** (HBY 793, **2**): a) By peptide coupling of **7** with **8**: *N*-Ethylmorpholine (0.343 L, 2.695 mol) was added at 0 °C to a solution of dihydrochloride **7** (0.750 kg, 1.31 mol) in DMF (11.8 L), and the solution was stirred for 5 min. (*S*)-DSNP-OOBt ester **8** (1.354 kg, 2.82 mol) was added in portions within 30 min at 0 °C, and the mixture was stirred for 1 h at 0 °C and then for 30 min at 20 °C. HPLC (250 × 4 mm C18 Nucleosil 5 µm, eluent A: AcOH/H_2O 95:5 +0.1% CF_3CO_2H, eluent B: AcOH/H_2O 5:95 +0.1% CF_3CO_2H, A:B = 65:35, flow 1.0 mL min^{-1}, 25 °C, det. 224 nm, injection of 0.5 mg mL^{-1}; t_{ret} = **2** 15.03 min) indicated complete reaction. The DMF was evaporated in vacuo (4 mbar) over 3 h at a bath temperature of 40–50 °C. The residue was dissolved in CH_2Cl_2 (6.6 L). The solution was washed with saturated aqueous $NaHCO_3$ solution (4.6 L), stirred for 15 min with Na_2SO_4 (0.5 kg), and the drying agent was filtered off. The filtrate was allowed to stand overnight without any change. The solvent was evaporated in vacuo, and the residue (pale yellow oil) was triturated with water (6.6 L); this led to crystallization. The crystals were collected by suction filtration, washed with water (2 L) and dried for 4 d in vacuo (50 mbar) at 40 °C to give a crude product (1.42 kg) with 2–3% H_2O content (Karl–Fischer titration) and 70–80% purity (HPLC). The crude product was dissolved in refluxing EtOH (98%, denatured with toluene, 2.9 L). The temperature was decreased to 74 °C, active charcoal (50 g) added, the mixture refluxed for 5 min and the charcoal removed by suction filtration of the hot mixture through a Seitz filtering pad. The filtrate was cooled and stirred 2 h at 5 °C. The crystals were collected by suction filtration, washed with cold EtOH (0.5 L), and then dried for 18 h in vacuo (100 mbar) at 40 °C to obtain a roughly purified product (0.90 kg) of 93–98% purity (HPLC). This was recrystallized from refluxing EtOAc (3.4 L) and dried in vacuo to give a product (0.78 kg, 53% yield) of 99–99.5% purity (HPLC); M.p. 189–190 °C; $[\alpha]_D^{20} = -23.8$ (c = 1.0 in MeOH); spectra and elemental analysis: vide infra.

b) By vanadium(II)-induced reductive pinacol coupling of **15c**: A solution of VCl_3 (678 g, 4.31 mol) in THF (18 L) was heated at reflux for 5 h. On laboratory scale this time could be reduced to 2 h without any influence on the quality of **2**. Zinc dust (160 g, 2.45 mol) was added in one portion at 20 °C. The mixture was stirred for 30 min at 25 °C, then heated to reflux, and 1,3-dimethyl-2-imidazolidinone (1.6 L), followed by a solution of aldehyde **15c** (1.20 kg, 2.12 mol) in THF (6 L) were added within 15 min. The reaction mixture was heated for 1 h at reflux. TLC (CH_2Cl_2/EtOAc/MeOH 15:5:1, R_f(**2**) = 0.3) indicates quantitative reaction. The mixture was cooled to 20 °C, diluted with 10% aqueous citric acid (19 L), stirred for 15 min, further diluted with EtOAc (18 L), and vigorously stirred for 10 min. The phases were separated, the organic phase was washed with water (3 × 3 L), dried over Na_2SO_4 (2.5 kg) and filtered, and the solvent was evaporated in vacuo. The residue was stirred with water (4 L), filtered under suction, and dried in vacuo. HPLC [250 × 4.0 mm RP18 Nucleosil 120 7 µm C18, eluent: H_2O/CH_3CN 40:60 +0.1% KH_2PO_4, 1.0 mL min^{-1}, 40 °C, det. 225 nm, t_{ret} = **2** ((*S,R,R,S*) configuration of central unit): 13.64 min, (*S,R,S,S*) diastereomer: 14.33 min, (*S,S,S,S*) diastereomer: 15.40 min] indicates a diastereomeric composition of (*S,R,R,S*)/(*S,R,S,S*)/(*S,S,S,S*) = 8.7:1.3:1.0. The crude product (2.4 kg) was dissolved in hot EtOH (8 L). Small amounts of undissolved solid were removed by filtration. The product was allowed to crystallize from the filtrate at 20 °C overnight. It was collected by filtration and recrystallized (only partially dissolved at reflux) from hot EtOAc (1 L). The colourless crystals were collected and dried in vacuo to give **2** (720 g, 60% yield). M.p. 189–190 °C; HPLC (RP18 Nucleosil 120, vide supra): purity >99%; HPLC (250 × 4.0 mm Spherisorb 5 µm ODS3, eluent A: H_2O/CH_3CN/85% aq. H_3PO_4 19:1:0.2 adjusted with NEt_3 to pH 3.0, eluent B: H_2O/CH_3CN/85% aq. H_3PO_4 4:18:0.2 adjusted with NEt_3 to pH 3.0, A:B = 38:62, 1.0 mL min^{-1}, 30 °C, det. 210 nm, run time 160 min, t_{ret} = **2** 35.1 min): purity 98.8%; ^1H NMR (400 MHz, [D$_6$]DMSO, 32 °C, TMS): δ = 0.68 (d, ^3J(H,H) = 6 Hz, 6H, CH_3), 0.76 (d, ^3J(H,H) = 7 Hz, 6H, CH_3), 1.10 (s, 18H, *t*Bu), 1.86 (oct, ^3J(H,H) = 7 Hz, 2H, CH), 2.70 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 5 Hz, 2H, CH), 2.79 (m, 4H, CH), 3.10 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 10 Hz, 2H, CH), 3.26–3.42 (m, 6H, CH_2 and CH), 3.58 (dd, ^3J(H,H) = 13 and 8 Hz, 2H, CH), 4.08 (t, ^3J(H,H) = 8 Hz, 2H, CH), 4.51 (td, ^3J(H,H) = 9 and 5 Hz, 2H, CH), 4.58 (brs, 2H, OH), 7.02 (t, ^3J(H,H) = 7 Hz, 2H, H_{arom}), 7.16 (t, ^3J(*H,H*) = 7 Hz, 4H, H_{arom}), 7.22 (d, ^3J(H,H) = 7 Hz, 4H, H_{arom}), 7.31 (d, ^3J(H,H) = 10 Hz, 2H, H_{arom}), 7.42 (m, 4H, H_{arom}), 7.51 (t, ^3J(H,H) = 7 Hz, 2H, H_{arom}), 7.57 (t, ^3J(H,H) = 7 Hz, 2H, H_{arom}), 7.79 (m, 2H, H_{arom}), 7.92 (d, ^3J(H,H) = 7 Hz, 2H, H_{arom}), 8.12 (d, ^3J(H,H) = 9 Hz, 2H, NH), 8.19 (d, ^3J(H,H) = 9 Hz, 2H, H_{arom}); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.18 (2 × CH_3), 19.23 (2 × CH_3), 22.34 (6 × CH_3), 30.16 (2 × CH), 34.75 (2 × CH_2), 38.59 (2 × CH_2), 39.70 (2 × CH), 45.97 (2 × CH_2), 50.28 (2 × CH), 58.26 (2 × C), 58.54 (2 × CH), 73.13 (2 × CH), 123.96 (2 × CH), 125.27 (2 × CH), 125.58 (4 × CH), 126.09 (2 × CH), 127.13 (2 × CH), 127.29 (2 × CH), 127.71 (4 × CH), 128.44 (2 × CH), 128.97 (4 × CH), 131.55 (2 × C), 133.34 (2 × C), 134.03 (2 × C), 138.87 (2 × C), 170.27 (2 × C), 171.90 (2 × C); IR (KBr): $\tilde{\nu}$ = 3660–3150 (O-H and N-H), 1675 (C=O), 1513 (N-C=O), 1295 and 1117 cm^{-1} (SO_2); MS (FAB): *m/z* (%) = 1153 (17) [*M* + Na^+], 1131 (94) [*M* + H^+], 1113 (19) [*M* + H^+ − H_2O], 716 (100) [*M* + H^+ − DSNP-NH-CH(*i*Pr)-CO], 416 (70) [DSNP-NH-CH(*i*Pr)-CO^+], 388 (92) [DSNP-NH-CH(*i*Pr)$^+$]; inductive coupled plasma (ICP) MS and atomic absorption spectrometry (AAS) measurements: 0.1–0.2 ppm vanadium, 14–21 ppm zinc; $C_{64}H_{82}N_4O_{10}S_2$ (1131.52): calcd. C 67.94, H 7.30, N 4.95, S 5.67; found C 68.0, H 7.4, N 4.8, S 5.6. On laboratory scale 65–72% yield was routinely attained with this procedure.

c) By niobium(III)-induced reductive pinacol coupling of **15c**: A solution of aldehyde **15c** (2.0 g, 3.54 mmol) in deaerated THF (5 mL) was added to a suspension of niobium complex **16** [22] (1.5 g, 5.18 mmol) in deaerated THF (50 mL). The mixture was refluxed and monitored by TLC (vide supra); this indicated quantitative reaction after 1 h. Workup as described for **6b** provides a crude product (1.8 g) with 80% (*S,R,R,S*) configuration and considerable content of by-products (HPLC, vide supra). Purification by flash chromatography and recrystallization from hot EtOAc furnished **2** (0.70 g, 35% yield), with physical constants and spectra identical to those obtained for samples of **2** prepared by V^{II}-induced pinacol coupling of **15c** or from dihydrochloride **5**.

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[(*N*-benzyloxycarbonyl-(*S*)-valinyl)amino]-3,4-dihydroxy-1,6-diphenylhexane (**6a**): a) By peptide coupling of **5** with **17a**: *N*-Benzyloxycarbonyl-(*S*)-valine (**17a**) (1.150 kg, 4.58 mol) was added to a suspension of (2*S*,3*R*,4*R*,5*S*)-2,5-diamino-1,6-diphenyl-3,4-hexanediol dihydrochloride (**5**) [10,13,20] (0.680 kg, 1.82 mol) in DMF (20.4 L), and the mixture was cooled to 0 °C. *N*-Ethyldiisopropylamine (2.47 L, 1.88 kg, 14.57 mol) was added within 5 min, and the mixture was stirred for 15 min at 0 °C to obtain a pale-brown solution. Ethyl cyanooximoacetate [14] (0.651 kg, 4.58 mol) was added, followed after 5 min by TOTU [14] (1.503 kg, 4.58 mol). This second addition was exothermic, and the reaction temperature rose to 7 °C. The mixture was stirred for 20 min at 10 °C and 2 h at 20 °C. DMF (≈18 L) was evaporated in oil-pump vacuo (1 mbar). Saturated aqueous $KHCO_3$ solution (34.0 L) was added to the oily residue leading to a spontaneous crystallization. The suspension was stirred for 30 min at 20 °C and then filtered by

suction. The crystals were washed thoroughly with $KHCO_3$ solution (34.0 L) and with water (34.0 L) and then dried in vacuo at 35 °C, initially with introduction of nitrogen (400 L h^{-1}) to give the crude product (1.44 kg). This was stirred with *tert*-butyl methyl ether (*t*BuOMe, 5.0 L), filtered and dried in vacuo to give colourless crystals (1.23 kg, 88% yield); M.p. 240–242 °C; $[\alpha]_D^{20} = -32.0$ ($c = 1.0$ in MeOH); $[\alpha]_D^{20} = -46.6$ ($c = 1.0$ in THF); ^{1}H NMR (200 MHz, [D$_6$]DMSO, 27 °C, TMS): $\delta = 0.64$ (d, ^3J(H,H) = 7 Hz, 6H, CH$_3$), 0.70 (d, ^3J(H,H) = 7 Hz, 6H, CH$_3$), 1.80 (m, 2H, CH), 2.60–2.83 (m, 4H, CH$_2$), 3.27 (brs, 2H, CH), 3.78 (dd, ^3J(H,H) = 9 and 7 Hz, 2H, CH), 4.47 (brt, ^3J(H,H) = 9 Hz, 2H, CH), 4.78 (brs, 2H, OH), 5.04 (AB system, ^2J(H,H) = 12 Hz, 4H, CH$_2$), 7.00–7.23 (m, 10H, H$_{arom}$), 7.23–7.42 (m, 10H, H$_{arom}$); the amide NH resonance was very broad ($\delta \approx 13$–20); MS (FAB): m/z (%) = 767 (100) [M + H$^+$], 749 (15) [M + H$^+$ − H$_2$O], 534 (14) [M + H$^+$ − Cbz-NH-CH(*i*Pr)-CO], 383 (11) [(M/2)$^+$].

b) By vanadium(II)-induced reductive pinacol coupling of **15a**: A solution of VCl_3 (12.5 g, 79.5 mmol) in THF (330 mL) was refluxed for 5 h and then cooled to 20 °C. Zinc powder (2.88 g, 44.0 mmol) was added and the mixture was stirred 30 min at 20 °C. DMI (29.5 mL, 266 mmol) was added. The mixture was heated to reflux again and a solution of aldehyde **15a** (15.0 g, 39.3 mmol) in THF (110 mL) was added dropwise within 10 min. After 1 h of reflux TLC (CH_2Cl_2/acetone 3:1, R_f(**15a**) = 0.76, R_f(**6a**) = 0.47, DMI 0.38) indicated quantitative, clean reaction. Saturated aqueous citric acid (200 mL) was added, and the mixture was allowed to stand for 12 h. EtOAc (300 mL) was added. The organic phase layer was separated, washed with water (2 × 300 mL), dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was triturated with *t*BuOMe (200 mL), the crystals were collected by filtration and dried in vacuo (9.6 g, 64% yield). M.p. 223–226 °C; HPLC [250 × 4 mm RP18 Nucleosil 100 7 µm, eluent: CH_3CN/H_2O 54:46 + 0.1% CF_3CO_2H, 1.0 mL min^{-1}, 40 °C, det. 210 nm, t_{ret} (*S,R,R,S*) dimer **6a** = 19.70 min, (*S,S,S,S*) und (*S,R,S,S*) dimer 21.1 and 21.5 min (not separated)] indicated a ratio (*S,R,R,S*):[(*S,S,S,S*) + (*S,R,S,S*)] = 70:30. Recrystallization from hot *t*BuOMe provides an analytical sample. M.p. 240–242 °C,with physical and spectral data identical with those of a sample prepared from **5** (vide supra).

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[(*N*-*tert*-butoxycarbonyl-(*S*)-valinyl)amino]-3,4-dihydroxy-1,6-diphenylhexane (6b): a) By vanadium(II)-induced reductive pinacol coupling of **15b**: A solution of VCl_3 (3.58 g, 22.8 mmol) in THF (95 mL) was refluxed for 5 h. It was cooled to 25 °C, zinc powder (0.82 g, 12.5 mmol) added and the mixture stirred for 30 min. DMI (8.4 mL, 76.8 mmol) was added, and the mixture was heated to reflux again. A solution of aldehyde **15b** (4.6 g, 13.2 mmol) in THF (30 mL) was added, and the reaction mixture was refluxed for 1 h. HPLC (125 × 4.0 mm Hyperchrome Shandon Hypersil 5 µm, eluent: cyclohexane/EtOAc 3:1, 1.5 mL min^{-1}, 25 °C, det. 254 nm, t_{ret} **15b** = 2.93 min, (*S,R,R,S*) dimer **6b** 11.39 min, (*S,S,S,S*) dimer [6a] 13.97 min, **19b** 16.38 min) indicated quantitative reaction and a (*S,R,R,S*):(*S,S,S,S*) ratio of 7:1. RP-HPLC (250 × 4 mm RP18 Nucleosil 120 7 µm, eluent A: H_2O + 0.1% CF_3CO_2H, eluent B: CH_3CN/H_2O 4:1 + 0.1% CF_3CO_2H, A:B = 35:65, 1.0 mL min^{-1}, 30 °C, det. 205 nm, t_{ret} (*S,R,R,S*) dimer **6b** = 17.97 min, (*S,S,S,S*) dimer [6a] 20.45 min, (*S,R,S,S*) dimer [6a] 20.72 min) indicated a ratio (*S,R,R,S*):[(*S,S,S,S*) + (*S,R,S,S*)] = 6.5:1. The mixture was cooled to 20 °C. The organic solution was washed twice with a solution of citric acid (8.0 g, 41.6 mmol) in water (20 mL). The organic phase was dried (Na_2SO_4), the solvent evaporated in vacuo and the residue purified by flash chromatography (SiO_2, 35–70 µm, cyclohexane/EtOAc 6:4) to furnish colourless crystals (3.30 g, 72% yield). M.p. 201 °C; ^{1}H NMR (270 MHz, [D$_6$]DMSO, 27 °C, TMS): $\delta = 0.56$ (d, ^3J(H,H) = 7 Hz, 6H, CH$_3$), 0.67 (d, ^3J(H,H) = 7 Hz, 6H, CH$_3$), 1.40 (s, 18H, *t*Bu), 1.68–1.82 (m, 2H, CH), 2.62 (dd, ^2J(H,H) = 18 Hz, ^3J(H,H) = 4 Hz, 2H, CH$_2$), 2.78 (dd, ^2J(H,H) = 18 Hz, ^3J(H,H) = 4 Hz, 2H, CH$_2$), 3.24–3.28 (brs, 2H, CH), 3.62–3.72 (m, 2H, CH), 4.45–4.55 (brm, 2H, CH), 4.70 (brs, 2H, OH), 6.55 (d, ^3J(H,H) = 8 Hz, 2H, NH), 7.05–7.25 (m, 10H, H$_{arom}$), 7.31 (d, ^3J(H,H) = 8 Hz, 2H, NH); IR ($CHCl_3$): $\tilde{\nu}$ = 3340 (O-H), 1690 and 1655 (C=O), 1520 cm^{-1} (N-C=O); MS (FAB): m/z (%) = 699 (77) [M + H$^+$], 599 (27) [M + H$^+$ − Boc], 499 (100) [M + H$^+$ − 2 Boc], 400 (50), 249 (86); $C_{38}H_{58}N_4O_8$ (698.9): calcd C 65.31, H 8.36, N 8.02; found C 65.6, H 8.5, N 7.7.

b) By niobium(III)-induced reductive pinacol coupling of **15b**: A solution of aldehyde **15b** (3.5 g, 10.0 mmol) in deaerated THF (10 mL) was added to a suspension of niobium trichloride dimethoxyethane complex **16** [22] (4.0 g, 13.8 mmol) in deaerated THF (20 mL). The mixture was refluxed and monitored by HPLC (vide supra), which indicated quantitative reaction after 1 h and > 85% (*S,R,R,S*) configuration of the pinacol products. Saturated aqueous citric acid (300 mL) and EtOAc (100 mL) were added. The mixture was stirred for 30 min. During this time a colour change from dark red to pale yellow was observed. The layers were separated and the aqueous phase extracted with EtOAc (100 mL). The combined extracts were washed with 2 N aq. NaOH (20 mL), 2 N aq. HCl (20 mL) and brine (20 mL), and dried (Na_2SO_4). The solvent was evaporated in vacuo to give an oil that crystallized within 2 d at 0 °C. It was purified by flash chromatography to furnish colourless crystals (1.8 g, 52% yield).

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[((*S*)-valinyl)-amino]-3,4-dihydroxy-1,6-diphenylhexane dihydrochloride (7): A suspension of **6a** (1.20 kg, 1.56 mol) in MeOH (37.5 L) was purged with nitrogen, 10% Pd on charcoal (containing 50% H_2O w/w, Degussa type E 10 R/W, 185 g) added and the N_2 purge continued. At 20–25 °C, hydrogen (150 L h^{-1}) was bubbled via a 5 µm frit through the suspension, and nitrogen (2000 L h^{-1}) was introduced above the suspension to avoid the formation of hazardous hydrogen/air mixtures. The pH was kept constant at 6 by the dropwise addition of 1 N methanolic hydrogen chloride. The suspension turned into a clear solution. TLC (CH_2Cl_2/MeOH 4:1, R_f(**6a**) = 0.80, R_f(**7**) = 0.32) indicated quantitative hydrogenolysis after 2.5 h. The solution was purged thoroughly with nitrogen. The catalyst was filtered off, and the solvent of the filtrate evaporated in vacuo. The residue was redissolved in MeOH (5.2 L), *i*PrOH (26.0 L) was added and the solution was slowly concentrated in vacuo. Crystallization of the dihydrochloride commenced at a residual volume of 15–20 L. After the suspension had been concentrated to 10 L, it was cooled for 1 h in an ice bath. The solid was filtered under suction, washed with *i*PrOH (2 × 1 L) and *t*BuOMe (2 × 2 L), and dried at 40 °C in vacuo to furnish colourless crystals (760 g, 85% yield); M.p. 195–210 °C decomp.; $[\alpha]_D^{20} = +32.0$ ($c = 1.0$ in 0.1 N HCl); HPLC (250 × 4.0 mm RP18 Nucleosil 120 7 µm, eluent A: H_2O + 0.1% CF_3CO_2H, eluent B: CH_3CN/H_2O 4:1 + 0.1% CF_3CO_2H, A:B linear from 95:5 to 20:80 within 20 min, 1 mL min^{-1}, 30 °C, det. 254 nm, t_{ret} = 11.93 min): purity 92%. An analytical sample was obtained by recrystallization of the crude product (9 g) from boiling *i*PrOH (30 mL), followed by cooling to 0 °C, filtration, washing of the crystals with MeO*t*Bu (20 mL) and drying in vacuo; purity 98% (HPLC); M.p. 206–208 °C decomp.; ^{1}H NMR (270 MHz, [D$_6$]DMSO, 27 °C, TMS): $\delta = 0.82$ (d, ^3J(H,H) = 7 Hz, 6H, CH$_3$), 0.87 (d, ^3J(H,H) = 7 Hz, 6H, CH$_3$), 2.01 (m, 2H, CH), 2.72 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 5 Hz, 2H, CH), 2.84 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 9 Hz, 2H, CH), 3.34 (brs, 2H, CH), 3.58 (d, ^3J(H,H) = 4 Hz, 2H, CH), 4.35 (m, 2H, CH), 5.04 (brs, 2H, OH), 7.02–7.32 (m, 10H, H$_{arom}$), 8.00 (brs, 6H, NH), 8.27 (d, ^3J(H,H) = 9 Hz, 2H, NH); $C_{28}H_{44}Cl_2N_4O_4$ (571.6): calcd C 58.84, H 7.76, Cl 12.40, N 9.80, O 11.20; found C 59.0, H 7.9, Cl 12.0, N 9.6.

3-(*S*)-(*tert*-Butylsulfonylmethyl)-2-(1-naphthyl)propionic acid OOBt ester (8): A solution of *N,N'*-dicyclohexylcarbodiimide (0.906 kg, 4.39 mol) in THF (2.1 L) was added dropwise to a precooled (− 5 °C) solution of (*S*)-DSNP-OH [15] (1.50 kg, 4.49 mol) in THF (8.4 L), at a speed that maintained the weakly exothermic reaction at between −5 and 0 °C. Depending on the viscosity of the reaction mixture additional THF (3.0–5.0 L) was added and stirring was continued for 15 min at −5 °C. 3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOOBt) [16] (22.5% on ®Dicalite, 3.20 kg, 4.41 mol) was added at −5 to 0 °C. The mixture was stirred for 1 h at 0 °C and for 3 h at 20 °C. The reaction progress was monitored by TLC (100% *t*BuOMe, R_f(DSNP-OH) = 0.0–0.6 (tailing), R_f(**8**) = 0.77). The mixture was cooled to 0 °C, the ®Dicalite was filtered off and washed with THF. The THF of the filtrate was evaporated in vacuo, and *t*BuOMe (10.0 L) added to the residue. The resulting suspension was stirred for 2 h at 0 °C. The precipitate was collected by filtration, washed with cold *t*BuOMe (2.0 L) and dried in vacuo to give pale yellow crystals (2.03 kg, 95% yield) that were used in the subsequent preparation of HBY 793 without further purification. ^{1}H NMR (270 MHz, $CDCl_3$, 27 °C, TMS): $\delta = 1.38$ (s, 9H, CH$_3$), 3.25 (dd, ^2J(H,H) = 13 Hz, ^3J(H,H) = 6 Hz, 1H, CH$_2$), 3.77 (m, 1H, CH$_2$), 3.77 [dd (superimposed on the multiplet with the same δ), ^2J(H,H) = 14, ^3J(H,H) = 7 Hz, 1H, CH$_2$], 3.93 (dd, ^2J(H,H) = 14, ^3J(H,H) = 7 Hz, 1H, CH$_2$), 4.04 (qui, ^3J(H,H) = 6–7 Hz, 1H, CH), 7.42–7.56 (m, 3H, H$_{arom}$), 7.62 (td, ^3J(H,H) = 8 Hz, ^4J(H,H) = 2 Hz, 1H, H$_{arom}$), 8.26 (t, ^3J(H,H) = 8 Hz, 2H, H$_{arom}$), 8.37 (dd, ^3J(H,H) = 8 Hz, ^4J(H,H) = 1 Hz, 1H, H$_{arom}$); IR (KBr): $\tilde{\nu}$ = 1812 (C=O), 1703 (C=O), 1295 and 1113 cm^{-1} (SO_2); MS (FAB): m/z (%) = 480 (100) [M + H$^+$].

Vanadium(II)-induced reductive pinacol coupling of *N*-(benzyloxycarbonyl)-(*S*)-phenylalaninal (14a) (according to procedure B; Table 1, entry 3): A solution of VCl_3 (6.45 g, 41.0 mmol) in THF (170 mL) was refluxed for 3 h. Zinc dust (1.5 g, 22.9 mmol) was added at 25 °C and the mixture was stirred for 30 min at 25 °C. The mixture was reheated to reflux, and DMI (16 mL) followed by a solution of aldehyde **14a** [10,11] (5.7 g, 20.1 mmol) in THF (50 mL) were added within 5 min. The reaction mixture was refluxed for 1 h. Aqueous citric acid (10%, 200 mL) and EtOAc (200 mL) were added at 25 °C, and the mixture was vigorously stirred for 30 min. The organic layer was washed with H_2O (2 × 200 mL) and then evaporated in vacuo. HPLC (250 × 4.0 mm RP18 LiChrospher 100 5 µm C18, eluent A: H_2O + 0.1% NH_4OAc, eluent B: CH_3CN/H_2O 3:1 + 0.1% NH_4OAc, A:B = 35:65, 1.0 mL min^{-1}, 40 °C, det. 215 nm) of the crude product indicated 91% of (2*S*,3*R*,4*R*,5*S*)-2,5-bis[*N*(benzyloxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane (t_{ret} = 16.47 min) and 9% for the sum of its (*S,R,S,S*) and (*S,S,S,S*) diastereomers (t_{ret} = 17.97 and 19.77 min). Trituration of the crude product with CH_2Cl_2 provided colourless crystals (4.2 g, 74% yield). M.p. 221 °C, $[\alpha]_D^{20} = -13$ ($c = 0.01$ in THF), $[\alpha]_D^{20} = -59$ ($c = 1.0$ in MeOH); ref. [10]: M.p. 219.5–220 °C, $[\alpha]_D^{20} = -12.8$ ($c = 0.0137$ in THF).

Vanadium(II)-induced reductive pinacol coupling of *N*-(*tert*-butoxycarbonyl)-(*S*)-phenylalaninal (14b): a) According to procedure A (Table 1, entries 4 and 5): Under argon, Zn powder (360 mg, 5.5 mmol) was added at 20 °C to a solution of $VCl_3(THF)_3$ [28] (3.4 g, 9.1 mmol) in CH_2Cl_2 (60 mL), and the mixture stirred for 30 min. This caused a colour change from red to green. Hexamethyl phosphorous triamide (4 mL, 22.0 mmol) was added followed, after 1 h, by a solution of **14b** [32] (1.0 g, 4.0 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 6 h at 20 °C. Aqueous sodium tartrate solution (10%, 100 mL) was added, and the mixture stirred for 30 min, leading to a decolourization of the organic layer. The layers were

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separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and then evaporated in vacuo. HPLC (125 × 4.0 mm RP18 Purospher 5 μm, eluent A: MeOH/H_2O 60:40, eluent B: MeOH/H_2O 80:20, gradient: 100% A for 6 min, then within 19 min linearly to 100% B; 1.0 mL min^{-1}, 30 °C, det. 215 nm) indicated a diastereomer composition of 60% of (2*S*,3*R*,4*R*,5*S*)-2,5-bis[*N*(*tert*-butoxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane (t_{ret} = 19.88 min), 20% of the (2*S*,3*S*,4*S*,5*S*)-isomer (t_{ret} = 17.52 min) and 20% of the (2*S*,3*R*,4*S*,5*S*)-isomer (t_{ret} = 18.12 min). Column chromatography (180 g SiO_2, 70–200 μm) led to the elution of a mixture of (*S*,*S*,*S*,*S*) and (*S*,*R*,*S*,*S*) isomer (325 mg, 33% yield), followed by the elution of pure (*S*,*R*,*R*,*S*) isomer (490 mg, 49% yield). M.p. 202 °C (ref. [11]: M.p. 200–202 °C), $[\alpha]_D^{28}$ = −8.6 (*c* = 1.0 in DMSO); ^{1}H NMR in accord with ref. [11]. When the reductive coupling of **14b** was conducted in refluxing CH_2Cl_2, HPLC indicated 70% of (*S*,*R*,*R*,*S*), 10% of (*S*,*S*,*S*,*S*), 20% of (*S*,*R*,*S*,*S*) diastereomers, and the total yield of diol products was 85%.

b) According to procedure B (Table 1, entries 6 and 7): A protocol analogous to that described for the coupling of **14a** (vide supra) provided a crude product, which, according to HPLC, was made up of (*S*,*R*,*R*,*S*), (*S*,*S*,*S*,*S*) and (*S*,*R*,*S*,*S*) diasteromers in a 66:11:23 ratio. When the coupling was conducted in THF at 20 °C the ratio was 64:18:18.

***N*-(Benzyloxycarbonyl)-(*S*)-valinyl-phenylalaninal amide (15a)**: DMSO (33 mL, 458 mmol) was added dropwise within 15 min at −70 °C to a solution of oxalyl chloride (30 mL, 358 mmol) in CH_2Cl_2 (1.12 L). The solution was stirred for 15 min at −70 °C. A solution of alcohol **19a** (80.5 g, 209 mmol) in a mixture of DMSO (56 mL) and CH_2Cl_2 (140 mL) was added dropwise over 30 min at −60 to −70 °C. The mixture was stirred at −70 °C for 30 min. NEt_3 (132 mL, 935 mmol) was added dropwise at −70 °C, and the mixture stirred for 15 min at −70 °C. The completeness of the oxidation may be verified by TLC (CH_2Cl_2/EtOAc/MeOH 15:5:1, R_f(**19a**) = 0.48, R_f(**15a**) = 0.61) of an aliquot that had previously been treated with an excess of aqueous citric acid. A solution of glacial acetic acid (53 mL, 926 mmol) in CH_2Cl_2 (160 mL) was added dropwise; this led to an increase in the reaction temperature to −50 °C. A solution of citric acid (53.0 g, 276 mmol) in water (160 mL) was added in one go without cooling; this led to a further increase in the temperature to −10 °C. The organic layer was separated, washed with water (2 × 500 mL), then with brine (300 mL), dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was triturated with iPr_2O. The crystals were filtered and dried in vacuo (72.0 g, 90% yield). M.p. 112–113 °C, $[\alpha]_D^{20}$ = −51.0 (*c* = 1.0 in MeOH); HPLC (250 × 4.0 mm RP18 Nucleosil 120 5 μm C18, eluent: H_2O/CH_3CN 55:45 + 0.1% CF_3CO_2H, 1.0 mL min^{-1}, 40 °C, det. 215 nm, run time 30 min, t_{ret} **15a** = 7.14 min): purity 91%; ^{1}H NMR (200 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 0.79 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 0.80 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 1.91 (oct, ^3J(H,H) = 7 Hz, 1H, CH), 2.80 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 9 Hz, 1H, CH_2), 3.16 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 5 Hz, 1H, CH_2), 3.87 (dd, ^3J(H,H) = 8 and 7 Hz, 1H, CH), 4.33 (m, 1H, CH), 5.02 (s, 2H, CH_2), 7.07–7.40 (m, 11H, H_{arom} and NH), 8.38 (d, ^3J(H,H) = 8 Hz, 1H, NH), 9.44 (s, 1H, CH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 17.93 (CH_3), 19.10 (CH_3), 30.07 (CH), 33.31 (CH_2), 59.52 (CH), 60.00 (CH), 65.32 (CH_2), 126.18 (CH), 127.56 (2 × CH), 127.66 (CH), 128.09 (2 × CH), 128.21 (2 × CH), 129.03 (2 × CH), 136.94 (C), 137.48 (C), 155.98 (C), 171.63 (C), 199.96 (CH); IR (KBr): $\tilde{\nu}$ = 3300 (N-H), 1732 (C=O), 1690 (C=O), 1640 (C=O), 1540 (N-C=O), 1250 cm^{-1} (C-O); MS (FAB): *m*/*z* (%) = 383 (100) [*M* + H$^+$]. The aldehyde was used for the pinacol coupling reaction without further purification. Trituration with EtOAc/*n*-heptane (2:1) furnished a sample (40% yield) of 96% purity (HPLC). M.p. 126 °C, $[\alpha]_D^{22}$ = −56.0 (*c* = 1.0 in MeOH).

***N*-(*tert*-Butoxycarbonyl)-(*S*)-valinyl-(*S*)-phenylalaninal amide (15b)**: DMSO (2.4 mL, 33.4 mmol) was added dropwise within 15 min at −70 °C to a solution of oxalyl chloride (2.1 mL, 25.0 mmol) in CH_2Cl_2 (80 mL). The solution was stirred 15 min at −70 °C. A solution of alcohol **19b** (5.85 g, 16.7 mmol) in a mixture of DMSO (4.0 mL) and CH_2Cl_2 (10.0 mL) was added dropwise and the reaction mixture was stirred for 30 min at −70 °C. NEt_3 (9.4 mL, 66.8 mmol) was added dropwise, and the reaction temperature increased to −60 °C. The mixture was stirred at −70 °C for 15 min. The completeness of the oxidation may be verified by TLC (cyclohexane/EtOAc 60:40, R_f(**19b**) = 0.05–0.3, R_f(**15b**) = 0.61; CH_2Cl_2/acetone 3:1, R_f(**19b**) = 0.46, R_f(**15b**) = 0.77). Aqueous citric acid (15% w/w, 200 mL) was added dropwise without cooling, and the reaction temperature increased to −20 °C. The mixture was stirred for 15 min while it warmed to 0 °C. The aqueous phase was separated, and the organic phase washed successively with saturated aqueous $NaHCO_3$ solution (200 mL), water (200 mL), brine (200 mL), and was then stirred with Na_2SO_4 (20 g) and active charcoal (1 g). The mixture was filtered under suction, and the filtrate was evaporated in vacuo to leave a colourless solid (5.13 g, 88% yield). M.p. 124–125 °C, $[\alpha]_D^{20}$ = −55.4 (*c* = 1.0 in MeOH); HPLC (250 × 4.0 mm RP18 Nucleosil 120 7 μm, eluent: MeOH/H_2O 56:44 + 0.1% CF_3CO_2H, 1.0 mL min^{-1}, 40 °C, det. 207 nm, run time 35 min, t_{ret} **15b** = 9.76 min): purity 92%; ^{1}H NMR (200 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 0.79 (d, ^3J(H,H) = 7 Hz, 6H, 2 × CH_3), 1.36 (s, 9H, *t*Bu), 1.86 (oct, ^3J(H,H) = 7 Hz, 1H, CH), 2.80 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 9 Hz, 1H, CH), 3.16 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 5 Hz, 1H, CH), 3.78 (t, ^3J(H,H) = 7 Hz, 1H, CH), 4.34 (m, 1H, CH), 6.62 (d, ^3J(H,H) = 9 Hz, 1H, NH), 7.12–7.33 (m, 5H, H_{arom}), 8.30 (d, ^3J(H,H) = 7 Hz, 1H, NH), 9.47 (s, 1H, CH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.01 (CH_3), 19.09 (CH_3), 28.07 (3 × CH_3), 30.17 (CH), 33.32 (CH_2), 59.47 (CH), 59.60 (CH), 77.95 (C); 126.18 (CH), 128.10 (2 × CH), 129.01 (2 × CH), 137.53 (C), 155.27 (C), 171.84 (C), 199.98 (CH); IR (KBr): $\tilde{\nu}$ = 1744 (C=O), 1668 (C=O), 1524 cm^{-1} (N-C=O); MS (FAB): *m*/*z* (%) = 349 (17) [*M* + H$^+$], 293 (57) [*M* + H$^+$ − (CH_3)$_2$C=CH_2], 249 (41) [*M* + H$^+$ − Boc], 150 (59), 120 (100). The aldehyde was used for the pinacol coupling reaction without further purification. Trituration with EtOAc/*n*-heptane (2:1) furnished a sample (54% yield) of 99% purity (HPLC). M.p. 125 °C, $[\alpha]_D^{22}$ = −61.9 (*c* = 1 in MeOH).

{[(3*S*)-*tert*-Butylsulfonylmethyl]-[2-(1-naphthyl)]-propionyl}-(*S*)-valinyl-(*S*)-phenylalaninal diamide (15c): DMSO (0.98 L, 13.81 mol) was added dropwise within 45 min at −60 °C to a solution of oxalyl chloride (0.363 L, 4.23 mol) in CH_2Cl_2 (9 L). The solution was stirred 15 min at −60 °C. A solution of alcohol **21** (1.50 kg, 2.65 mol) in CH_2Cl_2 (9 L) was added dropwise within 1 h at −60 °C. The mixture was stirred 30 min at −60 °C. NEt_3 (1.17 L, 8.47 mol) was added dropwise within 30 min at −60 to −55 °C, and the mixture was stirred 1 h at −60 °C. TLC (CH_2Cl_2/EtOAc/MeOH 15:5:1, R_f(**21**) = 0.4, R_f(**15c**) = 0.5; CH_2Cl_2/acetone 3:1, R_f(**21**) = 0.35, R_f(**15c**) = 0.66) of a sample taken after 45 min indicated quantitative reaction. Chlorosulfonic acid (85 mL, 1.28 mol) was added dropwise within 10 min at −60 °C. The cold mixture was transferred into a separatory flask with stirrer, containing 20% aqueous citric acid (6 L), and the mixture was stirred vigorously for 15 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 L). The combined organic layers were washed with water (2 × 6 L), dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo (bath temperature 30–35 °C) to a volume of 4 L; no precipitate was observed at this stage. EtOAc/*n*-heptane (2:1, 10 L) was added, followed by seeding crystals of **15c**. The mixture was cooled with continuous stirring (or rotation) for 1 h to +3 °C. The precipitate was filtered under suction, washed with EtOAc/*n*-heptane (2:1, 3 L) and dried in vacuo to furnish colourless crystals (1.08 kg, 72% yield). M.p. 178–179 °C; $[\alpha]_D^{20}$ = −34.5 (*c* = 1.0 in MeOH); HPLC (250 × 4.0 mm Si 60 LiChrosorb 7 μm, eluent A: *n*-heptane/$CHCl_3$/*i*PrOH 60:37:3 + 0.1% CF_3CO_2H, eluent B: *n*-heptane/$CHCl_3$/*i*PrOH 40:55:5 + 0.1% CF_3CO_2H, 12 min 100% A, within 1 min to 100% B, then 20 min 100% B, 1.0 mL min^{-1}, 25 °C, det. 282 nm, t_{ret} **15c** = 9.74 min, **21** 23.10 min): purity >99%, <0.5% starting material, no diastereomers visible; ^{1}H NMR (270 MHz, $CDCl_3$, 27 °C, TMS): δ = 0.67 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 0.83 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 1.33 (s, 9H, *t*Bu), 2.08 (oct, ^3J(H,H) = 6–7 Hz, 1H, CH), 2.86 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 8 Hz, 1H, CH_2), 3.07 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 7 Hz, 1H, CH_2), 3.16 (dd, ^3J(H,H) = 13 and 3 Hz, 1H, CH), 3.34–3.59 (m, 4H, CH_2), 4.16 (dd, ^3J(H,H) = 9 and 6 Hz, 1H, CH), 4.49 (qua, ^3J(H,H) = 7 Hz, 1H, CH), 5.92 (d, ^3J(H,H) = 9 Hz, 1H, NH), 6.02 (d, ^3J(H,H) = 7 Hz, 1H, NH), 7.00–7.07 (m, 2H, H_{arom}), 7.18–7.33 (m, 5H, H_{arom}), 7.51 (m, 1H, H_{arom}), 7.59 (m, 1H, H_{arom}), 7.73 (m, 1H, H_{arom}), 7.87 (m, 1H, H_{arom}), 8.11 (d, ^3J(H,H) = 8 Hz, 1H, H_{arom}), 9.48 (s, 1H, CH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.22 (CH_3), 19.13 (CH_3), 22.41 (3 × CH_3), 30.35 (CH), 33.31 (CH_2), 34.79 (CH_2), 39.72 (CH), 46.35 (CH_2), 57.98 (CH), 58.36 (C), 59.47 (CH), 123.89 (CH), 125.22 (CH), 125.55 (CH), 126.01 (CH), 126.18 (CH), 127.08 (CH), 127.30 (CH), 128.11 (2 × CH), 128.46 (CH), 128.98 (2 × CH), 131.55 (C), 133.33 (C), 134.02 (C), 137.48 (C), 171.25 (C), 171.81 (C), 199.98 (CH); IR (KBr): $\tilde{\nu}$ = 3295 (N-H), 1724 ((C=O of aldehyde), 1633 ((C=O of amide), 1530 (N-C=O), 1298 and 1114 cm^{-1} (SO_2); MS (FAB): *m*/*z* (%) = 565 (77) [*M* + H$^+$], 416 (100) [*M* + H$^+$ − $PhCH_2CH(NH_2)CHO$], 388 (57) ["416" − CO]; $C_{32}H_{40}N_2O_5S$ (564.8): calcd C 68.06, H 7.14, N 4.96, S 5.68; found C 68.2, H 7.2, N 4.9, S 5.5. On laboratory scale 78–85% yield was routinely attained with this procedure.

***N*-(Benzyloxycarbonyl)-(*S*)-valinyl-(*S*)-phenylalaninol (19a)**: Triethylamine (1.50 L, 10.8 mol) was added at 0 °C within 15 min to a solution of Cbz-valine (**17a**) (0.54 kg, 2.15 mol) in CH_2Cl_2 (5.5 L). L-Phenylalaninol (**18**) (0.328 kg, 2.17 mol) was added in portions. The mixture was stirred for 10 min to obtain a clear solution. A 50% solution of *n*-propyl phosphonic anhydride in EtOAc (1.79 kg, 1.72 L, 2.80 mol) was added dropwise within 1 h. The mixture was warmed to 20 °C and stirred for 2 h. Reaction progress may be monitored by TLC (CH_2Cl_2/MeOH 3:1, R_f(**17a**) = 0.80, R_f(**18**) = 0.15, R_f(**19a**) = 0.37). The mixture was poured into a stirred, cold (5 °C), saturated aqueous solution of $NaHCO_3$ (12.0 L) and vigorously stirred for 30 min. The organic layer was separated and washed with water (2 × 8 mL). The organic phase was stirred for 45 min with Na_2SO_4 (1 kg) and active charcoal (50 g). It was filtered through ®Celite, and the solvent of the filtrate was evaporated in vacuo. The residue was triturated with *n*-heptane (5 L) to give a crystalline product that was collected by filtration and dried in vacuo (0.71 kg, 86% yield). M.p. 155–156 °C; $[\alpha]_D^{20}$ = −46.5 (*c* = 1.0 in MeOH); HPLC (250 × 4.0 mm RP18 Nucleosil 120 5 μm, eluent: H_2O/CH_3CN 55:45 + 0.1% CF_3CO_2H, 1.0 mL min^{-1}, 40 °C, det. 215 nm, run time 30 min, t_{ret} **19a** = 6.50 min): purity 96%; ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C, TMS): δ = 0.82 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 0.91 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 2.10 (oct, ^3J(H,H) = 7 Hz, 1H, CH), 2.18 (brs, 1H, OH), 2.84 (AB part of ABX system, 2H, CH_2), 3.59 (AB part of ABX system, 2H, CH_2), 3.92 (dd, ^3J(H,H) = 8 and 7 Hz, 1H, CH), 4.18 (m, 1H, CH), 5.09 (s, 2H, CH_2), 5.15 (brd, ^3J(H,H) = 8 Hz, 1H, NH), 6.30 (brd, ^3J(H,H) = 8 Hz, 1H, NH), 7.13–7.32 (m, 5H, H_{arom}), 7.36 (s, 5H, H_{arom}); IR (KBr): $\tilde{\nu}$ = 3318/ 3290 (N-H), 1696/ 1654 (C=O), 1537 (N-C=O), 1248 cm^{-1} (C-O); MS (FAB): *m*/*z* (%) = 385 (100) [*M* + H$^+$], 367 (5) [*M* + H$^+$ − H_2O], 341 (9)

$[M - iPr]^+$. An analytical sample was obtained by recrystallization from *t*BuOMe. $C_{22}H_{28}N_2O_4$ (384.5):calcd C 68.73, H 7.34, N 7.29; found C 68.9, H 7.5, N 7.2.

N-(*tert*-Butoxycarbonyl)-(*S*)-valinyl-(*S*)-phenylalaninol amide (19b): NEt_3 (9.6 L, 68.9 mol) was added at 0 °C within 15 min to a solution of L-Boc-valine (**17a**) (3.0 kg, 13.8 mol) in CH_2Cl_2 (3.4 L). L-Phenylalaninol (**18**) (2.11 kg, 13.95 mol) was added in portions within 15 min, and the mixture was stirred until a clear solution was obtained (10 min). A 50% solution of *n*-propyl phosphonic acid anhydride in EtOAc (11.04 kg, 10.6 L, 17.3 mol) was added at 0 °C within 1 h. The mixture was warmed up to 20 °C and allowed to stir for 3 h. TLC (EtOAc/MeOH 95:5, R_f(**19b**) = 0.82) indicated quantitative reaction. The mixture was poured into cold, saturated aqueous $NaHCO_3$ solution (80 L) and stirred for 1 h. The organic layer was separated, then washed with water (2 × 55 L). Na_2SO_4 (1 kg) and active charcoal (0.25 kg) was added, the mixture was stirred for 30 min, filtered through ®Celite, and the filtrate was evaporated in vacuo. The solid residue was stirred with *t*BuOMe (25 L), filtered and dried in vacuo to give colourless crystals (4.54 kg, 94% yield); M.p. 153 °C; $[\alpha]_D^{20} = -52.3$ ($c = 1.0$ in MeOH); HPLC (250 × 4 mm C18 Nucleosil 100 7 µm, eluent A: H_2O/MeOH 80:20 +0.1% CF_3CO_2H, eluent B: H_2O/MeOH 20:80 +0.1% CF_3CO_2H, A:B = 40:60, flow 1.0 mL min^{-1}, 40 °C, det. 205 nm; t_{ret} **19b** = 11.04 min): purity 98.4%; ^{1}H NMR (270 MHz, $CDCl_3$, 27 °C, TMS): δ = 0.82 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 0.91 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 1.45 (s, 9H, *t*Bu), 2.10 (oct, ^3J(H,H) = 7 Hz, 1H, CH), 2.38 (br s, 1H, *OH*), 2.86 (dd, ^2J(H,H) = 13 Hz, ^3J(H,H) = 8 Hz, 1H, CH_2), 2.91 (dd, ^2J(H,H) = 13 Hz, ^3J(H,H) = 8 Hz, 1H, CH_2), 3.57 (dd, ^2J(H,H) = 12 Hz, ^3J(H,H) = 5 Hz, 1H, CH_2), 3.68 (dd, ^2J(H,H) = 12 Hz, ^3J(H,H) = 4 Hz, 1H, CH_2), 3.84 (dd, ^3J(H,H) = 8 Hz,, ^3J(H,H) = 7 Hz, 1H, CH), 4.19 (m, 1H, CH), 4.95 (br d, ^3J(H,H) = 8 Hz, 1H, NH), 6.29 (br d, ^3J(H,H) = 8 Hz, 1H, NH), 7.18–7.34 (m, 5H, H_{arom}); IR (KBr): $\tilde{\nu}$ = 3340/3295 (N-H), 1683/1658 (C=O), 1523 cm^{-1} (N-C=O); MS (FAB): *m/z* (%) = 351 (87) [$M + H^+$], 295 (100) [$M + H^+ - (CH_3)_2C{=}CH_2$], 251 (94) ["295" − CO_2]. An analytical sample was obtained by recrystallization from *t*BuOMe; $C_{19}H_{30}N_2O_4$ (350.5): calcd C 65.12, H 8.63, N 7.99; found C 65.3, H 8.8, N 7.9.

(*S*)-Valinyl-(*S*)-phenylalaninol amide hydrochloride (20): a) From **19b** by acidic cleavage of the Boc group: A gentle stream of HCl gas was bubbled through a suspension of **19b** (3.85 kg, 10.98 mol) in MeOH (11 L). The reaction temperature climbed slowly to 35 °C, gas evolution was observed, and a clear solution was formed. TLC (CH_2Cl_2/MeOH 95:5, R_f(**20**) = 0.05) after 2 h indicated quantitative reaction. The HCl stream was stopped and the solvent evaporated in vacuo. The solid residue was suspended in EtOAc (11 L) at 10 °C. The solid was filtered, washed with EtOAc (3 L) and with iPr_2O/EtOAc (4:1, 8 L), and dried in vacuo to give colourless crystals (2.85 kg, 91% yield); M.p. 83 °C (decomp.); $[\alpha]_D^{20} = +5.2$ ($c = 1.0$ in MeOH); $[\alpha]_D^{20} = +15.1$ ($c = 1.0$ in 0.1 N HCl); HPLC (column eluent, see **19b**, A:B = 90:10, 1.0 mL min^{-1}, 40 °C, det. 205 nm, t_{ret} **20** = 7.54 min): >99.5% purity; ^{1}H NMR (200 MHz, CF_3CO_2D, 27 °C, TMS): δ = 1.14 (d, ^3J(H,H) = 7 Hz, 6H, CH_3), 2.36 (oct, ^3J(H,H) = 7 Hz, 1H, CH), 2.99 (d, ^3J(H,H) = 8 Hz, 2H, CH_2), 3.98 (m, 2H, CH_2), 4.27 (d, ^3J(H,H) = 6 Hz, 1H, CH), 4.50 (m, 1H, CH), 7.17–7.43 (m, 5H, H_{arom}); IR (KBr): $\tilde{\nu}$ = 3660–2400 (br, OH and NH_3^+), 1687 cm^{-1} (C=O); MS (DCI): *m/z* (%) = 251 (100) [$M + H^+$], 233 (5) [$M + H^+ - H_2O$].

The free amine **20** was prepared by adjusting an aqueous solution of the hydrochloride to pH 9 with saturated aqueous Na_2CO_3 solution, extraction with EtOAc, stirring of the extract with Na_2SO_4 and active charcoal, filtration, concentration of the filtrate in vacuo, followed by precipitation with iPr_2O to furnish colourless crystals; M.p. 110 °C; $[\alpha]_D^{20} = -22.0$ ($c = 1.0$ in MeOH); $[\alpha]_D^{20} = +15.1$ ($c = 1.0$ in 0.1 N HCl); ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C, TMS): δ = 0.59 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 0.88 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 1.97 (br s, 3H, OH and NH_2), 2.19 (m, 1H, CH), 2.81 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 9 Hz, 1H, CH_2), 2.92 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 7 Hz, 1H, CH_2), 3.19 (d, ^3J(H,H) = 4 Hz, 1H, CH), 3.62 (dd, ^2J(H,H) = 11 Hz, ^3J(H,H) = 6 Hz, 1H, CH_2), 3.91 (dd, ^2J(H,H) = 11 Hz, ^3J(H,H) = 4 Hz, 1H, CH_2), 4.14 (m, 1H, CH), 7.11–7.35 (m, 5H, H_{arom}), 7.56 (br d, ^3J(H,H) = 6 Hz, 1H, NH); IR (KBr): $\tilde{\nu}$ = 3338 (O-H), 1635 (C=O), 1548 cm^{-1} (N-C=O); MS (DCI): *m/z* (%) = 251 (100) [$M + H^+$], 233 (7) [$M + H^+ - H_2O$]; $C_{14}H_{22}N_2O_2$ (250.3): calcd C 67.17, H 8.86, N 11.19; found C 67.2, H 8.9, N 11.1.

b) From **19a** by hydrogenolysis of the Cbz group: A procedure analogous to that for hydrogenolysis of **6a** (vide supra) furnishes **20** in 85% yield.

{[3(*S*)-*tert*-Butylsulfonylmethyl]-[2-(1-naphthyl)]-propionyl}-(*S*)-valinyl-(*S*)-phenylalaninol diamide (21): A solution of (*S*)-DSNP-OH [15] (1.21 kg, 3.61 mol) in EtOAc (5.0 L), followed by a solution of NEt_3 (0.50 L, 364 g, 3.61 mol) in EtOAc (5.0 L) were added at 22 °C to hydrochloride **20** (1.03 kg, 3.61 mol). At the resulting temperature of 27 °C *N,N'*-dicyclohexylcarbodiimide (0.85 kg, 4.1 mol) was added in two portions within 20 min, keeping the reaction temperature below 45 °C. The mixture was stirred for 2 h and monitored by TLC (CH_2Cl_2/MeOH/AcOH/H_2O 100:10:1:1, R_f(**21**) = 0.54) or by HPLC (250 × 4.0 mm C18 Nucleosil 100 7 µm, eluent A: H_2O/CH_3OH 80:20 +0.1% CF_3CO_2H; eluent B: CH_3OH/H_2O 80:20 +0.1% CF_3CO_2H, A:B = 26:74, 1.0 mL min^{-1}, 40 °C, det. 282 nm, t_{ret} **21** = 12.04 min). The mixture was filtered under suction through a clarifying pad and the solid was washed with EtOAc (7 L). The combined filtrates were washed with 1 N H_2SO_4 (2 × 5 L) and filtered again to attain a good phase separation. The organic layer was washed successively with $NaHCO_3$ solution (7 L), water (5 L) and brine (4 L). It was dried (Na_2SO_4), filtered, and the solvent was evaporated in vacuo to leave a solid residue (2.6 kg). It was largely dissolved in refluxing EtOAc (6 L) and filtered (while hot) to remove small amounts of residual solid. *n*-Heptane (6 L) was added to the hot filtrate, which was then allowed to slowly cool down to ambient temperature overnight. The suspension was stirred for 1 h at 5 °C, the crystals were filtered under suction, washed with iPr_2O/EtOAc (4:1, 4 L) and dried in vacuo to furnish a crude product (1.49 kg) of 92% purity (HPLC, vide infra). The mother liquor was evaporated in vacuo, and the residue (400 g) recrystallized from hot EtOAc/iPr_2O (1 L + 2.5 L) to give a second batch (0.21 kg). The combined first and second batches were recrystallized from EtOAc/iPr_2O to give the pure product (1.51 kg, 74% yield). M.p. 92 °C, $[\alpha]_D^{20} = -20.5$ ($c = 1.0$ in MeOH); HPLC (250 × 4 mm C18 Nucleosil 100 7 µm, eluent A: MeOH/H_2O 20:80 +0.1% CF_3CO_2H, eluent B: MeOH/H_2O 80:20 +0.1% CF_3CO_2H, A:B = 26:74, 1.0 mL min^{-1}, 40 °C, det. 224 nm, t_{ret} **21** = 12.14 min): purity 99.3%; ^{1}H NMR (270 MHz, $CDCl_3$, 27 °C, TMS): δ = 0.68 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 0.80 (d, ^3J(H,H) = 7 Hz, 3H, CH_3), 1.33 (s, 9H, *t*Bu), 2.08 (oct, ^3J(H,H) = 7 Hz, 1H, CH), 2.67 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 8 Hz, 1H, CH_2), 2.82 (dd, ^2J(H,H) = 14 Hz, ^3J(H,H) = 8 Hz, 1H, CH_2), 3.12 (m, 1H, CH), 3.40–3.63 (m, 6H, CH_2), 4.02 (dd, ^3J(H,H) = 7 and 8 Hz, 1H, CH), 4.07 (m, 1H, CH), 6.18 (d, ^3J(H,H) = 8 Hz, 1H, NH), 6.24 (d, ^3J(H,H) = 8 Hz, 1H, NH), 7.05–7.12 (m, 2H, H_{arom}), 7.15–7.29 (m, 3H, H_{arom}), 7.30–7.40 (m, 2H, H_{arom}), 7.47–7.63 (m, 2H, H_{arom}), 7.73–7.82 (m, 1H, H_{arom}), 7.84–7.89 (m, 1H, H_{arom}), 8.10 (d, ^3J(H,H) = 9 Hz, 1H, H_{arom}); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.35 (CH_3), 19.11 (CH_3), 22.40 (3 × CH_3), 30.43 (CH), 34.82 (CH_2), 36.34 (CH_2), 39.72 (CH), 46.25 (CH_2), 52.09 (CH), 58.35 (C), 58.52 (CH), 62.33 (CH_2), 123.87 (CH), 125.24 (CH), 125.57 (CH), 125.73 (CH), 126.04 (CH), 127.11 (CH), 127.28 (CH), 127.95 (2 × CH), 128.48 (CH), 128.96 (2 × CH), 131.54 (C), 133.34 (C), 133.98 (C), 138.98 (C), 170.22 (C), 171.67 (C); IR (KBr): $\tilde{\nu}$ = 3285 (O-H), 1642 (C=O), 1548 (N-C=O), 1290 and 1111 cm^{-1} (SO_2); MS (FAB): *m/z* (%) = 567 (100) [$M + H^+$], 549 (15) [$M + H^+ - H_2O$], 416 (68) [$M + H^+ - PhCH_2CH(NH_2)CH_2OH$], 388 (82) ["416" − CO]; $C_{32}H_{42}N_2O_5S$ (566.8): calcd C 67.82, H 7.47, N 4.94, S 5.66; found C 67.9, H 7.4, N 4.9, S 5.5.

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