Articles

Practical, Stereoselective Synthesis of Palinavir, a Potent HIV Protease Inhibitor

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Palinavir is a potent peptidomimetic-based HIV protease inhibitor. We have developed a highly convergent and stereoselective synthesis which is amenable to the preparation of multikilogram quantities of this compound. The synthetic sequence proceeds in 24 distinct chemical steps (with several integrated, multistep operations) from commercially available starting materials. No chromatographies are required throughout the process, and the final product is purified by crystallization of its dihydrochloride salt to >99% homogeneity.

Introduction

The human immunodeficiency virus (HIV) has been identified as the etiologic agent causing AIDS.[1] The HIV protease enzyme is an essential element of the virus's life cycle and is responsible for processing of the *gag* and *gag-pol* gene products into functional viral enzymes and proteins.[2] Inhibition of the protease leads to the formation of immature, noninfectious virions and results in repression of viral replication.[3] This enzyme is a member of the aspartyl protease family and has been found susceptible to inhibition by peptidomimetic structures.[4] In the last years, an extensive effort has been devoted to the design and development of HIV protease inhibitors as antiviral agents.[5a] Following demonstration of efficacy in human clinical trials, much excitement was raised with the recent approval of several members of this class of compounds for the treatment of AIDS.[5b,c] HIV protease inhibitors are now emerging as key components in therapeutic strategies directed against this deadly disease.

Despite the successes of peptidomimetic structures in producing highly potent inhibitors of HIV protease activity and of viral replication, this approach has usually produced synthetically complex molecules.[4,6] This has become a critical issue in the development of such compounds, since there are strong pressures to maintain treatment cost for AIDS patients at a reasonable level. Some progress has been achieved toward the development of structurally simpler, "nonpeptidic" HIV protease inhibitors; however, they have not yet reached a level of potency comparable to that of substrate-based inhibitors, and their efficacy in clinical trials remains to be demonstrated.[7] Most promising compounds to date incorporate three to six chiral centers within their framework, imposing a formidable challenge upon the synthetic chemist.[8]

We have been involved in the synthesis and evaluation of HIV protease inhibitors.[9] Recently, our efforts culminated in the discovery of palinavir (**1**) (Figure 1), a highly potent inhibitor of HIV-1 (K_i = 31 pM) and HIV-2 (K_i = 134 pM) protease activities and of viral replication *in*

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(1) (a) Barre-Sinoussi, F.; Chermann, J.-C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Brun-Vezinet, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868. (b) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. *Science* **1984**, *224*, 500.

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(4) (a) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491−2517. (b) Boehme, R. E.; Borthwick, A. D.; Wyatt, P. G. *Ann. Rep. Med. Chem.* **1995**, *30*, 139−149. (c) Thaisrivongs, S. *Annu. Rep. Med. Chem.* **1994**, *29*, 133−144. (d) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305−2314.

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(6) Kempf, D. J.; Sham, H. L. *Curr. Pharmaceut. Des.* **1996**, *2*, 225−246.

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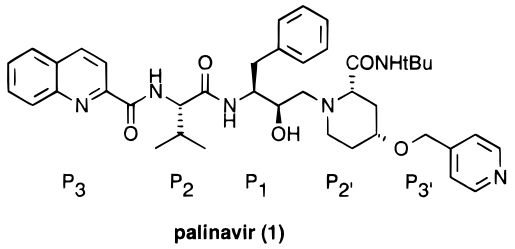


Figure 1.

vitro (EC_{50} = 3−30 nM).[10] Furthermore, palinavir was found to exhibit a favorable pharmacokinetic profile with good to excellent oral bioavailability in several laboratory animal species.[11] The encouraging biological and pharmacological properties of palinavir resulted in the selection of this compound for preclinical evaluation. In support of these studies, large quantities of this inhibitor were required, necessitating the development of a synthetic route to **1** that would be amenable to the preparation of multikilogram quantities. We describe herein the realization of this objective.

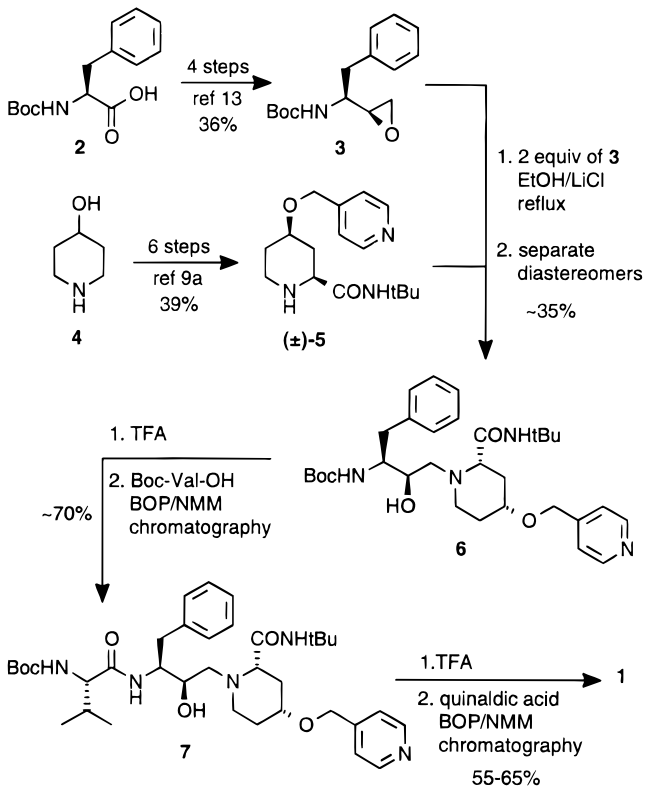
Results and Discussion

Original Synthesis of Palinavir. Palinavir is a peptidomimetic-type inhibitor which possesses five chiral centers (Figure 1). The structure incorporates an acylated L-valine residue in the P_3-P_2 positions, an (*R*)-hydroxyethylamine isostere which serves as the noncleavable transition state mimic, and a novel 4-substituted pipecolic acid amide moiety which interacts with the $S_{1'}$-$S_{3'}$ binding sites of the protease.[12]

The original synthesis of palinavir is depicted in Scheme 1.[9ab] Key Boc-epoxide **3** was prepared in four steps and 36% overall yield from **2** following a literature procedure.[13] Pipecolic amide derivative **5** was prepared in racemic form (six steps, 39% overall yield) from 4-hydroxypiperidine **4**.[9a] Coupling a two-fold excess of epoxide **3** with amine **5** was carried out in refluxing ethanol in the presence of LiCl. The 1:1 diastereomeric mixture of compounds produced was separated by chromatography to give the desired isomer **6** in ~35% yield from racemic **5**. Deprotection followed by coupling with *N*-Boc-L-valine using BOP[14] gave **7** after chromatography (70% yield). Finally, deprotection, followed by a second coupling to quinoline-2-carboxylic acid (quinaldic acid) using BOP, and purification by flash chromatography gave pure palinavir **1** in 55-65% yield from **7**.

While this scheme was used extensively during SAR studies leading to the discovery of palinavir, several aspects precluded its use for the preparation of large

Scheme 1



quantities (>10 g) of inhibitor. The preparation of epoxide **3** required the use of diazomethane, restricting the scale of this chemistry to limited amounts of this important building block. Requirements for excess **3** in the coupling with **5**, the racemic nature of the latter, the sequential coupling of valine and quinaldic acid, and the chromatographic purifications all contributed to a low overall efficiency for this process. As a result, a new synthetic scheme had to be elaborated that would be better suited for the preparation of large quantities of material.

Retrosynthetic Analysis. In designing a scaleable synthetic route to **1**, several issues had to be addressed. In addition to establishing effective stereochemical control and optimizing chemical yields, special emphasis was devoted to minimizing purification steps (avoiding chromatographic purifications), implementing integrated multistep procedures and restricting the use of hazardous reagents and/or reaction conditions.

Our convergent retrosynthetic analysis of **1** is shown in Scheme 2. Three key homochiral building blocks **3**, **8**, and **9** were identified as primary targets. Fragment **8** is a derivative of naturally occurring (2*S*,4*R*)-4-hydroxypipecolic acid. The transition state mimic would be introduced as in the original synthesis, in the form of epoxide **3**. Coupling of **3** with **5** leads to amine **10**, the deprotected form of **6** generated en route to **7** in the original synthesis (Scheme 1). Final conversion to palinavir would be acomplished by condensation of **10** with the acylated valine derivative **9**. Last, a protocol would have to be developed for the purification of large quantities of the final product to >99% homogeneity.

Preparation of Palinavir Fragments. Epoxide **3** is a key intermediate in the synthesis of several hydroxyethylamine-based HIV protease inhibitors.[6] Several approaches to this key building block have been reported in the literature and their suitability for large scale

(10) Lamarre, D.; Croteau, G.; Bourgon, L.; Thibeault, D.; Wardrop, E.; Clouette, C.; Vaillancourt, M.; Cohen, E.; Pargellis, C.; Yoakim, C.; Anderson, P. C. *Antimicrob. Agents Chemother.* **1997**, *41*, in press.
(11) Unpublished results.
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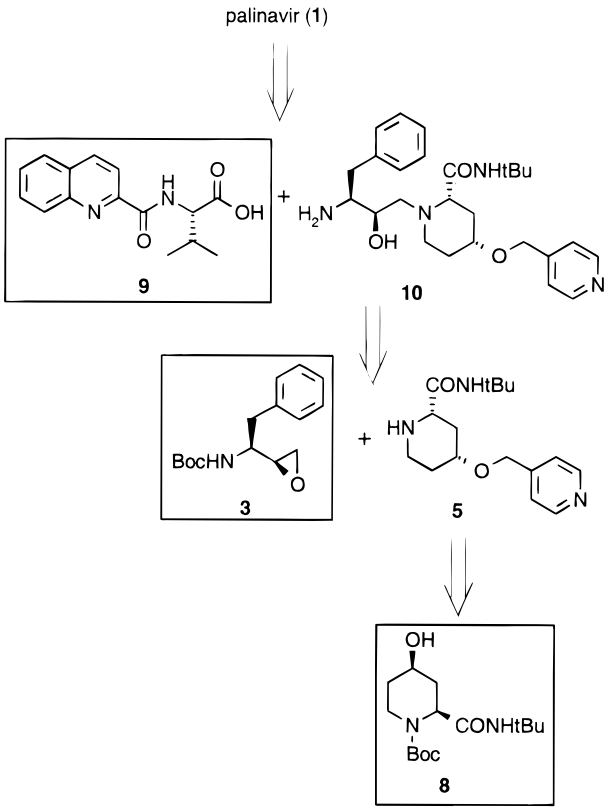
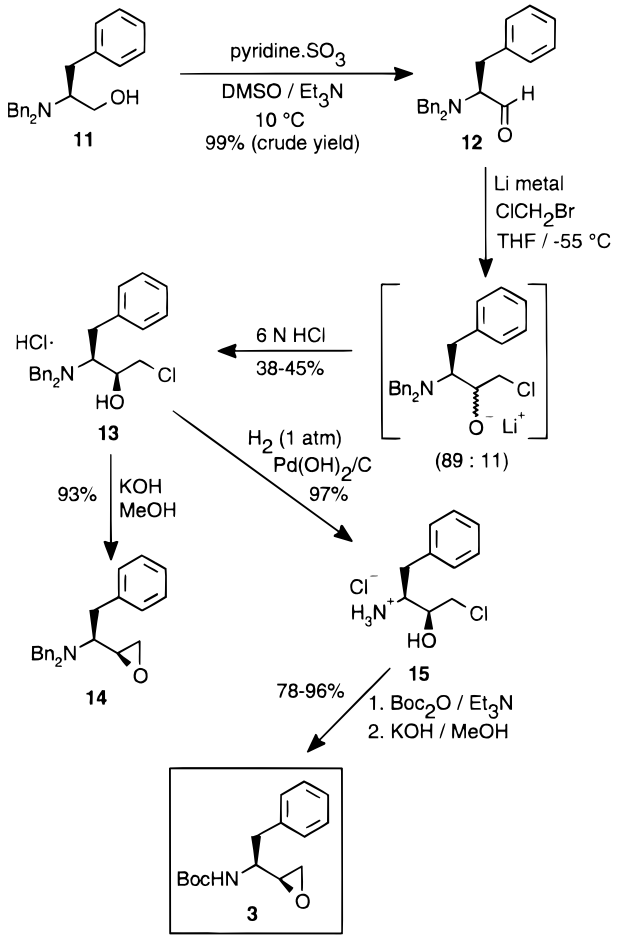
(14) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219.

Scheme 2



Scheme 3



preparations was assessed by us and others.[13,15] In our opinion, however, none of the published procedures appeared directly applicable to our needs. We have therefore developed a novel process for the large scale preparation of **3**, based on the diastereoselective addition of *in situ*-generated (chloromethyl)lithium to *N*,*N*-dibenzylphenylalaninal **12** (Scheme 3).[16] This four-step sequence begins with commercially available *N*,*N*-dibenzylphenylalaninol (**11**)[17] and proceeds in 28−35% yield overall on a kilogram scale, producing **3** in greater than 99.5% isomeric purity. Only one purification (recrystallization of **13**) is required in the sequence. In principle, **13** or *N*,*N*-dibenzylamino epoxide **14** could have been used directly to couple with pipecolic derivative **5**.[16b] However, selective removal of the *N*-benzyl protecting groups from the resulting *N*,*N*-dibenzyl derivative of **10** (Scheme 2) could not be realized in the presence of the picolyl ether substituent. Therefore, **13** was hydrogenolyzed to **15** which was converted to **3** in a two-step/one-pot procedure.

Elaboration of the molecule's right hand side required access to (2*S*,4*R*)-4-hydroxypipecolic acid derivatives. A survey of the literature did not yield useful methods that would have been amenable to scale-up.[18] Recently, we published a route to such derivatives (Scheme 4),[18a] which is based on an asymmetric version of an iminium ion cyclization originally developed by Hays.[19] A simple procedure relying on the selective crystallization of diastereomeric salts was used to provide lactone **17a** of high isomeric purity (93.4%) and 27−29% overall yield from **16**, without the need for chromatography. Lactone **17a** is a useful synthetic intermediate for the preparation of a variety of 4-substituted pipecolic acid derivatives in isomerically pure form, including fragment **8**.[18a] While this approach was amenable to scale-up, we found that a more efficient separation of diastereomers could be achieved at a latter stage of the sequence. The crude 60:40 mixture of lactones **17a**,**b** (prepared in 67−72% yield from alcohol **16**)[18] was converted to the highly crystalline hydroxy amides **18a**,**b** using the Brodroux procedure (*i*PrMgCl/*tert*-butylamine for *in situ* generation of *tert*-

(15) (a) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. K.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656 and references cited therein. (b) Shum, W. P.; Chen, J.; Cannarsa, M. J. *Chirality* **1994**, *6*, 681 and references cited therein. (c) Gurjar, M. K.; Devi, N. R. *Tetrahedron Asymm.* **1994**, *5*, 755. (d) Albeck, A.; Persky, R. *Tetrahedron* **1994**, *50*, 6333. (e) Pégorier, L.; Petit, Y.; Larchevêque, M. *J. Chem. Soc. Chem. Commun.* **1994**, 633. (f) Castejón, P.; Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1995**, *36*, 3019. (g) Green, B. E.; Chen, X.; Norbeck, D. W.; Kempf, D. J. *Synlett.* **1995**, 613. (h) Rotella, D. P. *Tetrahedron Lett.* **1995**, *36*, 5453. (i) Heinsoo, A.; Raidaru, G.; Linask, K.; Järv, J.; Zetterström, M.; Langel, Ü. *Tetrahedron Asymm.* **1995**, *6*, 2245. (j) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.

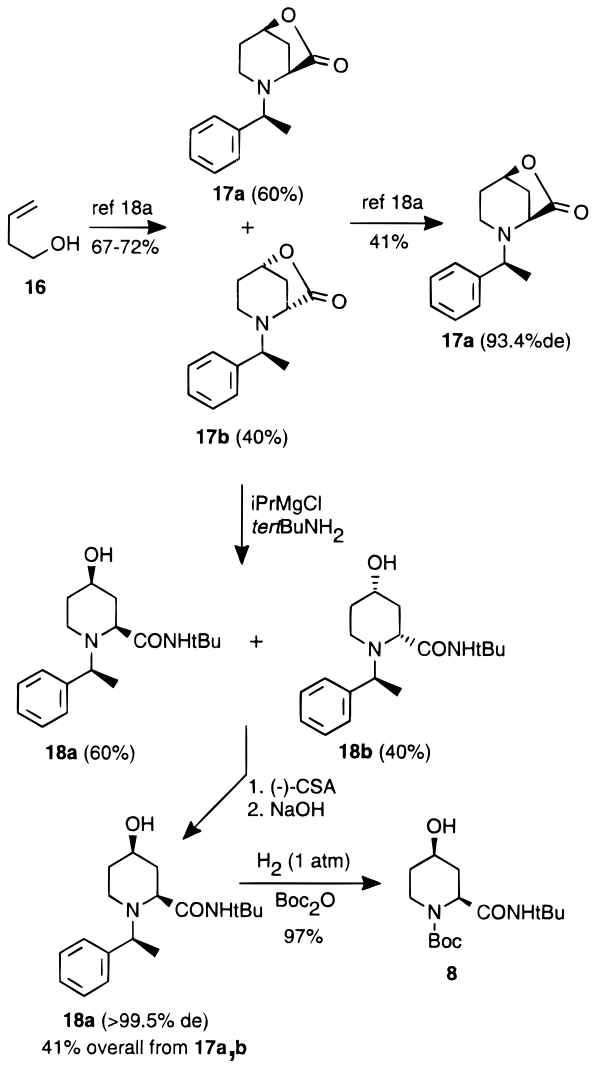
(16) (a) Beaulieu, P. L.; Wernic, D.; Duceppe, J.-S.; Guindon, Y. *Tetrahedron Lett.* **1995**, *36*, 3317. (b) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635. (c) Barluenga, J.; Baragaña, B.; Alonso, A.; Concellón, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 969. (d) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696. (e) NG, J. S.; Przybyla, C. A.; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* **1995**, *51*, 6397.

(17) *N*,*N*-Dibenzyl-L-phenylalaninol (**11**) is commercially available from the Nutrasweet Company.

(18) See references cited in: (a) Gillard, J.; Abraham, A.; Anderson, P. C.; Beaulieu, P. L.; Bogri, T.; Bousquet, Y.; Grenier, L.; Guse, I.; Lavallée, P. *J. Org. Chem.* **1996**, *61*, 2226−2231. (b) Skiles, J. W.; Giannousis, P. P.; Fales, K. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 963−966.

(19) Hays, S. J.; Malone, T. C.; Johnson, G. *J. Org. Chem.* **1991**, *56*, 4084.

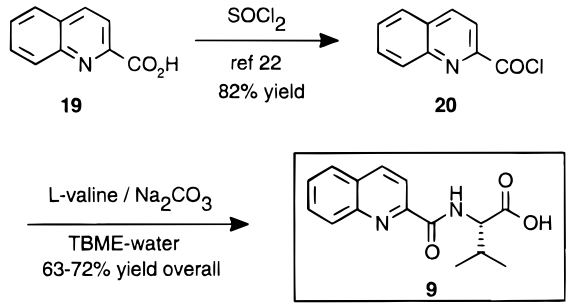
Scheme 4



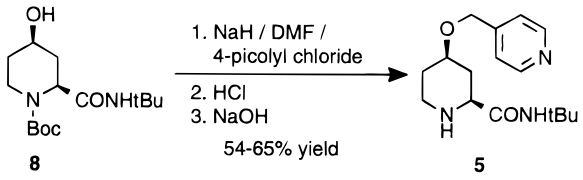
BuNHMgCl).[20] While separation of diastereomeric amides **18a**,**b** could be accomplished by selective crystallizations, recovery was rather poor due to preferential crystallization of the undesired diastereomer **18b**. A more efficient process consisted in salt formation between crude **18a**,**b** and (−)-camphorsulfonic acid (CSA), which allowed subsequent selective crystallization of the (2*S*,4*R*)-isomer **18a** adduct in pure form. Following neutralization with sodium hydroxide, (2*S*,4*R*)-**18a** was obtained in 41% yield overall from crude **17a**,**b** and >99.5% isomeric purity without need for purification. The overall yield from commercially available 3-buten-1-ol (**16**) was 27−29%. Attempts to prepare crystalline addition salts of **18a**,**b** with a variety of inorganic or achiral organic acids failed. However, the low cost of (−)-CSA coupled to the possibility of recycling the resolving agent[21] still made this process most attractive on a large scale.

To complete the synthesis of fragment **8**, we once again had to resort to a protecting group interchange since removal of the *N*-benzylic protecting group by hydrogenolysis was not compatible with the presence of the

Scheme 5



picolyl substituent which is present in compound **5**. Hydrogenolysis of **18a** under standard conditions,[18a] followed by addition of di-*tert*-butyl dicarbonate gave **8** in 97% yield (26−28% overall yield from 3-buten-1-ol, **16**). Crude intermediates were used throughout the synthesis, and the final product was obtained in >99.5% isomeric purity without need for purifications. This process was used to prepare multikilogram quantities of this intermediate. Elaboration to **5** was accomplished by an integrated three-step operation as shown in eq 1. Thus, the alkoxide of **8** was generated using NaH and alkylated with 4-picolyl chloride. The carbamate protecting group



(1)

was then cleaved under acidic conditions and after neutralization, fragment **5** was obtained as a stable, crystalline solid in 60−65% yield.

Preparation of the remaining left-hand side fragment of palinavir was accomplished by conversion of quinoline-2-carboxylic acid **19** to the known acid chloride **20** using thionyl chloride (Scheme 5).[22] This stable, crystalline acid chloride was then used to acylate L-valine using a biphasic system consisting of aqueous sodium carbonate and *tert*-butyl methyl ether (TBME). Acylation of the amino acid using this procedure, followed by crystallization, provided material of high enantiomeric purity (>99.5%) as judged by HPLC analysis on a chiral support and comparison to material derived in a similar fashion from D-valine (see Experimental Section for details). Fragment **9** was obtained as a stable crystalline solid in 63−72% yield overall from **19**.

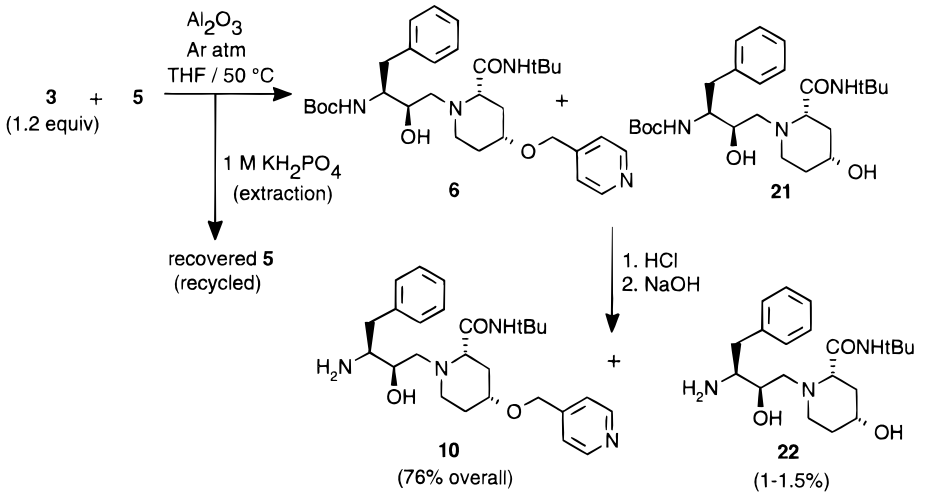
Coupling of Epoxide 3 with Pipecolic Derivative 5. Preparation of Compound 10. In the original synthesis of palinavir (Scheme 1), a two-fold excess of epoxide **3** was required for coupling to amine **5** by refluxing in ethanol in the presence of LiCl. Excess **3** was necessary due to extensive decomposition of the epoxide under these reaction conditions. The desired coupled product **6** was produced in ∼35% yield based on **5**, after separation of diastereomers by flash chromatography.[9a] Several alternative procedures for the preparation of amino alcohols from epoxides and amines were

(20) (a) Bassett, H. L.; Thomas, C. R. *J. Chem. Soc.* **1954**, 1188−1190. (b) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464. On a large scale, the amination of lactones and esters using the less reactive magnesium amides is less hazardous and less costly then the corresponding aluminum reagents.

(21) This is not a true resolution process *per se*, since hydroxy amides **18a**,**b** are diastereomeric in nature.

(22) Davis, J. W., Jr. *J. Org. Chem.* **1959**, *24*, 1691−1694. The acid chloride crystallized as pale yellow needles in 82% yield: mp 94−96 °C dec [lit. mp 96−97 °C].

Scheme 6



investigated.[23] After much experimentation, it was discovered that reaction of **3** (1.2 equiv) with **5** (1 equiv) in THF at 50 °C in the presence of 5× w/w basic alumina (deactivated with 2.5% w/w water),[23a] gave **6** in 76% yield after purification by flash chromatography (Scheme 6). When the reaction was repeated on a larger scale, analysis of the crude, unchromatographed reaction mixture indicated the presence of 10−15% of despicolyl compound **21** (Scheme 6). Reasoning that fragmentation of the picolyl ether might be a consequence of activation of the pyridine ring through *N*-oxide formation in the presence of air, the coupling procedure was performed in carefully degassed solvent, and an argon atmosphere was maintained throughout the reaction. Under these conditions, the formation of side product **21** was reduced to 1−2%. On a kilogram scale, despite a small excess of **3**, amine **5** was never completely consumed (due to partial decomposition of epoxide **3**). Washing of the reaction mixture with 1 M KH_2PO_4 allowed for the recovery and recycling of unreacted **5**. In practice, after removal of unreacted **5**, crude carbamate **6** was not isolated but was deprotected with concd HCl and, following basification with NaOH, crude amine **10** was isolated in 63−70% yield as a viscous syrup (84−97% yield based on recovered **5**). Crude amine **10** (84−97% homogeneous by HPLC and NMR) was contaminated with no more then 1−2% of despicolyl derivative **22** and was used as such for the final coupling leading to palinavir.

Preparation and Purification of Palinavir. Completion of the palinavir synthesis required coupling of amine **10** with valine derivative **9** (Scheme 2). It is difficult to avoid racemization during the coupling of *N*-acylated amino acid fragments due to facile ring formation of the configurationally labile oxazolone, following activation of the carboxyl group (Scheme 7).[24] Small scale experiments were conducted in order to optimize this step, and results are presented in Table 1. (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP),[14] 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU),[25] and DCC/HOBt,[26] all in the presence of *N*-methylmorpholine (NMM), in THF or DMF, gave palinavir **1** and 20−30% of epimer **24**. Activation using pivaloyl chloride[26] at −20 °C in the presence of NMM gave **1** along with 2.5−11% **24** and 6−13% of the pivalyl amide of amine **10** (resulting from coupling of **10** on the *tert*-butyl side of the unsymmetrical anhydride). Activation with isobutyl chloroformate (IBCF)[26] in THF at 0 °C in the

Scheme 7

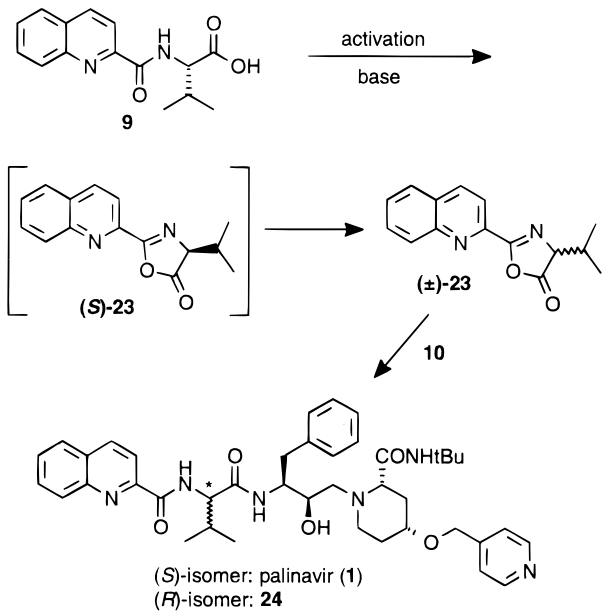


Table 1. Coupling of 10 and 9

coupling conditions	% **1**[a]	% **24**	% others
BOP/NMM/DMF/rt	50−60	30	
TBTU/NMM/DMF/rt	50−60	30	
DCC/HOBt/THF/rt	±70	20	
Me_3CCOCl/NMM/THF/rt	61−79	2.5−11	6−13[b]
$iBuO_2CCl$/NMM/THF/0 °C	60−70	5−10	
$iBuO_2CCl$/NMM/THF/−20 °C	80−85	3	

[a] Estimated by HPLC analysis. [b] Pivaloyl amide of **10**.

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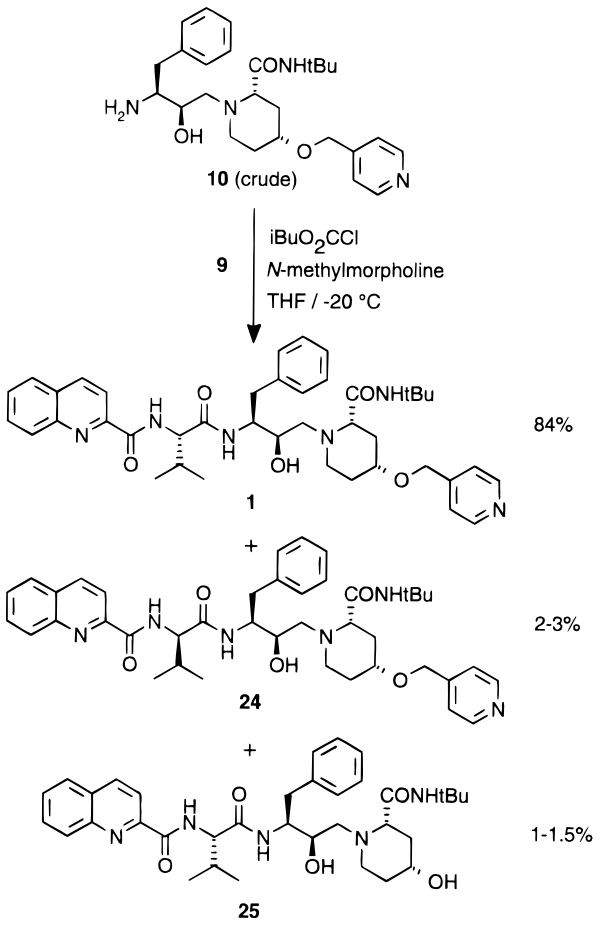
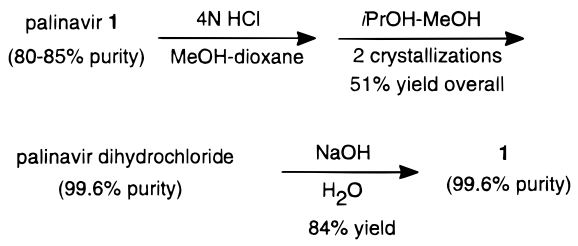
Scheme 8



Scheme 9



presence of NMM gave 60−70% palinavir with 5−10% of **24**. At −20 °C, however, racemization was minimized and formation of epimer **24** limited to ∼3%. On a kilogram scale, similar results were obtained, and **1** was produced with an homogeneity of 80−85% (Scheme 8; the crude product was contaminated with ∼3% of epimer **24** and 1−2% of despicolyl derivative **25**).

For toxicology studies, we desired material of >99% homogeneity. While palinavir was easily purified by flash chromatography on a small scale, this was not practical for large quantities. In a purified state, palinavir is a white amorphous solid that could not be crystallized despite numerous efforts. Purification of the crude material (80−85% homogeneity) resulting from our synthesis was achieved through formation of the crystalline dihydrochloride salt of **1** (Scheme 9). Two recrystallizations of this material (*i*PrOH/MeOH) provided palinavir dihydrochloride of 99.6% homogeneity (HPLC) in approximately 43% yield from **5**. The remaining contaminant (0.4%) was identified as **25** by comparison to an authentic sample. This impurity originates in the coupling of **5** with epoxide **3** (Scheme 6). It is therefore of crucial importance to minimize the fragmentation side reaction resulting in the formation of **21**, since this side product was incorporated in the synthetic sequence and the resulting **25** was the most difficult impurity to remove from palinavir. Careful crystallization of a small sample of the dihydrochloride of **1** in ethanol provided crystals for X-ray analysis, that allowed unambiguous proof of structure and absolute configuration of **1** (see Supporting Information).[27]

Regeneration of palinavir free base from the dihydrochloride was accomplished by slow addition of a dilute aqueous solution of the salt into a large volume of dilute aqueous sodium hydroxide to provide material of 99.6% homogeneity.[28]

Conclusion

Palinavir **1**, a potent HIV protease inhibitor, was prepared on greater than 1 kg scale through a highly convergent and stereoselective synthesis. Several of the necessary 24 chemical steps were combined through the use of multistep integrated sequences and one-pot operations. No chromatographies were required throughout the process, and the final product was purified to >99% homogeneity by recrystallization of the dihydrochloride of **1**. The chemistry described herein should allow preparation of large quantities of this HIV protease inhibitor.

Experimental Section

General. All reagents, solvents and starting materials were obtained from commercial sources and used as received. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR at 100 MHz unless stated otherwise.

(2*S*,4*R*)- and (2*R*,4*S*)-4-Hydroxypipecolic Amides 18a,b. A 3 L three-necked flask equipped with a mechanical stirrer and thermometer was charged with a 2 M solution of iPrMgCl in THF (952 mL, 1.905 mol, 2.2 equiv) and the solution cooled to 5−10 °C under an argon atmosphere. *tert*-Butylamine (209 mL, 1.992 mol, 2.3 equiv) was added dropwise over 1 h, maintaining an internal temperature <20 °C (caution, gas evolution!). The resulting slurry was then stirred for an additional 1 h at room temperature. The reaction mixture was cooled again in an ice−water bath and a 60:40 mixture of diastereomeric lactones **17a**,**b**[18a] (200 g, 0.866 mol) in THF (200 mL) was added dropwise over 1.5 h (internal temperature <20 °C). The reaction mixture was subsequently allowed to warm up to room temperature and stirred overnight.

After cooling in an ice−water bath, the reaction was hydrolyzed by dropwise addition of 4 N HCl (250 mL) over 1 h (internal temperature <30 °C). At this point, the reaction mixture solidified and another 350 mL of 4 N HCl was added more rapidly (30 min), followed by concd HCl until a pH of 7−8 was obtained (ca. 50 mL). The organic layer was separated and the still slightly turbid aqueous phase was extracted with EtOAc (3 × 500 mL). The combined organic phases were washed with water (500 mL), saturated aqueous $NaHCO_3$ (500 mL), and brine (500 mL). After drying ($MgSO_4$), volatiles were removed under reduced pressure to give a 60:40 mixture (determined by ^{1}H NMR) of crude diastereomeric amides **18a**,**b** (mass recovery of crude material was close to theoretical). An analytical sample of this mixture was obtained by flash chromatography on silica gel using 20:80

(27) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K.

(28) The order and rate of addition, the use of dilute solutions, and efficient stirring are important, to avoid precipitation of the monohydrochloride salt of **1**.

hexanes/EtOAc as eluent: R_f 0.40 (EtOAc). IR (KBr) ν 3600−3200, 1655, 1530 cm^{-1}. ^1H NMR and ^{13}C NMR: see below for spectral data on separated diastereomers. FAB-MS *m/z* 305 (MH^+). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.02; H, 9.33; N, 9.03.

When performed on a 2.2 kg batch of lactones **17a**,**b**, diastereomeric hydroxy amides **18a**,**b** were obtained in comparable yield and purity.

(2*S*,4*R*)-4-Hydroxypipecolic Amide 18a, (−)-Camphorsulfonic Acid Salt. The crude mixture of diastereomeric amides **18a**,**b** from above (assume 0.866 mol) was dissolved in absolute EtOH (250 mL) and the solution warmed to 50 °C. (−)-Camphorsulfonic acid (201 g, 0.866 mol) was dissolved in EtOH (200 mL) and the solution warmed to 50 °C and added in small portions (caution, exothermic!) into the pipecolic amide solution. The mixture was cooled to room temperature and then to 5 °C. After standing at 5 °C for 24−48 h, crystallized solids were collected by filtration, washed with 10% EtOH in TBME (3 × 250 mL), and dried under vacuo. Pure (−)-CSA salt of **18a** was obtained as a white crystalline solid (192.88 g, 38.6% yield based on 6.8% w/w EtOH content as determined by ^1H NMR): mp 136−145 °C. $[\alpha]^{25}_D$ −56.2° (*c* 1, MeOH). IR (KBr) ν 3800−2400, 1735, 1670, 1570 cm^{-1}. ^1H NMR (DMSO-d_6) EtOH content: 6.8% w/w. δ 9.87 (t, J = 8.0 Hz, 1H), 8.32 (s, 1H), 7.50 (m, 3H), 7.40 (m, 2H), 5.10 (broad s, 1H), 4.64 (q, J = 6.9 Hz, 1H), 3.69 (broad d, J = 12.0 Hz, 1H), 3.37 (m, 2H), 2.92 (d, J = 14.7 Hz, 1H part of an AB quartet), 2.77−2.67 (m, 1H), 2.49−2.40 (m, 1H), 2.41 (d, J = 14.7 Hz, 1H, part of an AB quartet), 2.23 (dt, J = 18.0, 4.0 Hz, 1H), 2.09 (broad d, J = 12.9 Hz, 1H), 1.94 (t, J = 4.5 Hz, 1H), 1.92−1.81 (m, 2H), 1.78 (d, J = 18.0 Hz, 1H), 1.72 (d, J = 6.9 Hz, 3H), 1.60 (q, J = 11.7 Hz, 1H), 1.38 (s, 9H), 1.32−1.25 (m, 1H), 1.07 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 216.1, 166.9, 131.5, 130.4, 130.0, 128.9, 63.9, 62.7, 62.0, 56.0, 51.0, 47.0, 46.7, 44.0, 42.2, 42.1, 37.4, 30.8, 28.1, 26.4, 24.1, 20.1, 19.5, 16.4. FAB-MS *m/z* 305 (MH^+ of **18a** free base). Anal. Calcd for $C_{28}H_{44}N_2O_6S$ (corrected for 6.8% w/w EtOH content as determined by ^1H NMR): C, 61.96; H, 8.59; N, 4.85. Found: C, 61.85; H, 8.80; N, 4.78. HPLC (Supelcosil LC-ABZ, 10−35% 1% TFA in MeCN/1% TFA gradient in 25 min, 1 mL/min flow rate): **18a** t_R 12.58 min (99.8%, 99.6% de); **18b** t_R 13.56 min (0.2%).

A second crop was isolated from the mother liquors (see below, after isolation of **18b** isomer).

(2*R*,4*S*)-4-Hydroxypipecolic Amide 18b. This material was isolated from the above reaction and used as analytical standard: Combined filtrates and washings from isolation of the (2*S*,4*R*)-isomer (above) were diluted with TBME (500 mL) and water (1 L). NaOH (10 N) (60 mL) was added (pH 10−11). The organic layer was separated and the aqueous phase extracted with TBME (500 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$-decolorizing charcoal), and concentrated under reduced pressure to give a tan-colored solid. This residue was dissolved in hot TBME (250 mL) and the solution allowed to stand overnight at room temperature. The crystallized **18b** was collected and washed with cold TBME (3 × 150 mL). The title compound (50.76 g, 19.3% yield) was obtained as a white crystalline solid: R_f 0.43 (EtOAc). Mp 144−145 °C dec. $[\alpha]^{25}_D$ +12.9° (*c* 1, MeOH). IR (CH_2Cl_2 film) ν 3600−3200, 1655, 1525 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35 (m, 4H), 7.29−7.23 (m, 1H), 6.85 (s, 1H), 4.02 (q, J = 6.7 Hz, 1H), 3.86 (m, 1H), 3.09 (dd, J = 5.6, 5.4 Hz, 1H), 2.92 (ddd, J = 14.1, 9.9, 3.2 Hz, 1H), 2.87 (d, J = 4.1 Hz, 1H), 2.63 (ddd, J = 13.2, 7.6, 2.9 Hz, 1H), 2.11 (dt, J = 13.7, 3.8 Hz, 1H), 1.87−1.78 (m, 2H), 1.47−1.38 (m, 1H), 1.36 (d, J = 7.0 Hz, 3H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.5, 143.7, 128.2, 126.7, 126.5, 66.3, 62.3, 57.1, 50.2, 40.1, 35.3, 31.6, 28.3, 13.9. FAB-MS *m/z* 305 (MH^+). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.17; H, 9.44; N, 9.21. HPLC (Supelcosil LC-ABZ, 10−35% 1% TFA in MeCN/1% TFA gradient in 25 min, 1 mL/min flow rate): **18a** t_R 12.75 min (<0.1%); **18b** t_R 13.28 min (>99.9%, >99.9% de).

A second crop of **18a**, (−)-CSA salt was obtained from the above mother liquors: The combined filtrate and washings from the recovery of **18b** were concentrated to a dark brown solid that was dissolved in hot absolute EtOH (60 mL). (−)-CSA (62 g, 0.267 mol) in hot EtOH (60 mL) was added slowly to the first solution (caution, exothermic!). A second crop of **18a**, (−)-CSA salt was isolated as described previously for the first crop (17.19 g, 12.5% yield based on assumed 6.8% EtOH content). The material had spectral data comparable to that of the first crop. HPLC analysis on a chiral support as described above gave a 97.8% de.

The combined overall yield of **18a** (−)-CSA salt was 210.07 g (42% yield overall from crude lactones **17a**,**b** based on a 6.8% EtOH content). When performed on a 2 kg scale, **18a** (−)-CSA salt was obtained in comparable yield and purity.

(2*S*,4*R*)-4-Hydroxypipecolic *tert*-Butylamide, 18a. 18a (−)-CSA salt (150.00 g, 0.261 mol based on 6.8% w/w EtOH content) was suspended in EtOAc (250 mL), and a solution of NaOH (12.31 g, 0.308 mol) in water (500 mL) was added. The mixture was stirred for 20 min after which the organic phase was separated. The aqueous layer was extracted with EtOAc (2 × 150 mL), the organic extracts combined and washed successively with 1 N NaOH (2 × 100 mL) and brine (100 mL). After drying ($MgSO_4$), volatiles were removed under reduced pressure and the oily residue coevaporated with ether−hexanes until a white solid was obtained. After drying in vacuo **18a** (78.06 g, 98% yield) was obtained, comparable to material previously reported.[18a] HPLC analysis on a chiral support as described previously[18a] and comparison to **18b** gave a 99.6% de. Similar results were obtained on >1 kg scale.

***N*-Boc-(2*S*,4*R*)-4-Hydroxypipecolic Acid *tert*-Butylamide, Fragment 8.** Following the previously described procedure,[18a] **18a** (72.93 g, 0.240 mol) was hydrogenolyzed to give (2*S*,4*R*)-4-hydroxypipecolic acid *tert*-butylamide (48.00 g, 100% yield) comparable to reported material.[18a] Starting from **18b**, (2*R*,4*S*)-4-Hydroxypipecolic acid *tert*-butylamide was also prepared for use as an analytical standard: mp 167−168 °C. $[\alpha]^{25}_D$ +17.9° (*c* 1, MeOH). IR, ^1H NMR, ^{13}C NMR, and MS data identical to that of the (2*S*,4*R*)-isomer. Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.75; H, 10.21; N, 14.02.

(2*S*,4*R*)-4-Hydroxypipecolic acid *tert*-butylamide (43.04 g, 0.215 mol) was converted to (2*S*,4*R*)-**8** as described previously.[18a] The product was obtained in two crops (62.95 g, 97% yield) and was of comparable purity to that reported (>99.5% ee by HPLC on chiral support).[18a] (2*R*,4*S*)-**8** was also prepared for use as an analytical standard: mp 131.5−133 °C. $[\alpha]^{25}_D$ +66.8° (*c* 1, MeOH). IR, ^1H NMR, ^{13}C NMR, and MS data identical to that of the (2*S*,4*R*)-isomer. Anal. Calcd for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.40; N, 9.33. Found: C, 59.93; H, 9.58; N, 9.28. The material was >99.5% ee by HPLC analysis on a chiral support.[18a]

Picolyl Ether 5. A 60% oil dispersion of NaH (312 g, 7.77 mol, 1.3 equiv) was washed with hexanes (2 × 1 L) and suspended in DMF (6 L) under a nitrogen atmosphere. After cooling to 0−5 °C in ice−water, (2*S*,4*R*)-**8** (1796 g, 5.98 mol) was added in portions under vigorous mechanical stirring. The mixture was then stirred for an additional 1.5 h. In the mean time, 4-picolyl chloride hydrochloride (1372 g, 8.37 mol, 1.4 equiv) was dissolved in water (1.5 L) and the solution cooled in ice. Ether (1 L) was added followed by cold 5 N NaOH (1.8 L). Solid $NaHCO_3$ (80 g) was added and the organic layer separated. The aqueous phase (pH 10) was extracted with ether (2 × 1 L), and the combined extracts were washed with brine and dried ($MgSO_4$). DMF (1.2 L) was added to the filtered ether solution and the ether removed under reduced pressure at room temperature.[29] The resulting DMF solution of 4-picolyl chloride was cooled to 5 °C and added dropwise over 2 h to the alcoholate solution, maintaining an internal temperature <10 °C. After completion, the cooling bath was removed and the reaction mixture stirred overnight at room temperature. The resulting brown slurry was poured into water (60 L) and the precipitated solid collected by suction filtration. The solid was washed successively with water (10 L), 10% *i*-PrOH in water (10 L), and water (10 L).

(29) The free base of 4-picoylyl chloride is unstable and polymerizes if the etheral solution is concentrated to dryness. Addition of DMF before removal of ether ensures the free base remains as a dilute solution, thus reducing the extent of self-condensation. The polymerization process is also minimized if the solutions are kept cold.

The resulting wet cake was placed in a 22 L flask, and cold concd HCl (2 L) was added slowly. The mixture was kept at ~15 °C by means of external cooling and stirred 3.5 h. After complete deprotection (as shown by HPLC analysis), the solution was further cooled to 5−10 °C and basified (pH 12) with 10 N NaOH (2.7 L). The mixture was extracted with EtOAc (4 × 1 L), and the combined extracts were washed with brine. After drying over $MgSO_4$-decolorizing charcoal, volatiles were removed under reduced pressure, and the residue was coevaporated twice with THF (1 L). The resulting oil was slowly poured into vigorously stirred hexanes (4 L) and allowed to crystallize. The solid was collected by filtration, washed with 1:1 ether−hexanes and dried in vacuo. The desired product **5** was obtained as a beige colored crystalline solid (944.4 g, 54% yield): R_f 0.28 (9:1 $CHCl_3$/MeOH). Mp 79−81 °C dec. $[\alpha]^{25}_D$ +8.7° (*c* 1, MeOH). IR (KBr) ν 3349, 3233, 2960, 1667, 1514 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.55 (broad, d, J = 4.5 Hz, 2H), 7.25 (broad d, J = 5.5 Hz, 2H), 6.67 (broad s, 1H), 4.64 (d, J = 13.4 Hz, 1H, part of AB), 4.54 (d, J = 13.4 Hz, 1H, part of AB), 3.47 (m, 1H), 3.19 (dt, J = 12.4, 3.8 Hz, 1H), 3.13 (dd, J = 11.2, 3.0 Hz, 1H), 2.67 (dt, J = 12.4, 2.9 Hz, 1H), 2.49 (m, 1H), 2.24 (broad s, 1H), 2.02 (m, 1H), 1.53−1.36 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 171.8, 149.6, 148.5, 121.9, 75.8, 67.1, 58.6, 50.0, 43.1, 36.1, 32.4, 28.5. FAB-MS *m/z* 292 (MH^+). Anal. Calcd for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found: C, 65.61; H, 8.68; N, 14.16. An authentic sample of (2*R*,4*S*)-**5** was prepared as described above but starting from (2*R*,4*S*)-**8** and used as analytical standard. An aliquot of both samples was converted to the corresponding *N*-trifluoroacetamide by heating for 10 min in TFAA and analyzed by HPLC (Chiralcel OD, 15% EtOH in hexane, isocratic, 0.5 mL/min flow rate): (2*S*,4*R*)-**5**, t_R 27.9 min (>99.5% isomeric purity), (2*R*,4*S*)-**5**, t_R 25.0 min (<0.5%).

Quinoline-2-carboxylic Acid L-Valyl Amide, Fragment 9. A 20 L reaction vessel was charged with Na_2CO_3 (916 g, 8.64 mol), water (8 L), and L-valine (503 g, 4.30 mol). After dissolution and cooling to 0 °C, quinoline-2-carboxylic acid chloride (**20**)[22] (747 g, 3.90 mol) was added followed by TBME (4.3 L). After 1 h, the organic layer was separated and extracted with water (2 L). The aqueous phases were combined, acidified with 6 N HCl (3.2 L), and extracted with EtOAc (4 L). The organic extract was washed with brine and dried over $MgSO_4$. Volatiles were removed under reduced pressure and the solid residue crystallized from EtOAc−hexanes to give **9** as a tan-colored crystalline solid in two crops (931 g, 88% yield): mp 135−136 °C. $[\alpha]^{25}_D$ +61.2° (*c* 1.22, MeOH). IR (KBr) ν 3500−2500, 3365, 1730, 1650, 1535, 1420 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.76 (d, J = 8.9 Hz, 1H), 8.31 (m, 2H), 8.17 (d, J = 8.3 Hz, 1H), 7.89 (dd, J = 8.0, 0.6 Hz, 1H), 7.78 (ddd, J = 7.0, 6.9, 1.9 Hz, 1H), 7.63 (ddd, J = 8.2, 7.0, 1.0 Hz, 1H), 4.83 (dd, J = 9.1, 5.0 Hz, 1H), 2.47 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.9, 164.9, 148.9, 146.5, 137.6, 130.1, 129.9, 129.4, 128.1, 127.6, 57.5, 31.4, 19.2, 17.9. CI-MS (isobutane) *m/z* 273 (MH^+). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.17; H, 5.95; N, 10.22. The enantiomeric purity of an aliquot of the product was assessed by HPLC on a chiral support (Chiralcel OD, 5% EtOH in hexane, isocratic, 1 mL/min flow rate) after conversion to the methyl ester (CH_2N_2): t_R 8.28 min, >99.5% (>99.5% ee).

Quinoline-2-carboxylic acid D-valyl amide was prepared from D-valine in an analogous fashion and used as analytical standard: mp 134−136.5 °C. $[\alpha]^{25}_D$ −59.7° (*c* 1.08, MeOH). IR, ^1H NMR, ^{13}C NMR, and MS data identical to that of L-enantiomer. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.08; H, 6.00; N, 10.30. HPLC of methyl ester (Chiralcel OD, 5% EtOH in hexane, isocratic, 1 mL/min flow rate): t_R 10.02 min.

Amine 10. Pipecolic derivative **5** (958 g, 3.29 mol) and epoxide **3**[16a] (1022 g, 3.88 mol, 1.18 equiv) were charged in a 22 L flask equipped with a reflux condenser and mechanical stirrer. THF (12 L) was added and the solution degassed by bubbling Ar through the solution for 1 h. The solution was then heated to 45−50 °C, and basic alumina (5 kg, deactivated by shaking with 2.5% w/w water for 18 h) was added. The resulting slurry was stirred 23 h at 45−50 °C under a slow stream of argon. After cooling to room temperature, the suspension was filtered (3 L of THF for rinses) and the product eluted from the alumina using 10% MeOH in EtOAc (20 L). The filtrate and washings were combined and evaporated under reduced pressure. The residue was dissolved in EtOAc (4 L), and unreacted **5** was extracted into 1 M KH_2PO_4 (3 × 2 L). The aqueous phase was saved for recovery of **5** (see below). The EtOAc layer was extracted with a solution of concd HCl (400 mL) in water (2 L). The aqueous phase was separated and washed with EtOAc (1 L), and concd HCl (1 L) was added. After stirring the aqueous solution for 1 h, deprotection was shown to be complete (TLC). The solution was cooled in an ice−water bath and basified to pH 12 with 10 N NaOH (3 L), maintaining the temperature <40 °C. The oily product was extracted with EtOAc (3 × 1.5 L), washed with water (2 L) and brine (2 L), and dried ($MgSO_4$). Removal of volatiles under reduced pressure and drying to constant weight in vacuo gave crude **10** as a burgundy-colored glass (944 g, 63% yield): R_f 0.48 (7:3 $CHCl_3$/MeOH). $[\alpha]^{23}_D$ −34.9° (*c* 1, MeOH). IR (KBr) ν 3600−2500, 1663, 1601, 1530 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.57 (dd, J = 4.4, 1.6 Hz, 2H), 7.36−7.18 (m, 7H), 6.50 (s, 1H), 4.62 (d, J = 13.4 Hz, 1H, part of AB), 4.53 (d, J = 13.4 Hz, 1H, part of AB), 3.78 (m, 1H), 3.46 (tt, J = 9.9, 4.3 Hz, 1H), 3.40 (dt, J = 12.7, 3.8 Hz, 1H), 3.10 (dt, J = 10.5, 3.8 Hz, 1H), 2.94−2.85 (m, 2H), 2.79 (dd, J = 13.4, 3.5 Hz, 1H), 2.55 (dd, J = 13.4, 10.5 Hz, 1H), 2.45 (dd, J = 13.0, 8.0 Hz, 1H), 2.36 (dd, J = 12.3, 1.9 Hz, 1H), 2.31 (dm, J = 10.2 Hz, 1H), 2.01−1.93 (m, 1H), 1.72−1.58 (m, 2H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 172.1, 150.0, 148.0, 138.7, 129.4, 129.0, 126.9, 122.0, 75.3, 72.3, 68.4, 67.1, 56.6, 56.7, 51.2, 50.5, 38.1, 33.8, 31.5, 30.0, 28.9. FAB-MS *m/z* 455 (MH^+). RP-HPLC (Supelcosil LC-ABZ; 0 → 20% 0.1% TFA−CH_3CN/0.1% TFA in 35 min, then 20 → 100% 0.1% TFA−CH_3CN/0.1% TFA in 10 min; 1.0 mL/min flow rate): **10** t_R 24.0 min (96.4%).

Recovery of unreacted **5**: The KH_2PO_4 extract from above (6 L) was basified to pH 10 with solid NaOH (300 g, 7.5 mol). NaCl (500 g) was added and the solution extracted with EtOAc (3 × 750 mL). The extracts were combined, dried (Na_2SO_4), and concentrated to an oil that was coevaporated with THF (2 × 250 mL). The residue was dissolved in THF (200 mL) and the solution added dropwise (over 3 h) to hexanes (2.5 L) under vigorous stirring. The crystallized solid was filtered, washed with 10% THF in hexanes (2 × 500 mL), and dried in vacuo to give **5** (200 g) of sufficient purity for recycling: mp 89−92 °C. $[\alpha]^{25}_D$ +11.7° (*c* 1, $CHCl_3$).

Crude Palinavir (1). Fragment **9** (980 g, 3.603 mol) and *N*-methylmorpholine (792 mL, 7.2 mol) were dissolved in THF (6 L), and the solution was cooled to −30 °C under a nitrogen atmosphere. Freshly distilled isoobutyl chloroformate (467 mL, 3.6 mol) was added dropwise over 15 min, maintaining an internal temperature <−20 °C. The reaction mixture was stirred for 0.5 h after completion of the addition. Crude amine **10** (1489 g, 3.275 mol) was dissolved in THF (5 L + 1 L rinse) and added as rapidly as possible (1 h), keeping the reaction temperature below −20 °C. The reaction mixture was then stirred 3 h, allowing the temperature to rise to 10 °C after which point it was quenched by addition of water (2 L). THF was removed under reduced pressure and the residue dissolved in EtOAc (3 L). The organic phase was separated and washed successively with water (2 L), 3 N NaOH (2 × 2 L), and water (2 L). Crude **1** was then extracted into a solution of concd HCl (1.6 L) in water (1.5 L). The EtOAc layer was extracted once more with concd HCl (200 mL) in water (500 mL), and the combined aqueous phases were washed with EtOAc (2 × 2 L). Basification to pH 11 with 10 N NaOH (4.5 L), extraction with EtOAc (2 × 1 L), drying ($MgSO_4$-decolorizing charcoal), and evaporation of the solvent under reduced pressure gave crude palinavir (**1**) as a thick brown oil (yield not determined). HPLC analysis (Supelcosil LZ-ABZ, 10−50% 1% TFA in MeCN/1% TFA in 25 min, 1 mL/min flow rate): **1**, t_R 17.80 min (84.1%); **24**, t_R 18.47 min (2.0%); **25**, t_R 19.97 min (1.45%).

Palinavir Dihydrochloride. Crude palinavir, derived as above from amine **10** (1971 g, 4.355 mol), was dissolved in MeOH (4 L) and the solution stirred vigorously as 4 N HCl in dioxane (2.25 L, 9.0 mol) was added. To the resulting hot solution of palinavir dihydrochloride was added 2-propanol (8

L) and the salt allowed to crystallize at room temperature over 24−48 h. The material was filtered using 1:1 2-propanol−acetone (12 L) for rinses and washings and the solid washed with an additional 15 L of acetone. HPLC analysis of this first crop (Supelcosil LZ-ABZ, 10−50% 1% TFA in MeCN/1% TFA in 25 min, 1 mL/min flow rate) gave an homogeneity for **1**·2HCl of 98.27% and 0.96% contamination by **25**. The material was recrystallized by dissolving in hot MeOH (4.5 L), adding 2-propanol (7 L), and allowing to stand at room temperature overnight. The crystallized salt was recovered and washed as above and air-dried overnight to give palinavir dihydrochloride (2018 g) that was shown to be 99.1% homogeneous by HPLC (**25**: 0.55% content). A second recrystallization from hot MeOH (3 L) and isopropanol (6 L), followed by air drying to constant weight gave palinavir dihydrochloride (1750 g, 51% yield) containing 0.25% w/w isopropanol (by ^{1}H NMR): mp 175−185 °C. $[\alpha]^{25}_D$ −13.0° (*c* 1, MeOH). $[\alpha]^{25}_{Hg365}$ +44.9° (*c* 1, MeOH). IR (KBr) ν 3700−2300, 1660, 1555, 1520 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 10.00 (broad s, 1H), 8.88 (d, J = 6.3 Hz, 2H), 8.61 (d, J = 8.4 Hz, 1H), 8.60 (s, 1H), 8.51 (d, J = 9.6 Hz, 1H), 8.35 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 6.0 Hz, 2H), 7.89 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.2 Hz, 2H), 7.08 (t, J = 7.5 Hz, 2H), 6.91 (t, J = 7.3 Hz, 1H), 4.86 (AB quartet, 2H), 4.37 (broad t, J = 7.8 Hz, 1H), 4.21 (d, J = 11.4 Hz, 1H), 4.11 (broad m, 1H), 3.96 (broad m, 1H), 3.80−3.65 (m, 2H), 3.26 (t, J = 7.4 Hz, 1H), 3.15−3.01 (m, 2H), 2.94 (broad d, J = 12.0 Hz, 1H), 2.62 (dd, J = 13.6, 10.6 Hz, 1H), 2.56 ((broad d, J = 12.0 Hz, 1H), 2.20−2.05 (m, 2H), 1.86 (m, 1H), 1.69 (q, J = 11.7 Hz, 1H), 1.31 (s, 9H), 0.81 (d, J = 6.3 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 170.4, 166.4, 163.3, 158.3, 149.5, 145.9, 141.9, 138.6, 138.2, 130.7, 129.3, 129.1, 129.0, 128.3, 128.2, 128.0, 125.9, 124.1, 118.6, 72.3, 68.8, 67.2, 64.8, 58.0, 57.8, 54.4, 51.3, 51.1, 35.4, 34.1, 31.1, 28.2, 19.5, 17.9. FAB-MS *m*/*z* 709 (MH^+ of free base). Anal. Calcd for $C_{41}H_{54}Cl_2N_6O_5$ (corrected for 8% water content as determined by Karl Fisher analysis and 0.25% w/w isopropanol as determined by ^{1}H NMR): C, 58.31; H, 7.29; N, 9.93. Found: C, 57.76; H, 7.25; N, 9.89. Titration of HCl content using NaOH: 2.09 ± 0.03 mol HCl. HPLC homogeneity (Supelcosil LC-ABZ, 10−50% 1% TFA in MeCN/1% TFA in 25 min, 1 mL/min flow rate): palinavir dihydrochloride, t_R 18.24 min (99.51%); **25** t_R 20.39 min (0.33%). HPLC homogeneity (Nova-Pak C_8, 20−80% MeCN/50 mM NaH_2PO_4 in 25 min, 1 mL/min flow rate): palinavir dihydrochloride, t_R 15.52 min (99.67%); **25** t_R 13.52 min (0.33%).

A sample of this material was crystallized slowly from EtOH and yielded crystals suitable for X-ray analysis (see Supporting Information).

Palinavir (1). Palinavir dihydrochloride (2694 g, 3.45 mol, >99% homogeneity) was dissolved in 1 N HCl (14 L) and the solution filtered using 16 L of water for rinses. The clear solution was added dropwise to a vigorously stirred solution of NaOH (800 g, 20 mol) in water (10 L). The resulting slurry was stirred for 1.5 h to ensure complete neutralization. The suspension was filtered and the product washed with water (50 L). Drying under vacuum for 72 h followed by blending and sieving (10 μ sieve) gave palinavir (**1**) as a white amorphous powder (1902 g, 84% yield): mp 100−107 °C. $[\alpha]^{25}_D$ −11.5° (*c* 1, MeOH). IR (KBr) ν 3700−3100, 1660, 1520, 1495 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 5.7 Hz, 2H), 8.48 (d, J = 8.6 Hz, 1H), 8.31 (d, J = 8.6 Hz, 1H, part of AB), 8.22 (d, J = 8.3 Hz, 1H, part of AB), 8.13 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 5.4 Hz, 2H), 7.13 (d, J = 7.3 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 6.57 (s, 1H), 4.61 (d, J = 13.4 Hz, 1H, part of AB), 4.51 (d, J = 13.4 Hz, 1H, part of AB), 4.32 (dd, J = 8.6, 6.4 Hz, 1H), 4.22 (m, 1H), 3.97 (m, 1), 3.47−3.33 (m, 2H), 2.94 (dd, J = 14.3, 4.1 Hz, 1H), 2.89 (d, J = 8.6 Hz, 1H), 2.79−2.72 (m, 1H), 2.77 (dd, J = 14.3, 10.8 Hz, 1H), 2.43 (dd, J = 13.4, 8.3 Hz, 1H), 2.40−2.25 (m, 3H), 1.95 (broad d, J = 12.4 Hz, 1H), 1.65 (q J = 11.8 Hz, 2H), 1.32 (s, 9H), 0.95 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.6, 171.2, 165.0, 149.8, 148.8, 147.9, 146.5, 137.6, 137.5, 130.3, 129.9, 129.5, 129.4, 129.0, 128.8, 128.5, 128.2, 127.7, 126.4, 121.7, 118.8, 75.0, 71.9, 68.1, 66.7, 59.4, 56.9, 54.6, 50.9, 50.2, 34.8, 33.3, 29.8, 29.7, 28.7, 19.6, 17.5. FAB-MS *m*/*z* 709 (MH^+). Anal. Calcd for $C_{41}H_{52}N_6O_5$ (corrected for 0.7% water content as determined by Karl Fisher analysis): C, 68.98; H, 7.42; N, 11.77. Found: C, 68.71; H, 7.47; N, 11.71. HPLC homogeneity (Supelcosil LC-ABZ, 10−50% 1% TFA in MeCN/1% TFA in 25 min, 1 mL/min flow rate): palinavir (**1**), t_R 17.83 min (99.59%); **25** t_R 20.00 min (0.41%). HPLC homogeneity (Nova-Pak C_8, 10−80% MeCN/50 mM NaH_2PO_4 in 25 min, 1 mL/min flow rate): palinavir (**1**), t_R 17.37 min (99.51%); **25** t_R 15.87 min (0.49%).

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Supporting Information Available: ORTEP drawing for palinavir dihydrochloride (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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