# A Highly Efficient Synthesis of Fibrinogen Receptor Antagonist L-734,217 via a Novel Chemoselective Silyl-Mediated Conjugate Addition of δ-Lactams to 4-Vinylpyridine

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A highly practical chromatography-free six-step synthesis of L-734,217 suitable for large scale preparation is described. The key chiral pyridine acid intermediate (*R*)-**1** was prepared in four steps based on a novel chemoselective silyl-mediated conjugate addition of ethyl (2-oxopiperidin-1-yl)acetate to 4-vinylpyridine and a highly productive, recyclable, kinetic resolution with quinine. Subsequent salt breaking/peptide coupling with benzyl 3-(*R*)-aminobutyrate (**2**) in a biphasic system, followed by concomitant hydrogenation of the pyridine ring and debenzylation afforded L-734,217 in 20% overall yield (30% with one recyle) from 2-piperidone. The mechanism of this key conjugate addition to 4-vinylpyridine was studied by $^{13}C$ NMR.

## Introduction

Vascular occlusion by thrombus formation has been implicated as a primary cause of a variety of cerebral and cardiovascular diseases that affect over one million patients within the United States each year.[1] In search of pharmacological inhibitors of these events, a strategy based on the inhibition of plasma fibrinogen binding with the platelet GPIIb/IIIa complex has been demonstrated to have wide-spectrum platelet inhibitory activity without side effects associated with other approaches.[2,3] Thus, extensive efforts have been directed toward the discovery and synthesis of such therapeutic agents.[3,4] L-734,217, a non-peptide, orally active fibrinogen receptor antagonist, was the result of such a search and is currently undergoing clinical studies.[5]

The initial synthetic route to this compound proceeded from 4-piperidineethanol via a 14-step sequence.[6] However, a more concise and practical route was desired. Herein we disclose novel chemistry leading to an efficient, highly practical six-step synthesis of L-734,217 that requires no chromatography and uses readily available starting materials (Scheme 5). The key chiral intermediate (*R*)-**1** was synthesized based on a novel chemoselective silyl-mediated conjugate addition of a 2-piperidone derivative to 4-vinylpyridine and a highly productive, recyclable, kinetic resolution with quinine. These new developments render alternate methods of asymmetric synthesis unnecessary.

Our retrosynthetic analysis is outlined in Scheme 1. We envisioned that a pyridylethylation reaction with a 2-piperidone derivative using 4-vinylpyridine would offer quick access to the racemic pyridine acid **1**, which after an efficient resolution should offer a practical route to (*R*)-**1**. The employment of 4-vinylpyridine not only resolved the availability issue of starting material but also significantly improved the efficiency of the route by having the pyridine moeity acting as a piperidine surrogate thereby avoiding the use of an expensive nitrogen protecting group. After peptide coupling of (*R*)-**1** with the commercially available chiral benzyl β-aminobutyrate **2**,[7,8] concomitant hydrogenation of pyridine to piperidine and debenzylation should afford L-734,217.

## Results and Discussion

**Preparation of Racemic Pyridine Acid 1**. Our initial approach to racemic **1** was to effect a classical conjugate addition[9] of 3-carbethoxy-2-piperidone (**3**) to 4-vinylpyridine followed by hydrolysis−decarboxylation of the carbethoxy group (Scheme 2). The conjugate addition of **3** to 4-vinylpyridine was carried out in refluxing ethanol with catalytic sodium ethoxide in the presence of a trace amount of hydroquinone. Without isolation, the resulting crude adduct **4** was directly saponified and decarboxylated to afford pure compound **5** in 77% overall yield after crystallization. Subsequent N-alkylation with ethyl bromoacetate followed by saponification of the resulting ester **11** afforded the pure racemic pyridine acid **1** in 70% overall yield. Despite the

† Department of Analytical Research.

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(1) (a) Nichols, A. J.; Ruffolo Jr., R. R.; Huffman, W. F.; Poste, G.; Samanen, J. *Trends Pharmacol. Sci.* **1992**, *13*, 413. (b) Coller, B. S. *N. Engl. J. Med.* **1990**, *322*, 248. (c) Ellis, S. G.; Bates, E. R.; Schaible, T.; Weisman, H. F.; Pitt, B.; Topol, E. J. *J. Am. Coll. Cardiology* **1991**, *17*, 89b.

(2) (a) Kleinman, N. S.; Ohman, E. M.; Keriakes, D. J.; Ellis, S. G.; Weisman, H. F.; Topol, E. J. *Circulation* **1991**, *84* (Suppl. II), 522. (b) Aiken, J. W.; Gorman, R. R.; Shebuski, R. J. *Prostaglandins* **1979**, 17, 483.

(3) Blackburn, B. K.; Gadek, T. R. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press, Inc.: San Diego, 1993; Vol. 28, Chapter 10, p 89.

(4) Cheng, S.; Craig, W. S.; Mullen, D.; Tschopp, J. F.; Dixon, D.; Pierschbacher, M. D. *J. Med. Chem.* **1994**, *37*, 1 and references therein.

(5) (a) Duggan, M. E.; Naylor-Olsen, A. M.; Perkins, J. J.; Anderson, P. S.; Chang, C. T.-C.; Cook, J. J.; Gould, R. J.; Ihle, N. C.; Hartman, G. D.; Lynch, J. J.; Lynch, R. J.; Manno, P. D.; Schaffer, L. W.; Smith, R. L. *J. Med. Chem.* **1995**, in press. (b) Duggan, M. E.; Egbertson, M. S.; Ihle, N.; Hartman, G. D.; Turchi, L. M.; Hoffman, W. F. U.S. Patent 5,281,585, Jan 5, 1994.

(6) The initial synthesis of L-734,217[5] required 17 steps (14 linear steps and 3 steps to prepare the *tert*-butyl ester analog of **2**), 11 chromatographies, and several raw materials and reagents that are not readily available in bulk.

(7) Chiral benzyl β-aminobutyrate **2** is commericially available from Celgene Corp., 7 Powder Horn Drive, Warren, NJ 07059.

(8) For a review on enantioselective synthesis of β-amino acids, see: Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3.

(9) Siperko, L. G.; Smith, F. X. *Synth. Commun.* **1979**, *9*, 383, and references therein.

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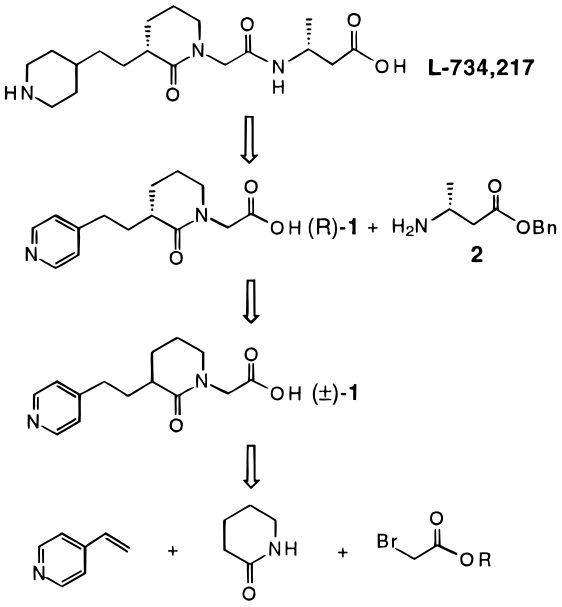
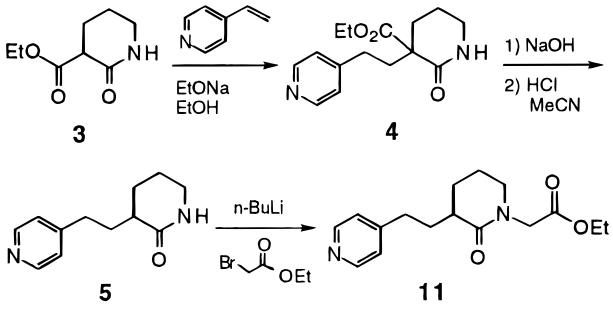
**Scheme 1**



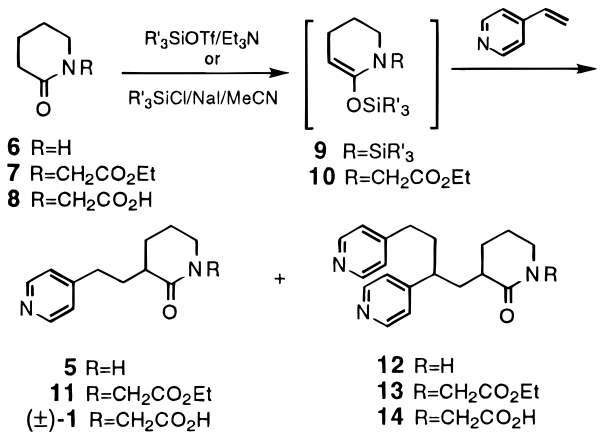

**Scheme 2**




success of this approach, it was not suitable for large scale use due to the hydrophilic nature of compound **5** which made its isolation rather cumbersome. In addition, compound **3** was not available in commercial quantities. Its preparation via Raney nickel reduction of the dimethyl malonate−acrylonitrile Michael adduct proved to be erratic.[10] This prompted us to search for a more direct means to prepare **1** without using **3**.

The obvious choice was to use the readily available 2-piperidone (**6**) as the starting material. However, initial attempts to prepare **5** by adding 4-vinylpyridine to the dianion of **6**[11] gave no reaction.[12] Reasoning that the hardness of the dianion was not compatible with 4-vinylpyridine, we then surmised that the "softer" *N*,*O*-disilyl ketene **9** should react with 4-vinylpyridine, especially if 4-vinylpyridine is further activated by N-silylation (Scheme 3). Thus, treatment of 2-piperidone with 2.2 equiv each of TMSOTf and $Et_3N$ or 2.2 equiv each of TMSCl, $Et_3N$, and NaI in acetonitrile at 0−22 °C gave the presumed silyl ketene *N*,*O*-acetal **9**, which without isolation was directly treated with 4-vinylpyridine at 0

**Scheme 3**




°C to afford pyridine-piperidone **5** in 75−80% assay yield after aqueous quench. Again, due to the high hydrophilic nature of **5**, the pure product was isolated in only 50% yield after extractive workup and purification by silica gel filtration.

One simple solution to this problem was to avoid **5** as an intermediate by reversing the reaction sequence of the conjugate addition and the alkylation step, which should provide the lipophilic compound **11** from piperidone-ester **7**. However, the chemoselectivity of the conjugate addition of **7** to 4-vinylpyridine was in question, since one would expect the addition to take place primarily at the ester α-carbon due to its higher acidity over the lactam α-carbon. Nevertheless, 2-piperidone was first N-alkylated with ethyl bromoacetate, and the resulting piperidone-ester **7** (84%) was reacted with 4-vinylpyridine under the above described conditions (2.2 equiv of silyl reagent). Pleasingly, a 65−70% assay yield of crude **11** was obtained after aqueous workup with negligible loss to the aqueous phase. The main byproducts were the bispyridyl adduct **13** and starting ester **7** at 15−20% and 10−15%, respectively. Surprisingly, none of the ester adduct was detected. The addition of 4-vinylpyridine appears to be completely selective toward the lactam α-carbon over the ester α-carbon. To our best knowledge, the silyl-mediated conjugate addition of 4-vinylpyridine and the observed chemoselectivity are unprecedented. This interesting chemoselectivity is contrary to the p$K_a$ values of carbonyl groups where one would expect that enolization of the ester would precede enolization of the lactam.[13]

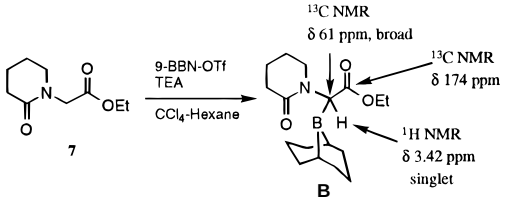
This reversal of expected chemoselectivity from ester to lactam in the silyl-mediated reaction is most likely due

(10) (a) Koelsch, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 2458. (b) Liebman, A. A.; Malarek, D. H.; Dorsky, A. M.; Kaegi, H. H. *J. Heterocycl. Chem.* **1974**, *11*, 1105.

(11) For preparation of the dianion of 2-piperidone, see: Yamamoto, Y.; Morita, Y. *Chem. Pharm. Bull.* **1984**, *32*, 2555.

(12) (a) Conjugate addition of *N*,*N*-dibutylpropionamide to 2-vinylpyridine in DMF at 110 °C with catalytic potassium *tert*-butoxide in 51% yield has been reported: Hintermeier, K.; Brachel, H. Ger. Offen. 2025009, Dec 9, 1971. (b) For various Michael reactions of amide and lactam enolates with enones, see: Heathcock, C. H.; Henderson, M. A.; Oare, D. A; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019.

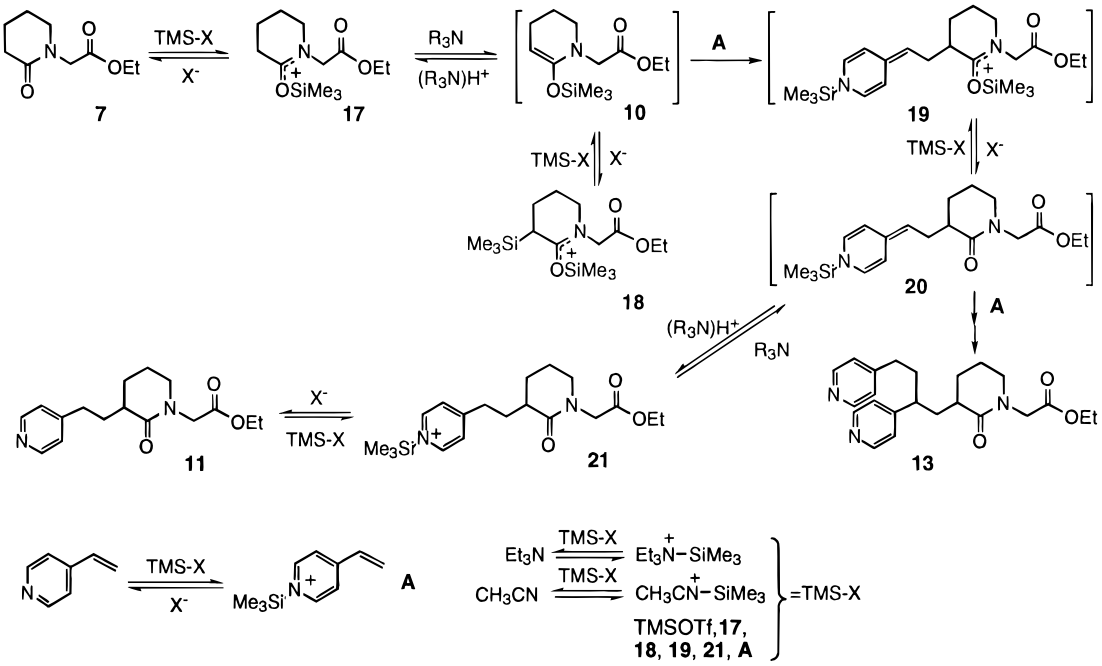
(13) Further support for this contra-thermodynamic phenomenon was that when **7** was treated with 9-BBN-OTf (1.05 equiv) and triethylamine (1.1 equiv) in $CCl_4$ it gave only the *C*-boronate of the ester **B**, presumably via the ester *O*-boronate.[14] None of the products derived from boronation of the lactam were detected.[15]




(14) Irreversible 1,3-boryl shifts are known: Paetzold, P.; Biermann, H.-P. *Chem. Ber.* **1977**, *110*, 3678.

(15) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.

**Scheme 4**



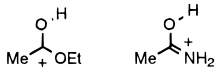

to the higher nucleophilicity[16] of the lactam toward trimethylsilyl triflate and the formation of the more stable imidate cation relative to the ester counterparts. Thus, the following deprotonation and alkylation with *N*-silyl-4-vinylpyridine (**A**) should go to the lactam α-C instead of that of the ester. This explanation seems consistent with $^{13}C$ NMR studies wherein *O*-silyl imidate cations **17** and **18** were observed[17] (see Figure 1 in the supporting information for C13 chemical shift assignments), and no intermediates resulting from silylation of the ester group were detected.

The proposed mechanism for this reaction is outlined in Scheme 4. $^{13}C$ NMR examination of a mixture of piperidone ester **7** and TMS-OTf (1.2 equiv) in $CD_3CN$ at 0 °C showed that lactam ester **7** was completely converted to imidate cation **17**. Upon addition of triethylamine, competition between lactam **7** and triethylamine for available silyl groups was indicated by line broadening in triethylamine and shift averaging in lactam **7** with no observable evidence for intermediate **10**. However, the formation of C,O-bis-silylated **18** was observed when $CD_2Cl_2$ was substituted for $CD_3CN$. In $CD_3CN$ at −20 °C, the α−carbon signal of **17** was notably broadened, possibly due to silyl exchange or to deuterium incorporation from the solvent. In addition, there was evidence of accompanying proton incorporation in the solvent spectral pattern. These observations suggested the formation of intermediate **10**. It appeared that rapid trapping of **10** by electrophiles (TMS-OTf in this case) present in the system could have precluded it from being detected.[18] Subsequent incremental addition of 4-vinylpyridine at 0 °C resulted in an averaged spectra of **21** and **11**, indicating they are in dynamic equilibrium. Presumably, the conjugate addition of **10** to **A** proceeded via **19** and **20**, which was then protonated to give **21** or alternatively underwent another conjugate addition with **A** to give the bis-adduct **13** side product. At the end of the reaction, as all **21** was converted to **11**, almost all triethylamine was silylated (as $R_3N^+SiMe_3$).

Differences between the two solvents used in the NMR study are of importance. A moderating effect of acetonitrile[19] upon the silylating activity of TMS-OTf may be responsible for the finite lifetime of silylated 4-vinylpyridine in that solvent. Such an effect could explain the relatively poor reaction yield in methylene chloride especially when $(i\text{-Pr})_2NEt$ (Hunig's base) was used, both of which have no moderating effect leading to rapid polymerization of 4-vinylpyridine and, thus, little of the desired product.

In an effort to improve the yield, we examined alternative solvents, bases, silylating agents, temperature, and stoichiometry. As mentioned above, a significant solvent effect was observed, with acetonitrile being the best solvent. Methylene chloride is also a good solvent; however, it only works well with sterically less hindered tertiary amine bases. The yield deteriorates with toluene, isopropyl acetate (IPAC), or ethereal solvents as the cosolvent with acetonitrile. $Et_3N$, $Me_2EtN$, and $(Me_2NCH_2)_2$ (TMEDA) all gave similar yield in acetonitrile, whereas Hunig's base almost completely shut down the reaction especially in dichloromethane. It appeared that small tertiary bases were needed to moderate the silylation activity[20] to prevent rapid polymerization of 4-vinylpyridine. Hindered bases such as Hunig's base could not be silylated and therefore have no moderating effect.

(16) Carbonyl oxygen of amides (lactam here) is more basic than that of esters. This is shown by their p$K_a$ values (Data from: *Organic Chemistry*; 3rd ed.; Streitwieser, A.; Heathcock, C. H., Eds.; Macmillan Publishing Co.: New York, 1985):




(17) For formation of *O*-silyl imidate cations, see: (a) Frick, U.; Simchen, G. *Liebigs Ann. Chem.* **1987**, 839. (b) Simchen, G.; Kober, W. *Synthesis* **1976**, 259.

(18) For iodotrimethylsilane-mediated 2-monohalogenation of 4-aza-5α-androstan-3-one steroids, see: King, A. O.; Anderson, R. K.; Shuman, R. F.; Karady, S.; Abramson, N. L.; Douglas, A. W. *J. Org. Chem.* **1993**, *58*, 3384.

(19) For silylation of acetonitrile by TMS-X, see: (a) Emde, H.; Simchen, G. *Synthesis* **1977**, 636. (b) Kira, M.; Hino, T.; Sakurai, H. *J. Am. Chem. Soc.* **1992**, *114*, 6697, footnote 6.

(20) For silylation of tertiary amines, see ref 21, pp 14−15.

Weaker bases such as pyridine do not work well, probably because they are not basic enough to deprotonate intermediate **17**. With regard to silylating agents,[21] TMSOTf and TMSCl/NaI performed with similar efficiency, whereas bis(trimethylsilyl)trifluoroacetamide/cat. TfOH and TMS-Br gave a slower rate of reaction. We found bulky silylating agents such as triethylsilyl, triphenylsilyl, and *tert*-butyldimethylsilyl triflate and also their iodides somewhat suppress the formation of bis-adduct **13** to a level of 10−15% and improve the yield of **11** to 75−80%. Bulky silyl triflates, in general, gave a 5−8% better yield than the corresponding iodides. On the basis of cost and availability, triethylsilyl chloride (TES-Cl)/NaI was chosen for further development.

We found slow addition of 4-vinylpyridine was necessary to minimize the formation of polymerization products. Typically an addition time of 2−3 h was used (0.01−10 mol scale). Attempts to drive the reaction to completion by charging more 4-vinylpyridine did not improve the yield. It appeared that 4-vinylpyridine reacted with both starting piperidone-ester and the product in such a way that there was no net increase of the product. The net result was increased formation of the polypyridyl adduct impurities. Attempts to minimize the formation of bis-adduct **13** by having excess triethylammonium triflate in the reaction, hoping to favor the protonation pathway of **20**, however, did not alter the product−impurity ratio. Also, in theory, the silylating agent is a catalyst; however, when 0.25 equiv of TESCl was used the yield dropped to 50−60%.

The current optimized procedure involves addition of TES-Cl (1.1 equiv) to a 1 M acetonitrile solution of lactam **7**, NaI (1.1 equiv), and $Et_3N$ (1.2 equiv) at 0 °C. After aging at 20 °C for 1 h, 4-vinylpyridine (1.15 equiv) was added over 2 h at 0 °C (0.1 mol), followed by aging for 2 h at the same temperature. The assayed yield at this point was 75%. After extractive workup, the crude pyridine-ester **11** was obtained in 70% assay yield as an 2-propanol (IPA) solution along with two impurities, **7** (8%), and bis-adduct **13** (9%) after a solvent switch. This mixture was used directly in the next step.

Due to the high water-solubility of **1**, the hydrolysis of **11** was carried out under near water-free condition to facilitate the isolation. The optimized procedure involves treating the above 2-propanolic solution of **11** with 50% aqueous NaOH (1.3 eq.). After pH adjustment with concentrated HCl to its isoelectric point (pH 5.5) and removal of NaCl by filtration, the filtrate was azeotropically dried and treated with hexane to crystallize the racemic pyridine acid **1** in 91% yield with 97% purity. The two acid impurities, **8** and **14**, derived from esters **7** and **13** were completely rejected in the crystallization.

**Resolution of Racemic Pyridine Acid 1.** With a practical synthesis of racemic pyridine acid **1** in hand, we next sought an efficient resolution.[22] Initial studies of the chiral phenethylamine diastereomeric salts of racemic **1** indicated that resolution by selective crystallization was possible; however, this material required four recrystallizations from IPA to achieve 96%+ ee in only 32% yield (maximum 50%).

Subsequently, five alkaloids were examined for their ability to form a crystalline solid with pure (*R*)-**1**. Three alkaloids, cinchonine, quinine, and strychnine, gave crystalline solids, whereas cinchonidine and quinidine gave oils. Quinine was chosen for further development based on solubility diffences between diastereomeric salts and cost, availability, and toxicity considerations. The resolution was carried out at a concentration of 3 mL of IPA/g of the salts at 0 °C, which gave 96−98% ee after crystallization and 42−46 wt % recovery. Thermodynamic solubility data have been obtained on both the diastereomeric salts **20** and **21** (Table 1). The data indicated that the solubility difference between the diastereomeric quinine salt is only 4.4 fold at 5.5 °C. At the concentrations used in the resolution (428 mg/g solvent), this would mean at equilibrium, the product crystallized would be 57% ee. However, the growth kinetic of the desired diastereomeric salt **20** is much faster than the undesired diastereomeric salt **21**. Data in Table 2 show that after a 14 h age at 0 °C, the supernatant contains 11 mg/mL of **20** and 162 mg/mL of **21**, which is a 14.7 fold difference between the two salts. These results indicated that the resolution is a kinetic phenomenon. On the basis of thermogravimetric and NMR studies, this large difference in the growth rates was subsequently determined to be related to the fact that the desired (*R*) diastereomeric salt forms an IPA solvate whereas the (*S*) diastereomeric salt does not. Further studies revealed that this kinetic ratio was stable at 0−10 °C for at least 15 h. Thus, there was sufficient time for isolation without disturbing the diastereomeric ratio. Also, it was found that the presence of water was deleterious due to the formation of water solvates which gave no resolution.

**Table 1. Thermodynamic Solubility of Diastereomeric Salts 20 and 21**

| temp (°C) | solubility of **20** (mg/mL of IPA) | solubility of **21** (mg/mL of IPA) | ratio (**21**/**20**) |
|---|---|---|---|
| 5.5 | 14.4 | 63.8 | 4.4 |

**Table 2. Resolution Based on Kinetics of Crystal Growth**

| temp (°C) | concn of **20** (mg/mL of IPA) | concn of **21** (mg/mL of IPA) | ratio (**21**/**20**) |
|---|---|---|---|
| 0 | 11 | 162 | 14.7 |

Based on these results, a reliable resolution procedure was developed. Pyridine acid **1**, quinine, and dry IPA (1 g/3 mL) were combined and then heated at 65 °C for 15 min. The mixture was seeded with >99% ee quinine salt at 45 °C and then aged at 22 °C for 15 h. The mixture was cooled to 10 °C within 30−45 min, and then the solid was filtered. After washing with 3−4 bed volumes of cold THF/hexane (1:1), the solid was vaccum dried. Since the (*R*) diastereomeric salt forms an IPA solvate, the final solid contain ca. 9% IPA.

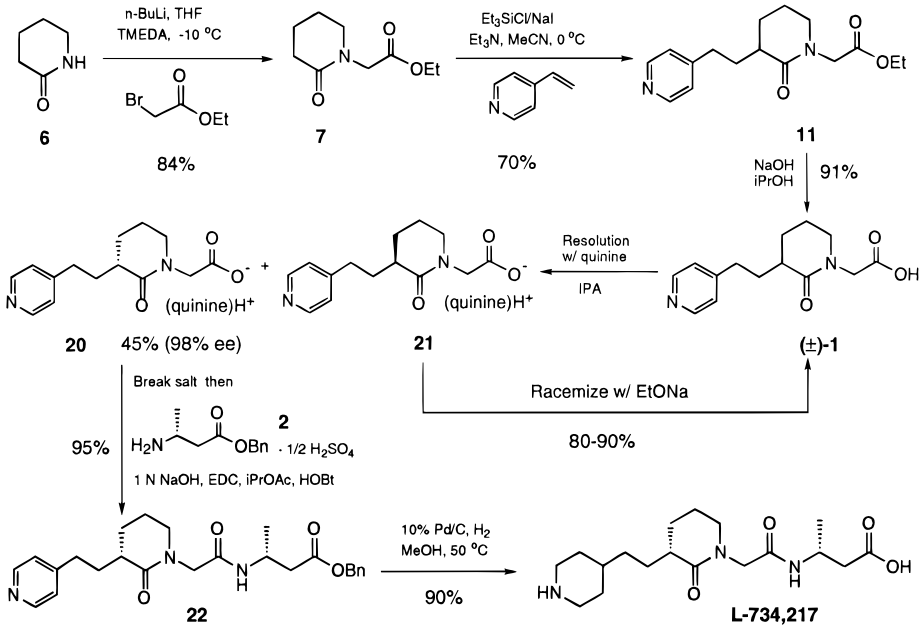
Purity of the resolved pyridine acid quinine salt was 89.5 wt % (40 wt % for pyridine acid alone) with 9.3 wt % of IPA and 1.2 wt % of NaCl. The optical purity of the chiral acid was determined to be 98% ee via the (*R*)-naphthylethylamine derivatives on a normal phase HPLC column (Zorbax SIL) using $CH_2Cl_2$/IPA/$NH_4OH$ (980/17/3) as the mobile phase. The (*R*)-naphthylethylamine derivatives was prepared directly from the quinine salt without having to break salt first, requiring only 10−15 min.

**Recycling of the Mother Liquor.** To further improve the efficiency, we found that the undesired (*S*) diastereomeric salt in the resolution mother liquor could be directly racemized without breaking the salt by

(21) For a review, see: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

(22) *Enantiomers, Racemates, and Resolutions*, Jacques, J.; Collet, A.; Wilen, S. H.; Eds.; John Wiley & Sons: New York, 1981.

**Scheme 5. Six-Step Synthesis of L-734,217**



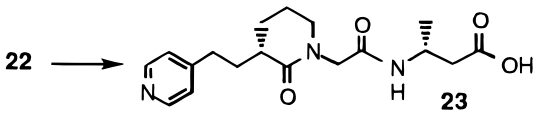

treatment with 2.0 equiv of NaOEt at 85 °C for 3−5 h. Preliminary results indicated that racemization does not take place with 1.2 equiv of NaOEt. After neutralization with concentrated HCl to pH 8.0−8.4 and dilution with THF, the NaCl was filtered. The filtrate was azeotropically dried and reconstituted to a concentration of 1 g of quinine salt per 3 mL of IPA. This mixture was resolved as described above to give the desired pyridine acid quinine salt in 36% yield and 97+% ee. THF was added to reduce the viscosity of IPA and to facilitate and filtration. It also decreased the solubility of NaCl in the solvents.

An attempt to directly racemize the quinine salt by heating the mother liqour in a sealed tube at 150 °C gave no racemization. About 20% of the pyridine acid decomposed.

**Salt Breaking, Peptide Coupling, and Hydrogenation.** With the chiral pyridine acid quinine salt in hand, the salt was partitioned between aqueous sodium hydroxide and IPAC or *tert*-butyl methyl ether (MTBE). After two extractions with IPAC, less than 1 mol % quinine was left in the aqueous layer.

This aqueous solution of pyridine acid (*R*)-**1** was then used directly in the 1-[3-(dimethylamino)propyl]ethylcarbodiimide hydrochloride (EDC)-mediated coupling with benzyl 3(*R*)-aminobutyrate (**2**) in the presence of IPAC as the second phase. In the absence of this organic phase, significant polyamidation of the product ester **22** by amine **2** took placed. This organic layer efficiently removed the product ester **22** from amine **2** as it formed in the aqueous layer, thus eliminating the amidation side reaction. After extractive workup of the reaction, the coupled product **22**, together with trace amount of the quinine left from the last step, was turned over to methanol and then hydrogenated over 10% palladium on carbon at 50 °C under 40 psi hydrogen. After the catalyst is removed, L-734,217 is then crystallized from a mixture of MeOH−$CH_3CN$. All the reduced quinine is rejected in this crystallization according to HPLC. Starting from 98% ee resolved pyridine acid and >99% ee benzyl 3(*R*)-aminobutyrate (**2**), the final product is >99% de and the overall yield is ca. 85% based on quinine salt **20**.

It is interesting to note that in the hydrogenation step, lowering the hydrogenation temperature to 20 °C provided selective debenzylation of **15** without reduction of the pyridine ring. By carefully monitoring the reaction and terminating the reaction after uptake of 1 equiv of hydrogen, product **23** was isolated in 86% yield after crystallization from a mixture of $CH_3CN$−MTBE (1:2).

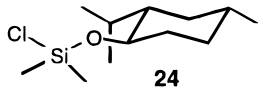



One remaining concern in the coupling reaction is the use of the expensive reagent EDC. Preliminary work with DCC showed that the major difficulty is dissolution of the two starting materials, pyridine acid, and 3-aminobutyrate, into a solvent that will also dissolve DCC. Toward that end, it was found that a 1:1 mixture of THF−$H_2O$ is a good solvent for the coupling reaction, and dicyclohexylurea is removed from the product solution in IPAC as a solid. The yield was nearly quantitative and subsequent hydrogenation gives L-734,217 with no significant difference in impurity profile. Thus, DCC is used as successfully as EDC.

In summary, a highly practical chromatography-free six-step synthesis of L-734,217 suitable for large scale preparation was developed (Scheme 5). The key chiral pyridine acid intermediate (*R*)-**1** was prepared in four steps based on a novel chemoselective silyl-mediated conjugate addition of ethyl (2-oxopiperidin-1-yl)acetate to 4-vinylpyridine and a highly productive, recyclable, kinetic resolution with quinine. Subsequent salt breaking/peptide coupling with benzyl 3(*R*)-aminobutyrate (**2**) in a biphasic system, followed by concomitant hydrogenation of the pyridine ring and debenzylation afforded L-734,217 in 20% overall yield (30% with one recyle) from 2-piperidone.

In an effort to further improve the synthesis, attempts to affect asymmetric conjugate addition of piperidone-ester **5** to 4-vinylpyridine with chiral chlorosilane were explored. Preliminary studies with dimethyl((−)-men-

thyloxy)silyl chloride **24**[23] gave 45% yield of pyridine-ester **7**, however, with no asymmetric induction.




**24**

## Experimental Section

**General.** All reactions were conducted under an atmosphere of dry $N_2$. As necessary, most of solvents and reagents were dried over 3 Å or 4 Å molecular sieves and residual water was determined by Karl Fisher titration. Melting points were uncorrected. $^1$H and $^{13}$C NMR spectra were collected at 250 and 63 MHz, respectively, from samples in the specified deuterated solvent. Assay yields of product were determined by HPLC analysis using the corresponding pure products as standards.

**Preparation of Ethyl (2-Oxopiperidin-1-yl)acetate (7).** A dry 5 L four-necked round bottom flask equipped with a mechanical stirrer, an addition funnel, nitrogen inlet, cooling unit, and thermometer probe was charged with 2-piperidone (160.00 g, 1.61 mol), anhydrous THF (3.36 L), and TMEDA (206.3 g, 1.78 mol). The solution was cooled to −10 °C, and *n*-butyllithium (1.6 M in hexane, 1.06 L, 1.70 mol) was slowly added over a 60 min period, while keeping the internal temperature less than 0 °C. After the addition, the reaction mixture was stirred at 0−5 °C for 1 h. The reaction mixture was cooled to −10 °C, and ethyl bromoacetate (283.1 g, 1.70 mol) was added over 15 min while maintaining the internal temperature less than 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then allowed to warm to 23 °C and aged at this temperature for a 2 h period. The reaction mixture was cooled to −5−0 °C and quenched into a solution of NaCl (170 g) in 2 N HCl (1.78 L), while keeping the internal temperature less than 20 °C. The resulting aqueous phase should be at pH 6. The mixture was transferred to a 12 L separatory funnel and the two layers were separated. The aqueous layer was extracted with isopropyl acetate (IPAC) (3 × 1 L). The combined organic layers were concentrated to near dryness and then azeotropically dried with $CH_3CN$ (3 × 600 mL) (50 °C, house vacuum). The mixture was filtered to remove a small amount of NaCl after the azeotropic distillation. The filter cake was washed with $CH_3CN$ (500 mL). The combined filtrate was assayed by HPLC showing 253.5 g of product (84% yield; 83−85 LC area % purity at 215 nm) as a 36 wt % solution. The water content was 0.06 mg/mL and contained <2 mol % of THF and IPAC by NMR. This brown solution was used as is in the next step. Pure solid product can be isolated by recrystallization from IPAC/hexanes: mp 70−71 °C; MS (EI) *m*/*z* 185 ($M^+$); $^1$H NMR ($CDCl_3$) $\delta$ 1.27 (t, $J$ = 7.1 Hz, 3 H), 1.85 (br m, 4 H), 2.42 (br m, 2 H), 3.35 (br m, 2 H), 4.10 (s, 2 H), 4.19 (q, $J$ = 7.1 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 21.3, 23.1, 32.1, 48.6, 49.2, 61.1, 169.1, 170.4. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.25; H, 8.51; N, 7.48.

**Preparation of Ethyl [(±)-3-[2-(Pyridin-4-yl)ethyl]-2-oxopiperidin-1-yl]acetate (11).** A 250 mL three-necked round bottom flask equipped with a stirrer, nitrogen inlet, cooling unit, and thermometer probe was charged with piperidone-ester **7** (55.6 g, 108.0 mmol; 36 wt % solution from above), $CH_3CN$ (63.0 mL), sodium iodide (17.8 g, 118.8 mmol), and triethylamine (13.1 g, 129.6 mmol). The mixture was stirred until all the solid dissolved. The solution was cooled to 0 °C, chlorotriethylsilane (17.9 g, 118.8 mmol) was added over 5 min, keeping the internal temperature below +5 °C, and then the mixture was stirred at 20 °C for 1−2 h. The resulting mixture was cooled to −5−0 °C, and 4-vinylpyridine (13.1 g, 124.2 mmol) was added dropwise over a 2 h period, while keeping the internal temperature below 0 °C. The reaction was aged at 0 °C for 1−2 h and then quenched by slow addition into a cold (0 °C) solution of 1 N HCl (140 mL), while keeping the internal temperature < 20 °C. The final pH should be 1.5−2.5. The acidic solution (pH ~ 2) was extracted with 1:1 IPAC/hexane (2 × 160 mL). The aqueous layer was assayed by HPLC showing 24 g of product **11** (76% yield), 1.2 g of **7** (6%) and 4.7 g of bis-pyridyl impurity **13** (11%). To the aqueous solution was added IPAC (120 mL), and the mixture was cooled to 5−10 °C. With vigorous stirring, it was then basified to pH 9.5−10 by the slow addition of solid sodium bicarbonate (10 g; to pH 6) and 5 N NaOH (~22 mL; to pH 9.7). The layers were separated, and the aqueous layer was extracted with toluene (2 × 150 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (3 × 50 mL). The organic layer was azeotropically dried by distillation at 60 °C under reduce pressure. After ~400 mL distilled out, distillation was terminated and 150 mL dry toluene (total volume = 200 mL) and 12 g of silica (60−200 mesh) were added. After stirring for 1 h, the mixture was filtered and the filter cake was washed with 100 mL toluene. The combined filtrate was assayed to contain 21.9 g (70% overall yield; 91.8% recovery) of product **11**. After distilling off most of the solvent, the batch was turnovered to an IPA solution with a final concentration of 25 wt % (86 g) in IPA. This solution was used as is in the next step. An analytically pure oily sample of **11** was prepared by flash chromatography: MS (EI) *m*/*z* 290 ($M^+$); $^1$H NMR ($CDCl_3$) $\delta$ 1.09 (t, $J$ = 7.1 Hz, 3H), 1.50 (m, 1H), 1.60−1.90 (m, 2H), 2.04 (m, 1H), 2.20 (m, 1H), 2.54 (m, 2H), 3.10−3.30 (m, 2H), 3.77 (A of AB, $J$ = 17.2 Hz, 1H), 4.01 (q, $J$ = 7.1 Hz, 2H), 4.03 (B of AB, $J$ = 17.2 Hz, 1H), 6.99 (d, $J$ = 6.0 Hz, 2H), 8.30 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 9.7, 17.3, 22.2, 27.9, 28.0, 36.2, 44.6, 44.9, 56.6, 119.5, 145.2, 146.6, 164.7, 168.2; HRMS calcd for $C_{16}H_{22}N_2O_3$ 291.1709, found 291.1713 ($MH^+$). Compound **13** (a mixture of four diastereomers; two peaks on HPLC): MS (EI) *m*/*z* 395 ($M^+$).

**Preparation of [(±)-3-[2-(Pyridin-4-yl)ethyl]-2-oxopiperidin-1-yl]acetic Acid ((±)-1).** To a 25 wt % solution of the pyridine-ethyl ester **11** (21.3 g, 73.35 mmol) in isopropyl alcohol was added 48.8% aqueous sodium hydroxide (7.82 g, 95.36 mmol) at 20 °C under nitrogen over a 5 min period. The reaction mixture was stirred for 2 h until complete consumption of **11** was observed as monitored by HPLC. The mixture was cooled to 5−10 °C, seeded with 50 mg of NaCl, and then quenched by the slow addition of 36.6% aqueous hydrochloric acid (9.50 g, 95.36 mmol) over a 10 min period, while maintaining the internal temperature <15 °C. The final pH was 5.45. To the resulting mixture was added MeOH (20 mL), THF (40 mL), and Solka-Floc (5 g). After stirring for 30 min at ambient temperature, the mixture was filtered through a pad of Solka-Floc (5 g, wetted with 10 mL of IPA). The filter cake was washed with a mixture of IPA/THF/MeOH (50 mL: 20 mL:10 mL). The combined filtrate contained acid (±)-**1** in quantitative yield as determined by HPLC analysis. The filtrate was dried by azeotropic distillation under vacuum at 50 °C. After most of the solvents were distilled, the mixture was flushed several times with IPA (3 × 50 mL) to give a final concentration of 30 wt % (final weight = 60 g) and a water content of <1 mg/mL. The mixture was seeded with (±)-**1** and stirred until a seed bed was formed. Hexane (30.5 mL) was then added over a 1 h period and then aged for 12 h. After cooling to 10 °C and stirring for 0.5 h, the solid was collected by filtration. The filter cake was washed with a 40:60 mixture of IPA:hexanes (50 mL) and vacuum-dried to give 18.3 g of (±)-**1** as a light beige crystalline solid. The purity was 96.6 wt %. Thus, the yield was 91.8% (17.7 g) from **11** or an overall yield of 62% from **7** for the two steps. Complete rejection of impurities was achieved in this solvent system. The washes and the mother liquors contained about 10% (2 g) product (±)-**1**, 15% (3.95 g) bis-pyridyl-acid **14**, and 0.9% (0.1 g) piperidone-acid **8**. Pure (±)-**1**: mp 144−145 °C; MS (CI) *m*/*z* 263 ($MH^+$); $^1$H NMR ($CDCl_3$) $\delta$ 1.70 (m, 1H), 1.80−2.05 (m, 4H), 2.20 (m, 1H), 2.40 (m, 1H), 2.78 (t, $J$ = 8.0 Hz, 2H), 3.35 (m, 1H), 3.47 (m, 1H), 3.90 (A of AB, $J$ = 17.1 Hz, 1H), 4.32 (B of AB, $J$ = 17.1 Hz, 1H), 7.27 (d, $J$ = 6.2 Hz, 2H), 8.49 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 17.4, 22.4, 28.1, 28.4, 36.3, 44.9, 45.1, 120.4, 142.7, 149.8, 167.7, 168.3. Anal. Calcd for $C_{14}H_{18}O_3N_2$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.15; H, 7.16; N, 10.66.

(23) Kaye, P. T.; Learmonth, R. A. *Synth. Commun.* **1989**, *19*, 2337.

**Preparation of Quininium [3(*R*)-(−)-[2-(Pyridin-4-yl)-ethyl]-2-oxopiperidin-1-yl]acetate Mono-2-propanol Solvate (20)**. In a 250 mL round bottom flask, pyridine acid (±)-**1** (12.04 g, 96.6% pure, 44.34 mmol), quinine (14.89 g, 45.90 mmol), and IPA (80.8 mL) were combined. The mixture was heated at 65 °C for 15 min under a nitrogen atmosphere to dissolve all the solid. The resulting solution was then allowed to cool slowly to ambient. When the solution reached 45 °C, it was seeded with ∼10 mg of quinine salt **20** (99.5% ee). Soon after the seeding, crystallization began as the temperature slowly cooled. After stirring overnight at 20 °C, the mixture was cooled to 5−6 °C and aged for 0.5−1 h. The solid was collected on a medium porosity fritted funnel under a nitrogen blanket. The filter cake was washed with 50 mL of cold (5−10 °C) THF:hexane (50:50) and then dried under vacuum with a nitrogen sweep to give 12.72 g of **20** as a white solid. The weight % of the free acid was 42.2%; thus, the yield of free acid was 46.1% based on 44.34 mmol of (±)-**1**. The optical purity of the free acid was 98% ee, which was determined by normal phase HPLC analysis via the chiral amides of (*R*)-(+)-1-(1-naphthyl)ethylamine: Column: 4.6 × 250 mm Zorbax Silica; Eluent: 980:17:3 $MeCl_2$/IPA/15 M aqueous $NH_4$-OH; flow rate:1.0 mL/min; injection: 20 $\mu$L; detection: 260 nm. Multiple recrystallization gave an analytically pure sample with >99.5% ee: Compound **20** is a metastable species. Upon exposure to air, IPA is graduately replaced by water: mp 103−105 °C; $[\alpha]^{22}_{Na} = -115.5°$ (*c* 1.1, MeOH). Anal. Calcd for $C_{34}H_{42}N_4O_5 \cdot 1.5H_2O \cdot 0.2C_3H_8O$: C, 66.41; H, 7.51; N, 8.95. Found: C, 66.52; H, 7.24; N, 8.75.

**Recycling of the Resolution Mother Liquor. Preparation of Quininium [3(*R*)-(−)-[2-(Pyridin-4-yl)ethyl]-2-oxopiperidin-1-yl]acetate (20). Racemization and Resolution.** A 3 L three-necked round bottom flask equipped with a mechanical stirrer, condenser, nitrogen gas inlet, and thermometer probe was charged with pyridine acid quinine salt mother liquor from the resolution step (1.84 L, 77.7 g/L, 545 mmol) and solid sodium ethoxide (67 g, 981 mmol). The mixture was heated at reflux (83−85 °C) for 5 h. The resulting mixture was cooled to 15 °C, and 37% hydrochloric acid (56 mL) was slowly added until pH 8.1−8.3 (at 23 °C). To the batch was added THF (1.84 L) and Solka-Floc (80 g). After stirring for 1 h, the mixture was filtered through a a layer of Solka-Floc (40 g, prewetted with THF) in a sintered glass funnel (medium porosity) to remove NaCl and then washed with THF (300 mL). The filtrate was concentrated under vacuum at 45 °C and flushed with toluene (3 × 300 mL) to remove water, followed by isopropyl alcohol (3 × 300 mL) to remove toluene. The water content of the mixture should be less than 500 mg/mL after the flushes. Isopropyl alcohol (750 mL) was added to the batch to give a final concentration of 3 mL of IPA/gram of the quinine salt. The mixture was heated at 70−75 °C for 15−30 min under a nitrogen atmosphere to dissolve all the solid. The resulting solution was allowed to cool gradually to ambient. When the batch temperature reached 45 °C, the mixture was seeded with 0.1 g of 99.5% ee quinine salt **20**. After stirring overnight at 22 °C, the mixture was cooled to 5−10 °C and aged for 0.5 h. The batch was filtered through a sintered glass funnel, and the wet cake was washed with cold hexane/THF (1:1, 10 °C, 2 × 350 mL) and then dried under vacuum under a nitrogen blanket. A 114−132 g amount of **20** (32−37% yield) was obtained with ∼89.5 wt % purity (9 wt % IPA, 1 wt % NaCl) and 98+% ee.

**Preparation of *N*-[[3(*R*)-(−)-[2-(Pyridin-4-yl)ethyl]-2-oxopiperidin-1-yl]acetyl]-3(*R*)-methyl-β-alanine Benzyl Ester (22). A. Salt Breaking**. In a three-necked flask charged with IPAC (37 L) was added pyridine acid quinine salt **20** (6711 g, 39.8 wt % of pyridine acid, 10.2 mol). To this stirred suspension was slowly added 1 N NaOH (10.1 L). The final pH of the aqueous solution was 9.5. After separation of two layers, the aqueous layer was extracted with IPAC (8.5 L). The pH of the aqueous layer was adjusted to 10.4 with 1 N NaOH (245 mL) and again extracted with IPAC (1.4 L). The recovery of the chiral acid (*R*)-**1** in the aqueous layer was quantitative. Quinine should be <1.5% in the aqueous layer before proceeding, otherwise another extraction is required. Alternatively, MTBE should be use in place of IPAC, if hydrolysis of IPAC is a problem. An analytically pure sample of (*R*)-**1** (>99.5% ee) was prepared by crystallization (IPA): mp 128−129 °C; $[\alpha]^{20}_{Na} = -21.4°$ (*c* 1.01, MeOH).

**B. Amide Bond Formation**. To the stirred solution of the sodium salt of pyridine acid (*R*)-**1** (10.2 mol) from above was added benzyl 3(*R*)-aminobutyrate hemisulfate (2500 g, 10.3 mol), IPAC (10.2 L), HOBT (103.2 g, 0.76 mol), and 1-[3-(dimethylamino)propyl]3-ethylcarbodiimide hydrochloride (2346 g, 12.2 mol). The mixture was stirred at room temperature overnight. The reaction mixture was extracted with IPAC (2 × 10.2 L). The combined organic layers was washed with saturated sodium bicarbonate solution (10 L) and then with water (2 × 20 L). The combined organic solution, contained ∼95% yield of ester **22**, which was used directly in the next reaction. An analytical sample was obtained by concentrating the organic solution to dryness to give an oily **22**: $[\alpha]^{20}_{Na} = -1.4°$ (*c* 1.03, MeOH); MS (CI) *m*/*z* 437 ($M^+$); $^1$H NMR ($CDCl_3$) $\delta$ 1.19 (d, *J* = 6.7 Hz, 3H), 1.54−2.05 (m, 5H), 2.15−2.4 (m, 2H), 2.48 (ABq, *J* =15.5, 5.5 Hz, 1H), 2.55 (ABq, *J* =15.5, 5.5 Hz, 1H), 2.69 (m, 2H), 3.32 (m, 2H), 3.81 (d, *J* = 15.2 Hz, 1H), 4.03 (d, *J* = 15.2 Hz, 1H), 4.33 (m, 1H), 5.07 (ABq, *J* = 13.9, 12.3 Hz, 2H), 6.76 (br d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 6.0 Hz, 2H), 7.32 (s, 5H), 8.46 (d, *J* = 6.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.1, 21.7, 26.5, 32.4, 32.6, 40.0, 40.9, 42.0, 49.5, 51.7, 66.3, 123.9, 128.2, 128.3, 128.6, 135.6, 149.7, 150.9, 167.9, 171.3, 173.0; HRMS calcd for $C_{25}H_{32}N_3O_4$ 438.2393, found 438.2367 ($MH^+$).

**Preparation of *N*-[[3(*R*)-(−)-[2-(Piperidin-4-yl)ethyl]-2-oxopiperidin-1-yl]acetyl]-3(*R*)-methyl-β-alanine (L-734,217).** The pyridine amide benzyl ester **22** solution in IPAC from the last step was concentrated under vacuum (≤40 °C pot temperature) to a volume of 8 L, and then 10 L of MeOH was added and the solution concentrated again to 8 L. The flush (temperature ≤50 °C, 10 cmHg) was repeated four times until all the IPAC was replaced with MeOH (maximum IPAC content = 50 mol % relative to benzyl ester). The resulting solution was divided into two equal portions and each subjected to the following hydrogenation conditions.

To a 5-gal stirred autoclave was added the pyridine amide benzyl ester (2231 g, 5.1 mol) solution in MeOH (total volume was adjusted to 17.6 L) and acetic acid (27.5 mL). To this solution was added 10% Pd/C (211.5 g). The mixture was heated to 50 °C and hydrogenated at 40 psi for 20 h. After the mixture was cooled to room temperature, it was filtered through ca. 5 in. thick Solka-Floc (1 kg dried in vacuum oven, prewashed with 4 × 2 L MeOH), and the solid was washed with MeOH ( 2 × 2.5 L). The assayed amount of L-734,217 was 3325 g (MW 353, 9.4 mol, 92% from pyridine acid quinine salt). The filtrate was concentrated under vacuum, and the total volume was adjusted to 15.3 L (12 L MeOH + 3325 g L-734,217). This solution was heated to reflux under nitrogen, and $CH_3CN$ (20 L) was added while the solution was at reflux. The solution was seeded with L-734,217 (0.6 g), and $CH_3CN$ (5 L) was added. The mixture was then stirred for 1 h without heating during which time the temperature dropped from 61 °C to 52 °C. The mixture was stirred at room temperature overnight and then filtered. The solid was washed with $CH_3$-CN (6 L). The solid was dried *in vacuo* (50 °C, 10 cmHg) overnight to give 3082 g of L-734,217 as a white, fluffy solid (MW 353.45, 8.72 mol, 85.5% yield based on pyridine acid quinine salt). HPLC assay showed ca. 203 g of L-734,217 in the mother liquor. The solid L-734,217 was 99.8% de. No other impurity peak was observed by HPLC. L-734,217: mp 237−239 °C; $[\alpha]^{25}_{405} = -57.2°$ (*c* 1.0, $H_2O$); $^1$H NMR ($CD_3OD$) $\delta$ 1.14 (d, *J* = 6.7 Hz, 1H), 1.33 (m, 4H), 1.50−1.90 (m, 5H), 1.93 (m, 4H), 2.29 (dd, *J* = 14.3, 6.7 Hz, 1H), 2.38 (dd, *J* = 14.3, 6.0 Hz, 1H), 2.40 (m, 1H), 2.95 (dt, *J* = 12.8, 2.9 Hz, 2H), 3.38 (m, 4H), 3.91 (d, *J* = 16.3 Hz, 1H), 4.02 (d, *J* = 16.3 Hz, 1H), 4.14 (sextet, *J* = 6.7 Hz, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 20.7, 22.5, 27.2, 29.6, 30.0, 30.2, 34.2, 35.0, 42.5, 44.5, 44.7, 45.2, 50.8, 51.7, 169.5, 175.5, 179.5. Anal. Calcd for $C_{18}H_{31}N_3O_4$: C, 61.17; H, 8.84; N, 11.89. Found: C, 61.22; H, 9.00; N, 11.90.

**Preparation of *N*-[[3(*R*)-(−)-[2-(Pyridin-4-yl)ethyl]-2-oxopiperidin-1-yl]acetyl]-3(*R*)-methyl-β-alanine (23).** A solution of the benzyl ester **22** (1220 g, 2.79 mol) in MeOH (11 L) and acetic acid (184 mL) was hydrogenated in a stirred

autoclave at rt under 40 psi hydrogen over 10% Pd/C (60 g). The hydrogen uptake was carefully monitored until 1.0 equiv of hydrogen was consumed (2.0 h), and the reaction was stopped. The palladium was removed by filtration through dry Solka-Floc and washed with MeOH (5 L). The filtrate was concentrated under vacuum to an oil residue and flushed with anhydrous $CH_3CN$ (4 L). The residue started crystallizing at the end and it was stirred with a mixture of anhydrous $CH_3CN$ (2.5 L) and anhydrous MTBE (5 L) overnight. The white solid was collected by filtration and was washed with a 1:2 mixture of $CH_3CN$/MTBE (750 mL) and MTBE (2 × 1 L). It was dried in vacuum oven at 50 °C yielding 835 g (86%) of **23**. HPLC analysis showed the sample is about 97% pure containing trace amount of L-734,217 (~2%). An analytically pure sample was obtained by recrystallization from 1:7 MeOH/$CH_3CN$. **23**: mp 142−143 °C; $[\alpha]^{20}_{Na} = -14.2°$ (*c* 1.0 MeOH); $^1$H NMR ($CD_3OD$) $\delta$ 1.22 (d, $J = 6.7$ Hz, 3H), 2.25−1.65 (m, 7H), 2.60−2.35 (m, 3H), 2.77 (m, 2H), 3.35 (m, 2H), 3.96 (d, $J = 15$ Hz, 1H), 4.03 (d, $J = 15$ Hz, 1H), 7.35 (d, $J = 6.1$ Hz, 2H), 8.24 (d, $J = 6.1$ Hz, 2H); $^{13}$C NMR ($CD_3OD$) $\delta$ 20.4, 22.5, 27.3, 33.5, 33.6, 41.4, 42.1, 43.9, 50.7, 51.4, 125.8, 138.0, 149.6, 154.7, 169.8, 175.0, 175.1. Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.09. Found: C, 61.95; H, 7.10; N, 12.16.

**Acknowledgment.** We would like to thank K. Mistry and T. M. Dowling for analytical support.

**Supporting Information Available:** Figure 1, which contains C-13 NMR chemical shift assignments for **7**, **11**, **17**, **18**, bis-silylated **11** (**24**), **A**, 4-vinylpyridine, triethylamine, and silylated triethylamine (2 pages). 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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