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A Practical Synthesis of the Platelet Fibrinogen Antagonist, Elarofiban

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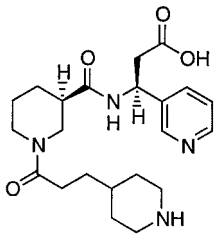
Abstract:

Elarofiban is a novel, nonpeptide, orally active fibrinogen receptor antagonist useful for the treatment of platelet mediated thrombotic disorders (Costanzo, M. J.; Hoekstra, W. J.; Maryanoff, B. E. WO, 97/41102, 1997). Herein we describe the process research that was carried out for the synthesis of elarofiban that eventually led to the development of a safe and cost-effective commercial scale process.



elarofiban

Introduction

Integrins are heterodimeric molecules composed of α and β subunits which combine to form ligand-specific receptors.[1−3] Antagonists of the glycoprotein GPIIb/IIIa integrin (of the $\alpha_{IIb}\beta_3$ subunit found on the surface of platelets) were shown to be effective as platelet aggregation inhibitors.[4] As part of our research towards the synthesis of orally active, nonpeptide GPIIb/IIIa antagonists, we identified a novel series of nipecotamide analogues which are potentially useful in the treatment of platelet-mediated thrombotic disorders such as re-occlusion of an artery following thrombolytic therapy, acute myocardial infarction, and unstable angina.[2] The lead compound in this series, elarofiban, was chosen for further development because it can be dosed both intravenously and orally, has a good duration of action, and demonstrated excellent safety characteristics.

To prepare the necessary supplies of drug substance to support both toxicological and clinical studies, we needed to develop an efficient large-scale process. We began by evaluating the existing synthetic method developed by Drug Discovery (Scheme 1),[5] which presented many challenges for the preparation of material in large quantity. Specifically, we needed to address the following areas: (1) Enantiomerically enriched β-amino ester **3** was prepared in low overall yield via enzymatic resolution of 3-phenylacetylamino-3-pyridin-3-ylpropionic acid; however, this procedure was both volume inefficient and expensive; (2) Although the coupling of β-amino ester **3** and *N*-boc-(*R*)-nipecotic acid (**4**) proceeded in good yield, the use of expensive 2-[1*H*-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) coupling reagent was required to prevent racemization. Furthermore, purification of the resulting product **5** was difficult as it is a thick oil thus requiring column chromatography; (3) In the final coupling step, HBTU was again required to avoid epimerization and the product **7** was purified by column chromatography; (4) Elarofiban was isolated as an amorphous dihydrochloride salt in low overall yield (approximately 7%); and (5) In addition to these issues, we needed to eliminate the use of hazardous solvents such as chloroform and dioxane. Therefore, a strong need for the development of a more efficient synthesis existed.

Synthesis Strategy. As shown in Scheme 2, there are two coupling strategies possible for assembling elarofiban. Route A, used in the original Drug Discovery synthesis, was problematic on large-scale production for reasons mentioned above. After preliminary evaluation, we determined Route B to be the more efficient one to prepare large quantities of drug substance for two main reasons. First, the starting materials and intermediates are crystalline solids easily purified by recrystallization, thus avoiding column chromatography. Second, the most expensive starting material, methyl (*S*)-3-amino-3-(3-pyridyl)propionate is used at the end of the process which lowers the cost of production. Herein, we describe the process research that was carried out for the synthesis of elarofiban using Route B, which eventually

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‡ Cilag AG Pharmaceutical and Chemical Operations.

|| Current address: 19502 Encino Gap, San Antonio, TX 78259.

(1) Costanzo, M. J.; Hoekstra, W. J.; Maryanoff, B. E. WO, 97/41102, 1997.

(2) Shinagawa, S.; Kanamaru, T.; Asai, M.; Okazaki, H. *J. Med. Chem.* **1987**, *30*, 1458.

(3) Scott, V. R.; Boehme, R.; Matthews, T. R. *Antimicrob. Agents Chemother.* **1988**, *32*, 1154.

(4) Kawabata, N.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiot.* **1992**, *45*, 513.

(5) Hoekstra, W. J.; Maryanoff, B. E.; Damiano, B. P.; Andrade-Gordon, P.; Cohen, J. H.; Costanzo, M. J.; Haertlein, B. J.; Hecker, L. R.; Hulshizer, B. L.; Kauffman, J. A.; Keane, P.; McComsey, D. F.; Mitchell, J. A.; Scott, L.; Shah, R. D.; Yabut, S. C. *J. Med. Chem.* **1999**, *42*, 5254.

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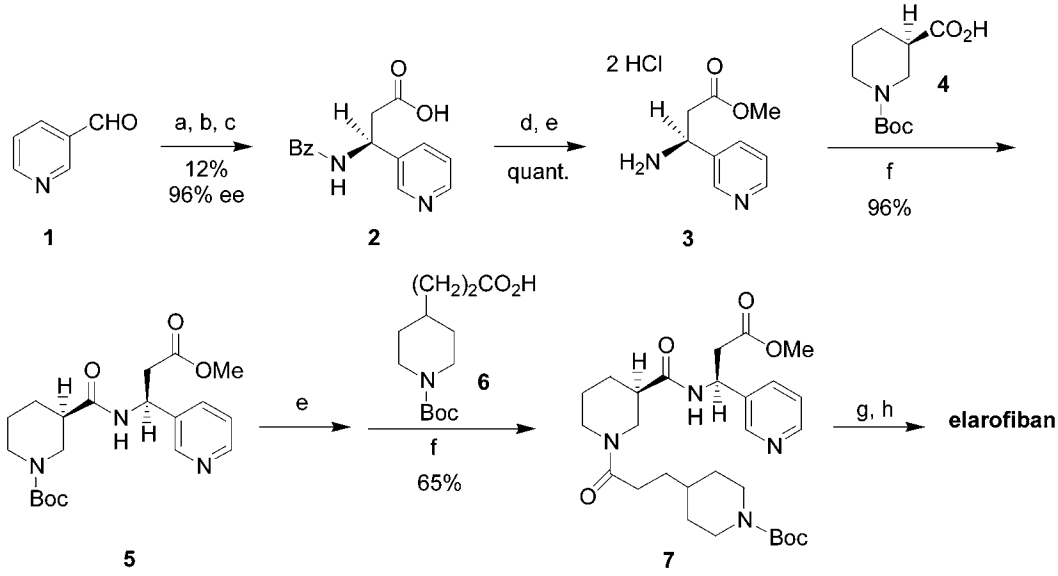
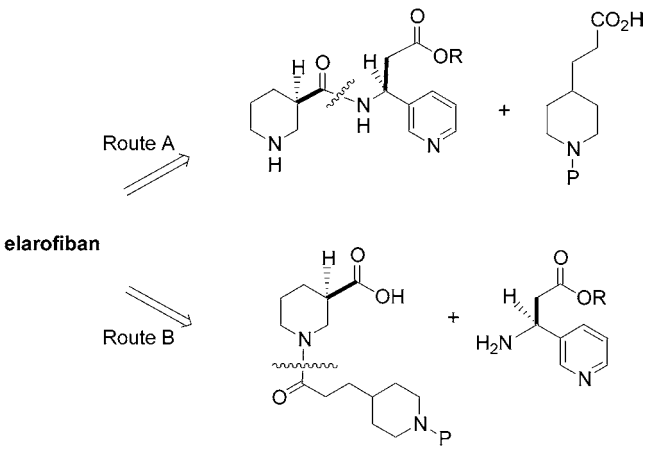
Scheme 1 [a]



[a] Reagents and conditions: (a) $CH_2(CO_2H)_2$, NH_4OAc, EtOH; (b) $PhCH_2COCl$, NEt_3, aq Me_2CO; (c) penicillin amidase, chromatography; (d) 6N HCl, reflux; (e) HCl, MeOH; (f) HBTU, HOBT, chromatography; (g) LiOH, aq THF; (h) HCl, dioxane, chromatography.

Scheme 2



led to the development of a safe and cost-effective commercial scale process.[6]

Results and Discussion

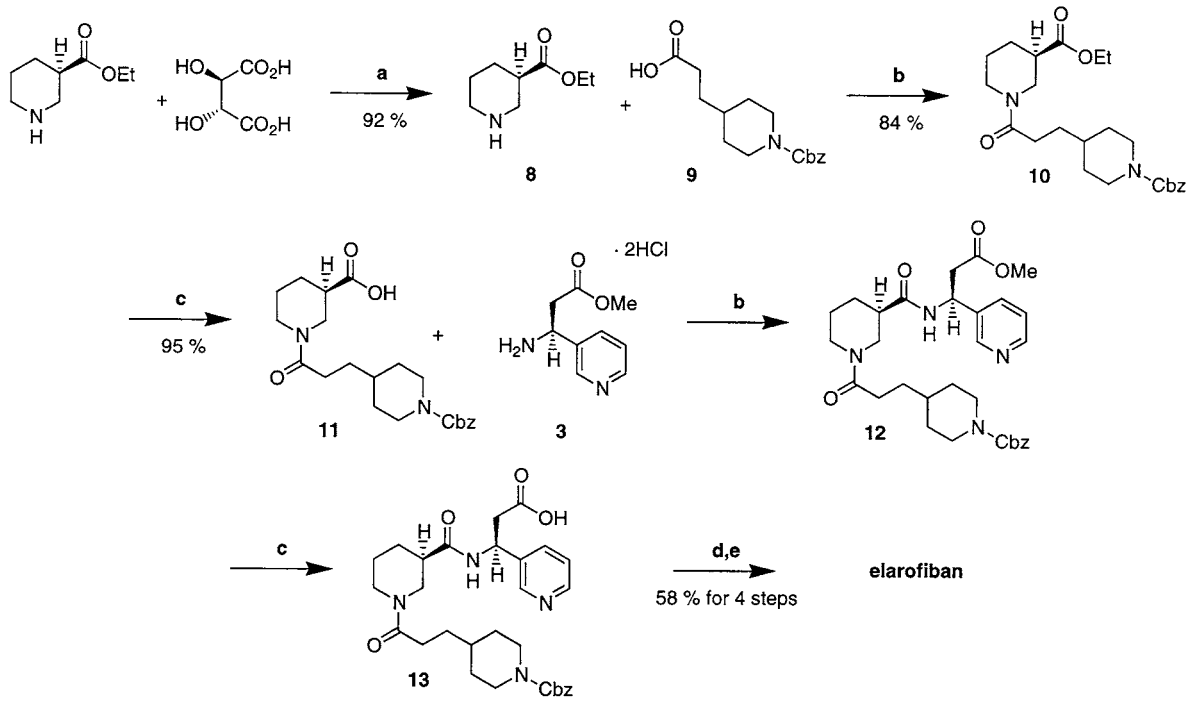
Initially, we needed to prepare 1 kg of drug substance for early toxicological and clinical studies in a very short time frame. Therefore, we concentrated on preparation of the required drug substance without optimization of reaction parameters, using the process outlined in Scheme 3. *R*-Ethyl nipecotate (**8**) was obtained from the commercially available tartrate salt and reacted with acid **9** (prepared according to a modified literature procedure).[7] The resulting ester **10** was saponified with LiOH to afford the corresponding crystalline acid **11**. Coupling of acid **11** with methyl (*S*)-3-amino-3-(3′-pyridyl)propionate dihydrochloride (**3**) (prepared via classical resolution of the corresponding 3-(*tert*-butoxycarbonyl)amino-3-(3′-pyridyl)propionic acid)[8] afforded intermediate **12**. The ester was saponified using LiOH, and finally the Cbz group was removed via catalytic hydrogenation to afford crude elarofiban which was purified via recrystallization from *n*-BuOH.

While this process was suitable for the preparation of the initial supplies of drug substance, it identified other issues that needed to be addressed for the production of larger quantities of material. Specifically: (1) the use of expensive PtO_2 catalyst and formation of a dimeric byproduct during the protection step in the synthesis of 3-(*N*-benzyloxycarbonyl-4-piperidyl)propionoic acid (**9**); (2) development of a more cost-effective method to prepare the enantiomerically pure β-amino ester **3**; (3) the use of enantiomerically enriched *R*-ethyl nipecotate tartrate since there was only one commercial supplier and the material was very expensive; and (4) increase in the overall yield of the process to make it more cost-efficient.

Synthesis of 3-(*N*-Benzyloxycarbonyl-4-piperidyl)propionoic (9). In 1966, DeGraw and Kennedy reported the synthesis of acid **9** via catalytic hydrogenation of 4-pyridinelacrylic acid with PtO_2 in 2N HCl followed by protection of the resulting amine using benzyl chloroformate (CbzCl).[7] However, upon scale-up, we encountered several problems with isolation of the water-soluble acid **9** from the large volume of aqueous solvent, thus requiring an exhaustive extractive workup. We therefore modified this procedure so the intermediate 3-(4-piperidyl)propionic acid HCl salt was isolated from the reduction and then treated with *N*-(benzyloxycarbonyloxy)succinimide (CbzOSu) and triethylamine in EtOAc to eliminate the use of aqueous reaction conditions. However, when this sequence was used on a 1.2 kg scale, reaction of **9** with CbzOSu followed by *N*-

(6) Cohen, J. H.; Justus, M.; Maryanoff, C. A.; Rossler, A.; Schroder, F.; Sorgi, K. L.; Villani, F. J., Jr.; Weh, C. U.S. Patent 6,515,130, B1, 2003.
(7) DeGraw, J. I.; Kennedy, J. G. *J. Heterocycl. Chem.* **1966**, *3*, 90.
(8) Boesch, H.; Cesco-Cancian, S.; Hecker, L. R.; Hoekstra, W. J.; Justus, M.; Maryanoff, C. A.; Scott, L.; Shah, R. D.; Solms, G.; Sorgi, K. L.; Stefanick, S. M.; Thurnheer, U.; Villani, F. J., Jr.; Walker, D. G. *Org. Process Res. Dev.* **2001**, *5*, 23.

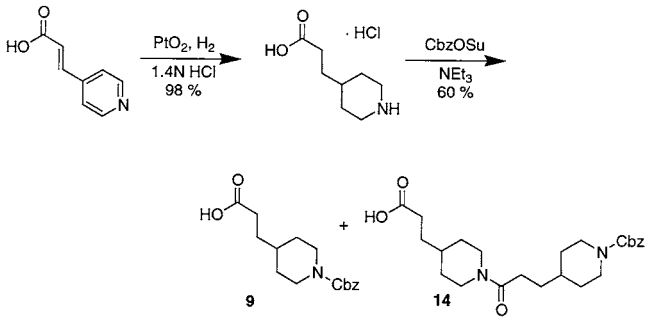
Scheme 3 [a]



[a] Reagents and conditions: (a) K_2CO_3; (b) DCC, MeCN, HOBT; (c) LiOH, aq THF; (d) Pd/C, H_2, MeOH; (e) recrystallization (*n*-BuOH).

hydroxysuccinimide resulted in formation of an activated ester, which during the long reaction time, was coupled to a molecule of 3-(4-piperidyl)propionic acid, leading to byproduct **14**. To minimize formation of this difficult-to-remove by-product, we stopped the reaction prior to completion and isolated the acid **9** as a thick oil in approximately 60% overall yield with only a trace amount of **14** present (Scheme 4).

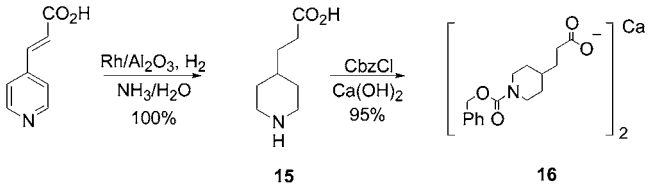
Scheme 4



For large-scale production, we still needed to improve this process to remove the expensive PtO_2 catalyst as well as increase the overall yield. After much investigation, we found that reduction under neutral conditions using a Rh/Al_2O_3 catalyst[9] proved very effective (Scheme 5). This allowed isolation of 3-(4-piperidyl)propionic acid (**15**) as a crystalline solid in quantitative yield after precipitation from acetonitrile. The acid was then suspended with $Ca(OH)_2$ in aqueous acetonitrile and treated with CbzCl to afford the calcium salt **16** in 95% overall yield. This improved process led to an increase in overall yield from 60 to 95%, used less expensive reagents, and allowed isolation of the product as a crystalline calcium salt.

(9) Freifelder, M. U.S. Patent 3,159,639, 1964.

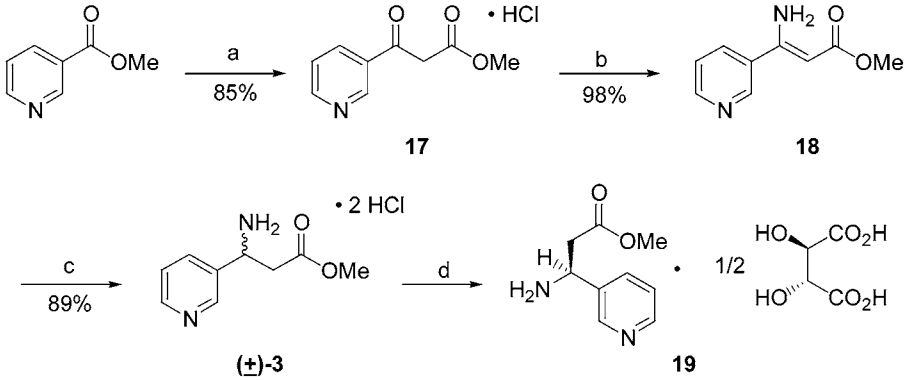
Scheme 5



Synthesis of Methyl (*S*)-3-Amino-3-(3′-pyridyl)propionate 3. While the initial process[8] to prepare β-amino ester **3** via classical resolution of the corresponding 3-[(*tert*-butoxy)carbonyl]amino-3-(3′-pyridyl)propionic acid with (−)-ephedrine afforded the desired material, we needed to develop a more cost-efficient, large-scale process which would not require an expensive protection/deprotection sequence. We surveyed the literature and found several methods reported for the synthesis of β-3-pyridyl alanine esters;[10−13] however, for reasons of cost, low overall yield, low reaction temperature, or general patent issues, none of these procedures would be useful as a large-scale process. As part of our process research, we evaluated different approaches for the preparation of **3** and thus developed several methods, including both an asymmetric synthesis[14] and a classical resolution. However, we found the more cost-effective process was classical resolution of the correspond-

(10) Bovy, P. R.; Rico, J. G.; Lindmark, R. J.; Rogers, T. E.; Tjoeng, F. S.; Zablocki, J. A. U.S. Patent 5,254,573, 1993.
(11) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.
(12) Behling, J. R.; Boys, M. L.; Cain-Janicki, K. J.; Colson, P. J.; Doubleday, W. W.; Duran, J. E.; Farid, P. N.; Knable, C. N.; Muellner, F. W.; Nugent, S. T.; Topgi, R. S. U.S. Patent 5,840,961, 1998.
(13) Jiang, J.; Schumacher, K. K.; Joullie, M. M.; Davis, F. A.; Reddy, R. E. *Tetrahedron Lett.* **1994**, *35*, 2121.
(14) Zhong, H. M.; Cohen, J. H.; Abdel-Magid, A. F.; Kenney, B. D.; Maryanoff, C. A.; Shah, R. D.; Villani, F. J., Jr.; Zhang, F. *Tetrahedron Lett.* **1999**, *40*, 7721.

Scheme 6 [a]



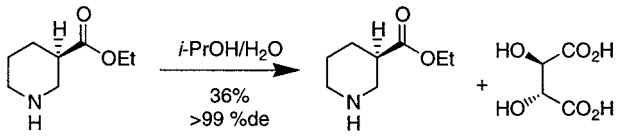
[a] Reagents and conditions: (a) NaOMe, toluene, methyl acetate, 65 °C, 13 h, extraction and azeotropic removal of water, then HCl 0−10 °C; (b) toluene, NaOAc, MeOH, acetic acid, 65 °C, NH_3, 4 h; (c) $NaBH_4$, THF, HOAc, −5 °C, 5 h; MeOH, −5 °C, 30 min, followed by HCl, 5 °C; (d) MeCN, NEt_3, 35 °C, 2 h, then EtOH/H_2O, (+)-tartaric acid, RT.

ing racemic β-amino ester because the racemate was easily prepared in high yield/purity and the enantiomerically pure resolving agent, (+)-tartaric acid, was commercially available and inexpensive (Scheme 6).

The synthesis of β-ketoester **17** was reported in the literature by treatment of methyl nicotinate with a base (sodium hydride[15] or sodium ethoxide[16,17]), followed by addition of methyl acetate. We found sodium methoxide was a better base for this step, leading to increased yield and purity in addition to being safer to use on large scale. Isolation of the β-ketoester via precipitation of the hydrochloride salt from the toluene phase after extractive workup afforded **17** in 85% yield. Treatment with gaseous ammonia in a mixture of toluene and *i*-PrOH at elevated temperature under acid catalysis afforded **18**, which was crystallized directly from the reaction mixture in excellent yield (89%) and purity (99.5%). The reduction of enamine **18** to give β-amino ester (±)-**3** was carried out using either catalytic hydrogenation (Pd/C, AcOH) or borohydride reagents ($NaBH_4$/AcOH/THF). However, it was necessary to carry out the hydrogenation under water-free conditions since wet catalysts led to lower yields resulting from partial hydrolysis of the enamine as was evident by the formation of the corresponding β-hydroxy ester after reduction. Thus, it was more efficient to carry out the reduction using $NaBH_4$ in the presence of AcOH. After quenching the reaction with methanol and subsequent treatment with gaseous HCl, the racemic dihydrochloride salt (±)-**3** was obtained in 74% overall yield and then easily converted to the free amine via treatment with triethylamine in acetonitrile prior to the classical resolution. The optimal condition for the resolution in terms of yield and throughput was achieved using 0.25 equiv of (+)-tartaric acid in a mixture of EtOH/water. This precipitated the diastereomerically enriched hemi-tartrate salt, which was then purified by slurrying in EtOH/water to afford **19** in 28% yield and >98% de.

Synthesis of *R*-(−)-Ethyl Nipecotate (+)-Tartrate. Although *R*-ethyl nipecotate was commercially available as the (+)-tartrate salt, it was very expensive. Thus, to minimize cost, (±)-ethyl nipecotate was resolved using *L*-(+)-tartaric acid as shown in Scheme 7. According to the procedure by Akkerman et al.,[18] the resolution was carried out using 1 equiv of *L*-(+)-tartaric acid in EtOH. However, it required five recrystallizations from ethanol to obtain >99% de in 31% overall yield using approximately 45 L of solvent per kilogram of material. We developed a better alternative by carrying out the resolution in aqueous *i*-PrOH which provided the (+)-tartrate salt in >99% de after only 1 slurry requiring 15.5 L of solvent per kilogram of material with an increased overall yield (36%).

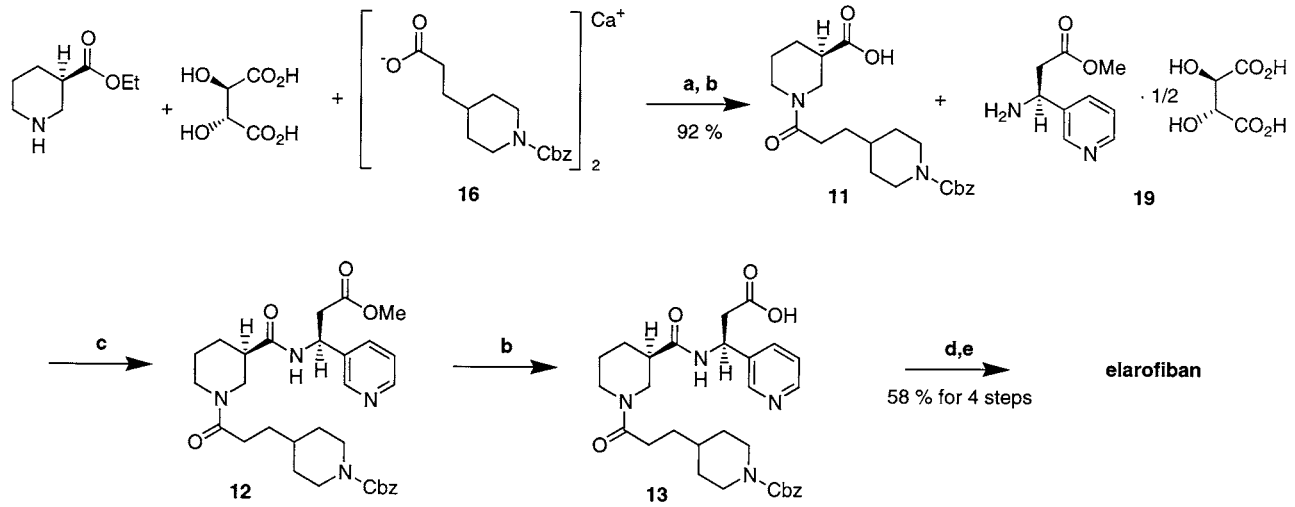
Scheme 7



Synthesis of Elarofiban. With the preparation of the key starting materials and intermediates in place, we completed the synthesis of elarofiban as shown in Scheme 8. Typically, the formation of an amide bond is carried out by reacting a carboxylic acid with an amine (either in its free form or as a salt) in the presence of a coupling agent and base. When the amine used is in the form of a carboxylate salt, a separate step is added in which the amine salt is converted to a free amine prior to coupling, as the carboxylate anion may interfere with the coupling, resulting in undesired side products.[19] However, for the preparation of elarofiban, we were able to take advantage of the unique physical−chemical properties of calcium tartrate to eliminate this extra step. By mixing the calcium salt **16** with *R*-(−)-ethyl nipecotate (+)-tartrate in the presence of $Ca(OH)_2$ in calcium tartrate precipitated from the aqueous THF reaction mixture and was easily removed via filtration. The filtrate, which contains no tartrate anion, was then treated with DCC/HOBT to afford the coupled ester without racemization or formation of any by-products or racemization. The ester was not isolated but converted directly to acid **11** upon hydrolysis with LiOH and acidification in excellent yield (92%) and purity (>98%

(15) Wenkert, E.; Orito, K.; Simmons, D. P. *J. Org. Chem.* **1983**, *48*, 5006.
(16) Strong, F. M.; McElvain, S. M. *J. Am. Chem. Soc.* **1933**, *55*, 816.
(17) Stein, M. L.; Burger, A. *J. Am. Chem. Soc.* **1957**, *79*, 154.
(18) Akkerman, A. M.; de Jongh, D. K.; Veldstra, H. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 899.
(19) Bodansky, M. *Principles of Peptide Synthesis*, 2nd ed.; Springer-Verlag: Berlin, Germany, 1993.

Scheme 8 [a]



[a] Reagents and conditions: (a) $Ca(OH)_2$, DCC, HOBT, aq THF; (b) LiOH, aq THF; (c) phosphate buffer, aq THF, $Ca(OH)_2$, DCC 0−5 °C; (d) Pd/C, H_2, MeOH, 2 h; (e) *n*-BuOH.

ee). Acid **11** was then reacted with the β-amino ester hemitartrate salt **19** using similar reaction conditions[20] as the previous coupling step to yield fully protected elarofiban (**12**). Finally, the ester was hydrolyzed with aqueous LiOH, the Cbz group was removed via catalytic hydrogenation, and the crude product was recrystallized from *n*-BuOH to afford pure elarofiban in 58% overall yield for the four steps.

Conclusion

In summary, we have developed a very efficient commercial scale process to prepare elarofiban which offers several advantages over the original Drug Discovery synthesis. This new synthetic strategy avoids the use of chromatography for isolation/purification by using crystalline starting materials and intermediates, reduces the overall number of steps by introducing a novel procedure for free amine liberation from the corresponding tartrate salts employing $Ca(OH)_2$ followed by direct coupling with carboxylic acids under mild conditions to produce the amide products with no racemization or formation of by-products, eliminates all hazardous solvents, reduces the overall cost by using less expensive reagents, and improves the overall yield.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 300, 300 MHz spectrometer. The chemical shifts are expressed as δ units with Me_4Si as the internal standard (multiplicities in ^{1}H NMR are referred to as: s for singlets, d for doublets, t for triplets, q for quartets, and m for multiplets). All reactions were carried out under a nitrogen or an argon atmosphere. Solvents and reagents were obtained from commercial sources and used without further treatment or purification.

3-(4-Piperidyl)propionic Acid (15). A suspension of 3-(4-pyridine)acrylic acid (18 kg, 2.7 mol) in 75 kg of water was neutralized (pH 7.5) with 25% aq ammonia (6.8 kg). A slurry of Rh/Al_2O_3 (0.9 kg) in 5 kg of water was added, and the reaction mixture was hydrogenated under 3−3.5 bar of pressure at 85−95 °C. When no further change in pressure was observed (∼8 h), the mixture was cooled to 25−35 °C. The catalyst was filtered and washed with 4.0 kg of water. The filtrate was concentrated under vacuum at 80−90 °C, and the product began to precipitate. Acetonitrile (116 kg) was added, and then the mixture was again concentrated (ca. 50%) under vacuum to remove residual ammonia. Additional acetonitrile (57.1 kg) was added to aid in crystallization, and the mixture was stirred for 1−4 h at ambient temperature. The product was isolated via filtration and dried under vacuum at 45−55 °C to afford 19.1 kg (100%) of **15**, which was identical to the literature.[9]

(*R*)-(−)-Ethyl Nipecotate (+)-Tartrate (20). *L*-(+)-Tartaric acid (47.74 g, 318 mmol) was suspended in 265 g of *i*-PrOH 16.91 g of water and heated to 60−65 °C to afford a homogeneous solution. The mixture was treated with (±)-ethyl nipecotate (50 g, 318 mmol) and heated to 70−75 °C for 20−30 min. The mixture was then cooled to 60 °C, and seed crystals of (*R*)-(−)-ethyl nipecotate-*L*-(+)-tartrate (25 mg, 0.08 mmol) were added. Upon cooling to ambient temperature, a white solid precipitated which was isolated (62.0 g, 94.8% de) and washed twice with a mixture of *i*-PrOH (21.05 g) and water (1.34 g). The crude product was slurried in a mixture of *i*-PrOH (188 g) and water (12 g), heated to 73−77 °C for 10−20 min, and then cooled to ambient temperature. The product was isolated by filtration and washed twice with a mixture of *i*-PrOH (21.05 g) and water (1.34 g) to afford 35.2 g (36%) of **20** as a white powder, which was identical to the literature:[18] mp 155−156 °C. By HPLC analysis this material was greater than 98.8% de.[21]

(*R*)-1-[3-(1-Benzyoxycarbonyl-4-piperidyl)-propionyl]-3-piperidinecarboxylic Acid (11). Compound **15** (5.3 g,

(20) To obtain a high yield for this coupling reaction, the pH needs to be maintained between 6.5 and 7.0. Initially this was done via constant addition of either base or acid throughout the reaction. However, to simplify this process, a buffer system was developed which maintained the desired pH and thus afforded **12** in high yield and purity.

(21) Rustum, A. M. *J. Chromatogr., A* **1995**, *696*, 75.

33.9 mmol) and calcium hydroxide (4.0 g, 53.7 mmol) were suspended in 16 g water/65 g acetonitrile and then cooled to 0−10 °C. Benzyl chloroformate (6.8 g, 39.6 mmol) was added within 30 min, and the reaction was stirred at 0−5 °C for 2 h. The product precipitated during the reaction and was isolated (as a mixture with calcium hydroxide and calcium chloride) by filtration to afford 3-(*N*-benzyloxycarbonyl-4-piperidyl)propionic acid calcium salt (**16**). Crude **16** (21.9 g, 32.2 mmol), **20** (21.7 g, 70.8 mmol), and hydroxy benzyltriazole (HOBT) (1.30 g, 9.65 mmol) were suspended in water (40 g)/THF (80 g), and the resulting suspension was adjusted to pH 7 with $Ca(OH)_2$. The precipitated calcium tartrate was collected by filtration and washed with 10 g of THF. The filtrate was cooled to 0−5 °C and treated with a solution of DCC (19.9 g, 96.5 mmol) in 40 g of THF. The mixture was warmed slowly to ambient temperature, and *N*,*N*′-dicyclohexylurea (DCU) precipitated. After 4 h, the DCU was removed by filtration and washed with 8 g of THF. The filtrate was again cooled to 0−5 °C and treated with a solution of lithium hydroxide (6.67 g, 159.0 mmol) in 60.38 g of water. The resulting pale yellow solution was warmed to ambient temperature. After 3 h, ethyl acetate (45.4 g) was added and the pH was adjusted to 4.0 with ca. 18.6 g of concentrated HCl. DCU precipitated and was filtered from the mixture. The aqueous layer was separated and washed twice with 31.8 g of ethyl acetate. The combined organic layers were washed twice with 50 mL of saturated brine, the ethyl acetate layer was separated, and the solvent was removed by distillation under vacuum at or below 55 °C. *tert*-Butyl methyl ether (MTBE) (70.8 g) was added, and the suspension was stirred for 30 min at 45−50 °C, then cooled to ambient temperature and stirred for 1 h until crystallization was complete. The product was filtered, washed with 6.3 g of MTBE, and then dried under vacuum at 40−50 °C to afford 11.9 g (87%) of **11**: mp 134−135 °C. ^{1}H NMR (DMSO) δ (ppm): 0.9−1.1 (2H, m), 1.31−1.75 (8H, m), 1.86−2.00 (1H, m), 2.20−2.50 (3H, m), 2.65−2.85 (2H, m), 2.94−3.05 (1H, m), 3.25−3.35 (1H, m), 3.70−3.84 (1H, m), 4.34−4.43 (1H, m), 3.95−4.02 (2H, m), 5.05 (2H, s), 7.27−7.40 (5H, m), 12.40 (1H, s). MS (ESI) *m*/*z*: 403 (MH^+).

Methyl 3-Amino-3-(3-pyridyl)-2-propenoate (18). Methyl nicotinoyl acetate (88 g, 0.5 mol) was dissolved in toluene (200 g), *i*-PrOH (200 g), and formic acid (98−100%, 1.22 g, 0.03 mol) and heated to 60−65 °C. Gaseous ammonia (23 g, 1.35 mol) was bubbled through the solution for 15 min, and the resulting white suspension was stirred at 65 °C until a homogeneous solution formed. The solution was stirred for 2 h at 65 °C and then was concentrated (ca. 200 g) at 65 °C. The residue was cooled to −5 °C with stirring, and methyl 3-amino-3-(3-pyridyl)-2-propenoate crystallized as colorless needles. The process of reducing the volume to 50% followed by cooling was repeated three times with the mother liquors. Filtration, washing with toluene, and drying at 30 °C resulted in 77.74 g (88.8%) of **18** as colorless crystals: mp 118−120 °C. ^{1}H NMR (DMSO) δ (ppm): 3.61 (3H, s), 4.87 (1H, s), 7.50 (1H, dd, J_a = 4.6 Hz, J_b = 8.0 Hz), 8.01 (1H, dt, J_a = 8.0 Hz, J_b = 4.6 Hz), 8.68 (1H, dd, J_a = 1.5 Hz, J_b = 4.6 Hz), 8.82 (1H, d, J = 2.3 Hz). MS (ESI) *m*/*z*: 179 (MH^+).

Methyl 3-Amino-3-(3-pyridyl)propanoate Dihydrochloride (±)-3. Procedure A. Glacial acetic acid (526.9 g, 8.78 mol) was added dropwise at −5 °C to a suspension of **18** (0.45 mol) and sodium borohydride (44.3 g, 1.17 mol) in THF (500 g), and the resulting reaction mixture was stirred at −5 to 0 °C. After 5 h, methanol (600 g) was added dropwise to the solution followed by gaseous HCl (163 g, 4.47 mol) after an additional 0.5 h. After 8 h, the white precipitate was collected by filtration and dried at 40 °C to yield 101.6 g (89%) of (±)-**3** as a white crystalline solid.

Procedure B. Dry palladium on charcoal (0.54 g, manufactured by Degussa, 5% Pd/C) was added to a solution of **18** (5.4 g, 30 mmol) in dry acetic acid (13 g) in a 450-mL Pyrex high-pressure bottle and hydrogenated at 3−3.2 bar. After 1.5−2 h, the catalyst was filtered and washed with 20 g of *i*-PrOH until the wash solvent was no longer yellow. Gaseous HCl (10.6 g, 0.3 mol) was bubbled through the stirred filtrate at 5−15 °C, and the resulting suspension was cooled to 0−5 °C for 2 h. The product was isolated by filtration, washed with 5 g of *i*-PrOH, and dried at 45 °C to yield 5.95 g (78.4%,) of (±)-**3** as a white crystalline solid: mp 187.5−189 °C. ^{1}H NMR (D_2O) δ (ppm): 3.19 (1H, dd), 3.28 (1H, dd), 3.62 (3H, s), 5.05 (1H, t), 8.08 (1H, m), 8.66 (1H, m), 8.80 (1H, m), 8.91 (1H, s). MS (ESI) *m*/*z*: 181 (MH^+).

Methyl (*S*)-3-Amino-3-(3-pyridyl)propanoate Hemitartrate (19). (±)-**3** (150 g, 0.563 mol) was suspended in acetonitrile (425 g) and treated with triethylamine (125.3 g, 1.239 mol) at 35 °C or less. The reaction was stirred for 2 h at 20 °C, then cooled to 5 °C. After 0.5 h, the resulting triethylamine hydrochloride was removed via filtration and washed with 50 g of acetonitrile. The filtrate was evaporated to dryness under vacuum to afford crude methyl 3-amino-3-(3-pyridyl)propanoate. The free base (ca. 105 g) was dissolved in 80 g of ethanol and treated with a solution of (+)-tartaric acid (21.1 g, 0.141 mol) in 80 g EtOH/5 g water. The mixture was stirred for 4 h at ambient temperature and then cooled slowly to 10−15 °C for an additional 2 h. The precipitate was collected via filtration and washed with 30 g of ethanol. The crude hemi-tartrate salt was slurried at 35−40 °C for 2 h in a mixture of 150 g of ethanol and 4.6 g of water and then cooled to ambient temperature. The resulting precipitate was isolated via filtration, washed with 30 g of ethanol, and dried under vacuum to afford 35.5 g (28%) of **19** as a white crystalline solid: mp 139−141 °C. ^{1}H NMR (DMSO) δ (ppm): 2.90 (2H, m), 3.55 (3H, s), 3.97 (1H, s), 4.45 (1H, t, J = 8.0 Hz), 7.39 (1H, dd, J_a = 4.6 Hz, J_b = 8.0 Hz), 7.89 (1H, dt, J_a = 8.0 Hz, J_b = 3.8 Hz), 8.49 (1H, dd, J_a = 1.5 Hz, J_b = 4.6 Hz), 8.62 (1H, d, J = 2.3 Hz). MS (ESI) *m*/*z*: 181 (MH^+ free base).

[*S*-(*R,*S**)]-*β*-[[[1-[1-Oxo-3-(4-piperidinyl)propyl]-3-piperidinyl]carbonyl]amino]-3-pyridine Propanoic Acid (Elarofiban). 11** (60 kg, 149 mol), **19** (41.8 kg, 164 mol), and HOBT (1.98 kg, 14.8 mol) were suspended in a cold solution (0−5 °C) of KH_2PO_4 (7.4 kg, 42.6 mol) and Na_2HPO_4 (4.3 kg, 30 mol) in water (95 kg)/THF (55 kg).

The pH was adjusted to 6.0−6.4 using calcium hydroxide, and the resulting suspension was cooled to 0−5 °C. The reaction mixture was treated with a solution of DCC (37.2 kg, 180.3 mol) in THF (110 kg) and stirred for 1 h at 0−5 °C, then warmed to ambient temperature. After 4 h, the suspension was cooled to 0−5 °C and ethyl acetate (2 kg) was added. The precipitate (a mixture of DCU and calcium tartrate) was removed via filtration and washed with pre-cooled THF (60 kg). The organic layer was separated, washed with 5% $NaHCO_3$ (50 kg), and then concentrated at 40−50 °C. The residual oil was dissolved in THF (50 kg) and evaporated to dryness to afford **12** as an oil. Crude **12** was dissolved in 163 kg of THF at 45 °C, cooled to 0−5 °C, and treated with a solution of lithium hydroxide monohydrate (14.3 kg, 340.8 mol) in 151 kg of water. The resulting pale yellow solution was stirred for 2 h at ambient temperature, and then the pH was adjusted to 4.1 with HCl (36−38%, 38 kg). NaCl (7.2 kg) was added, and the layers were separated. The organic layer was washed twice with a solution of 36.4 kg of NaCl in 72.6 kg of water. The organic layer was concentrated under vacuum, and the resulting oil was dissolved in 75 kg of THF. (This process was repeated until a water content of <2% was achieved.) The precipitated inorganic salts were removed and washed with 9 kg of THF. The filtrate was evaporated under vacuum at 45 °C to afford **13** as an oil. Crude **13** was dissolved in 312 kg of methanol, treated with a suspension of 60 kg of methanol and 15 kg of Pd/C (wet), and then hydrogenated under pressure (2−3 bar) with stirring at 38−42 °C. When the hydrogenation was finished, the catalyst was filtered through Hyflo SuperCel and washed with 39 kg of methanol. The filtrate was concentrated under reduced pressure at 40−50 °C, and the resulting crude oil was dissolved in 756 kg of *n*-butyl alcohol and heated to 75−85 °C for 15−20 min, then cooled to 20−30 °C. *tert*-Butylamine (0.7 kg) was added, and the mixture was cooled to 0−5 °C for an additional hour. The precipitate was isolated, washed with 102 kg of MTBE, and dried under vacuum at 60−80 °C to yield 36 kg (58%) of elarofiban as a white crystalline solid: mp 157−159 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.2−2.0 (m, 12 H), 2.3 (m, 3 H), 2.5 (m, 1 H), 2.8 (m, 5 H), 3.2 (d, J = 8 Hz, 2 H), 3.8 (m, 2 H), 4.2 (m, 2 H), 5.2 (m, 1 H), 7.8 (t, J = 4 Hz, 1 H), 8.3 (t, J = 4 Hz, 1 H), 8.5 (m, 1 H), 8.7 (m, 1 H), 8.9 (m, 2 H); MS *m*/*e*: 417 (MH^+).

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