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Pilot Scale Synthesis of a Novel Nonpeptide Angiotensin II Receptor Antagonist

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Abstract:

FR143187 is a novel nonpeptide angiotensin II receptor antagonist under development at Fujisawa Pharmaceutical Co. for the treatment of hypertension. Development of a process for preparation on a large scale is described. The optimized process is 10 steps in length and uses only commercially available materials for each step. Efficient methylation of the 2-position of a pyrrole derivative was achieved by reduction of a Mannich base via the quaternary ammonium salt. Selective cyanation directed by a solvent effect was also investigated. Process improvement efforts focused on optimized reaction conditions for each step, leading to a high-quality product according to a new and concise synthetic route.

Introduction

Angiotensin II (Ang II) receptor antagonists, such as Losartan[1] (Dupont-Merck) or Candesartan[2] (Takeda) which block the receptor site of angiotensin II, have been developed as a new generation of more effective and selective drugs for the treatment of hypertension than the well-known angiotensin-converting enzyme (ACE) inhibitors such as Captopril (BMS)[3] or Enalapril (Merck)[4] (Figure 1). This discovery of non-peptide Ang II receptor antagonists having exceptionally high antihypertension effects prompted our own search for agents with high activity. Amongst many types of Ang II receptor antagonists synthesized in Fujisawa, several pyrrole derivatives showed highly potent activity.[5] Amongst these compounds, FR143187 (**1**) was shown to be especially effective. For the purposes of complete pharmacological and toxicological evaluation of FR143187 (**1**), we needed an efficient synthetic route to large quantities. The results described herein outline a new process for the synthesis of FR143187 (**1**) and remove several major obstacles in the original process that prevented large-scale synthesis. The new route uses readily available commercial materials, requires relatively simple equipment, and produces a high-quality product. Herein, we report the studies on the process development of FR143187 (**1**) amenable to a large-scale synthesis.

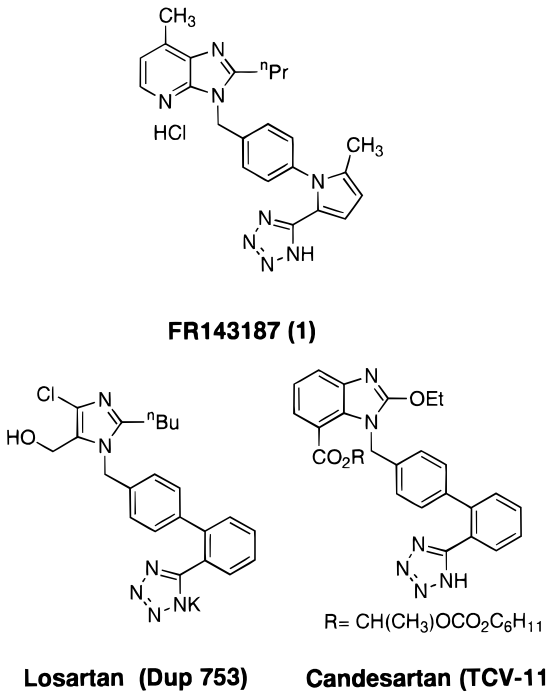

Figure 1. **Nonpeptide angiotensin II receptor antagonists.**

Results and Discussion

Synthetic Route Investigation. 1-(4-Ethoxycarbonylphenyl)-5-methylpyrrole-2-carbonitrile (**6a**) is a key intermediate for the preparation of **1**. The original synthetic approach[5] to **6a** involved regioselective cyanation of a protected hydroxymethylpyrrole derivative followed by reduction of the hydroxymethyl moiety to a methyl group (Scheme 1). However, this route had severe disadvantages for large-scale synthesis. A major problem was that hydroxymethylpyrrole derivatives as intermediates were too unstable to be handled on a large scale. These compounds were initially purified by column chromatography on silica gel, but on a scale above 100 g, most of the product decomposed during this procedure. Another problem was that this 6-step route is conceptually inefficient. For example, protection and deprotection of the hydroxymethyl group requires two extra steps,

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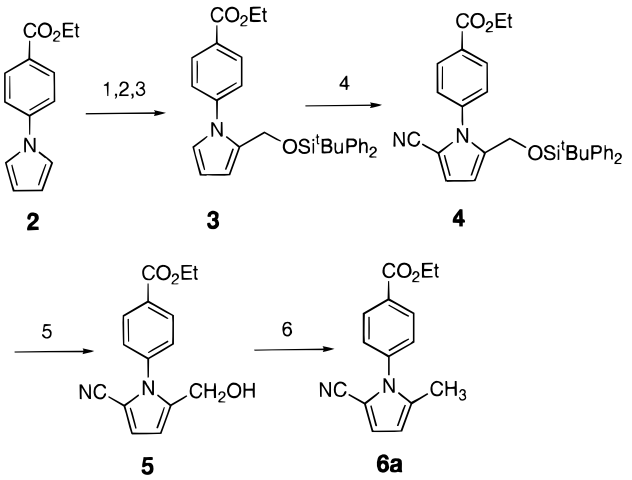
Scheme 1. **Original route to key intermediate 2-cyanopyrrole (6a) (route A)[a]**



[a] Reagents and conditions: 1. $POCl_3$/DMF; 2. $NaBH_4$/EtOH; 3. ^{t}BuPh$_2$SiCl/Et_3N, DMAP; 4. $ClSO_2NCO$/DMF; 5. ^{n}Bu$_4$NF; 6. Et_3SiH, TFA.

compared with a direct cyanation approach. Furthermore, protecting reagents such as *tert*-butylchlorodiphenylsilane are expensive and not readily available on a bulk scale. Amongst several postulated synthetic routes, we were particularly interested in the route outlined in Scheme 2, since in this route no special or expensive reagents ought to be required and fewer potentially unstable intermediates are involved. Moreover, according to route B, only 4 steps are required in principle to convert **2** into **6a**, compared with 6 steps in the previous route (route A). Therefore, our interest in developing a rapid and inexpensive preparative method for **1** promoted us to explore and develop this new synthetic route (route B).

Step 1: Pyrrole Ring Formation. In early investigations, the Wasley procedure[6] (AcOH solvent) was used for preparation of 1-(4-ethoxycarbonylphenyl)pyrrole (**2**). The desired product was obtained in 47% yield; however, it contained tar by-products which made the purification procedure extremely tedious. We endeavoured to improve the reaction conditions and found that the presence of water in the reaction leads to decomposition of the desired product. Use of a 1:1 mixture of toluene and glacial acetic acid as solvent, and continuously removing water by azeotropic distillation, significantly improved the quality and yield of product. Crystallization of **2** from 2-propanol then gave the product in good yield and satisfactory purity (78% chemical yield; 99% chemical purity).

Step 2: Mannich Reaction and Quaternary Ammonium Salt Formation. We applied standard Mannich reaction conditions (37% aqueous CH_2O, Me_2N·HCl−EtOH) to prepare the dimethylamino precursor of **7**, but the yield (47%) was unacceptably low. Knowing that the product and starting material were possibly unstable in an aqueous system, as was observed in the previous step, we investigated reaction in nonaqueous conditions (paraformaldehyde−Me_2N·HCl−EtOH) and found that reaction proceeded quantitatively. Next, the product was converted into the stable quaternary trimethylammonium salt. According to these procedures, we could prepare a product of satisfactory quality (93% chemical yield from **2**; 95% chemical purity)

Table 1. **Reduction of 7[a]**

reagent	yield (%)	molar ratio	temp. (°C)	time (h)
$NaBH_3CN$	73	8	70	18
Me_2N·BH_3	0[c]	8	100	4
NMM·BH_3[b]	70	8	100	4
pyridine·BH_3	78	8	100	2
pyridine·BH_3	63	2.2	100	2
$NaBH(CH_3CO_2)_3$	0[d]	8	70	2

[a] All reactions were carried out in *N*,*N*′-dimethylimidazolidinone. [b] NMM = *N*-methylmorpholine. [c] Major product was the Mannich base (removal of MeI). [d] Starting material recovery.

Step 3: Reduction with Borane−Pyridine Complex. Itoh and co-workers[7] reported methylation of aromatic compounds by reduction of quaternary salts of Mannich bases with sodium cyanoborohydride. It is well-known that sodium cyanoborohydride is capable of reducing a number of functional groups chemoselectively in the presence of a range of sensitive functional groups.[8] Despite this usefulness, it is not acceptable for industrial synthesis because of a lack of commercial availability on a bulk scale and the difficulty in effecting complete decomposition of excess reagent under mild acidic conditions. The evolution of hydrogen cyanide gas during the reaction also necessitates elaborate safety precautions and therefore causes many procedural problems when employing the use of this reducing agent on a large scale. As an alternative reagent available in bulk quantities, borane−dimethylamine complex[9] was investigated for reduction of **2**, but the results were unsatisfactory. The obtained products were mainly the Mannich base with several related by-products. In the course of further studies, it was found that dramatically superior results could be obtained by using borane−pyridine complex. As shown in Table 1, use of excess borane−pyridine complex improved the yield. However, the use of excess reagent also made the workup procedure cumbersome. After completion of the reaction, the organic layer was washed with water and most of the unreacted borane−pyridine complex was thereby removed. A small amount of remaining borane−pyridine complex in the organic layer was completely decomposed by washing with dilute formalin. Removal of solvent under reduced pressure afforded an oil which contained **8** in 64% yield. The reaction allowed complete starting material consumption in 2 h, leading to **8** and a major by-product (33 area % by HPLC). However, the quality of **8** was not influenced since this unknown by-product was cleanly removed in the aqueous layer. For the pilot plant scale synthesis, we obtained the pre-prepared borane−pyridine complex from the Morton International Co.; however, with the goal of gaining a more rapid access to **8** in a manner amenable to production scale use in the future, we endeavoured to prepare the borane−

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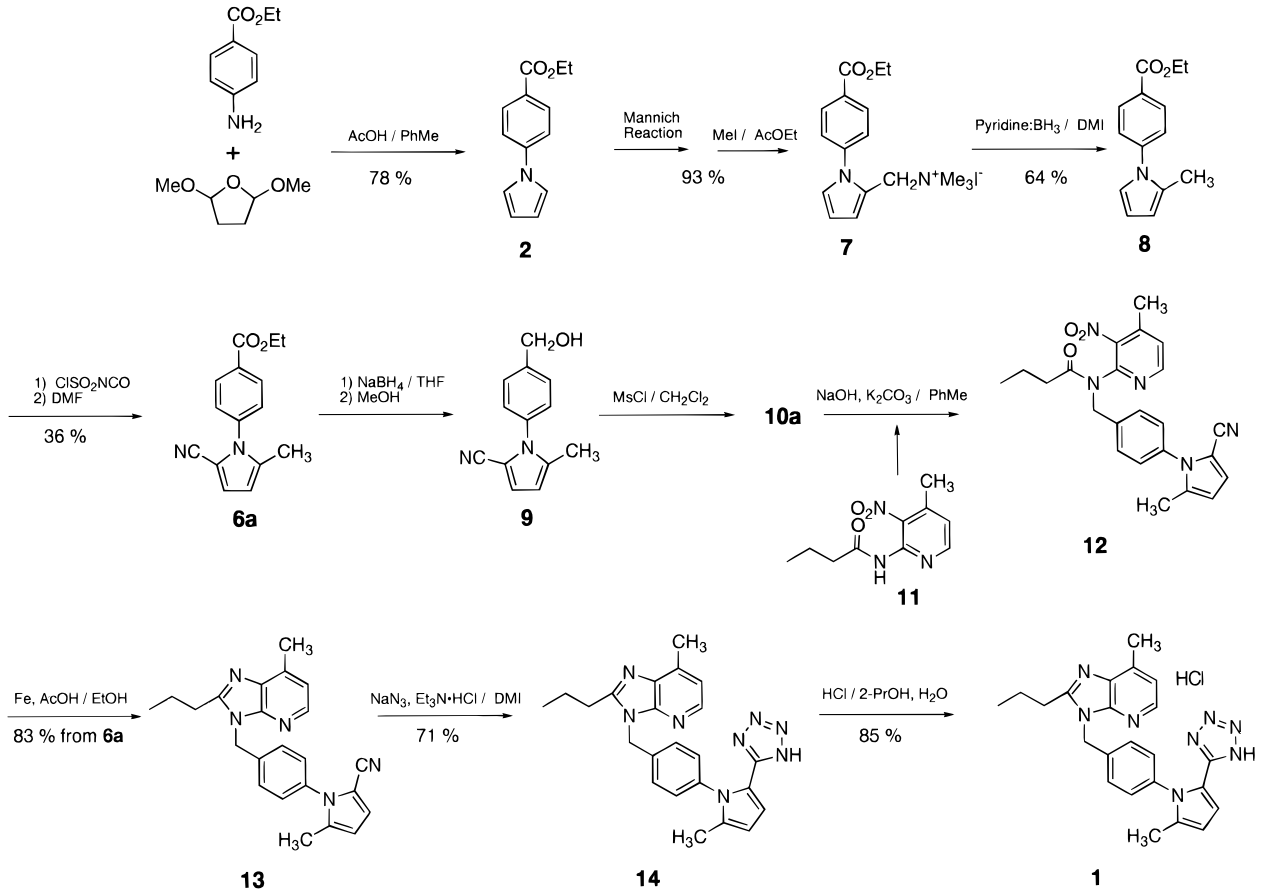
Scheme 2. **New synthetic route to FR143187 (1) (route B)**



pyridine complex in situ. Whilst amine borane reagents have been proven to act as alternatives to sodium cyanoborohydride[10] and have remarkable stability[11] and handling convenience, they have failed to gain widespread use in synthetic chemistry. Furthermore, inexpensive and practical processes for borane−pyridine complex on a large scale are not well-known, in common with other amine borane reagents. In an attempt to develop a viable process on a large scale, we first improved the preparative method for borane−pyridine complex reported by Taylor[12] and explored the simple and efficient reduction system outlined schematically in Scheme 3. The preparative method was as follows. Reaction of pyridinium chloride, which was easily prepared from pyridine and hydrogen chloride, with sodium borohydride afforded borane−pyridine complex in situ and without isolation; the quaternary ammonium species **7** could be reduced to the corresponding methyl compound **8** by addition to the borane solution. Removal of solvent under reduced pressure afforded an oil which contained **8** in 68% yield. This was the same result as when pre-prepared borane−pyridine complex was used.

Step 4: Regioselective Cyanation. We next examined the regioselective cyanation of **8**. Compound **6a** was anticipated to be readily prepared via treatment of **8** with chlorosulfonylisocyanate in methylene chloride followed by addition of *N*,*N*-dimethylformamide (DMF) (Scheme 4). However, when standard methods were used,[13] considerable amounts of **6b** were also formed (Table 2). The similar nature of **6a** and **6b** prevented efficient separation by usual methods such as recrystallization, extraction, and column chromatography. In addition, **6a** never crystallized in the presence of **6b** (up to 10 mol %). In continuous studies, it became clear that there was a correlation between solvent polarity and the amount of **6b** produced. Amongst several solvents screened, *n*-heptane was found to be most suitable (Table 2), but in order to avoid gummy by-products, the addition of toluene after reaction completion served to facilitate the isolation and purification procedure. Crude **6a**, which was triturated from isopropyl ether, along with a small amount of **6b** (∼2%) was purified by recrystallization from aqueous isopropyl alcohol to afford **6a** with satisfactory quality (36% chemical yield; 98% chemical purity).

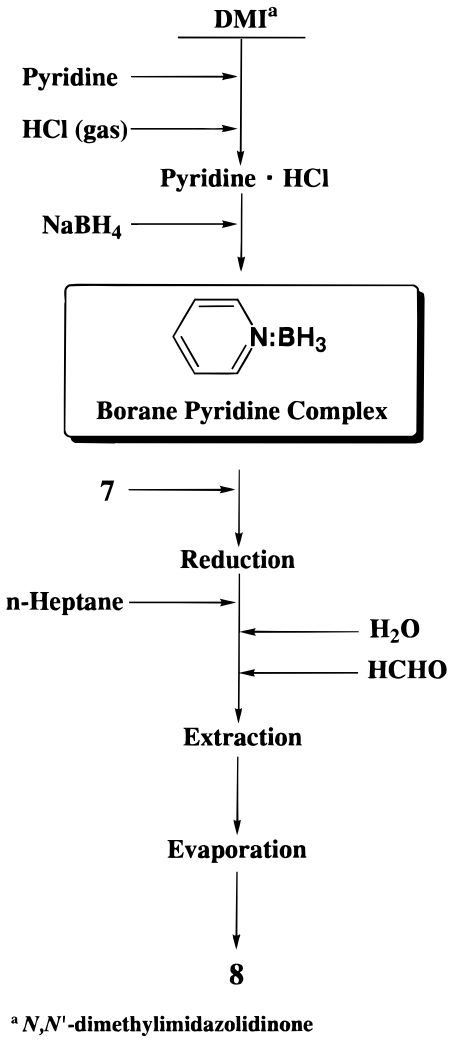
Table 2.

solvent	product ratio[a] 8	6a	6b
CH_2Cl_2	12	78	10
PhMe	6	87	7
n-heptane	10	86	4

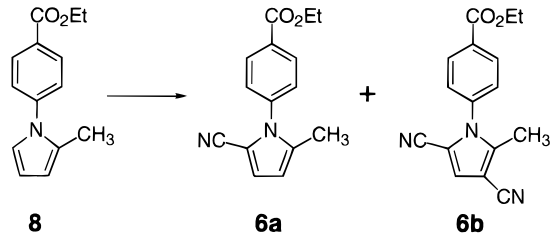
[a] Ratio of products was determined by HPLC.

(10) Pelter, A.; Rosser, R. M.; Mills, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 717.
(11) Ryschkewitsch, G. *J. Am. Chem. Soc.* **1960**, *82*, 3290.
(12) Taylor, M. D.; Grant, L. R.; Sands, C. A. *J. Am. Chem. Soc.* **1955**, *77*, 1506.
(13) Lohaus, G. *Org. Synth.* **1970**, *50*, 52.

Scheme 3. **Reduction of 7 with borane−pyridine complex**



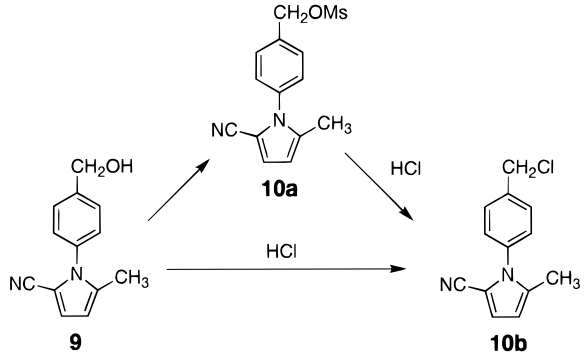
Scheme 4. **Solvent effect on cyanation of 8**



Step 5: Reduction of Ethyl Ester to Alcohol. This reaction proceeded smoothly by adding methanol dropwise to a mixture of **6a** and $NaBH_4$ in tetrahydrofuran maintaining high-temperature conditions (∼60 °C). However, since the control of hydrogen evolution was difficult on a large scale, we searched for appropriate conditions and found that reaction proceeded even at 45−55 °C. The resulting alcohol **9** was then used directly in the next step.

Step 6: Coupling 9 with 11. (*a*) *Activation of* ***9*** *with Methanesulfonyl Chloride*. Activation of **9** was easily achieved with methanesulfonyl chloride (MsCl). However, in our early studies, the product contained 10% of the chloromethyl impurity **10b**. This by-product did not undergo coupling with **11** under the low-temperature conditions investigated. By-product **10b** was readily removed in the mother liquor during the filtration procedure leading to **12**. Our investigations on the inhibition of production of **10b** showed that the resulting amount of **10b** depended on the quantity and speed of addition of MsCl and the internal reaction temperature (Scheme 5). Considering the heat balance during the reaction on a pilot plant scale preparation, it was estimated that 30 min would be best for introduction of MsCl to the reaction mixture, whilst maintaining the temperature at 5−10 °C. In this way, optimized reaction conditions (MsCl (1 equiv)), temperature of 5−10 °C, addition time of ca. 30 min) gave the desired product along with 1.5% of **10b** and 2.5% of the starting material. Extraction from the reaction mixture with methylene chloride, followed by condensation under reduced pressure, afforded crude **10a** as oil. The mesylate **10a** was suitable for direct coupling with readily prepared pyridine derivative **11** (see the Experimental Section) according to the following procedure.

Scheme 5. **Inhibition of 10b**



(*b*) *Coupling* ***10a*** *with* ***11***. In our first experiment on a lab scale, we coupled **10a** with **11** to prepare **12** in the presence of sodium hydride in DMF. However, in this system the use of excess sodium hydride resulted in the decomposition of the desired product, whilst in the case of exact molar equivalents, large amounts of starting material remained. In both experiments, the yields were poor (∼50%). Furthermore, the known instability of NaH−DMF mixtures precluded any development of a large-scale process.[14] We thus investigated methods to improve this reaction system and found that by utilizing a mixture of powdered potassium carbonate and granulated sodium hydroxide as the base under low-temperature conditions (3−5 °C), the desired adduct could be prepared in excellent yield as an oil (90% from **6a**).

Step 7: Reductive Cyclization. The reductive cyclization, leading to imidazole ring formation was carried out in ethanol in the presence of acetic acid and fine iron powder. The most difficult problem in this step was the observation that, on both laboratory and pilot scale, the reaction would sometimes suddenly stop, leaving variable amounts of unchanged starting material. The reason for this problem was not clear; however, extensive studies showed that periodic addition of further iron powder or acetic acid could reinitiate the reaction. In pilot manufacturing, we added acetic acid to finish the reaction at a point 2 h from initiation.

(14) Laird, T. *Chem. Ind.* **1986**, *17*, 134.

After the removal of residual iron powder and complete removal of solvents, the resultant oil was dissolved in ethyl acetate and purified by column chromatography on silica in order to improve the color of product and ensure the complete removal of iron powder. The eluent was concentrated to an oil and crystallized from 2-propanol to afford **13** in high yield and quality (83% chemical yield from **6a**; 99% chemical purity).

Step 8: Tetrazole Reaction. One of the most useful functional groups to be introduced into Ang II receptor antagonists is the tetrazole group, functioning as a carboxylic acid isostere. Whilst a number of methods for introducing a tetrazole group have been reported,[15] the coupling reaction of a cyano group with sodium azide in the presence of an ammonium salt has been the most widely used.[16] This reaction usually proceeds smoothly, but in the case of a large-scale synthesis, there is a major safety consideration which must be kept in mind. Hydrogen azide (HN_3) is extremely sensitive towards explosion, especially in the presence of heavy metals, as well as being harmful.[17] In pilot plant manufacturing, we rigorously ensured that no heavy metals were present in the starting material using an X-ray microanalyzer and also in the reaction vessel. Concerning residual sodium azide, we planned to decompose it using sodium nitrite under acidic conditions (pH = <1). However, almost all of the product decomposed under these conditions. Therefore, we had to investigate new procedures for the decomposition of azide. To prevent the decomposition of the product, we envisaged that rigorous control of pH would allow selective removal of azide. Ethyl acetate was first added to the reaction mixture, followed by an excess amount of sodium nitrite, and the aqueous layer was then carefully maintained at pH = 4.5−5.0. In our investigation, only when the reaction was carried out at relatively high-temperature conditions (25−30 °C) did decomposition of residual azides completely finish. In pilot plant manufacturing, complete decomposition of azides was analyzed by ion chromatography (N_3^- was checked) as well as the conventional method[18] using dilute iron(III) chloride in water. After this treatment, the organic layer was washed with 10% brine, and replacing the organic layer by acetonitrile gave the desired high quality product **14** (85% chemical yield; 99% chemical purity).

Step 9: Hydrogen Chloride Salt. In early studies, we attempted conversion of **14** into the hydrogen chloride salt form **1** using 35% hydrogen chloride in water, ethanol, or 2-propanol. However, variable amounts (1.5−1.7%) of residual solvent could not be removed under reduced pressure. We investigated crystallization from a mixture of 2-propanol and water and found that, at a high ratio (up to 64%) of water, satisfactory quality product (residual 2-propanol = 0.5%, 99% purity) could be obtained in 85% yield. The product prepared by this method has proven to be acceptable for pharmaceutical and toxicological evaluation.

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(17) Lenga, R. E. *Sigma-Aldrich Library of Chemical Safety Data*, 2nd ed.; Sigma-Aldrich Chemical Co., Inc.: Milwaukee, WI; Vol. 2, p 3129D.
(18) Azzam, A. A. *Mikrochim. Acta* **1937**, 283.

Conclusions

We have succeeded in developing a new large-scale synthesis of FR143187, a non-peptide angiotensin II receptor antagonist. Key features of this work are as follows:

1. We focused on maintaining safety for the pilot scale tetrazole reaction, one of the most dangerous and difficult reactions for large scale, by ensuring that no heavy metals were present and also the complete decomposition of residual azide compounds. The final process was safely implemented on a pilot plant scale. The described methods are useful for reactions in which use of azide reagents is unavoidable and especially for a large-scale synthesis.

2. A practical, efficient, and inexpensive preparative method for the borane−pyridine complex suitable for a large-scale synthesis was investigated. Borane−pyridine complex is a safe reagent, is easy to handle, and can function as a substitute for sodium cyanoborohydride.

3. Selective cyanation of a methylpyrrole derivative was achieved by modification of reaction conditions.

4. It is worth emphasizing that process improvement efforts focused on safe and optimized reaction conditions for each step with the aim of a large-scale synthesis giving satisfactory quality products and of a final product suitable for pharmaceutical and toxicological evaluation.

Experimental Section

General Methods. Ethyl 4-aminobenzoate was commercially available from the Midori Chemical Co. 2,5-Dimethoxytetrahydrofuran was commercially available from BASF Co. *N,N′*-dimethylimidazolidinone (DMI) was obtained from Mitsui Toatsu Chemical Co., and chlorosulfonylisocyanate was from Kuraray Co. All other chemicals were obtained from the usual commercial suppliers. HPLC analyses were performed using a YMC GEL ODS 120 Å S-7 column and an acetonitrile/water phase. The water component was adjusted with KH_2PO_4 and Na_2HPO_4 to pH = 7.8. Purity of each obtained product was determined by comparison with purified authentic samples using quantitative HPLC. X-ray microanalyses were performed on a HORIBA EMAX-5770. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 200 MHz in $CDCl_3$ or DMSO-d_6. Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard. Ion chromatography measurements were performed on a Yokogawa Model IC-7000. IR spectra were recorded on a HITACHI IR-260-10 spectrometer. Mass spectra were measured on a Hitachi Model M-80 mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer.

1-(4-Ethoxycarbonylphenyl)pyrrole (2). A solution of ethyl 4-aminobenzoate (220 kg, 1332 mol) and 2,5-dimethoxytetrahydrofuran (176 kg, 1332 mol) in a mixture of glacial acetic acid (660 L) and toluene (660 L) was heated to reflux for 3 h with removal of water of reaction by azeotropic distillation. After the reaction was complete, the reaction mixture was washed consecutively with water (440 L, 220 L, 220 L), saturated sodium hydrogen carbonate (220 L), and then evaporated under reduced pressure. The residue

was dissolved in 2-propanol (220 L) and evaporated again to ensure the complete removal of acetic acid. The residual product was dissolved in 2-propanol (880 L), heated to reflux for 1 h and cooled to 0 °C. After additional overnight stirring at ambient temperature, the precipitate was filtered off, washed with cooled 2-propanol (220 L) and dried under reduced pressure to yield **2** (224 kg, 78% yield) of 99% purity; mp 74−75 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, 3H, J = 7.1 Hz), 4.39 (q, 2H, J = 7.1 Hz), 6.38 (t, 2H, J = 2.2 Hz), 7.15 (t, 2H, J = 2.2 Hz), 7.44 (d, 2H, J = 8.8 Hz), 8.10 (d, 2H, J = 8.8 Hz); IR (Nujol) 1705, 1608, 1523, 1476, 1428, 1334, 1282 cm^{-1}; MS (EI) *m*/*z* 216 $(M+H)^+$, 75. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.55; H, 6.10; N, 6.46.

1-(4-Ethoxycarbonylphenyl)pyrrole-2-methyltrimethylammonium Iodide (7). A solution of **2** (220 kg, 1022 mol), dimethylammonium chloride (125 kg, 1533 mol) and paraformaldehyde (138 kg, 4595 mol) in ethanol (660 L) was heated to reflux (83 °C) for 3 h and cooled to 30 °C. To this reaction mixture were added sequentially ethyl acetate (660 L), water (220 L), and 12% sodium hydroxide in water (440 L) whilst the temperature was maintained below 15 °C. The aqueous layer was separated, and the organic layer was washed with water (440 L, 220 L). Aqueous layers were combined and extracted with ethyl acetate (220 L). The combined ethyl acetate layers were washed with saturated brine (220 L), and to this layer was added methyl iodide (290 kg, 2043 mol) at 35 °C. After 2 h of stirring at ambient temperature, the reaction mixture was cooled to 0 °C and stirred overnight. The precipitate was filtered off, washed with a mixture of ethyl acetate (352 L) and ethanol (88 L), and dried under reduced pressure to yield **7** (394 kg, 93% yield) of 95% purity: mp 287−289 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.35 (t, 3H, J = 7.1 Hz), 2.78 (s, 9H), 4.37 (q, 2H, J = 7.1 Hz), 4.37 (s, 2H), 6.42 (t, 1H, J = 3.4 Hz), 6.74 (dd, 1H, J = 3.6, 1.6 Hz), 7.26 (dd, 1H, J = 2.8, 1.7 Hz), 7.62 (d, 2H, J = 8.5 Hz), 8.12 (d, 2H, J = 8.5 Hz); IR (Nujol) 1698, 1605, 1470, 1379, 1333, 1280, 1174, 1130 cm^{-1}; MS (EI) *m*/*z* 242, 228, 214, 75. Anal. Calcd for $C_{17}H_{23}N_2O_2I \cdot 0.86\ H_2O$: C, 47.51; H, 5.80; N, 6.52. Found: C, 47.65; H, 5.57; N, 6.64.

1-(4-Ethoxycarbonylphenyl)-5-methylpyrrole (8). *Pilot Plant Scale Synthesis.* A mixture of **7** (130 kg, 314 mol) and borane−pyridine complex (64.2 kg, 691 mol) in DMI (400 L) was heated to 104−113 °C for 2 h and then cooled to 30 °C. To this reaction mixture was added consecutively *n*-heptane (650 L) and water (390 L). The layers were separated, the aqueous layer was extracted with fresh *n*-heptane (390 L), and the combined organic layers were washed with 12% formalin (390 L) until no borane−pyridine complex was detected (HPLC). The organic layer was washed with water (390 L) and concentrated under reduced pressure to give **8** as an oil (46.1 kg, 64% yield, 91 area % by HPLC).

Improved Synthesis on Lab Scale. Pyridinum chloride was easily prepared from pyridine (45.75 g, 578 mmol) and hydrogen chloride (20.20 g, 554 mmol) and was then treated with sodium borohydride (20.05 g, 530 mmol) in DMI (300 mL) under nitrogen atmosphere to afford borane−pyridine complex. To this reagent was added **7** (100 g, 241 mmol), the mixture heated to 105 °C for 2 h and then cooled to 30 °C. To this reaction mixture was added consecutively *n*-heptane (500 mL) and water (300 mL). After the layers were separated, the aqueous layer was extracted with fresh *n*-heptane (300 mL) and the combined organic layer was washed with 12% formalin (300 mL) until no borane−pyridine complex was detected (HPLC). The organic layer was washed with water (300 mL) and concentrated to an oil under reduced pressure which contained **8** (37.6 g, 68% yield, 91 area % by HPLC).

1-(4-Ethoxycarbonylphenyl)-5-methypyrrole-2-carbonitrile (6a). A mixture of **8** (46 kg, 201 mol) and *n*-heptane (920 L), cooled to −10 °C, was treated dropwise with chlorosulfonylisocyanate (39.8 kg, 281 mol) maintaining the temperature at −10 °C, and the reaction was continued at ambient temperature for an additional 1 h. To this solution were added cooled toluene (0−10 °C, 460 L) and cooled DMF (0−10 °C, 138 L), and the mixture was stirred for 1 h at −5 °C. To the reaction mixture was added 12% hydrogen chloride in water (230 L) maintaining the temperature under 0 °C. The layers were separated, and the aqueous layer was extracted with a mixture of *n*-heptane (230 L) and toluene (115 L). The combined organic layers were washed consecutively with water (230 L) and saturated sodium hydrogen carbonate (230 L). The organic layer was concentrated under reduced pressure, and to the residue were added isopropyl ether (595 L) and *n*-heptane (595 L). After the organic layer was separated by decantation, the residual waxy products were dissolved in isopropyl ether (595 L) and extracted with *n*-heptane (595 L). The combined organic layers were concentrated to an oil under reduced pressure, and the residual oil was dissolved in hot isopropyl ether (198 L) and cooled to 0 °C. Purified **6a** (132 g) was added, and after complete precipitation at ambient temperature, the precipitate was filtered off and dried under reduced pressure to afford crude **6a** (33.6 kg, 66% yield) of 91% purity. The crude **6a** (33.6 kg) was recrystallized from a mixture of 2-propanol (67 L) and water (17 L) to afford purified **6a** (18.4 kg, 55% yield) of 98% purity. 1-(4-Ethoxycarbonylphenyl)-5-methypyrrole-2-carbonitrile (**6a**): mp 56−57 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, 3H, J = 7.0 Hz), 2.18 (s, 3H), 4.42 (q, 2H, J = 7.0 Hz), 6.11 (d, 1H, J = 4.5 Hz), 6.90 (d, 1H, J = 4.5 Hz), 7.40 (d, 2H, J = 9.0 Hz), 8.21 (d, 2H, J = 9.0 Hz); IR (Nujol) 2212, 1715, 1604, 1513, 1479, 1407, 1371, 1328 cm^{-1}; MS (EI) *m*/*z* 255 $(M + H)^+$, 209, 141, 75. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.68; H, 5.52; N, 10.96. 1-(4-Ethoxycarbonylphenyl)-5-methypyrrole-2,4-dicarbonitrile (**6b**) was obtained by preparative TLC: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, 3H, J = 7.1 Hz), 2.33 (s, 3H), 4.44 (q, 2H, J = 7.1 Hz), 7.15 (s, 1H), 7.41 (d, 2H, J = 8.6 Hz), 8.27 (d, 2H, J = 8.6 Hz); MS (EI) *m*/*z* 280 $(M + H)^+$, 259, 167, 101, 75.

2-(Butyrylamino)-4-methyl-3-nitropyridine (11). A mixture of 2-amino-4-methyl-3-nitropyridine (45.7 kg, 298 mol) and *N*,*N*-dimethylaniline (72.3 kg, 597 mol) in toluene

(229 L) was heated at 95 °C under nitrogen atmosphere. To this solution was slowly added butyryl chloride (35.0 kg, 328 mol), and the mixture was stirred at 100 °C for 7 h. After cooling to 25 °C, methylene chloride (451 L) and water (229 L) were added. The organic layer (lower layer) was separated and washed twice with water (229 L, 229 L). The organic layer was concentrated under reduced pressure to ~229 L and *n*-heptane (457 L) added. The solution was concentrated again to ~457 L, and *n*-heptane (215 L) added, followed by concentrated to ~457 L. To this residue was added *n*-heptane (215 L), and the solution was heated at 45−50 °C for 30 min and cooled under 10 °C. The precipitate was filtered off, washed with *n*-heptane (137 L), and dried to afford **11** (56.0 kg, 84% yield) of 100% purity: mp 109−110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.5 Hz), 1.64−1.85 (m, 2H), 2.43 (t, 2H, J = 7.5 Hz), 2.48 (s, 3H), 7.10 (d, 1H, J = 5.0 Hz), 8.26 (br s, 1H), 8.35 (d, 1H, J = 5.0 Hz); IR (KBr) 3296, 3020, 2962, 2929, 2875, 1674, 1603, 1556, 1533, 1512, cm^{-1}; MS (EI) m/z 224 $(M + H)^+$, 154, 73. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.94; H, 5.89; N, 18.61.

3-[4-[1-(2-Cyano-5-methylpyrrolyl)]benzyl]-7-methyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine (13). To a mixture of **6a** (50.0 kg, 197 mol) and sodium borohydride (22.3 kg, 590 mol) in tetrahydrofuran (250 L) was added methanol (100 L) over 1 h maintaining the temperature at 45−55 °C. The reaction mixture was heated to reflux over 1 h followed by cooling to 20−25 °C. After addition of water (150 L) to the reaction mixture, the layers were separated and the aqueous layer was re-extracted with methylene chloride (250 L, 50 L). The combined organic layers were washed with water (150 L, 150 L) and concentrated to an oil under reduced pressure. The residue was dissolved in methylene chloride (418 L), treated with triethylamine (23.9 kg, 237 mol), and cooled to 5 °C. To this solution was added methanesulfonyl chloride (22.6 kg, 197 mol) as fast as possible (over about 30 min on this scale) keeping the internal temperature under 10 °C. After the completion of the reaction, water (209 L) was added over 30 min maintaining the temperature in the range of 5−10 °C. The layers were separated, and the organic layer was washed with 6% hydrogen chloride in water (209 L) and concentrated under reduced pressure to give crude **10a** as an oil. 1-(4-Methanesulfonyloxymethylphenyl)-5-methypyrrole-2-carbonitrile (**10a**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (s, 3H), 3.03 (3H, s), 5.31 (2H, s), 6.10 (d, 1H, J = 4.5 Hz), 6.89 (d, 1H, J = 4.5 Hz), 7.37 (d, 2H, J = 9.0 Hz), 7.59 (d, 2H, J = 9.0 Hz). 1-(4-Chloromethylphenyl)-5-methypyrrole-2-carbonitrile (**10b)** was obtained by preparative TLC: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H), 4.65 (2H, s), 6.08 (d, 1H, J = 3.9 Hz), 6.87 (d, 1H, J = 3.9 Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.54 (d, 2H, J = 8.4 Hz); MS (EI) m/z 230 (M^+), 195, 154, 127, 89. Compound **10b** was also confirmed to contain chlorine as an element. Anal. Calcd for $C_{13}H_{11}ClN_2$: Cl, 15.37. Found: Cl, 14.62.

To a solution of **11** (44.0 kg, 197 mol) in toluene (125 L) were added granulated sodium hydroxide (15.8 kg, 395 mol) and powdered potassium carbonate (81.7 kg, 591 mol), and the mixture was adjusted to 3−5 °C. To this mixture was added the previously prepared solution of **10a** in toluene over 15 min. The reaction was then continued overnight (12 h) at ambient temperature and then heated to 25−30 °C for 2.5 h. After completion of the reaction, water (314 L) was slowly added keeping the temperature below 30 °C, and then the mixture was heated to 50 °C. The layers were separated, and the aqueous layer was re-extracted with toluene (125 L). The combined organic layer was washed with water (125 L) and concentrated under reduced pressure to afford an oil which contained **12** (72.2 kg, 88% yield from **6a**). To a portion of the residual oil (62.0 kg, 149 mol) were added ethanol (310 L), acetic acid (62 L), and iron powder (62.0 kg), and the mixture was then heated to reflux for 2 h. Additional acetic acid (62 L) was then added, and the reaction was continued for a further 3 h, followed by cooling to room temperature. The iron powder was filtered off, the filter cake was washed with ethanol (124 L), and the filtrate was concentrated to an oil under reduced pressure. To ensure the complete removal of acetic acid, the residual oil was dissolved in toluene (62 L), and the mixture was re-concentrated. After removal of small amounts of insoluble products contained in **13** by dissolving in ethyl acetate (186 L) and filtration, the filtrate was purified by column chromatography on silica gel (62.0 kg) eluting with additional ethyl acetate (248 L). The effluent was concentrated to an oil under reduced pressure and dissolved in 2-propanol (248 L) at 65 °C, followed by cooling to 0 °C. After overnight stirring at ambient temperature, the precipitate was filtered off, washed with cooled 2-propanol (62 L), and dried in vacuo overnight to afford **13** (45.5 kg, 83% yield) of 99% purity. The product was confirmed as containing no heavy metals by the X-ray analyzer: mp 150−151 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.0 Hz), 1.69−1.91 (m, 2H), 2.10 (s, 3H), 2.72 (s, 3H), 2.87 (t, 2H, J = 7.0 Hz), 5.57 (s, 2H), 6.06 (d, 1H, J = 4.5 Hz), 6.86 (d, 1H, J = 4.5 Hz), 7.08 (d, 1H, J = 5.0 Hz), 7.28 (s, 4H), 8.23 (d, 1H, J = 5.0 Hz); IR (Nujol) 2216, 1608, 1519, 1410, 1378, 1327, 1243 cm^{-1}; MS (EI) m/z 370 $(M + H)^+$. Anal. Calcd for $C_{23}H_{23}N_5$: C, 74.77; H, 6.27; N, 18.96. Found: C, 74.37; H, 6.25; N, 18.82.

7-Methyl-3-[4-[1-(5-methyl-2-1*H*-tetrazol-5-yl)pyrrolyl]-benzyl]-2-propyl-3*H*-imidazo[4,5-*b*]pyridine (14). The reaction vessel was rigorous cleaned and confirmed as having no residual heavy metals, holes, or cracks by measuring electric insulation. A mixture of **13** (16.8 kg, 45.5 mol), triethylamine hydrogen chloride (31.3 kg, 227 mol), and sodium azide (11.8 kg, 181 mol) in DMI (118 L) was heated to 120 °C for 8 h and then cooled to room temperature. To this reaction mixture were added water (84 L) and sodium nitrite (18.8 kg, 272 mol) in water (42 L), maintaining temperature at 20−25 °C, followed by cooling to less than 10 °C. Ethyl acetate (168 L) was added, and the mixture was treated with cooled 6% hydrogen chloride in water to adjust the pH to 4.5−5.0 (caution: evolution of nitrogen gas). The reaction was continued until tests using ion chromatography measurement confirmed no remaining azide compounds. To this solution was added 4% sodium hydroxide

in water (84 L), and the layers were separated. The organic layer was re-extracted with 4% sodium hydroxide in water (42 L), and the aqueous layers were combined. To this aqueous layer were added ethyl acetate (168 L) and 36% hydrogen chloride in water to adjust the pH to 4.5−5.0 whilst the temperature was maintained at 13−17 °C. The separated organic layer was concentrated to ∼84 L under reduced pressure. To this residual organic solution was added acetonitrile (84 L), and the resulting solution was then re-concentrated to ∼84 L under reduced pressure. After additional overnight stirring at 3−7 °C, the precipitate was filtered off and washed with acetonitrile (16.8 L) to afford **14** (13.3 kg, 71% yield) of 99% purity: mp 184−185 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.90 (t, 3H, J = 7.5 Hz), 1.57−1.79 (m, 2H), 1.99 (s, 3H), 2.57 (s, 3H), 2.82 (t, 2H, J = 7.5 Hz), 5.60 (s, 2H), 6.18 (d, 1H, J = 4.5 Hz), 6.80(d, 1H, J = 4.5 Hz), 7.10 (d, 1H, J = 5.0 Hz), 7.22 (s, 4H), 8.19 (d, 1H, J = 5.0 Hz); IR (Nujol) 1608, 1539, 1520, 1463, 1391, 1360, 1284, 1233 cm^{-1}; MS (EI) m/z 413 (M + H)$^+$, 385, 287, 205, 127, 105, 75. Anal. Calcd for $C_{23}H_{24}N_8$: C, 66.97; H, 5.86; N, 27.16. Found: C, 66.51; H, 5.84; N, 26.96.

7-Methyl-3-[4-[1-(5-methyl-2-1*H*-tetrazol-5-yl)pyrrolyl]-benzyl]-2-propyl-3*H*-imidazo[4,5-*b*]pyridine Hydrochloride (1) (FR143187). A solution of **14** (12 kg, 29.1 mol) in a mixture of 2-propanol (42 L) and purified water (14 L) at 82 °C was purified by filtration through a 0.45 μm filter. After confirming that no crystals had precipitated, 36% hydrogen chloride in water (3.6 L) was added to this solution above 60 °C and was followed by addition of purified water (60 L). To this solution was added purified **1** (12.0 g) at 30−35 °C. After the precipitation of **1**, stirring was continued at the same temperature for 30 min and at 3−5 °C for 2.5 h. The precipitate was filtered off, washed with a cooled mixture of 2-propanol (6.0 L), purified water (12 L), and 36% hydrogen chloride (0.6 L), and dried under reduced pressure to afford purified **1** (11.1 kg, 85% yield) of 99% purity: mp 244−246 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.91 (t, 3H, J = 7.4 Hz), 1.69 (m, 2H), 2.00 (s, 3H), 2.70 (s, 3H), 3.23 (t, 2H, J = 8.0 Hz), 5.82 (s, 2H), 6.19 (d, 1H, J = 3.1 Hz), 6.94 (d, 1H, J = 3.7 Hz), 7.27 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.50 (d, 1H, J = 5.1 Hz), 8.54 (d, 1H, J = 4.9 Hz); IR (Nujol) 1600, 1529, 1513, 1356, 1220 cm^{-1}; MS (EI) m/z 413, 385, 287, 205, 127, 105, 75. Anal. Calcd for $C_{23}H_{25}N_8Cl$: C, 61.53; H, 5.61; N, 24.96. Found: C, 61.32; H, 5.61; N, 24.89.

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