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Development of a New Synthetic Route of a Non-Peptide CCR5 Antagonist, TAK-779, for Large-Scale Preparation

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Abstract:

A new large-scalable preparation of TAK-779 (1), a non-peptide CCR5 antagonist, has been developed. The route selection was focused on in the process research. The selective reduction of commercially available benzonitrile derivative (4) as the starting material with sodium bis(2-methoxyethoxy)aluminum hydride followed by the Wittig reaction, hydrogenation, and intramolecular acylation gave benzocycloheptanone (7) in good yield. The conversion of α,β-unsaturated carboxylic acid (8) led from 7 to benzyl alcohol (9) and shortened the number of steps using non-protected 4-aminobenzyl alcohol. The reductive alkylation of Me_2NH and tetrahydro-4*H*-pyran-4-one (12) smoothly gave a tertiary amine (3). The coupling of 2 chlorinated 9, and 3 successfully led to an ammonium chloride (1). A new inexpensive preparation which did not require a chromatographic method was achieved.

Introduction

In recent years, the β-chemokine receptor CCR5 has been shown to act as a major coreceptor for fusion and entry of macrophage-tropic HIV-1 into the host cell.[1] This new generation, having a novel mechanism, differs from well-known chemotherapy, for example, HIV-1 reverse transcriptase[2] and protease inhibitors,[3] and has been attractive as a strong candidate for the therapy of HIV-1. In the search of derivatives of many types, small-molecule non-peptide compounds synthesized by Takeda chemists, anilido derivatives, showed highly potent activities. In particular, *N*,*N*-dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride (TAK-779, **1**) was found to be especially effective.[4] Hence, an efficient preparation of **1** on large scale was required to support toxicological evaluation. Two independent preparations of **1** comprising the ammonium chloride moiety have been reported.[4b,c] One method uses methylation of a tertiary amine followed by anion exchange, and the other uses the reaction of benzyl chloride (**2**) and tertiary amine (**3**) as shown in Scheme 1. The latter synthesis produced a high-quality product, since this treatment afforded only ammonium chloride without contamination by other counterions. However, the original synthesis involved several limitations from the standpoint of large-scale preparation, for example, utilization of expensive reagents, requirement of a protective process, and repeated tedious chromatographic methods, and lower yield. To advance the practical preparation, we tried to develop an alternative synthesis of **1** using inexpensive reagents. Here, we report a new preparation of TAK-779 (**1**) that was amenable to scale-up, and in which protective processes and repeated chromatographic methods were not required, as outlined in Scheme 2.

Results and Discussion

Alternative Synthesis of 7-Tolylbenzocycloheptanone (7). In an early report,[4b,c] 3-(4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**7**) was synthesized by cyclization of 5-(4-bromophenyl)pentanoic acid prepared from bromobenzene as the starting material, followed by the aryl-aryl cross-coupling using arylboronic acid. However, intramolecular acylation of 5-(4-bromophenyl)pentanoic acid using PPA produced 3-bromo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one in 67% yield accompanied with a tar product, thus requiring chromatographic purification. To resolve the hazardous problem described above, we attempted to change the electron donor group from bromide as the substituted group, that is, the cyclization of 5-(4-methylphenyl)pentanoic acid (**6**), since it was known that the substituted groups in aromatic compounds affected the yields of the intramolecular acylation. First, 4-(4-methylphenyl)benzaldehyde (**5**) as an intermediate of **6** was prepared in about 50% yield from the treatment of 4-methylphenylbenzene with

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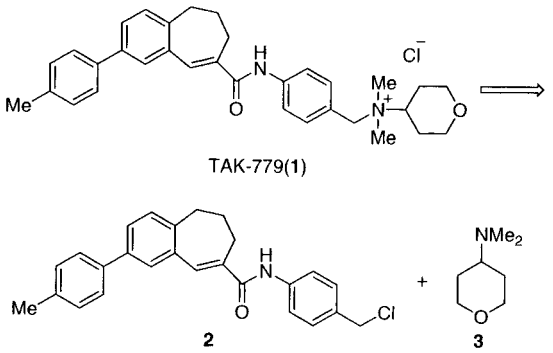
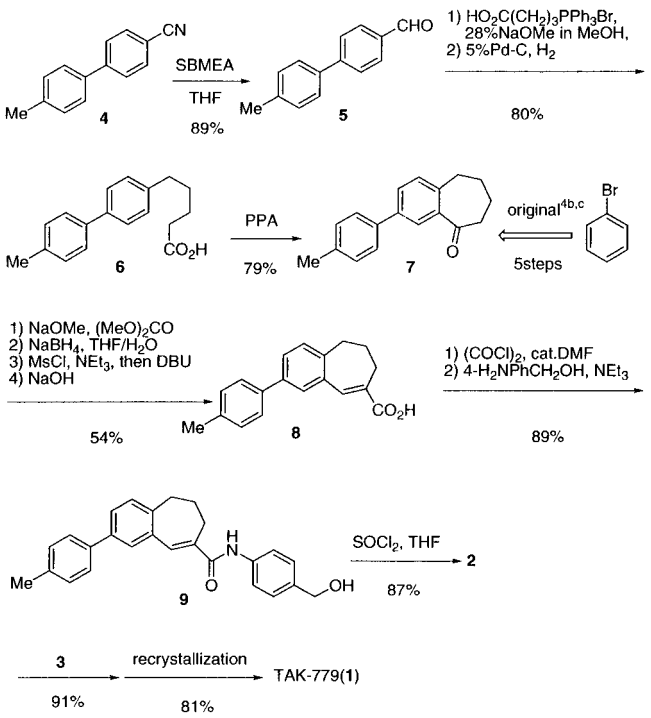
Scheme 1. **Retrosynthesis of TAK-779 (1)**



Scheme 2. **New preparation for TAK-779 (1)**



hexamethylenetetramine in TFA,[5a] not prepared by the Vielsmier reagent.[5b] When the selective reduction of commercially available 4-(4-methylphenyl)benzonitrile (**4**) was also carried out, the reaction using sodium bis(2-methoxyethoxy)aluminum hydride (SBMEA)[6] in THF at −20 °C gave benzaldehyde (**5**) in 98% yield (89% yield in pilot-scale preparation) as shown in Table 1, although the yield of **5** by DIBAL[7] in toluene solution was lower. The Wittig reaction of **5** followed by hydrogenation led to **6** in 80% yield. The acylation of **6** using PPA smoothly gave cycloheptanone (**7**) in 79% isolated yield without the byproduct. Friedel-Crafts acylation of acid-chloride of **6** with $AlCl_3$ led to contamination by inorganic products to inhibit the crystallization of **7**. Moreover, our approach did not require the tedious aryl-aryl cross-coupling conditions.

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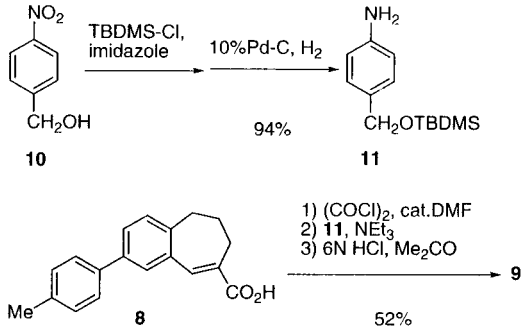
Table 1. **Reduction of 4 with SBMEA[a]**

entry	solvent	conditions	yield (%)
1	THF	−20 °C, 3 h	98
2	toluene	−20 °C, 3 h	91
3	DME	−10 °C, 3 h	87
4	THF	−10 °C, 3 h	96
5	THF	0 °C, 3 h	89

[a] SBMEA (1.0 equiv) was used.

Scheme 3. **Original synthesis to benzylalcohol (9)[4b,c]**



Short-Step Synthesis of Benzyl Alchohol (9). The original synthetic approach to cinnamic acid derivative (**8**) involved reduction with $NaBH_4$ of the β-ketoester prepared by the treatment of **7** and dimethyl carbonate in the presence of NaOMe, followed by dehydration with $MsCl/Et_3N$/DBU and hydrolysis. However, the reduction of the β-ketoester was performed in the hazardous dichloromethane solution using the tedious, portionwise additions of $NaBH_4$ and gave the desired hydroxyester with a hydroxy-hydroxymethyl derivative, which was an excess reductant. In view of these results, chromatographic purification was required. To solve this problem for large-scale preparation, optimization of the reduction was examined. As a result, the reaction of the β-ketoester with $NaBH_4$ at −10 °C in THF/water (10/1) afforded the target with a hydroxy-hydroxymethyl derivative. Subsequently, the dehydration of the resulting mixture, followed by the hydrolysis by NaOH solution, led to the crude **8**. The purification of **8** was performed by extraction with NaOH solution and crystallization from acetone to get the high-quality **8** in 54% isolated yield from **7** without a chromatographic method.

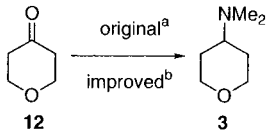
In the original procedure, benzyl alchohol derivative (**9**) was obtained by the amidation of **8** and expensive *O*-TBDMS-protected 4-aminobenzyl alcohol (**11**), followed by the deprotection with HCl (Scheme 3). The chemoselective coupling of **8** and the commercially available 4-aminobenzyl alcohol was carried out. The treatment of carboxylic acid (**8**) and a DMF catalytic oxalyl chloride (2.0 equiv) in THF followed by concentration and the reaction with 4-aminobenzyl alcohol (1.1 equiv) smoothly proceeded to give directly the desired **9** in 95% yield. However, this procedure showed inconstant yields, in pilot scale. It was thought that the remaining oxalyl chloride reacted with 4-aminobenzyl alcohol to give undesired effects, because the ester of **8** remained in about 50% yield when the reaction mixture using acid-chloride prepared from 2.0 equiv of oxalyl chloride

Table 2. **Reaction of 8 with 4-aminobenzyl alcohol**[a]

entry	$(COCl)_2$ (equiv)	ratio of products[b] 8	9	ester of 8
1	1.00	4.6	90.4	ND[c]
2	1.04	5.5	88.4	ND
3	1.10	0.1	95.3	0.2
4	1.14	0.1	93.8	ND
5	2.00	0.2	31.7	48.0

[a] 4-Aminobenzyl alcohol (1 equiv) was used, and the reaction mixture was quenched by MeOH. [b] Analyzed by HPLC at 254 nm. [c] ND = not detected.

Scheme 4. **Improved synthesis of tertiary amine (3)**[a]



12 3

[a] Reagents and conditions. a:[4b,c] HCO_2H, DMF, water, 100 °C, 6 h, 29%. b: 5% Pd−C, Me_2NH in THF, 2 kgf/cm^2 H_2, rt, 4 h, 75%.

was quenched by MeOH. The amidation was, therefore, optimized without concentration of the acid-chloride solution, as shown in Table 2. As a result, the amidation using acid-chloride prepared from 1.1 equiv of oxalyl chloride gave **9** in 89% yield in multikilogram preparation. Separately, we sought an alternative preparation of benzyl chloride derivative (**2**). The acid-chloride of **8** reacted with aniline to give *N*-phenyl-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-carboxamide quantitatively. However, the chloromethylation of the resulting anilide was not entirely successful with the reagents, for example, HCl/HCHO and chloromethyl methyl ether/Lewis acids.[8]

Convenient Synthesis of Tertiary Amine (3). In previous synthesis, the result of the treatment of tetrahydro-4*H*-pyran-4-one (**12**) with formic acid and DMF was unsatisfactory, giving 4-dimethylaminotetrahydro-*2H*-pyran-4-one (**3**) in 29% yield. This outcome was thought to result from the difficult extraction due to the high solubility of tertiary amine (**3**) in water. It was therefore considered that an alternative preparation of **3** was required without the extraction. The reductive alkylation[9] of **12** and Me_2NH in THF under conditions of 2 kgf/cm^2 hydrogen atmosphere, followed by only distillation produced **3** in 75% isolated yield (the yield of **3** was almost quantitative by GC). The decreased yield in distillation was caused by the lower boiling point (bp_{29} 75−82 °C[1c]) and large amounts of forerun as the water azeotrope (Scheme 4).

Synthesis of TAK-779 (1). The chlorination of **9** with thionyl chloride in THF instead of the previously reported solvent $CHCl_3$ at room temperature for 2 h gave benzyl chloride (**2**) in 87% yield. In the final stage, the coupling of benzyl chloride (**2**) and a tertiary amine (**3**) in DMF at 50 °C smoothly gave the desired **1** in 89% yield (99.8% purity), although the reaction at room temperature gave a small residual quantity of **2** as shown in Table 3. Subsequently, recrystallization from 15% aqueous EtOH successfully prepared the high-quality **1** in 81% yield.

Table 3. **Condensation of 2 and 3**[a]

entry	conditions	yield(%) of 1	purity(%) of 1
1	25 °C, 3 h	92	97.6
2	40−45 °C, 2 h	91	97.2
3	50−55 °C, 2 h	89	99.8
4	55−60 °C, 2 h	89	99.8
5	65−70 °C, 2 h	87	99.5

[a] **3** (1.5 equiv) was used.

In conclusion, we have been able to achieve practical preparation of **1** for large scale using commercially available reagents. The process development focused on a search for a suitable route selection of **1**. This alternative synthesis has been used to prepare multikilogram quantities of the bulk substance for toxicological trials.

Experimental Section

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H NMR spectra was recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. HPLC was performed on a YMC-Pack ODS-A302 column (6 i.d. × 150 mm) with 0.05 M KH_2PO_4 aqueous solution-MeCN (2:8, 3:7, 4:6, and 7:3) at 25 °C. Detection was effected with a Shimadzu SPD-10A spectrophotometric detector at 254 nm. Elemental analysis was carried out by Takeda Analytical Research Laboratories, Ltd.

4-(4-Methylphenyl)benzaldehyde (5). A solution of 70% sodium bis(2-methoxyethoxy)aluminum hydride in toluene (16.5 kg) was added dropwise over 1 h to a solution of 4-(4-methylphenyl)benzonitrile (**4**, 11.0 kg) in THF (110 L) keeping the temperature at −15 to −5 °C under nitrogen atmosphere, and the resulting mixture was stirred for 2 h under the same conditions. After the reaction was completed, the whole was added to a solution of concentrated H_2SO_4 (36 kg) in water (88 L) at −5−5 °C, and then water (110 L) and AcOEt (110 L) were added to the mixture. The mixture was stirred at 40−50 °C and allowed to stand. After the layers were separated, the aqueous layer was extracted with a mixture of THF (11 L) and AcOEt (33 L). The organic layers were combined, washed successively with 5% NaCl solution (55 L) and 7% $NaHCO_3$ solution (55 L), concentrated, and diluted with 2-propanol (39 L). The mixture was stirred under refluxing condition for 1 h and then at −5−5 °C for 4 h. The resulting crystals were collected by filtration, washed with cold 2-propanol (5 L), and dried under reduced pressure at 40−60 °C to give **5** (10.0 kg, yield 89%) as a white crystalline powder: mp 111−112 °C. Anal for $C_{14}H_{12}O$. Calcd: C, 85.68; H, 6.16. Found: C, 85.61; H, 6.01. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 2.41 (3H, s), 7.29 (2H, d, J = 8.1 Hz), 7.54 (2H, d, J = 8.1 Hz), 7.74 (2H, d, J =

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8.4 Hz), 7.93 (2H, d, J = 8.4 Hz), 10.04 (1H, s). IR (KBr, cm^{-1}) 1700, 1602, 1209, 1186, 1166, 809.

5-[4-(4-Methylphenyl)phenyl]-4-pentenoic acid. A solution of 28% NaOMe in MeOH (29.5 kg) and a solution of **5** (10.0 kg) in THF (100 L) were successsively added to a suspension of (3-carboxypropyl)triphenylphosphonium bromide (32.7 kg) and THF (330 L) at about 60 °C, and the resulting mixture was stirred at 55−60 °C for 1 h. After the reaction was completed, a solution of KOH (8.6kg) and water (300 L) and diisopropyl ether (130 L) were successively added to the reaction mixture at 20−40 °C, and the resulting mixture was allowed to stand. The layers were separated, and the organic layer was extracted twice with a solution of KOH (9.3 kg) and water (200 L). After the aqueous solution was combined, THF (200 L) and AcOEt (200 L) were added to the mixture, and then the resulting mixture was acidified (pH = 1.5) with 6 N HCl. After the mixture was allowed to stand, the organic layer was separated, washed with 10% NaCl solution(300 L), and concentrated under reduced pressure. The concentrate was diluted with EtOH (94 L) and water (40 L), and stirred at 5−30 °C for 1 h and then at 0−5 °C for 1 h. The resulting crystals were collected by filtration, washed with a mixture of EtOH (35 L) and water (15 L), and dried under reduced pressure at 40−60 °C to give 5-[4-(4-methylphenyl)phenyl]-4-pentenoic acid (11.5 kg, yield 85%) as a white crystalline powder: mp 198−199 °C. Anal for $C_{18}H_{18}O_2$. Calcd: C, 81.17; H, 6.81. Found: C, 81.20; H, 6.68. ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 2.34 (3H, s), 2.39−2.41 (4H, m), 6.27−6.39 (1H, m), 6.46 (1H, d, J = 15.6 Hz), 7.26 (2H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.1 Hz), 7.54−7.60 (4H, m), 12.13 (1H, brs). IR (KBr, cm^{-1}) 2730, 2653, 2578, 1691, 1496, 1255, 790.

5-[4-(4-Methylphenyl)phenyl]-4-pentanoic Acid (6). To a solution of 5-[4-(4-methylphenyl)phenyl]-4-pentenoic acid (11.5 kg) in THF (231 L) was added 5% Pd-C (wet, 0.6 kg) at 35−40 °C under nitrogen atmosphere. The whole was stirred for 1.5 h at 35−40 °C under the condition of 1.5 kgf/cm^2 hydrogen pressure. After the reaction was completed, Pd-C was filtered off and washed with THF (23 L). The filtrate and washings were combined and concentrated under reduced pressure. The concentrate was diluted with diisopropyl ether (46 L) and stirred at 0−5 °C for 1.5 h. The resulting crystals were collected by filtration, washed with diisopropyl ether (23 L), and dried under reduced pressure at 50−60 °C to give **6**(10.9 kg, yield 94%) as a white crystalline powder: mp 175−176 °C. Anal for $C_{18}H_{20}O_2$. Calcd: C, 80.56; H, 7.51. Found: C, 80.67; H, 7.41. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 1.69−1.73 (4H, m), 2.38−2.40 (5H, m), 2.64−2.68 (2H, m), 7.21−7.24 (4H, m), 7.43−7.48 (4H, m). IR (KBr, cm^{-1}) 1700, 1500, 810.

3-(4-Methylphenyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (7). To polyphosphoric acid (221kg) was added **6** (10.9kg) at 70−90 °C, and the whole was stirred for 12 h at 95−105 °C. After the reaction was completed, ice (145 kg) was added to the reaction mixture keeping the temperature at 40−85 °C, and toluene (73 L) was added to the mixture at 30−50 °C. The resulting mixture was allowed to stand, and the layers were separated. After the aqueous layer was extracted with toluene (18 L), the organic layers were combined, washed successively with water (55 L × 2), 25% ammonia solution (145 L), and water (73 L), concentrated under reduced pressure, and dissolved in acetone (8 L). The seed crystals (5 g) were added to the solution at 0−10 °C, and then the mixture was diluted with MeOH (8 L) and water (16 L) and stirred at 0−10 °C for 40 min. The resulting crystals were collected by filtration, washed with a mixture of acetone (6 L), MeOH (6 L) and water (12 L), and dried under reduced pressure at 30−40 °C to give **7** (8.0 kg, yield 79%) as a white crystalline powder: mp 61−64 °C. Anal for $C_{18}H_{18}O$. Calcd: C, 86.36; H, 7.25. Found: C, 86.54; H, 7.25. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 1.83−1.92 (4H, m), 2.38 (3H, s), 2.76 (2H, m), 2.96 (2H, m), 7.22−7.26 (3H, m), 7.50 (2H, d, J = 8.0 Hz), 7.62−7.64 (1H, m), 7.95 (1H, d, J = 2.0 Hz). IR (KBr, cm^{-1}) 1660, 1486, 819.

2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-carboxylic acid (8). To a solution of **7** (8.0 kg) in dimethyl carbonate (40 L) was added NaOMe (8.6 kg), and the whole was refluxed for 2 h. After the reaction was completed, the reaction mixture was cooled to 0−10 °C and acidified (pH = 1) with 6 N HCl. After diisopropyl ether (31 L) and water (15 L) were added to the mixture, the resulting mixture was allowed to stand. The organic layer was separated, washed with water (15 L), and concentrated under reduced pressure.

To a solution of the residue in a mixture of THF (44 L) and water (4 L) was added $NaBH_4$ (1.86 kg) at −15 to −5 °C under nitrogen atmosphere, the whole was stirred for 2.5 h under the same conditions. After the reaction was completed, water (44 L) and diisopropyl ether (44 L) were added to the reaction mixture under the same conditions, and the resulting mixture was allowed to stand. After the layers were separated, the aqueous layer was extracted with diisopropyl ether (44 L). The organic layers were combined, washed successively with 1 N HCl (46 L × 2) and water (46 L), concentrated under reduced pressure, and dissolved in THF (46 L).

To the resulting solution was added NEt_3 (10.0 kg), and the whole was cooled to 0−10 °C. MsCl (5.7 kg) was added dropwise to the mixture at the same temperature, and the whole was stirred for 2 h at 20−30 °C. DBU (10.0 kg) was added to the mixture at 20−30 °C, and the resulting mixture was stirred for 3 h at the same temperature. After the reaction was completed, water (46 L) and diisopropyl ether (46 L) were added to the reaction mixture, and the resulting mixture was allowed to stand. After the layers were separated, the aqueous layer was extracted with diisopropyl ether (46 L). The organic layers were combined, washed successively with 1 N HCl (46 L), 1 N NaOH (46 L), and water (46 L × 2), concentrated under reduced pressure, and dissolved in THF (49 L).

To the resulting solution were added MeOH (49 L) and 1 N NaOH (49 L), and the whole was stirred for 2 h at 55−60 °C. After the reaction was completed, toluene (31 L) was added to the reaction mixture at 50−60 °C, and the resulting mixture was allowed to stand at the same temperature. The aqueous layer was separated, washed with toluene (31 L × 2) at the same temperature, cooled to 0−20 °C, and acidified

(pH = about 1.5) with concentrated HCl. The resulting crystals were collected by filtration and washed with water (80 L).

The resulting wet crystals were dissolved in acetone (123 L) at 50−60 °C, and then activated charcoal was added to the solution. After the mixture was stirred for 45 min at the same temperature, the charcoal was filtered off at the same temperature and washed with warm acetone (15 L, about 50 °C). The filtrate and washings were combined and concentrated under reduced pressure to 45 L, and the resulting concentrate was gradually cooled to −5−0 °C for 1.5 h. The resulting crystals were collected by filtration and washed with cold acetone (8 L, about −10 °C), and dried at about 35−45 °C to give **8** (4.8 kg, yield 54%) as a white crystalline powder: mp 186−188 °C. Anal for $C_{19}H_{18}O_2$. Calcd: C, 81.99; H, 6.52. Found: C, 81.91; H, 6.52. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 2.07−2.13 (2H, m), 2.39 (3H, s), 2.67−2.71 (2H, m), 2.86−2.89 (2H, m), 7.20−7.26 (4H, m), 7.43−7.55 (3H, m), 7.91 (1H, s). IR (KBr, cm^{-1}) 2923, 1671.

***N*-(4-Hydroxymethylphenyl)-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-carboxamide (9).** Oxalyl chloride (1.5kg) was added dropwise to a solution of **8** (3.0 kg) and DMF (30 mL) in THF (24 L) at 0−10 °C, and the whole was stirred for 1 h at 20−30 °C. After the reaction was completed, the reaction mixture was added dropwise to a solution of 4-aminobenzyl alcohol (1.6 kg) and NEt_3 (4.5 L) in THF (30 L) at 0−10 °C. The whole was stirred for 1.5 h at the same temperature. After the reaction was completed, water (12 L) was added dropwise to the reaction mixture at the same temperature, and the resulting mixture was allowed to stand. The layers were separated, and the aqueous layer was extracted with AcOEt (60 L). The organic layers were combined, washed successively with 7% $NaHCO_3$ solution (12 L) and 30% NaCl solution (18 L), 1 N HCl (18 L × 3), and 15% NaCl solution (18 L × 4). The resulting organic layer was concentrated under reduced pressure, and AcOEt (24 L) was added to the concentrate, and then the mixture was concentrated again under reduced pressure. After AcOEt (48 L) was added intermittently without interruption of the concentration, the resulting concentrate was stirred for about 1 h at 10−30 °C. The resulting crystals were collected by filtration and washed with AcOEt (9 L), and dried under reduced pressure at about 40 °C to give **9** (3.7 kg, yield 89%) as a white crystalline powder: mp 184−185 °C. Anal. for $C_{26}H_{25}NO_2$. Calcd: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.19; H, 6.40; N, 3.63. ^{1}H NMR ($CDCl_3$, δ, 300 MHz); 2.16 (2H, tt, J = 6.8, 5.8 Hz), 2.39 (3H, s), 2.72 (2H, t, J = 6.8 Hz), 2.88 (2H, t, J = 5.8 Hz), 4.67 (2H, s), 7.21−7.63 (12H, m). IR (KBr, cm^{-1})1649, 1519.

***N*-(4-Chloromethylphenyl)-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-carboxamide(2).** To a suspension of **9** (3.6 kg) in THF (36 L) was added dropwise $SOCl_2$ (1.7 kg) at 0−10 °C, and the whole was stirred for 2 h at 20−30 °C. After the reaction was completed, AcOEt (36 L) and 10% NaCl solution (15 L) were added to the reaction mixture at 0−10 °C, and the resulting mixture was allowed to stand. The layers were separated, and the aqueous layer was extracted with AcOEt (22 L). The organic layers were combined, washed successively with 7% $NaHCO_3$ solution (22 L) and 10% NaCl solution(17 L), and 30% NaCl solution (24 L × 2). To the resulting organic layer was added $MgSO_4$ (7.0 kg), and the resulting suspension was stirred for about 10 min. The magnesium sulfate was filtered off and washed with a mixture of THF (4.5 L) and AcOEt(4.5 L). The filtrate and washings were combined and concentrated under reduced pressure, and AcOEt (64 L) was added intermittently without interruption of the concentration. After the resulting mixture was stirred for about 2 h at 0−10 °C, the resulting crystals were collected by filtration and washed with a mixture of AcOEt (3 L) and diisopropyl ether (6 L), and dried under reduced pressure at about 40 °C to give **2** (3.2 kg, yield 87%) as a white crystalline powder: mp 173−175 °C. Anal for $C_{26}H_{24}NOCl$. Calcd: C, 77.70; H, 6.02; N, 3.48; Cl, 8.82. Found: C, 77.69; H, 6.13; N, 3.43; Cl, 8.69. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 2.13−2.19 (2H,m), 2.39 (3H, s), 2.68−2.72 (2H, m), 2.85−2.89 (2H, m), 4.58 (2H, s), 7.20−7.69 (12H, m). IR(KBr, cm^{-1}) 3336, 1644, 1517.

***N*,*N*-Dimethyl-*N*-tetrahydro-2*H*-pyran-4-ylamine(3).** Dimethylamine(4.3kg) was dissolved in THF (15.1kg) at 0−10 °C. To the resulting solution were added tetrahydro-4*H*-pyran-4-one (**12**, 3.0 kg) and 5% Pd-C (wet, 0.3 kg) under nitrogen atmosphere, and the whole was stirred for 4 h under the conditions of 2 kgf/cm^2 hydrogen. After the reaction was completed, Pd-C was filtered off and washed with THF (5 L). The filtrate and washings were combined and concentrated at 15−45 °C under reduced pressure (50−100 mmHg). The concentrate was distilled under reduced pressure, the fraction boiling at 60−80 °C/30−40 mmHg was collected to give **3** (2.9 kg, yield 75%) as a colorless oil. Anal for $C_7H_{15}NO{\cdot}H_2O$. Calcd: C, 64.16; H, 11.70; N, 10.70. Found: C, 64.02; H, 11.44; N,11.03. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 1.5−1.6 (2H, m), 1.7−1.8 (2H, m), 2.1−2.4 (7H, m), 3.3−3.5 (2H, m), 3.9−4.1 (2H, m). IR (neat, cm^{-1}) 2952, 2836, 2771, 1213, 1135.

***N*,*N*-Dimethyl-*N*-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2*H*-pyran-4-aminium chloride (TAK-779, 1).** A solution of **2** (3.1 kg) in DMF (16 L) was added dropwise to a solution of **3** (1.5 kg) in DMF (16 L) at 50−60 °C, and the resulting mixture was stirred for 2 h at the same temperature. After the reaction was completed, acetone (31 L) was added to the reaction mixture at the same temperature. The resulting mixture was stirred for about 30 min at the same temperature, cooled to 20−30 °C, and stirred for about 1 h at the same temperature. The resulting crystals were collected by filtration and washed with acetone (13 L), and dried under reduced pressure at about 40 °C to give crude **1** (3.8 kg, yield 91%) as a white crystalline powder.

To a solution of crude **1** (2.9 kg) and purified water (4.5 L) in EtOH (25.5 L) was added activated charcoal (87 g) at 60−80 °C, and the resulting suspension was stirred for about 15 min at the same temperature. The charcoal was filtered off and washed with a mixture of EtOH (0.7 L) and purified water (0.1 L). The filtrate and washings were combined and filtered through N_{66}POSIDYNE to remove pyrogens, and

then the N_{66}POSIDYNE was washed with a mixture of EtOH (0.7 L) and purified water (0.1 L). The filtrate and washings were combined and gradually cooled to 0−10 °C. The resulting crystals were collected by filtration, washed with ethanol (5 L), and dried under reduced pressure at about 40 °C to give **1** (2.3 kg, yield 81%) as a white crystalline powder: mp 222−223 °C (dec). Anal for $C_{33}H_{39}N_2O_2Cl$. Calcd: C, 74.62; H, 7.40; N, 5.27; Cl, 6.67. Found: C, 74.37; H, 7.32; N, 5.23; Cl, 6.53. ^{1}H NMR (DMSO-d_6, δ, 300 MHz) 1.85−2.18 (6H, m), 2.34 (3H, s), 2.64 (2H, m), 2.78 (8H, m), 3.35 (2H, m), 3.50−3.75 (1H, m), 4.04−4.07 (2H, m), 4.46 (2H, s), 7.26−7.88 (12H, m), 10.22 (1H, s). IR (KBr, cm^{-1}) 1652, 1521.

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