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Practical Synthesis of an Orally Active CCR5 Antagonist, 7-{4-[2-(Butoxy)-ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide

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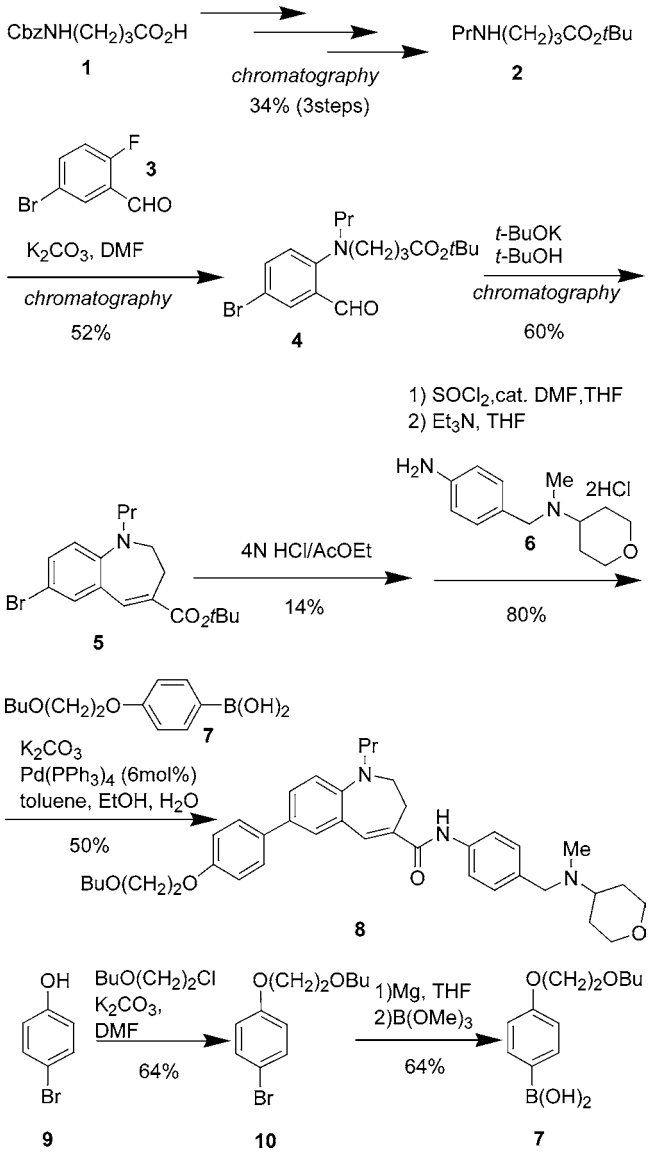
Abstract:

A practical method of synthesizing 7-{4-[2-(butoxy)ethoxy]-phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}-phenyl)-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (8), an orally active CCR5 antagonist, has been developed. Methyl 7-bromo-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-caboxylate (14a) was synthesized in good yield by the esterification of 4-[(4-bromo-2-formylphenyl)(propyl)amino]butanoic acid (13) followed by an intramolecular Claisen type reaction with 28% sodium methoxide in dimethyl carbonate as a solvent in one pot. The Suzuki−Miyaura reaction of 14a and 1-bromo-4-(2-butoxyethoxy)benzene (10) followed by hydrolysis and amidation gave 8. A new inexpensive method without chromatographic purification was established.

Introduction

In recent years, CC chemokine receptor 5 (CCR5) has been shown to act as a coreceptor for the entry of macrophage-tropic human immunodeficiency virus type 1 (HIV-1) into the host cell.[1] CCR5 antagonists as inhibitors of HIV-1 entry, having a novel mechanism, differ from well-known agents for chemotherapy, for example, HIV-1 reverse transcriptase and protease inhibitors, and have potential in the treatment of HIV-1. Shiraishi et al. reported a small molecule, the nonpeptide CCR5 antagonist TAK-779,[2] as an anti-HIV-1 agent for injection. Subsequently, 2,3-dihydro-1*H*-1-benzazepine derivatives showed markedly strong activity as orally active CCR5 antagonists.[3] In particular, 7-{4-[2-(butoxy)ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (**8**) was found to be especially effective.[3b] Hence, an efficient preparation of **8** on a large scale was required to support a toxicological evaluation. The previous synthetic route is shown in Scheme 1.[3b] However, this procedure had several limitations for large-scale production, for example, the utilization of expensive materials, the requirement of multiple steps, repeated tedious chromatographic purification, lower yield, and the use of a large amount of heavy metal (palladium) in the Suzuki−Miyaura reaction. To advance the practical preparation, we tried to develop an alternative method of producing **8** using inexpensive materials. Here, we report a new way to prepare **8**

Scheme 1. **Previous synthesis of 8**



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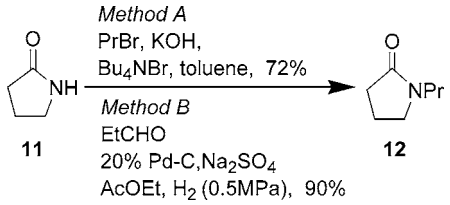
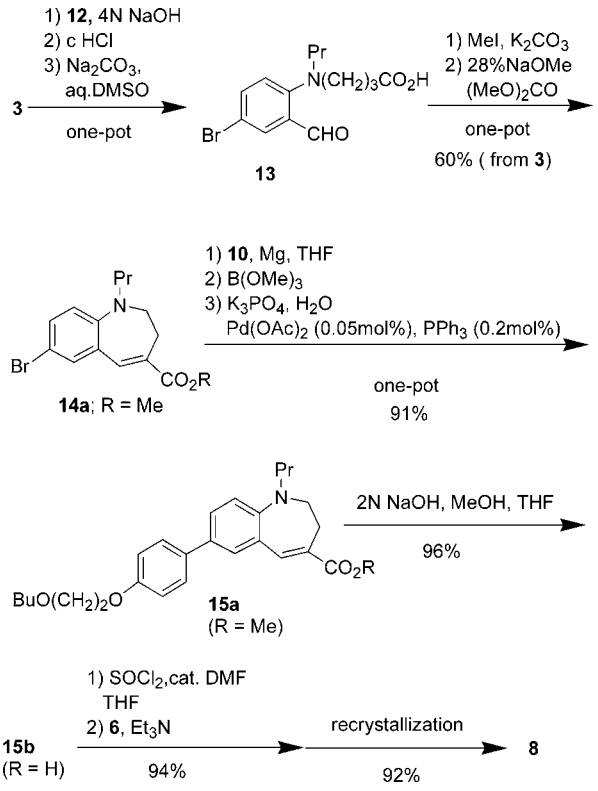
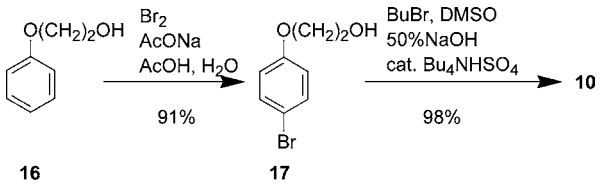
Scheme 2. **Efficient synthesis of 12**



Scheme 3. **New synthesis of 12**



Scheme 4. **Improved synthesis of 10**



in short steps that is amenable to scale-up without chromatographic purification, as outlined in Schemes 2−4.

Results and Discussion

Efficient Synthesis of 1-Propylpyrrolidin-2-one (12). We had already reported an efficient method of synthesizing 2,3-dihydrobenzazepine derivatives via an intramolecular Claisen type reaction of 4-[(2-formylaryl)alkylamino]butanoic acid, which was prepared from *o*-halogenobenzaldehyde and 4-(alkylamino)butanoic acid starting with 1-alkylpyrrolidin-2-one, using dialkyl carbonate as a solvent.[4] According to the reported method, we first studied the synthesis of **12** (Scheme 2). Many procedures for the synthesis of **12** have been reported, for example, alkylation of pyrrolidone (**11**) by 1-halogenopropane[5] or 1-propanol in the presence of additives,[6] amidation of γ-butyrolactone by 1-aminopropane,[7] the reduction of *N*-propylsuccinimide,[8] and Rh-catalyzed carbonylation of cyclopropylamine.[9] We chose the alkylation of **11** with 1-bromopropane in the presence of KOH and a phase transfer catalyst (PTC) in toluene (Method A)[10] because this method did not require special equipment and expensive reagents. The alkylation under anhydrous conditions (using the KOH pellet) gave **12** in 72% yield in a small-scale reaction. However, the reaction conditions were not suitable for large-scale production, since a resulting hard solid mass clogged a valve at the bottom of the vessel. Hence, alkylation under aqueous conditions (using 50% aqueous KOH) was examined and afforded **12** in 66% yield without a hard solid mass in a small-scale operation. However, alkylation under the same conditions on a large scale decreased the yield of **12** (44%). It was presumed that hydrolysis of **12** and losses in the aqueous layer caused the decrease in yield. Therefore, an alternative method, the reductive alkylation of **11** and propionaldehyde by 20% Pd−C and hydrogen in the presence of Na_2SO_4 in AcOEt,[11] was examined (Method B, Table 1). The reaction under 0.5−4 MPa of hydrogen pressure smoothly proceeded to give **12** in high yield (entry 1−4). However, the reaction in the presence of 20% Pd−C (5 wt %) was not complete (entry 5). As a result, the reductive alkylation was carried out smoothly in the presence of 20% Pd−C (10 wt %) under a lower hydrogen pressure (0.5 MPa) with high conversion (entry 4). A simple workup (filtration of Pd−C and Na_2SO_4, concentration, and distillation under reduced pressure) gave **12** in 90% yield (purity 97.9%).

Table 1. **Preparation of 12 by a reductive alkylation of 11**[a]

entry	H_2 pressure (MPa)	propionaldehyde (equiv)	Pd−C/**11** (wt %)	ratio by GC (%) **12**	ratio by GC (%) **11**	isolated yield of **12** (%)
1	4	4	25	92.9	ND[b]	94
2	0.5	4	25	94.6	0.9	90
3	0.5	2	25	93.9	ND[b]	90
4	0.5	2	10	93.8	0.2	90
5	0.5	2	5	65.8	7.1	*c*

[a] The mixture of **11** (1.0 equiv), propionaldehyde, 20% Pd−C (wet), and Na_2SO_4 (1.6 equiv) in AcOEt was stirred for 4 h at 105 °C. [b] ND = not detected. [c] **12** was not isolated.

Practical Synthesis of 14a. Next, we studied the synthesis of **14a** (Scheme 3). Hydrolysis of **12** with 4 N NaOH gave 4-(propylamino)butanoic acid in high conversion (80−90%, determined by ^{1}H NMR). After neutralization of the reaction mixture with concentrated HCl, sodium carbonate and 5-bromo-2-fluorobenzaldehyde (**3**) in DMSO were added and

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Table 2. **Preparation of 13**

entry	base	solvent	method [a]	yield (%)
1	Na_2CO_3	37% aq DMSO	A	88[b]
2	Na_2CO_3	50% aq DMSO	A	80[b]
3	Na_2CO_3	37% aq DMSO	B	86[c]
4	Na_2HPO_4	37% aq DMSO	A	86[c]

[a] (A) After **12** was hydrolyzed and neutralized, base, **3**, and DMSO were added. The whole mixture was refluxed. (B) After **12** was hydrolyzed and neutralized, base and DMSO were added. A solution of **3** in DMSO was added dropwise under refluxing conditions, and the whole mixture was refluxed. [b] Isolated yield. [c] Determined by HPLC.

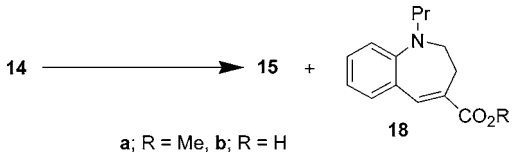
the whole mixture was refluxed to afford **13** smoothly in a one-pot small-scale reaction (Table 2, entry 1). However, this reaction was not suitable for large-scale production, since the viscous reaction mixture swelled 2- or 3-fold due to the resulting carbon dioxide. Though the utilization of 50% aqueous DMSO as a solvent produced a fluid suspension of the reaction mixture and improved the stirring, this condition decreased the yield of **13** slightly (entry 2). The reaction with Na_2HPO_4 as a base generated no carbon dioxide and gave **13** in high yield (entry 4). However, in this case, the separation of the organic layer and the aqueous layer in the workup was impossible due to a large amount of precipitate. As a result, slow addition of a solution of **3** in DMSO in the reaction mixture under refluxing conditions caused the slow evolution of carbon dioxide and improved the stirring solution to provide **13** in 86% yield in one pot (entry 3). Crude **13** (a pale yellow oil), which was obtained by extraction with aqueous Na_2CO_3 followed by neutralization, extraction with a mixture of AcOEt and THF, and concentration, was used directly in further reactions without purification.

The esterification of crude **13** with MeI in the presence of K_2CO_3 in DMF followed by an intramolecular Claisen type reaction triggered by the addition of dimethyl carbonate and 28% sodium methoxide in one pot gave **14a** very smoothly without a byproduct. After the workup, crystallization from MeOH afforded high quality **14a** (purity 99.8%) in 60% yield (from **3**).

Practical Synthesis of 8. Our attention was focused on developing a facile process for the synthesis of biaryl compounds. We tried using the Suzuki−Miyaura reaction in one pot[12] with **14a** and **10**, instead of **7**. In the previous method,[3b] the arylbromide derivative **10** was prepared from **9** and an expensive material, 2-chloroethyl *n*-butyl ether. It was therefore considered that an alternative method of preparing **10** was required without the need for expensive materials (Scheme 4). Hence, we chose 2-phenoxyethanol (**16**) as a starting material. Bromination of **16** with bromine in the presence of sodium acetate in a mixture of AcOH and water gave **17** quantitatively. Compound **17** was crystallized by addition of water to the reaction mixture and refined by filtration (yield 91%, purity 99.4%). Alkylation of **17** with 1-bromobutane using 50% aqueous NaOH as a base in the presence of PTC[13] proceeded quantitatively to give **10** in 98% yield (purity 99.9%) after distillation under reduced pressure.

Next, the Suzuki−Miyaura reaction in one-pot using **14a** and **10** was examined. The treatment of **10** was carried out with magnesium in THF under refluxing conditions and followed by the addition of trimethylborate at −10 °C. The whole mixture was reacted with **14a**, base, water, and Pd catalyst under refluxing conditions to give **15a** in high conversion (Table 3). To decrease the amount of palladium catalyst, this reaction was examined in the presence of several bases and catalysts. The coupling reactions using K_2CO_3 as a base in the presence of palladium catalyst (1 mol %) proceeded slowly and required 5.5−8.5 h to complete (entry 1−3). The utilization of K_3PO_4 as a base accelerated the reactions (entry 4−8) and reduced the amount of palladium catalyst. In particular, the combination of $Pd(OAc)_2$, PPh_3, and K_3PO_4 diminished the amount of palladium catalyst (0.05 mol %, entry 8) and provided **15a** in 91% yield (purity 99.5%, residual palladium 0.3 ppm). A Suzuki−Miyaura

Table 3. **Preparation of 15**[a]



entry	R	catalyst	base	time (h)	ratio by HPLC **15**	**18**	**14**	yield[b](%)
1	Me	$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	K_2CO_3	8.5	78.8	0.9	ND[c]	81
2	Me	$PdCl_2(PPh_3)_2$ (1 mol %)	K_2CO_3	7	80.7	2.5	0.3	84
3	Me	$PdCl_2(PPh_3)_2$ (1 mol %), PPh_3 (2 mol %)	K_2CO_3	5.5	85.8	0.9	1.1	89
4	Me	$PdCl_2(PPh_3)_2$ (1 mol %), PPh_3 (2 mol %)	K_3PO_4	1	86.2	0.7	1.0	91
5	Me	$PdCl_2(PPh_3)_2$ (0.1 mol %), PPh_3 (0.2 mol %)	K_3PO_4	2	86.2	1.0	0.1	92
6	Me	$PdCl_2(PPh_3)_2$ (0.05 mol %), PPh_3 (0.1 mol %)	K_3PO_4	4	49.4	0.6	38.6	*d*
7	Me	$Pd(OAc)_2$ (0.1 mol %), PPh_3 (0.4 mol %)	K_3PO_4	3	88.4	0.2	1.0	93
8	Me	$Pd(OAc)_2$ (0.05 mol %), PPh_3 (0.2 mol %)	K_3PO_4	5	88.1	1.7	1.0	91
9	H	$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %)	K_2CO_3	4	64.1	16.2	2.7	73

[a] Under an argon atmosphere, the treatment of **10** (2.0 equiv) was carried out with magnesium in THF under refluxing conditions followed by addition of trimethylborate at −10 °C. To the whole mixture was added catalyst, base in water, and **14**, and the resulting mixture was refluxed. [b] Isolated yield. [c] ND = not detected. [d] **15** was not isolated.

reaction using acid **14b** (R = H), which was prepared by hydrolysis of **14a**, increased the formation of the impurity **18b** and decreased the yield of desired **15b** (entry 9). Therefore, ester **14a** was suitable as the substance for this reaction.

Hydrolysis of **15a** was carried out with 2 N NaOH in a mixture of MeOH and THF to give **15b** in 95% yield (purity 99.8%). The treatment of **15b** with thionyl chloride in the presence of a catalytic amount of DMF in THF followed by a reaction with 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline dihydrochloride (**6**)[14] gave the desired **8** quantitatively. Crude **8** was crystallized by addition of aqueous NaOH and MeOH to the reaction mixture and refined by filtration without chromatographic purification (yield 92%). Subsequently, recrystallization of crude **8** from aqueous acetone afforded high-quality **8** in 90% yield (purity 99.3%) on a large scale.

In conclusion, we have been able to achieve the practical synthesis of **8** in short steps for large-scale production without chromatographic purification. 2,3-Dihydrobenzazepine derivative **14a** was synthesized by a convenient intramolecular Claisen type reaction of **13**, which was prepared from **3** and **12**. The Suzuki−Miyaura reaction in one pot using **14a** and **10** was smoothly carried out with the palladium catalyst (0.05 mol %) to give **15a** in excellent yield. The main route of this new method consisted of six steps, as compared with eight steps in the previous method.[3b]

Experimental Section

Melting points were recorded on a Büchi B-540 micromelting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. HPLC was performed on a YMC-Pack ODS-A302 column (4.6 × 150 mm^2) with 0.05 M KH_2PO_4 aqueous solution−MeCN (3:7) at 25 °C. Detection was effected with a Shimadzu SPD-10A spectrophotometric detector at 254 nm. Gas chromatography was carried out using a Shimadzu GC-14A gas chromatograph equipped with an FID detector and Gaskuropack 54 column (1 m × 3 mm) (injector temperature 240 °C, helium flow rate 50 mL/min, oven temperature 230 °C). The microanalyses and mass spectral analyses were carried out by Takeda Analytical Research Laboratories, Ltd.

1-Propylpyrrolidin-2-one (12). 2-Pyrrolidone (**11**) (40 g, 470 mmol), propionaldehyde (54.6 g, 940 mmol) and AcOEt (470 mL) were added to a 1-L autoclave. Sodium sulfate (106 g, 748 mmol) and 20% Pd−C (4.0 g, containing 50% H_2O, N. E. Chemcat corporation) were added, and the whole mixture was stirred at 105 °C for 4 h under 0.5 MPa of hydrogen pressure. After the mixture was cooled to 20−30 °C, Pd−C and sodium sulfate were filtered off and washed with AcOEt (120 mL). The filtrate and washing were combined and concentrated under reduced pressure. The concentrate was distilled under reduced pressure, and the fraction boiling at 63−66 °C/6 mmHg was collected to give **12** (53.8 g, yield 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 0.90 (3H, t, J = 7.4 Hz), 1.48−1.61 (2H, m), 1.96−2.07 (2H, m), 2.39 (2H, t, J = 7.9 Hz), 3.24 (2H, t, J = 7.5 Hz), 3.38 (2H, t, J = 7.0 Hz) [lit.[15] (δ) 0.96 (3H), 1.13−1.69 (2H), 1.85−2.42 (4H), 3.20 (2H), 3.34 (2H)]. IR (neat, cm^{-1}) 1673, 1465, 1427. EIMS: *m*/*z* 127 (M^+). HRMS (EI): *m*/*z* 127 (M^+) $C_7H_{13}NO$ calcd 127.0997, found 127.0990.

2-(4-Bromophenoxy)ethanol (17). To a solution of 2-phenoxyethanol (**16**) (440 g, 3.19 mol) and AcONa (340 g, 4.14 mol) in a mixture of AcOH and water (7/3, 880 mL) was added dropwise a solution of bromine (515 g, 3.22 mol) in a mixture of AcOH and water (7/3, 1760 mL) at 15−20 °C, and the whole mixture was stirred for 0.5 h at 10−20 °C. A 10% aqueous Na_2SO_3 solution (6 mL) and water (6.6 L) were added, and the resulting mixture was stirred for 2 h. The resulting crystals were collected by filtration, washed with water (3 L), and dried under reduced pressure to give **17** (631 g, yield 91%) as a white crystalline powder. Mp 54−55 °C. Anal. Calcd for $C_8H_9O_2Br$: C, 44.27; H, 4.18; Br, 36.81. Found: C, 44.21; H, 4.32; Br, 36.84. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 2.13 (1H, s), 3.95−3.98 (2H, m), 4.03−4.06 (2H, m), 6.77−6.82 (2H, m), 7.35−7.40 (2H, m). IR (KBr, cm^{-1}) 3350, 1486, 1241.

1-Bromo-4-(2-butoxyethoxy)benzene (10). To a solution of **17** (603 g, 2.78 mol), 1-bromobutane (761 g, 5.56 mol), and nBu$_4$NHSO$_4$ (47.2 g, 0.14 mol) in DMSO (3.02 L) was added dropwise a 50% aqueous NaOH solution (1111 g, 13.9 mol) at 25−50 °C, and the whole mixture was stirred for 1.5 h at 35−40 °C. Water (6.03 L) was added, and the mixture was extracted with a mixture of toluene (4.5 L) and THF (1.26 L). The organic layer was washed succesively with water (6.03 L), a 20% aqueous NaCl solution (3.02 L), and water (6.03 L) and concentrated under reduced pressure. The residue was distilled under reduced pressure, and the fraction boiling at 125−130 °C/2 mmHg was collected to give **10** (740.6 g, yield 98%) as a colorless oil. Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.76; H, 6.27; Br, 29.25. Found: C, 52.85; H, 6.27; Br, 29.29. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 0.92 (3H, t, J = 7.4 Hz), 1.30−1.45 (2H, m), 1.52−1.67 (2H, m), 3.52 (2H, t, J = 6.6 Hz), 3.76 (2H, t, J = 5.0 Hz), 4.07 (2H, t, J = 5.0 Hz), 6.80 (2H, d, J = 9.0 Hz), 7.35 (2H, d, J = 9.0 Hz) [lit.[3b] ($CDCl_3$, δ, 200 MHz) 0.92 (3H, t, J = 7.4 Hz), 1.27−1.65 (4H, m), 3.53 (2H, t, J = 6.6 Hz), 3.74−3.79 (2H, m), 4.05−4.11 (2H, m), 6.81 (2H, d, J = 9.0 Hz), 7.36 (2H, d, J = 9.0 Hz)]. IR (neat, cm^{-1}) 2958, 2871, 1488.

4-[(4-Bromo-2-formylphenyl)(propyl)amino]butanoic Acid (13). A solution of **12** (500 g, 3.93 mol) in 4 N NaOH (1.97 L, 7.86 mol) was refluxed for 8 h. After the solution was cooled to 40 °C, concentrated HCl (655 mL, 7.86 mol) was added. After addition of DMSO (5 L) and Na_2CO_3 (834 g, 7.86 mol) to the resulting mixture at 20−30 °C, a solution of **3** (399 g, 1.97 mol) in DMSO (1 L) was added dropwise

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to the whole mixture for 1 h under refluxing conditions. The mixture was refluxed for 4 h. After it was cooled to 30 °C, the mixture was treated with 4 N HCl (4.6 L) until the pH was adjusted to 3.4 and extracted with a mixture of AcOEt and THF (4/1, 3 L × 2). The organic layers were combined and washed with a 20% aqueous NaCl solution (3 L). The organic layer was extracted with a 10% aqueous Na_2CO_3 solution (9 L × 2), and the aqueous layers were combined and washed with AcOEt (1 L). The aqueous layer was treated with 6 N HCl (2 L) until the pH was adjusted to 3.3 and extracted with a mixture of AcOEt and THF (4/1, 2 L × 2). The organic layers were combined and washed successively with a 20% aqueous NaCl solution (1 L × 2) and water (1 L) and concentrated under reduced pressure to give crude **13** (613 g) as a brown oil, which was used directly in further reactions without purification. An analytically pure sample of **13** was obtained by chromatography on silica gel as a yellow oil. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 0.83 (3H, t, J = 7.4 Hz), 1.47−1.54 (2H, m), 1.81−1.88 (2H, m), 2.34 (2H, t, J = 7.2 Hz), 3.06−3.11 (2H, m), 3.18−3.22 (2H, m), 7.07 (1H, d, J = 8.7 Hz), 7.57 (1H, dd, J = 2.5, 8.7 Hz), 7.90 (1H, d, J = 2.5 Hz), 10.22 (1H, s). IR (neat, cm^{-1}) 2962, 1708, 1683. FABMS: m/z 328 (MH^+), 350 (MNa^+). HRMS (FAB): m/z 350 (MNa^+) $C_{14}H_{18}NO_3BrNa$ calcd 350.0368, found 350.0332.

Methyl 7-Bromo-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (14a). To a solution of crude **13** and K_2CO_3 (300 g, 2.17 mol) in DMF (1.6 L) was added dropwise a solution of MeI (336 g, 2.36 mol) in DMF (300 mL) at 25−40 °C, and the mixture was stirred for 1 h at the same temperature. After addition of dimethyl carbonate (3.9 L) to the mixture, 28% NaOMe in MeOH (912 g, 4.73 mol) was added and the whole mixture was stirred for 0.5 h at 50 °C. After the mixture was cooled to 5 °C, 2 N HCl (2 L) was added, and the whole mixture was concentrated and extracted with toluene (2 L × 2). The organic layers were combined and washed successively with 1 N NaOH (0.5 L × 3), a 20% aqueous NaCl solution (1 L × 3), and water (1 L) and concentrated under reduced pressure. The residue was dissolved in MeOH (1.5 L) at 40 °C. After it was cooled to 0 °C, the mixture was stirred for 2 h at the same temperature. The resulting crystals were collected by filtration, washed with cold MeOH (300 mL), and dried under reduced pressure to give **14a** (379 g, yield 60% from **3**) as a yellow crystalline powder. Mp 51−52 °C. Anal. Calcd for $C_{15}H_{18}NO_2Br$: C, 55.57; H, 5.60; N, 4.32; Br, 24.65. Found: C, 55.69; H, 5.71; N, 4.37; Br, 24.74. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 0.94 (3H, t, J = 7.4 Hz), 1.65−1.72 (2H, m), 2.78−2.81 (2H, m), 3.19−3.25 (4H, m), 3.79 (3H, s), 6.67 (1H, d, J = 8.9 Hz), 7.22 (1H, dd, J = 2.4, 8.9 Hz), 7.41 (1H, d, J = 2.4 Hz), 7.56 (1H, s). IR (KBr, cm^{-1}) 1700, 1496, 1251.

Methyl 7-[4-(2-Butoxyethoxy)phenyl]-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (15a). Under an argon atmosphere, to a suspension of magnesium (1.85 g, 76.1 mmol) in THF (80 mL) was added dropwise a solution of **10** (20.22 g, 74.02 mmol) in THF (28 mL) under refluxing conditions, and the whole mixture was refluxed for 1.5 h. After the mixture was cooled to −10 °C, a solution of trimethylborate (7.69 g, 74.02 mmol) in THF (28 mL) was added dropwise and the resulting mixture was stirred for 0.5 h at the same temperature. After the mixture was warmed to 20 °C, $Pd(OAc)_2$ (4.2 mg, 0.0185 mol) and PPh_3 (19.4 mg, 0.074 mmol) were added and the whole mixture was stirred for 0.5 h at the same temperature. Next, **14a** (12.0 g, 37.0 mmol) and a solution of K_3PO_4 (41.24 g, 194 mmol) in water (64 mL) were added, and the mixture was refluxed for 5 h. After it was cooled to 20 °C, 3 N HCl (150 mL) was added and the mixture was separated. The aqueous layer was extracted with toluene (136 mL). The organic layers were combined and washed successively with water (120 mL), 2 N NaOH (120 mL × 2), and water (120 mL × 2). Activated charcoal (1.2 g) and tri-*n*-butylphosphine[16] (1.2 mL) were added to the organic layer, and the mixture was stirred for 0.5 h. The charcoal was filtered off and washed with toluene (60 mL). The filtrate and washing were combined and concentrated under reduced pressure. The residue was dissolved in *i*-Pr_2O (40 mL) under refluxing conditions. After it was cooled to 0 °C, the mixture was stirred for 2 h at the same temperature. The resulting crystals were collected by filtration, washed with cold *i*-Pr_2O (32 mL), and dried under reduced pressure to give **15a** (14.7 g, yield 91%) as a yellow crystalline powder. Mp 81−82 °C. Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 73.99; H, 7.86; N, 3.11. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 0.90−0.97 (6H, m), 1.35−1.43 (2H, m), 1.57−1.63 (2H, m), 1.69−1.76 (2H, m), 2.81 (2H, t, J = 4.5 Hz), 3.26−3.33 (4H, m), 3.54 (2H, t, J = 6.7 Hz), 3.57−3.80 (2H, m), 3.78 (3H, s), 4.14 (2H, t, J = 4.7 Hz), 6.86 (1H, d, J = 8.7 Hz), 6.97 (2H, d, J = 6.7 Hz), 7.39 (1H, dd, J = 2.2, 8.7 Hz), 7.45 (2H, d, J = 6.7 Hz), 7.50 (1H, d, J = 2.2 Hz), 7.79 (1H, s). IR (KBr, cm^{-1}) 1706, 1504, 1241.

7-[4-(2-Butoxyethoxy)phenyl]-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic acid (15b). To a solution of **15a** (720 g, 1.65 mol) in a mixture of THF (2.88 L) and MeOH (7.2 L) was added 2N NaOH (1.65 L, 3.29 mol) and the mixture was refluxed for 3 h. After the mixture was cooled to 20 °C, activated charcoal (72 g) and tri-*n*-butylphosphine[16] (72 mL) were added and the mixture was stirred for 0.5 h. The charcoal was filtered off and washed with a mixture of MeOH, THF, and water (20/8/5, 1.26 L). The filtrate and washing were combined. To the whole mixture was added dropwise 1.5 N HCl (2.3 L, 3.45 mol) at 20−30 °C, and the resulting mixture was stirred for 1 h at 0−5 °C. The resulting crystals were collected by filtration, washed with a mixture of MeOH and water (1/1, 3 L) and dried under reduced pressure to give **15b** (670 g, yield 96%) as a yellow crystalline powder. Mp 148−149 °C. Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.72; H, 7.71; N, 3.23. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 0.90−1.00 (6H, m), 1.36−1.43 (2H, m), 1.56−1.64 (2H, m), 1.70−1.78 (2H, m), 2.83 (2H, t, J = 4.4 Hz), 3.28−3.34 (4H, m), 3.55 (2H, t, J = 4.9 Hz), 3.82 (2H, t, J = 4.7 Hz), 4.15 (2H, t, J = 5.2 Hz), 6.87 (1H, d, J = 8.7 Hz), 6.99 (2H, d, J = 6.7 Hz), 7.42 (1H, dd, J = 2.2, 8.7 Hz), 7.47 (2H, d, J =

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6.7 Hz), 7.52 (1H, d, J = 2.2 Hz), 7.88 (1H, s). IR (KBr, cm^{-1}) 1664, 1504, 1249.

7-{4-[2-(Butoxy)ethoxy]phenyl}-*N*-(4-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]methyl}phenyl)-1-propyl-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (8). To a solution of **15b** (150 g, 345 mmol) and DMF (1.9 mL, 25 mmol) in THF (650 mL) was added dropwise thionyl chloride (63.2 g, 531 mmol) at 0−5 °C, and the mixture was stirred for 1 h at 20−30 °C. The resulting mixture was added dropwise to a mixture of 4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]aniline dihydrochloride (**6**) (125 g, 425 mmol) and triethylamine (346 mL, 2.48 mol) in THF (750 mL) at 25−50 °C, and the whole mixture was stirred for 1.5 h at 45−55 °C. To the mixture was added dropwise 0.65 N NaOH (2.18 L) and MeOH (750 mL) at the same temperature. After it had cooled to 20 °C, the mixture was stirred for 16 h. The resulting crystals were collected by filtration, washed with a mixture of MeOH and water (1/1, 1.5 L), and dried under reduced pressure to give crude **8** (209 g, yield 94%) as a yellow crystalline powder.

Crude **8** (150 g) was dissolved in a mixture of purified water (340 mL) and acetone (1.91 L) at 60 °C, and the mixture was filtered through filter paper. After the filtrate had cooled to 30 °C, water (375 mL) was added and the whole mixture was stirred for 3 h. The resulting crystals were collected by filtration, washed with a mixture of acetone and water (1/1, 1.5 L), and dried under reduced pressure to give **8** (139 g, yield 92%) as a yellow crystalline powder. Mp 123−125 °C (lit.[3b] mp 118−121 °C). Anal. Calcd for $C_{39}H_{51}N_3O_4$: C, 74.85; H, 8.21; N, 6.71. Found: C, 74.81; H, 8.30; N, 6.66. ^{1}H NMR ($CDCl_3$, δ, 300 MHz) 0.93 (3H, t, J = 7.3 Hz), 0.99 (3H, t, J = 7.5 Hz), 1.31−1.45 (2H, m), 1.564−1.82 (8H, m), 2.20 (3H, s), 2.55−2.70 (1H, m), 2.80−2.93 (2H, m), 3.23−3.40 (6H, m), 3.50−3.60 (4H, m), 3.80 (2H, t, J = 4.7 Hz), 3.98−4.07 (2H, m), 4.14 (2H, t, J = 4.7 Hz), 6.88 (1H, d, J = 8.7 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.35−7.41 (2H, m), 7.42−7.50 (3H, m), 7.54 (2H, d, J = 8.4 Hz), 7.63 (1H, s). IR (Nujol, cm^{-1}) 2954, 2923, 1639, 1517.

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