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PREPARATION OF A 1-UNSUBSTITUTED-2,3-DIHYDRO-1-BENZAZEPINE DERIVATIVE

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Abstract – We developed a three-step method of producing a 1-unsubstituted-2,3-dihydro-1-benzazepine derivative (**2**) from **11**. The alkylation of **9**, obtained from **11**, and the subsequent intramolecular condensation of **12** in dialkyl carbonate with a metal alcoholate were conducted in one pot to afford 1-benzazepine (**13**) in good yield. **13** was then hydrolyzed to give **2** in 48% overall yield from **11**. Furthermore, we synthesized the orally active CCR5 antagonist intermediate **18** from **2**.

INTRODUCTION

In order to develop orally active CC chemokine receptor (CCR5) antagonists, medium ring heterocycles were investigated by Baba and Shiraishi *et al.*,[1] and a 2,3-dihydro-1-benzazepine system (**Figure 1**, **A**) was selected as one of the scaffolds. The intermediate (**1**) was utilized for the preparation of various derivatives (**Figure 1**).

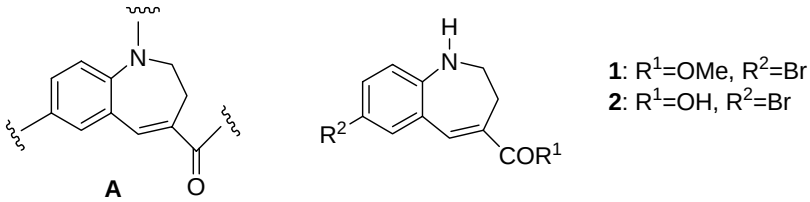
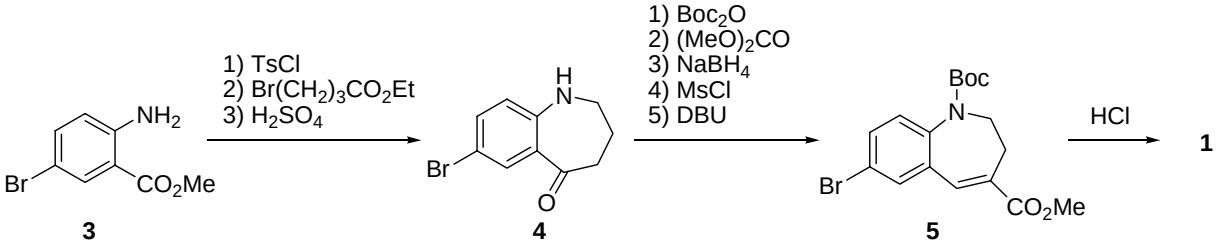


Figure 1

In their research,[1f] the intermediate (**1**) was prepared through a ketone (**4**) in good quality, however, there were several drawbacks to large scale production as follows (**Scheme 1**); 1) The preparation of **1** was a multistep process and the yield was considerably low (9 steps, 7% yield), 2) the process was inefficient owing to the application of two protective groups (tosyl and Boc groups), and 3) chromatographic

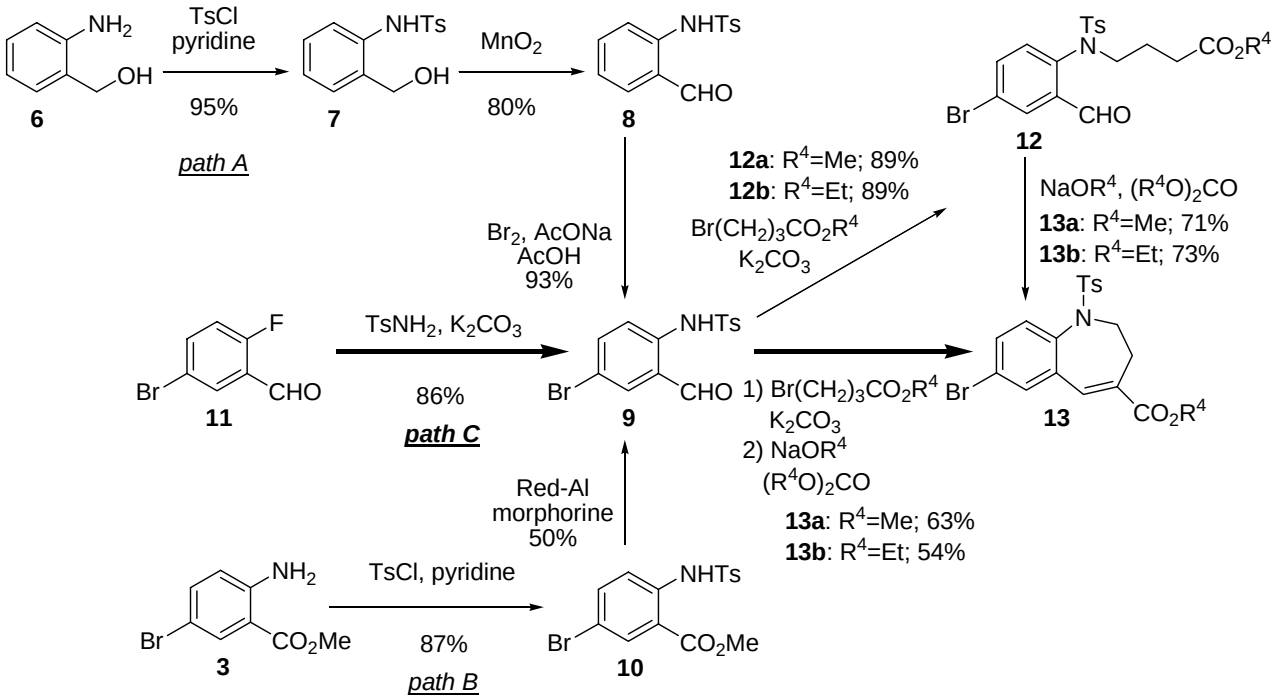
purification unsuitable for mass-production was needed. Therefore, we focused on the facile preparation of **1** or its equivalent compound (**2**).



Scheme 1

RESULTS AND DISCUSSION

During our investigation of intramolecular Claisen-type condensation, we had already found that the reaction using a metal alcoholate in dialkyl carbonate was effective at producing 2,3-dihydro-1-benzazepines in high yield.[2] However, all of the benzazepines obtained were *N*-alkylated. Hence, we planned to synthesize *N*-unsubstituted benzazepines via intramolecular cyclization of *N*-tosylated *o*-formylanilinobutyrates.



Scheme 2

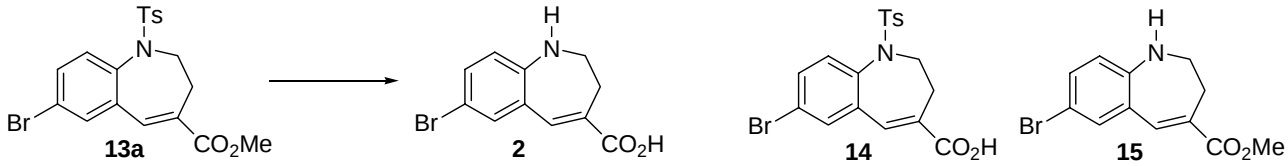
To establish an efficient synthetic route, we attempted to prepare an intermediate (**9**) from three different materials as follows (**Scheme 2**, *paths A, B* and *C*). First of all, amino alcohol (**6**) as a starting material was treated with TsCl and pyridine[3] followed by MnO_2 to give aldehyde (**8**). The intermediate (**9**) was obtained after bromination of **8** using Br_2 and AcONa in acetic acid in 70% yield from **6** (path A).

In path B,[4] *o*-anilinobenzoate (**3**) was subjected to tosylation followed by Red-Al reduction at –10 ℃ to produce **9** in 50% yield, while the reduction of ester (**10**) with 2 equivalents of DIBAL-H at –78 ℃ gave a mixture of **9** and the corresponding alcohol.

In path C, formylphenylfluoride (**11**) could be efficiently converted to **9** using $TsNH_2$ and K_2CO_3 in DMSO in 86% yield. Therefore, path C was favorable as a shorter, high-yielding process.

The alkylation of **9** with alkyl 4-bromobutyrate and K_2CO_3 in DMF gave **12** in excellent yield. The intramolecular condensation of **12** proceeded smoothly in the presence of sodium alcoholate in dialkyl carbonate to give **13** in good yield. Moreover, these two-step reactions, alkylation of **9** and the subsequent intramolecular condensation, could be performed in one-pot to give **13**.[5]

Table 1. Deprotection of **13a**

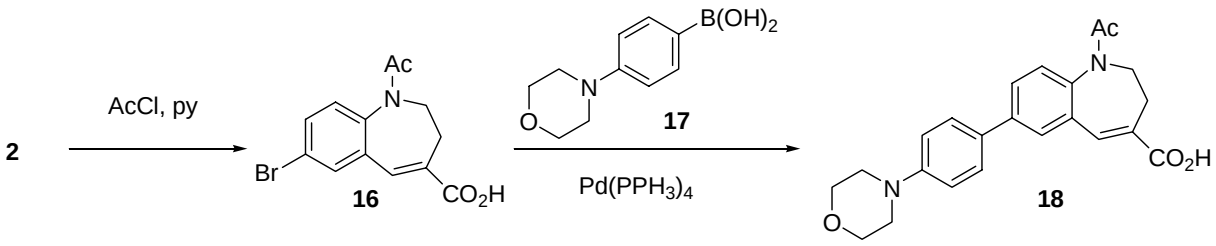


Entry	Acids (v/w)	Temp. (°C)	Ratio of Products[a] **13**	**14**	**15**	**2**	Yield (%)
1	conc. HCl (3), AcOH (5)	90	8	81	-	8	
2	60% $HClO_4$ (3), AcOH (5)	100	1	63	1	34	
3	MsOH (2), AcOH (5),	90	5	48	1	41	
4	conc. H_2SO_4 (5), AcOH (10),	90	-	1	6	81	
5	conc. H_2SO_4 (2) / H_2O (0.2), AcOH (4)	90	-	-	3	91	88

[a] HPLC area % (measured at 254 nm).

The deprotection of **13** by several kinds of acids was examined (**Table 1**). The treatment of **13** with conc. HCl in acetic acid mainly afforded carboxylic acid (**14**) since the ester moiety was predominantly hydrolyzed (entry 1). The reaction using $HClO_4$ or MsOH did not proceed completely to give the mixture of **2** and **14** (entries 2, 3). The conc. H_2SO_4 and H_2O in acetic acid could lead to smooth detosylation of **13** to give **2** in high yield (entries 4, 5).[7] The desired acid **2** was isolated easily by crystallization from the reaction mixture in 88% yield.

The preparation of the CCR5 antagonist intermediate (**18**) from **2** was subsequently investigated (**Scheme 3**). Carboxylic acid (**16**) was afforded in 84% yield by acetylation of **2** with AcCl and pyridine. Suzuki-Miyaura coupling of **16** and boronic acid (**17**) with a catalytic amount of $Pd(PPh_3)_4$ in EtOH provided **18** in 87% yield.



Scheme 3

In conclusion, we accomplished the effective synthesis of **2** by intramolecular Claisen-type condensation that was performed with sodium alcoholate in alkyl dicarbonate. Three different approaches were undertaken, and the desired product (**2**) was synthesized in only three steps via the most efficient path C without any chromatographic purification. In addition, a CCR5 antagonist intermediate (**18**) was obtained from **2** in good yield.

EXPERIMENTAL

General

Melting points were recorded on a Yanagimoto micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker DPX-300. ^{1}H NMR spectra are reported as follows: chemical shifts in ppm (δ) downfield from tetramethylsilane as an internal standard, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad and m, multiplet), coupling constants spectra (Hz) and integration. ^{13}C NMR spectra were recorded in ppm (δ) relative to the central line for $CDCl_3$ at 77 ppm and DMSO-d_6 at 39.7 ppm. Column chromatography was performed with a Wakogel C-200 (75-150mm). Elemental analyses and mass spectra were carried out by Takeda Analytical Research Laboratories Limited.

[*path A*]

***N*-[2-(Hydroxymethyl)phenyl]-4-methylbenzensulfonamide** (**7**)

To a solution of 2-aminobenzyl alcohol (**6**) (30.0 g, 244 mmol) and pyridine (39.4 mL, 488 mmol) in THF (150 mL) was added a solution of TsCl (46.4 g, 244 mmol) in THF (150 mL) below 10 °C, and the mixture was stirred for 1.5 h at rt. It was then quenched with water and extracted with AcOEt. The organic solution was washed with 2M HCl and brine. The solution was dried over Na_2SO_4, concentrated, and triturated with diisopropyl ether for 0.5 h at rt to give **7** (64.5 g, 95%) as a white solid. Mp 148-150 °C. Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.41; H, 5.55; N, 4.95. Found: C, 60.41; H, 5.55; N, 4.95. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (1H, brs), 2.38 (3H, s), 4.40 (2H, s), 7.00-7.09 (2H, m), 7.20-7.28 (4H, m), 7.43 (1H, d, *J* = 8.0 Hz), 7.65 (2H, d, *J* = 8.3 Hz). IR (KBr, cm^{-1}): 3438, 3072, 1457, 1317, 1153, 1091, 1031, 717, 563.

***N*-(2-(Formylphenyl)-4-methylbenzensulfonamide** (**8**)

To a solution of **7** (20.0 g, 72.1 mmol) in acetone (300 mL) was added activated MnO_2 (36.4 g, 418.3 mmol), and the mixture was stirred for 15 h at rt. The solid was filtered off and washed with acetone, and the combined mother solution was concentrated. The resulting residue was triturated with diisopropyl ether and filtrated to give **8** (15.8 g, 80%) as a pale yellow solid. Mp 136-137 °C. Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 60.88; H, 4.70; N, 4.93. ^{1}H NMR (300 MHz, $CDCl_3$,): δ = 2.36 (3H, s), 7.12-7.26 (3H, m), 7.47-7.52 (1H, m), 7.58 (1H, d, *J* = 6.0 Hz), 7.67 (1H, d, *J* = 9.0 Hz), 7.77 (2H, d, *J* = 6.0 Hz), 9.82 (1H, s), 10.76 (1H, brs). IR (KBr, cm^{-1}): 1673, 1494, 1409, 1340, 1157, 1087, 929, 840, 759, 565.

***N*-(4-Bromo-2-formylphenyl)-4-methybenzenesulfonamide** (**9**) from **8**

To a mixture of **8** (1.0 g, 3.63 mmol) and AcONa (0.33 g, 4.00 mmol) in 90% aq. AcOH (10 mL) was added Br_2 (0.22 mL, 4.36 mmol), and the mixture was stirred for 2 h at rt. Subsequently, Br_2 (0.44 mL, 8.72 mmol) was added and the mixture was again stirred for 2 h. To the reaction mixture was added 0.5M $Na_2S_2O_3$ (10 mL), and the stirring was continued for 0.5 h. The resulting solid was filtrated and washed with water to give **9** (1.2 g, 93%) as a pale yellow solid. Mp 130-131 °C. Anal. Calcd for $C_{14}H_{12}NO_3BrS$: C, 47.47; H, 3.41; N, 3.95. Found: C, 47.77; H, 3.45; N, 3.89. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (3H, s), 7.26 (2H, d, *J* = 9.0 Hz), 7.57-7.71 (3H, m), 7.76 (2H, d, *J* = 9.0 Hz), 9.76 (1H, s), 10.65 (1H, s). IR (KBr, cm^{-1}): 1679, 1479, 1186, 1162.

[*path B*]

Methyl 5-bromo-2-{[(4-methylphenylsulfonyl)amino]benzoate (**10**)

To a solution of methyl 5-bromo-2-aminobenzoate (**3**) (200 g, 869 mmol) in pyridine (600 mL) was added TsCl (174 g, 913 mmol), and the mixture was stirred for 3 h at rt. It was then quenched with water and extracted with AcOEt. The organic solution was washed with 2M HCl, brine, and water. The solution was concentrated and triturated with diisopropyl ether to give **10** (291 g, 87%) as a pale yellow solid. Mp 122-123 °C. Anal. Calcd for $C_{15}H_{14}NO_4BrS$: C, 46.89; H, 3.67; N, 3.65. Found: C, 46.88; H, 3.54; N, 3.60. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (3H, s), 3.88 (3H, s), 7.23 (2H, d, *J* = 8.2 Hz), 7.53 (1H, dd, *J* = 8.9, 2.3 Hz), 7.61 (1H, d, *J* = 8.9 Hz), 7.72 (2H, d, *J* = 8.2 Hz), 8.03 (1H, d, *J* = 2.3 Hz), 10.50 (1H, s). IR (KBr, cm^{-1}): 1698, 1479, 1434, 1394, 1340, 1305, 1247, 1157, 1087.

9 from **10**

To a solution of Red-Al® (37.5 g, 130 mmol) in toluene (35 mL) was added a solution of morpholine (12.5 mL, 143 mmol) in toluene (25 mL) at 0-5 °C under an argon atmosphere. This Red-Al®–morpholine solution was added to a solution of **10** (5.0 g, 13.0 mmol) in toluene (50 mL) at –10 °C, and the mixture was stirred for 2 h. After 20% sulfuric acid (500 mL) was added, the reaction mixture was extracted with

AcOEt. The organic solution was washed with water, concentrated, and purified by silica-gel chromatography (toluene) to give **9** (2.3 g, 50%).

[*path C*]

9 from **11**

To a suspension of *p*-tosylamide (1.7 g, 10.0 mmol) and K_2CO_3 (1.4 g, 10.0 mmol) in 50% aq. DMSO (10 mL) was added **11** (1.0 g, 5.0 mmol), and the mixture was stirred for 1 h at 130 °C. To the reaction mixture was added 2M HCl (7.5 mL), and the stirring was continued for 1 h at the same temperature. The mixture was cooled to rt, and stirred for 3 h. The resulting solid was filtrated and washed with water to give **9** (1.5 g, 86%).

Ethyl 4-{(4-bromo-2-formylphenyl)[(4-methylphenyl)sulfonyl]amino}butanoate (**12b**)

To a solution of **9** (3.0 g, 8.47 mmol) and ethyl 4-bromobutyrate (1.82 mL, 12.7 mmol) in DMF (9 mL) was added K_2CO_3 (1.7 g, 12.7 mmol), and the mixture was stirred for 4 h at 70 °C. It was then quenched with 2M HCl and extracted with AcOEt. The organic solution was washed with brine and water. The solution was dried over Na_2SO_4 and concentrated. The resulting solid was triturated with diisopropyl ether for 1 h at rt to give **12b** (3.5 g, 89%) as a white solid. Mp 99-100 °C. Anal. Calcd for $C_{20}H_{22}NO_5BrS$: C, 51.29; H, 4.73; N, 2.99. Found: C, 51.29; H, 4.70; N, 2.90. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (3H, t, *J* = 7.1 Hz), 1.72-1.82 (2H, m), 2.35 (2H, t, *J* = 7.1 Hz), 2.44 (3H, s), 3.30-3.40 (1H, m), 3.8-3.95 (1H, m), 4.09 (2H, q, *J* = 7.1 Hz), 6.60 (1H, d, *J* = 8.5 Hz), 7.27 (1H, d, *J* = 2.6 Hz), 7.30 (1H, s), 7.42-7.45 (2H, m), 7.56-7.61 (1H, m), 8.14 (1H, d, *J* = 2.4 Hz), 10.36 (1H, s). IR (KBr, cm^{-1}): 1740, 1684, 1596.

Methyl 4-{(4-bromo-2-formylphenyl)[(4-methylphenyl)sulfonyl]amino}butanoate (**12a**)

Using a similar procedure above (preparation of **12b**). Yield 89%. Mp 137-138 °C. Anal. Calcd for $C_{19}H_{20}NO_5BrS$: C, 50.23; H, 4.44; N, 3.08. Found: C, 50.22; H, 4.47; N, 3.04. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67-1.82 (2H, m), 2.34-2.38 (2H, m), 2.44 (3H, s), 3.31-3.45 (1H, m), 3.63 (3H, s), 3.82-3.91 (1H, m), 6.60 (1H, d, *J* = 8.5 Hz), 7.28 (2H, d, *J* = 8.6 Hz), 7.43 (2H, d, *J* = 8.6 Hz), 7.58 (1H, dd, *J* = 8.5, 2.4 Hz), 8.12 (1H, d, *J* = 2.4 Hz), 10.34 (1H, s). IR (KBr, cm^{-1}): 1743, 1683, 1597.

Ethyl 7-bromo-1-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (**13b**) from **12b**

To a solution of **12b** (1.00 g, 2.14 mmol) in diethyl carbonate (20 mL) was added NaOEt (20% EtOH solution, 0.87 g, 2.56 mmol), and the mixture was stirred for 3 h at rt. It was then neutralized with 2M HCl and extracted with AcOEt. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was crystallized from 2-PrOH and filtrated to give **13b** (0.70 g, 73%)

as a pale yellow crystal. Mp 109-110 °C (2-PrOH). Anal. Calcd for $C_{20}H_{20}NO_4BrS$: C, 53.34; H, 4.48; N, 3.11. Found: C, 53.18; H, 4.45; N, 3.00. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (3H, t, *J* = 7.0 Hz), 2.35 (3H, s), 2.86 (2H, t, *J* = 5.7 Hz), 3.86 (2H, t, *J* = 5.7 Hz), 4.18 (2H, q, *J* = 7.0 Hz), 7.13 (2H, d, *J* = 8.0 Hz), 7.18 (1H, s), 7.41 (2H, d, *J* = 8.0 Hz), 7.44-7.53 (3H, m). IR (KBr, cm^{-1}): 1714, 1348, 1243, 1162, 1087.

Methyl 7-bromo-1-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (**13a**) from **12a**

Compound **13a** was prepared from **12a** and NaOMe in dimethylcarbonate using a similar procedure to above (preparation of **13b**). A pale yellow solid. Yield 71%. Mp 138-139 °C (^{i}Pr$_2$O). Anal. Calcd for $C_{19}H_{18}NO_4BrS$: C, 52.30; H, 4.16; N, 3.21. Found: C, 52.14; H, 4.21; N, 3.12. ^{1}H NMR (300 MHz, $CDCl_3$); δ = 2.38 (3H, s), 2.84-2.88 (2H, m), 3.73 (3H, s), 3.84-3.88 (2H, m), 7.12-7.26 (3H, m), 7.42-7.53 (5H, m). IR (KBr, cm^{-1}): 1708, 1629, 1433.

13a from **9** (one-pot reaction)

To a solution of **9** (1.00 g, 2.82 mmol) and methyl 4-bromobutyrate (0.77 g, 4.23 mmol) in DMF (3 mL) was added K_2CO_3 (0.58 g, 4.23 mmol), and the mixture was stirred for 4 h at 90 °C. It was then cooled to rt. Dimethyl carbonate (20 mL) and NaOMe (28% MeOH solution, 1.09 g, 5.65 mmol) were added and the reaction mixture was stirred for 3 h at rt. It was neutralized with 2M HCl and extracted with AcOEt. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was crystallized from diisopropyl ether and filtrated to give **13a** (0.78 g, 63%).

13b from **9** (one-pot reaction)

Compound (**13b**) was prepared from **9** and methyl 4-bromobutyrate using a similar procedure to above (preparation of **13a**). Yield 54%.

7-Bromo-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic acid (**2**) from **13b**

To a suspension of **13b** (1.0 g, 2.22 mmol) in AcOH (4 mL) was added conc. H_2SO_4 (2 mL), and the mixture was stirred for 2 h at 90 °C. Subsequently, water (0.2 mL) was added and the reaction mixture was stirred for 6 h. It was then concentrated, 10% aqueous NaOH (32 mL) and water (10 mL) were added. The resulting solid was filtered off and washed with water. The combined mother solution was adjusted to pH 3.0-3.5 with 2M HCl. The solid was filtrated to give **2** (0.5 g, 86%) as a pale yellow solid. Mp 213-214°C. Anal. Calcd for $C_{11}H_{10}NO_2Br$: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.24; H, 3.76; N, 5.20. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.69 (2H, t, *J* = 4.3Hz), 3.20 (2H, t, *J* = 4.3Hz), 6.67 (1H, d, *J* = 8.7Hz), 6.92 (1H, brs), 7.16 (1H, dd, *J* = 8.7, 2.0 Hz), 7.40 (1H, d, *J* = 2.0 Hz), 7.45 (1H, s). IR (KBr, cm^{-1}); 1660, 1282, 1180.

In addition, **2** was prepared from **13a** using a similar procedure to above (preparation of **2** from **13b**). Yield 88%.

1-Acetyl-7-bromo-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic acid (**16**)

To a solution of **2** (4.0 g, 15.0 mmol) and pyridine (5.9 g, 75.0 mmol) in *N*-methylpyrrolidone (32 mL) was added AcCl (3.2 mL, 45.0 mmol) at 5-10 °C, and the mixture was stirred for 0.5 h at rt. After 6M HCl (16 mL) was added to the reaction mixture at 25-35 °C, the solution was extracted with toluene. The organic solution was washed with water and extracted with 1M NaOH. The aqueous solution was adjusted to pH 1-2 with 6M HCl. The resulting solid was filtrated to give **16** (3.9 g, 84%) as a pale yellow solid. Mp 200-201 °C. Anal. Calcd for $C_{13}H_{12}NO_3Br$: C, 50.34; H, 3.90; N, 4.52. Found: C, 50.38; H; 3.85, N, 4.49. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.92 (3H, s), 2.73 (3H, m), 4.51 (1H, m), 7.28-7.30 (1H, m), 7.56-7.58 (2H, m), 7.84-7.87 (1H, m). IR (KBr, cm^{-1}): 3467, 3436, 1656, 1621, 1294.

1-Acetyl-7-(4-morpholin-4-ylphenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic acid (**18**)[1f]

To a suspension of **16** (250 mg, 0.81 mmol), **17** (250 mg, 1.21 mmol), K_2CO_3 (334 mg, 2.42 mmol) in water (1 mL), EtOH (1 mL) and toluene (4 mL) was added $Pd(PPh_3)_4$ (47 mg, 0.04 mmol) under an atmosphere of argon, and the mixture was refluxed for 1.5 h. It was then cooled to rt and extracted with 1M NaOH. The aqueous solution was adjusted to pH 2.8 with 6M HCl and extracted with AcOEt. To the organic solution were added Na_2SO_4 and activated charcoal, and the mixture was stirred for 10 min. The solid was filtered off and washed with AcOEt. The combined mother solution was concentrated, and crystallized from MeOH. The resulting solid was filtrated to give **18** (276 mg, 87%) as a pale yellow solid. Mp 263-264 °C (MeOH). Anal. Calcd for $C_{23}H_{24}N_2O_2$•0.2 H_2O: C, 70.39; H, 6.16; N, 7.14. Found: C, 69.75; H, 6.21; N, 7.07. ^{1}H NMR (DMSO-d_6): δ = 1.95 (3H, s), 2.75 (3H, m), 3.14-3.19 (4H, m), 3.73-3.76 (4H, m), 4.56 (1H, m), 7.01 (2H, d, *J* = 8.7 Hz), 7.44 (1H, d, *J* = 8.2 Hz), 7.62-7.65 (3H, m), 7.74 (1H, s), 7.87 (1H, s). IR (KBr, cm^{-1}): 3388, 1704, 1623, 1606, 1492, 1228, 1216.

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3. In the early stages of this work, the alkylation of Boc-protected (**5**) or pivaloyl-protected (**5**) did not proceed completely. Thus, we chose the tosyl group for *N*-protection in this series.
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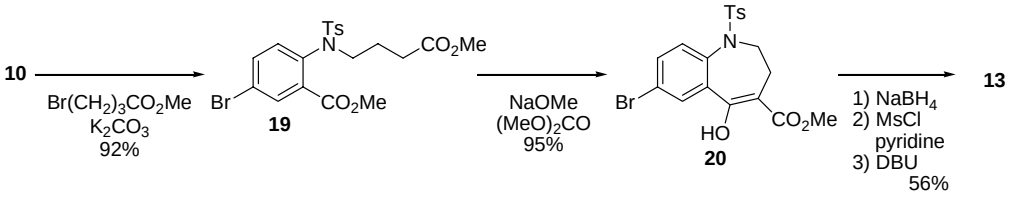
5. This reaction condition was also effective for the intramolecular condensation of the diester (**19**) that was afforded by the alkylation of **10** with methyl 4-bromobutyrate and K_2CO_3 in 92% yield. The cyclization of **19** under the typical conditions of Dieckmann condensation, using ^tBuOK in ^tBuOH at 50 °C, afforded **20** in only 54% yield.[6] In contrast, our method using the combination of NaOMe and dimethyl carbonate gave a drastically increased yield, 91%. The reduction of **20** followed by a one-pot reaction consisting of mesylation and β-elimination gave **13** in 56% yield. (Although the reduction of **20** by $NaBH_4$ provided the corresponding alcohol accompanied by an overreduced diol, the crude mixture was subjected to the next reaction without any purification.)



Methyl 5-bromo-2-{(4-methoxy-4-oxobutyl)[(4-methylphenyl)sulfonyl]amino}benzoate (**19**)

To a solution of **10** (30.0 g, 78.1 mmol) and methyl 4-bromobutyrate (17.0 g, 93.7 mmol) in DMF (120 mL) was added K_2CO_3 (21.6 g, 156.2 mmol), and the mixture was stirred for 8 h at 90 °C. It was then quenched with water and extracted with AcOEt. The organic solution was washed with brine and water, and concentrated. The resulting solid was triturated with diisopropyl ether for 2 h

at rt to give **19** (34.9 g, 92%) as a white solid. Mp 100-101 °C. Anal. Calcd for $C_{20}H_{22}NO_6BrS$: C, 49.59; H, 4.58; N, 2.89. Found: C, 49.56; H, 4.57; N, 2.82. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86-1.90 (2H, m), 2.41 (3H, s), 2.41-2.48 (2H, m), 3.40-3.80 (2H, m), 3.64 (3H, s), 3.83 (3H, s), 6.76 (1H, d, *J* = 8.5 Hz), 7.23-7.26 (2H, m), 7.43-7.46 (2H, m), 7.53 (1H, dd, *J* = 8.5, 2.4 Hz), 7.99 (1H, d, *J* = 2.4 Hz). IR (KBr, cm^{-1}): 1736, 1722, 1351.

Methyl 7-bromo-5-hydroxy-1-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (**20**)

To a solution of **19** (30.0 g, 61.9 mmol) in dimethyl carbonate (300 mL) was added NaOMe (28% MeOH solution, 9.2 g, 170.2 mmol), and the mixture was stirred for 2 h at 70 °C. It was then neutralized with 2M HCl and extracted with AcOEt. The organic solution was washed with brine and water, and concentrated. The resulting residue was crystallized from MeOH and filtrated to give **20** (26.5 g, 95%) as a white crystal. Mp 137-138 °C (MeOH). Anal. Calcd for $C_{19}H_{18}NO_5BrS$: C, 50.45; H, 4.01; N, 3.10. Found: C, 50.45; H, 4.02; N, 3.01. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (2H, t, *J* = 6.3 Hz), 2.40 (3H, s), 3.72 (3H, s), 4.07 (2H, t, *J* = 6.3 Hz), 7.15-7.18 (2H, m), 7.36-7.45 (3H, m), 7.60-7.64 (2H, m), 11.8 (1H, s). IR (KBr, cm^{-1}): 1619, 1581, 1481.

13a from **20**

To a solution of **20** (20.0 g, 44.2 mmol) in THF (200 mL) and water (20 mL) was added $NaBH_4$ (3.3 g, 88.4 mmol) at –10 to –5 °C, and the mixture was stirred for 2 h. It was then neutralized with 2M HCl and extracted with AcOEt. The organic solution was washed with brine, saturated aqueous $NaHCO_3$, and water, and concentrated. The resulting residue was dissolved with THF (200 mL), and NEt_3 (24.6 mL, 170.8 mmol) was added. To the solution was added MsCl (6.8 mL, 88.4 mmol) in an ice bath, and the mixture was stirred for 2 h at rt. Subsequently, DBU (33.5 mL, 221.0 mL) was added, and stirred for 1 h. It was then quenched with water and extracted with AcOEt. The organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The resulting residue was crystallized from MeOH and filtrated to give **13a** (10.8 g, 56%, based on **20**).

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