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A Scalable Process for the Synthesis of 2-Methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine Monohydrate and 4-[(Biphenyl-2-ylcarbonyl)amino]benzoic Acid: Two New Key Intermediates for the Synthesis of the AVP Antagonist Conivaptan Hydrochloride

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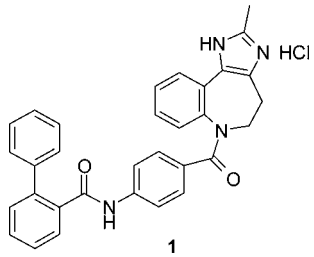
Abstract:

A process for the multikilogram synthesis of the dual vasopressin-receptor antagonist, conivaptan hydrochloride, has been developed. This method relies on the introduction of operationally simple chemistry during the final stages of the process when two key intermediates, isolated by crystallization, are reacted to assemble the final molecule. A three-stage sequence has been developed for the synthesis of the first key amine hydrate intermediate, and modifications of the original process are described here. Major strategic improvements have been made in defining the final route to the "side chain" precursor molecule, which is the second key intermediate. These advances revolve around the acylation of an unprotected amino benzoic acid and subsequent high-yield telescoped processes for the synthesis of 4-[(biphenyl-2-ylcarbonyl)amino]benzoic acid. This novel method leads to a 4-fold increase in the overall yield of the target materials, circumvents the restricted synthetic intermediates, and constitutes a safe, reliable, adaptable, environmentally friendly, and cost-effective approach with improved manipulability.

Introduction

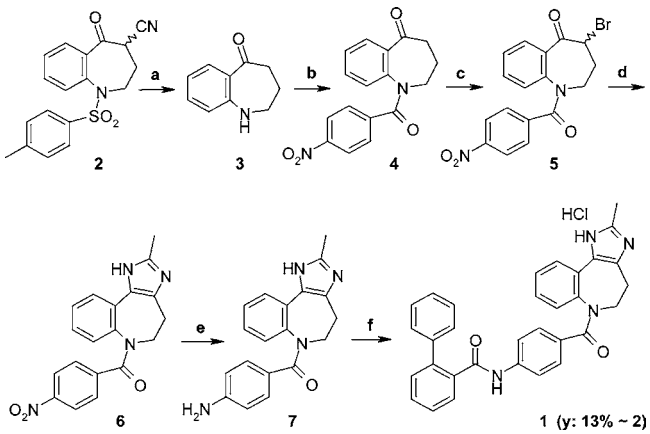
Arginine vasopressin (AVP) is a neurohypophysial hormone that has been shown to play important physiological roles in vasoconstriction and antidiuresis. It exerts its effects through binding to specific receptors that are coupled to distinct second messengers. Thus, small-molecule inhibitors of AVP are promising agents for the treatment of cardiovascular pathologies, such as congestive heart failure and renal disease.[1] Conivaptan hydrochloride (**1**; Figure 1) is a newly synthesized potent nonpeptide antagonist of the AVP V_{1A} and V_2 receptors.[2] We reported previously our first-generation route for **1**, which involved the elimination of chromatographic purification and crystallizations from highly inflammable solvents.[3] However, both the overall yield and the problems associated with this route made it unsuitable for use as a cost-effective method of synthesis to develop a competitive drug candidate (Scheme 1). This approach used chlorinated solvents at several stages and included a catalytic-reduction technique that required specialized facilities. Furthermore, some of the intermediates might infringe upon existing patents. Consequently, we sought to establish a more suitable synthetic strategy for **1** by manufacturing this compound via a novel route.



1
Conivaptan hydrochloride

Figure 1. **Chemical structure of 1.**

Scheme 1. **Published route for 1**[a]



[a] Reagents and conditions: (a) acetic acid, hydrochloric acid, 43%; (b) i. 4-nitrobenzoyl chloride, triethylamine, dichloromethane; ii. crystallization: chloroform, methanol, 75%; (c) bromine, chloroform, 88%; (d) i. ethanimidamide monohydrochloride, potassium carbonate, chloroform, 67%; (e) H_2, Raney nickel, methanol, DMF, 94%; (f) i. biphenyl-2-carboxylic acid, oxalyl chloride, DMF, dichloromethane; ii. acetonitrile, **7**, pyridine; iii. hydrogen chloride in ethyl acetate, 74%.

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(1) Naitoh, M.; Suzuki, H.; Murakami, M.; Matsumoto, A.; Arakawa, K.; Ichihara, A.; Nakamoto, H.; Oka, K.; Yamamura, Y.; Saruta, T. *Am. J. Physiol.* **1994**, *267*, H2245. Okada, H.; Suzuki, H.; Kanno, Y.; Yamamura, Y.; Saruta, T. *Clin. Sci.* **1994**, *86*, 399.

(2) Yatsu, T.; Tomura, Y.; Tahara, A.; Wada, K.; Tsukada, J.; Uchida, W.; Tanaka, A.; Takenaka, T. *Eur. J. Pharmacol.* **1997**, *321*, 225. Tahara, A.; Tomura, Y.; Wada, K.; Kusayama, T.; Tsukada, J.; Takanashi, M.; Yatsu, T.; Uchida, W.; Tanaka, A. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 301. Tahara, A.; Saito, M.; Sugimoto, T.; Tomura, Y.; Wada, K.; Kusayama, T.; Tsukada, J.; Ishii, N.; Yatsu, T.; Uchida, W.; Tanaka, A. *Naunyn-Shmiedeberg's Arch. Pharmacol.* **1998**, *357*, 63. Tahara, A.; Tomura, Y.; Wada, K.; Kusayama, T.; Tsukada, J.; Ishii, N.; Yatsu, T.; Uchida, W.; Tanaka, A. *Peptides* **1998**, *19*, 691.

(3) Tsunoda, T.; Yamazaki, A.; Iwamoto, H.; Sakamoto, S. *Org. Process Res. Dev.* **2003**, *7*, 883.

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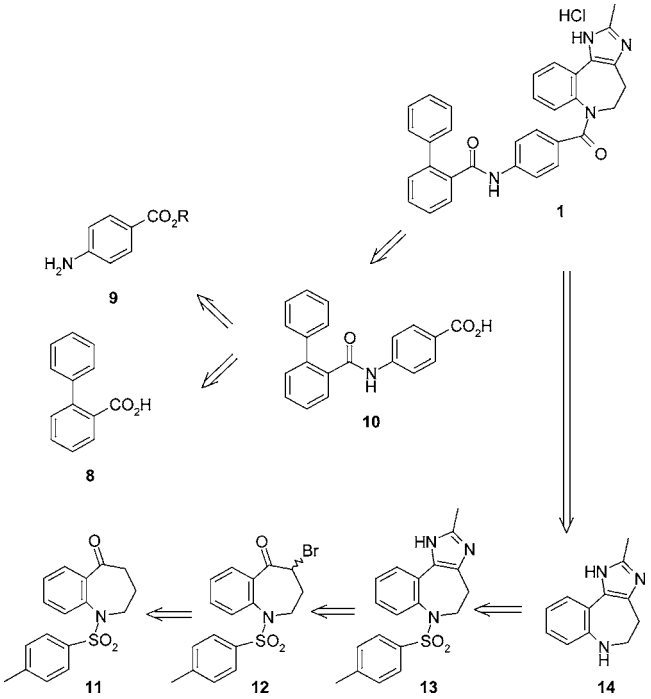
Scheme 2. **New synthesis route for 1**



Results and Discussion

As target material, **1** has a unique imidazobenzazepine structure; our strategy was to introduce an imidazole synthon into a readily available benzazepine compound and eliminate the catalytic reduction step, thus reducing the costs of the process. Moreover, the two key intermediates, 4-[(biphenyl-2-ylcarbonyl)amino]benzoic acid (**10**, YM-175043) and 2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine monohydrate (**14**, YM-53132 monohydrate), in the proposed convergent synthesis can be produced separately in different reactors, thus providing a more competitive system for large-scale production by reducing the manufacturing period (Scheme 2). This approach enhanced the overall yield of **1** to 56% from 13%, that in the original synthesis, after the completion of the process development described below.

Imidazole-Ring-Formation Stage. The known compound 1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**11**) was selected as the source of the benzazepine skeleton for the alternative route, as it can be produced using the method reported by Proctor and colleagues, and McCall and co-workers.[4] High-quality 4-bromo-1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**12**) was produced by the bromination of **11** with pyridinium hydrobromide perbromide[5] in chloroform, following recrystallization from ethanol.

Previously, we reported a novel imidazole-ring-formation approach.[3,6] Although this method might be applicable to the reaction of **12** to give **13** (Scheme 3), it required further optimization to obtain a routine production method due to the low manipulability of the process.

Table 1. **Imidazole-ring formation of 12 in chloroform[a]**

H_2O[b] in K_2CO_3	H_2O[c] charged	reaction[d] (**13**:**16**:**12**)	reaction time (h)	yield (%)
0	−	49:35:6	190	20
5	−	84:11:0	60	74
10	−	89:5:0	50	78
15	−	88:7:1	60	76
0	5	83:10:1	70	73
0	10	91:3:0	24	79
0	15	85:5:1	24	75

[a] Ethanimidamide monohydrochloride and K_2CO_3 at 5 and 6 mol per mol of **12**, respectively. [b] Amount of water absorbed in K_2CO_3 (w/w %).[7] [c] Amount of liquid water charged in the reaction system (w/w % based on the weight of K_2CO_3). [d] Monitored by HPLC.

Scheme 3. **Target and byproduct of imidazole-ring formation from 12**

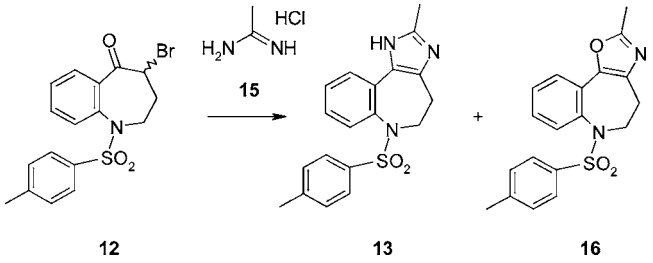


Table 1 summarizes the findings of our investigation into the imidazole-ring formation by the reaction of **12** with ethanimidamide (**15**). The reactions with moist potassium carbonate produced similar results to those observed in our previous research, although the reactants were different.[3] Considerable side-reaction formation of the oxazole byproduct (**16**) (Scheme 3) was seen in the reaction with fresh potassium carbonate; this side reaction decreased when 5−15% moist potassium carbonate[7] was employed. This confirmed that our theory was sufficiently robust to be applied to the reaction of various α-bromoketones. By contrast, the reaction of **12** with fresh potassium carbonate in the presence of liquid water produced imidazole **13** in good yield and also shortened the reaction time when 10 or 15% liquid water was employed. This approach allowed us to manufacture the novel imidazobenzazepine, **13**, with a consistently good yield, through to kilogram-scale production whilst eliminating the awkward moisture-absorption process.

The fact that **12** is a mutagen,[8] together with increased environmental concerns, led us to consider a modified method; imidazole-ring formation in non-chlorinated solvents and omission of the crystallization of **12** were both investigated.

In the first study, the reaction of **12** in toluene produced the largest quantity of **13**, although none of the reactions in non-chlorinated solvents produced results superior to those obtained in chloroform (Table 2). In the second study,

(4) Proctor, G. R.; Thomson, R. H. *J. Chem. Soc.* **1957**, 2312. McCall, I.; Proctor, G. R.; Purdie, L. *J. Chem. Soc. C* **1970**, 1126.
(5) Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 417.
(6) Although the importance of the small amount of water in the reaction was not discussed, a report of the reaction between α-bromopropiophenone and benzamidine has been reported, see: Krieg, B.; Brandt, L.; Carl, B.; Manecke, G. *Chem. Ber.* **1967**, *100*, 4042.
(7) Moist potassium carbonate, containing 5−15% of water, was prepared by the exposure of anhydrous potassium carbonate to the ambient humidity in the air. Up to 16% water was observed, which is the level reported for the 1.5 hydrate of this material.
(8) The result for the Ames test for **12** was positive.

Table 2. **Imidazole formation in non-chlorinated solvents compared to that in chloroform[a,b]**

solvents	reaction[c] (**13**:**16**:**12**)	reaction time (h)
toluene	77:7:0	2
2-butanone	68:16:1	25
MeCN	66:11:0	25
acetone	56:20:2	26
DMF	53:1:0	20
EtOH	24:0:0	23
MeOH	10:0:1	23
$CHCl_3$	91:3:0	24

[a] Ethanimidamide monohydrochloride and K_2CO_3 at 5 and 6 mol per mol of **12**, respectively. [b] In the presence of 10 w/w% liquid water (based on the weight of K_2CO_3) at reflux (for toluene; at 100 °C). [c] Monitored by HPLC.

Table 3. **Sequential reaction of 11 to 13[a,b]**

solvents[c]	product[d] (**13**:**16**:**12**)	yield[e] (%)
toluene	99:0:0	69
$CHCl_3$	99:0:0	77

[a] Ethanimidamide monohydrochloride and K_2CO_3 at 5 and 6 mol per mol of **12**, respectively. [b] In the presence of 10 w/w% liquid water (based on the weight of K_2CO_3) at reflux (for toluene; at 100 °C). [c] Reaction solvent for imidazole-ring formation. [d] Monitored by HPLC. [e] Total yield of two steps (bromination and imidazole-ring formation). 2-Propanol and ethanol were used as salt-formation solvents in the studies with toluene and chloroform, respectively.

successive reactions consisting of bromination and imidazole-ring formation in both chloroform and toluene were investigated. As expected, the reaction in chloroform produced a greater yield and a better quality of **13** than that in toluene during the first run. However, modifications of the post-treatment process in the experiments with toluene, which involved using a back-extraction with an aqueous acid solution and replacing ethanol with 2-propanol in the salt-formation process, improved the yield of **13** and provided material of comparable quality to that obtained by reaction in chloroform (Table 3).

Although the sequential reaction in chloroform remained superior to that in toluene in terms of yield, environmental concerns compelled us to choose the latter approach.

Consequently, we produced a safer, more environmentally favorable, and highly reproducible technique for the manufacture of **13**.

Hydrolysis Stage. Several previous studies have investigated the cleavage of aryl sulfonamides.[9,10] Initially, the detosylation of novel compound **13** (Scheme 4) was carried out using the method described for benzazepinone (**11**), which was reported to be generally applicable to aryl sulfonamides (Table 4, run 1).[10] However, the reaction of **13a** was incomplete, and more than 3% of the starting material persisted for 50 h after the reaction was initiated. Consequently, we sought an alternative method for the detosylation of **13**. Using concentrated sulfuric acid as the reagent, the reaction proceeded remarkably rapidly, despite the lower temperature.[11] This method was applicable to both forms of **13** (free base (**13a**) and hydrochloride salt (**13b**)) obtained during the development of the preceding imidazole-ring-formation stage.

(9) Proctor, G. R. *J. Chem. Soc.* **1961**, 3989.

(10) Lennon, M.; McLean, A.; McWatt, I.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1828. Carpenter, P. D.; Lennon, M. *J. Chem. Soc., Chem. Commun.* **1973**, 664.

Table 4. **Detosylation of 13**

run	form of **13**	conditions reagents, temperature	reaction time[a] (h)
1	free	c.H_2SO_4/AcOH,[b] 70 °C	50
2	free	NaOH aquous, 90 °C	(NR)
3	free	c.HCl, 70 °C	(NR)
4	free	c.H_2SO_4,[c] 60 °C	1
5	HCl salt	c.H_2SO_4,[c] 60 °C	1

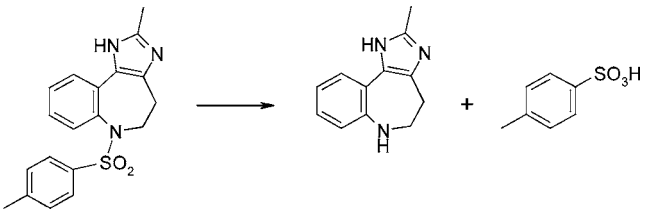
[a] The time at which the residual starting material could no longer be detected by HPLC (for **13a**; not more than 4%). NR = no reaction. [b] Concentrated sulfuric acid and glacial acetic acid at 2 and 3 volumes per weight of **13a**, respectively. [c] Concentrated sulfuric acid at 6 volumes per weight of **13a** or **13b**.

Table 5. **Efficacy of various solvents in the extraction of 14 from a basic solution**

solvents[a]	**14**[b] (%)
toluene	76
dichloromethane	29
chloroform	19
ethyl acetate	12
2-butanone	2

[a] The ratio of the volume of the solvent to the original basic solution was 0.5:1.0. [b] The amount of **14** remaining in the aqueous solution as a percentage of the initial volume detected by HPLC.

Scheme 4. **Target and byproduct of the detosylation of 13**



13a: free
13b: monohydrochloride

14 **17**

As **14** is highly water soluble, it was difficult to isolate it from the aqueous solution obtained after the reaction; thus, the efficiency of the extraction of **14** was investigated after the neutralization of the reaction mixture. As shown in Table 5, 2-butanone had the greatest effect on the extraction of **14** and minimized expansion of the batch scale.

In these experiments, the use of 2-butanone for the extraction afforded sufficient amounts of the crystalline product **14**, which was subsequently recrystallized from ethyl acetate. Although optimizing the solvent for the extraction minimized the batch volume, the reaction in concentrated sulfuric acid required a huge amount of water to dissolve the sodium sulfate that was produced during the post-treatment processes. This led us to investigate the use of dilute sulfuric acid for detosylation of **13b**, which now represented the chosen form of the product of the imidazole-ring-formation stage.

(11) Wiese, M.; Schmalz, D.; Seydel, J. K. *Arch. Pharm. (Weinheim, Ger.)* **1996**, *329*, 161.

Table 6. **Detosylation of 13b in sulfuric acid**

reagents[a]	temperature (C°)	time[b] (h)	batch-scale[c] (mL/g)
c.H_2SO_4	60	1	210
80% H_2SO_4	80	1	130

[a] c.H_2SO_4: concentrated sulfuric acid. 80% H_2SO_4: v/v%. [b] The time point at which the residual starting material could no longer be detected by HPLC. [c] The maximum volume in a batch per volume of product **14**.

Table 7. **Crystallization solvents for 14**

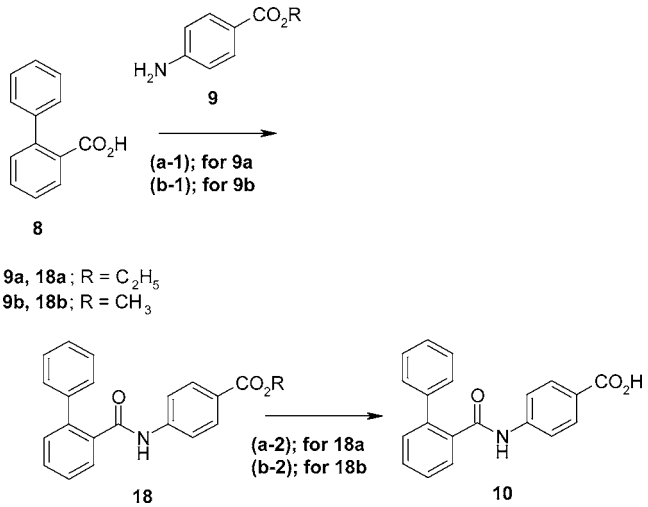
solvents[a]	yield (%)	product[b] (**14**:**17**)
EtOH−H_2O(3:5)	63	99.7:0.1
2-butanone	70	99.1:0.5
AcOEt	77	99.0:0.5
MeCN−H_2O(3:10)	90	99.9:0.0

[a] Crystallization solvents expressed in volumes. [b] Monitored by HPLC.

As shown in Table 6, the detosylation of **13b** in 80% sulfuric acid was accomplished within 1 h and reduced the batch scale by almost half; the reaction would fail if the sulfuric acid content of the solution was less than 80%, due to the low solubility of **13b**. Finally, to optimize both the quality and yield of **14**, a suitable crystallization solvent was required. **14** could be crystallized from an aqueous ethanol solution, 2-butanone, or ethyl acetate; however, aqueous acetonitrile solution produced higher quality **14**, in excellent yield, thus optimizing the detosylation stage (Table 7).

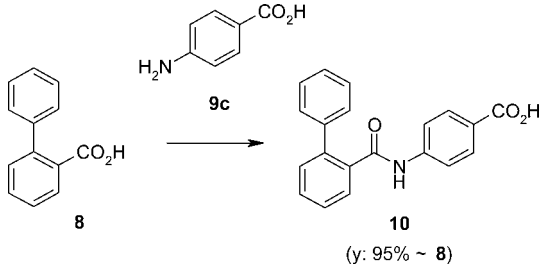
Production of a Synthon of 10. Initially, we chose not to explore this pathway, because the existing methods for the preparation of **10** did not appear attractive for the manufacturing process. For example, using ethyl[12] and methyl[13] benzoates as intermediates produced **10** in 7 and 48% yields, respectively (Scheme 5). However, the reaction

Scheme 5. **Published routes to 10**[a]



[a] Reagents and conditions: (a-1) i. **9a**, WSC, HOBT, tetrahydrofuran; ii. ethyl acetate; iii. Silica gel chromatography: chloroform/methanol; iv. crystallization: ethanol, 8%; (a-2) i. sodium hydroxide, ethanol; ii. water, diethyl ether, hydrochloric acid, 86%; (b-1) i. oxalyl chloride, dichloromethane; ii. **9b**, *N*,*N*-diisopropylethylamine; iii. *n*-hexane, 50%; (b-2) i. ethanol, sodium hydroxide, water, 96%.

Scheme 6. **Applied process for 10**[a]



[a] Reagents and conditions: i. thionyl chloride, DMF, toluene; ii. **9c**, *N*,*N*-dimethylaniline, acetone, water; iii. DMF, water, 95%.

Table 8. **Comparison of recrystallization solvents for 10**

solvents[a]	recovery (%)	purity[b] (%)	batch-scale[c] (mL/g)
2-PrOH	88	−	59
MeCN	−	−	50<
MeCN−H_2O(1:1)	−	−	40<
MeOH	75	−	40
EtOH	78	91[d] → 99	40
DMF−H_2O(1:1)	95	83[e] → 99	10

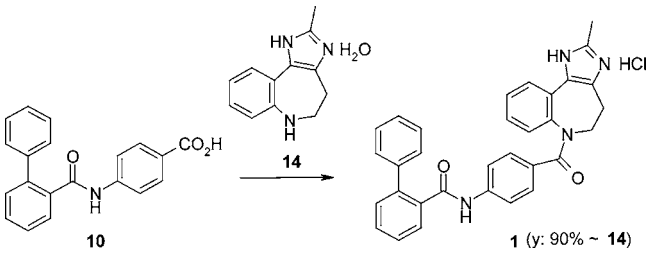
[a] Crystallization solvents expressed in volumes. [b] The purity (crude → purified) of **10** before and after recrystallization as detected by HPLC. [c] The maximum volume in a batch per amount of crude **10**. [d] Samples of 10 mol % of **8** and **9c** were spiked. [e] Samples of 20 mol % of **8** and **9c** were spiked.

of biphenyl-2-carboxylic acid (**8**) with unprotected 4-amino benzoic acid (**9c**) produced **10** in a sufficiently high yield using *N*,*N*-dimethylaniline as a base (Scheme 6).[14,15] Although the fluidity of the resultant suspension reduced the efficiency of agitation, it was suitable for use in the synthesis of **10** for the production of conivaptan hydrochloride. The low fluidity of the reaction mixture may result, on production scale, in large quantities of the starting materials **8** and **9c** remaining at the end of the reaction; therefore, a suitable purification method for the reliable generation of high-quality **10** was sought. As shown in Table 8, recrystallization of **10** in the 1:1 mixture of *N*,*N*-dimethylformamide and water removed any unreacted **8** and **9c**, even in cases beyond the expectation in extremely high yield with the smallest batch scale. Using this simple method (Scheme 6), high-quality **10** was generated in high yield during kilogram-scale production.

Final Reaction Stage. The synthetic strategy described in our previous paper was applied to the regioselective acylation of **14** with **10**.[3,16] Sufficiently high-quality **1** has been manufactured in a kilogram-scale process in high yield, using these two key intermediates produced in pilot plants (Scheme 7).

(12) Matsuhisa, A.; Koshio, H.; Sakamoto, K.; Taniguchi, N.; Yatsu, T.; Tanaka, A. *Chem. Pharm. Bull.* **1998**, *46*, 1566.
(13) Albright, J. D.; Venkatesan, A. M.; Delos Santos, E. G.; U.S. Patent 5,849,735, 1998.
(14) Bredereck, H.; Von Shuh, H. *Chem. Ber.* **1948**, *81*, 215.
(15) Thionyl chloride replaced oxalyl chloride which was used as a reagent for acyl halide formation in ref 3 due to the unit price.
(16) Tsunoda, T.; Koshio, H.; Taniguchi, N.; Asakura, T. Jpn. Kokai Tokkyo Koho JP 200287962, 2002.

Scheme 7. **Final reaction step for 1**[a]



[a] Reagents and conditions: i. thionyl chloride, acetonitrile, then toluene; ii. **14**, acetonitrile; iii. ethanol, 90%.

Conclusion

A process for the multikilogram production of **1** has been developed based on a convergent synthesis involving the key intermediates **14** and **10**, and has been implemented at a pilot plant. This method leads to a 4-fold increase in the overall yield of **1**, circumvents the restricted synthetic intermediates, and provides a safe, reliable, flexible, environmentally friendly, and cost-effective approach with improved manipulability.

Experimental Section

All reagents and solvents were used as received from commercial suppliers, unless otherwise stated. All equipment was inspected visually for cleanliness and integrity before use.

Analytical HPLC was performed on a Hitachi D-2500 system with UV detection at a wavelength of 220 or 240 nm using a YMC-pack ODS-A A-302 150 mm × 4.6 mm column, and elution with 0.2 M ammonium chloride aqueous solution−acetonitrile (2:1) to (2:3) or 0.05 M Na_2HPO_4 aqueous solution adjusted to pH 5.7−acetonitrile (2:3). ^{1}H NMR spectra were recorded on a JEOL JNM-AL400, AL500, or A500 spectrometer with chemical shifts given in ppm relative to TMS at $\delta = 0$. Mass spectra were determined on a Hitachi M-80, JEOL LX-2000, JMS-DX300, or 700T spectrometer. Melting points were determined using a Yanagimoto micro-melting-point apparatus and are uncorrected. All of the potassium carbonate used in this research was in powder form with a particle size of less than 105 μm and was purchased from commercial suppliers. The water content of the potassium carbonate was determined using the loss-on-ignition test described in Japan Industrial Standard (JIS) K 0067.

4-Bromo-1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (12). Pyridinium hydrobromide perbromide (25.7 g, 80.3 mmol) was added to a solution of 1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one **11**[4] (25.3 g, 80.2 mmol) in chloroform (230 mL), and the mixture was stirred at an internal temperature of 15−30 °C for 1 h, washed with water (180 mL, then 110 mL), 5% aqueous sodium bicarbonate solution (110 mL), and water (110 mL), successively, and then concentrated to dryness at 40 °C. The resultant residue was dissolved in ethanol (300 mL) at reflux, cooled to 0 °C, and stirred for 16 h. The resultant crystals were isolated by filtration and dried at 25−40 °C to give **12** (28.1 g, 89%) as a yellowish-white powder. Mp: 128−130 °C.[9] HPLC assay: 96.0% (area). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (m, 1H), 2.42 (s, 3H), 2.66 (m, 1H), 3.70 (m, 1H), 4.36 (m, 1H), 4.58 (q, 1H), 7.25−7.59 (m, 8H). MS *m*/*z*: 394 ($M^+ + 1$).

2-Methyl-6-[(4-methylphenyl)sulfonyl]-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine Monohydrochloride (13b). Bromine (13.7 g, 85.6 mmol) was added to a mixture of **11**[4] (27.0 g, 85.6 mmol) and 48% hydrobromic acid (1.5 g, 8.9 mmol) in acetic acid (260 g) at an internal temperature of 25−35 °C over 1 h, and the mixture was stirred for 1 h at the same temperature. Water (880 mL) and toluene (880 mL) were added, and the mixture was stirred. The organic and aqueous layers were separated, and the former was washed with 5% aqueous sodium carbonate solution (880 mL) and water (880 mL), and then toluene (340 mL) was added. Ethanimidamide monohydrochloride (36.5 g, 386 mmol), water (7.5 g, 417 mmol), and potassium carbonate (67.1 g, 485 mmol) were added to the toluene solution, and the mixture was heated at 95−110 °C for 3 h before cooling to 35−45 °C. Methanol (310 mL), water (430 mL), and concentrated hydrochloric acid (67.6 g) were added, and the mixture was stirred before the organic and aqueous layers were separated. The aqueous layer was basified with sodium carbonate (20.4 g) and extracted with ethyl acetate (two extractions of 800 mL). The organic layer was washed with water (two washes of 410 mL) and then concentrated to dryness at 40 °C. The resultant residue was dissolved in 2-propanol (210 mL), concentrated hydrochloric acid (7.0 g) was added at 20−30 °C, and the mixture was cooled to 0−5 °C. The resultant crystals were filtered and dried at 60 °C to give **13b** as grayish-white crystals (22.9 g, 69%). Mp > 250 °C. HPLC assay: 99.5% (area). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.34 (s, 3H), 2.57 (s, 3H), 3.14 (br s, 2H), 3.44 (br s, 2H), 7.22−7.95 (m, 8H), 14.7 (br s, 2H). Anal. Calcd for $C_{19}H_{19}N_3O_2S\cdot HCl$: C, 58.53; H, 5.17; N, 10.78; S, 8.22; Cl, 9.09. Found: C, 58.19; H, 5.14; N, 10.59; S, 8.17; Cl, 9.43. MS *m*/*z*: 354 ($M^+ + 1$).

Chloroform Method. Bromine (1.21 g, 7.55 mmol) was added to a mixture of **11**[4] (2.38 g, 7.55 mmol) and 48% hydrobromic acid (0.13 g, 0.75 mmol) in chloroform (21 mL) below −15 °C, and the mixture was stirred for 24 h at 15 °C. Water (11 mL) was added, and the mixture was stirred. The organic and aqueous layers were separated, and the former was washed with 5% aqueous sodium bicarbonate solution (11 mL) and water (11 mL), and then chloroform (100 mL) was added. Ethanimidamide monohydrochloride (3.57 g, 37.7 mmol), water (0.73 g, 40.6 mmol), and potassium carbonate (6.57 g, 47.5 mmol) were added to the chloroform solution, and the mixture was heated at reflux for 25 h before cooling to 25 °C. Water (60 mL) was added, and the mixture was stirred before the organic and aqueous layers were separated. The organic layer was washed with water (60 mL) and then concentrated to dryness at 40 °C. The resultant residue was dissolved in ethanol (11 mL), concentrated hydrochloric acid (0.76 g) was added at 20−30 °C, and the mixture was cooled to 0−5 °C. The resultant crystals were filtered and dried at 45 °C to give **13b** as grayish-white crystals (2.28 g, 77%). Mp > 250 °C. HPLC assay: 98.7% (area).

2-Methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine Monohydrate (14, YM-53132 Monohydrate). *N*-Substituted imidazobenzazepine **13b** (22.4 g, 57.5 mmol) was heated in 80 v/v% sulfuric acid (227 g) at an internal temperature of 80 °C for 1 h. The mixture was cooled, poured into water (270 mL) below 30 °C, and basified with 20% aqueous sodium hydroxide solution (860 g) before 2-butanone (200 mL) was added. The organic and aqueous layers were separated, and the organic layer was concentrated to dryness at 40 °C. Acetonitrile (58 mL) and water (58 mL) were added to the resultant residue, which was then concentrated to dryness at 60 °C; then acetonitrile (34 mL) and water (115 mL) were added to the resultant residue and heated at reflux. The resultant solution was cooled to 0−5 °C. The resultant crystals were filtered and dried at 60 °C to give **14** as brownish-yellow crystals (11.2 g, 90%). Mp: 189−191 °C. HPLC assay: 99.9% (area). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.26 (s, 3H), 2.82 (t, 2H), 3.17 (q, 2H), 3.40 (br s, 2H), 5.84 (br s, 1H), 6.69−6.88 (m, 3H), 7.94 (br s, 1H), 11.6 (br s, 1H). Anal. Calcd for $C_{12}H_{13}N_3 \cdot H_2O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.39; H, 6.92; N, 19.33. MS *m*/*z*: 200 ($M^+ + 1$).

4-[(Biphenyl-2-ylcarbonyl)amino]benzoic Acid (10, YM-175043). Thionyl chloride (10.4 g, 87.4 mmol) was added to a mixture of biphenyl-2-carboxylic acid **8** (15.0 g, 75.7 mmol) and *N*,*N*-dimethylformamide (0.28 g, 3.83 mmol) in toluene (72 mL) at an internal temperature of 40 °C. The mixture was stirred at this temperature for more than 2 h. After completion of the reaction, the mixture was concentrated to dryness at 60 °C. The resultant residue was then diluted with toluene (36 mL) and concentrated to dryness at 60 °C, and the process was repeated again to give biphenyl-2-carbonyl chloride as an oil. Acetone (100 mL) was added to the oil, and 4-amino benzoic acid (**9c**; 10.4 g, 75.8 mmol) and *N*,*N*-dimethylaniline (10.1 g, 83.3 mmol) were added to the resultant solution at 25 °C. The mixture was stirred at this temperature for more than 2 h. Water (100 mL) was then poured into the mixture, and it was stirred at 25 °C for more than 1 h. The resultant crystals were filtered and dissolved in *N*,*N*-dimethylformamide (100 mL) at 25 °C. The solution was then filtered to remove insoluble materials, water (100 mL) was poured into the filtrate, and it was stirred at 25 °C for more than 2 h. The resultant crystals were filtered and dried at 40 °C to give **10** as white crystals (22.7 g, 95%). Mp: 246−248 °C. HPLC assay: 98.7% (area). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.28−7.87 (m, 13H), 10.55 (s, 1H), 12.71 (br s, 1H). Anal. Calcd for $C_{20}H_{15}NO_3 \cdot 0.1H_2O$: C, 75.27; H, 4.80; N, 4.39. Found: C, 75.30; H, 4.77; N, 4.56. MS *m*/*z*: 318 ($M^+ + 1$).

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