Synthesis of Methyl 7,9-Dimethyl-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxylate and Its Analogues

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Abstract: A high-yielding five-step synthesis of the title compound, methyl 7,9-dimethyl-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxylate, starting from 2,4-dimethylaniline was developed. This synthesis involved N-alkylation of 2,4-dimethylaniline with ethyl 4-bromobutyrate to obtain ethyl 4-[(2,4-dimethylphenyl)amino]butanoate. Carbamoylation of the latter followed by hydrolysis of the resulting ester provided 4-[(2,4-dimethylphenyl)(methoxycarbonyl)amino]butanoic acid. Activation of the carboxylic acid using thionyl chloride followed by intramolecular cyclization via a Friedel–Crafts reaction using aluminum trichloride provided the title compound in good yield. Analogues of the title compound were also prepared similarly.

Key words: alkylation, carbamoylation, hydrolysis, Friedel–Crafts reaction

Benzo-fused seven-membered nitrogen heterocyclic rings, broadly termed as benzazepines, represent a particularly interesting class of heterocylces.[1] The benzazepine moiety constitutes the core structure of numerous pharmacologically important compounds.[2] Several members of this class have exhibited biological activity toward various targets such as enzymes, ion channels, and G-protein coupled receptors (GPCRs).[3,4] As a part of an ongoing project on cholesteryl ester transfer protein (CETP) inhibitor,[5] Evacetrapib, multi-kilogram quantities of the title compound **1** (Figure 1) were required for development. Although, we had reported the synthesis of **1** and 7,9-dimethyl-1,2,3,4-tetrahydro-5*H*-benzo[*b*]azepin-5-one (**2**) from 2,4-dimethylaniline (**3**),[6] the poor isolated yield of **1** (38–49%) necessitated the development of a practical process to meet the multi-kilogram requirement of **1**. Herein we report the details of a high-yielding and practical synthesis of **1**.

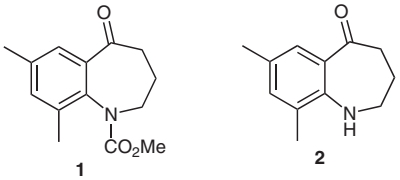
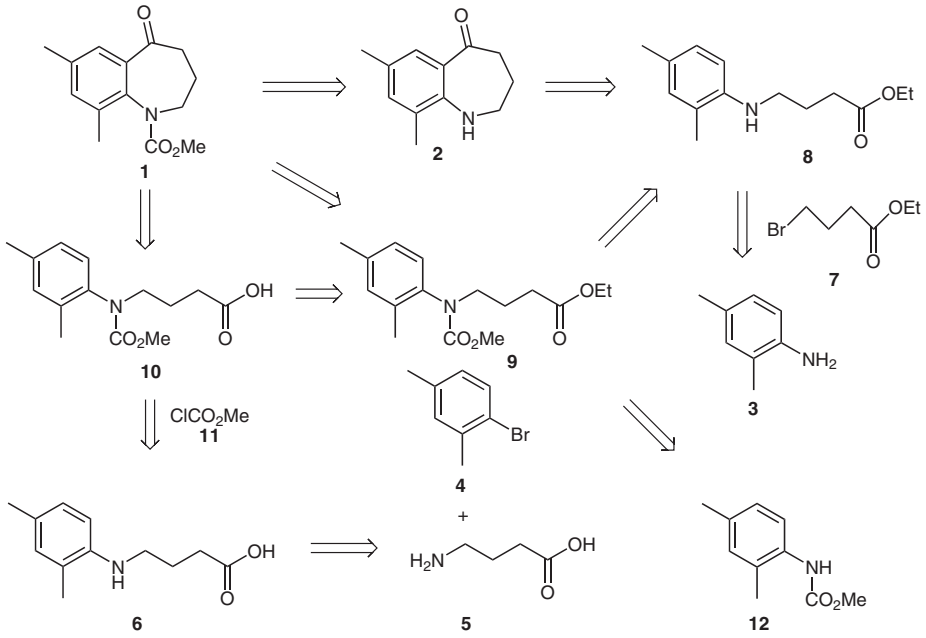


Figure 1 Structure of compounds **1** and **2**



Scheme 1 Retrosynthetic pathways for **1**

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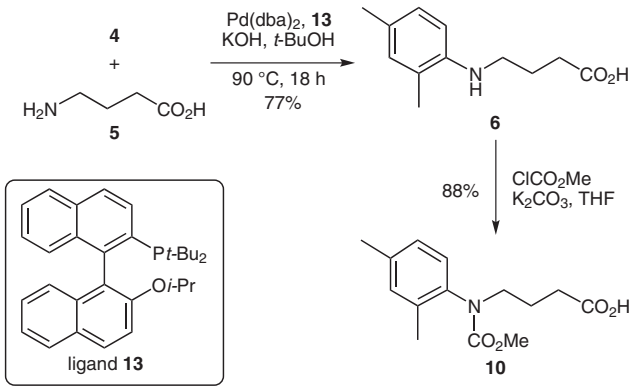
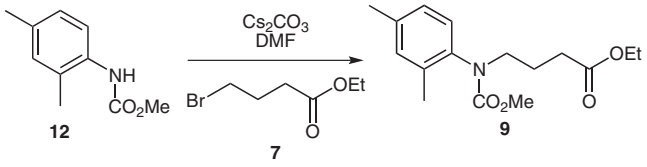
A retrosynthetic analysis of **1** revealed that its synthesis might be achieved by intramolecular Friedel–Crafts reaction of **6**, **8**, **9**, or **10** (Scheme 1). Compound **6** might be obtained by direct metal-catalyzed coupling of **4** and **5**. Compound **10** could be obtained either by carbomylation of **6** or by hydrolysis of **9**. Synthesis of **9** could be achieved by a) N-alkylation of **3** with **7** followed by carbamoylation of resulting product **8** or b) alkylation of **12** with **7**.

Following the literature precedent,[7] the synthesis of **6** was successfully achieved by coupling **4** with **5** using $Pd(dba)_2$ and ligand **13** in 77% yield (Scheme 2). Compound **10** was obtained by treating **6** with methyl chloroformate and potassium carbonate. We were unsuccessful in finding a commercially available ligand as a replacement for **13**. Thus, due to limited large-scale availability of ligand **13** and its tedious synthesis,[8] we explored other pathways for the synthesis of **10** as shown in Scheme 1.



Scheme 2 Synthesis of **10**

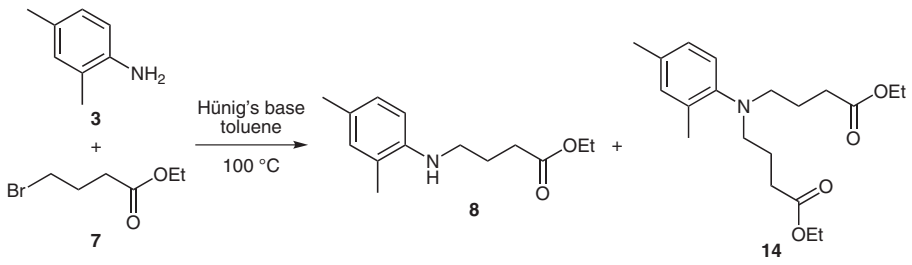
A survey of the literature revealed that N-alkylation of unsubstituted or N-substituted carboxamides with alkyl halides under basic conditions can be accomplished in good yield.[9–12] Thus, the synthesis of **9** was attempted by alkylation of **12** with **7** using powdered metal hydroxides or carbonates. Synthesis of **9** using metal hydroxides or powdered sodium or potassium carbonate was unsuccessful. Synthesis of **9** was, however, successful using cesium carbonate in *N*,*N*-dimethylformamide under dilute conditions (20 volumes) in 60% yield (Scheme 3). Due to the environmental concern for the disposal of cesium waste and large volumes of *N*,*N*-dimethylformamide required, we explored the synthesis of **9** from **8**.



Scheme 3 Synthesis of **9**

Thus, the synthesis of **8** was explored by N-alkylation of **3** with **7** (Scheme 4). The treatment of **3** with **7** in Hünig's base (DIPEA) as solvent at 100 °C provided a mixture of desired mono-N-alkylated product **8** along with bis-N-alkylated product **14**. Significantly higher amounts of **14** were observed as the scale of reaction was increased. Therefore, the impact of other parameters such as type of base, temperature, and solvent on the selectivity was examined in the formation of **8**. The reaction was performed in triethylamine at 75 °C with slow addition of **7** over 24 hours in order to minimize the levels of **14**. However, these modifications resulted in an extended reaction time of >70 hours. Even with an additional charge of **7**, the level of **3** could not be driven to the desired target of <3%, without a concomitant increase in levels of **14**.

Several alternative bases including pyridine, *N*-methylmorpholine, and potassium carbonate were screened, but alkylation results were poor. A more detailed comparison study of triethylamine and Hünig's base were undertaken. The alkylation was much worse in Hünig's base at both 75 and 100 °C. The reaction rate was slow and bis-alkylation was three times higher as compared to the alkylation reaction performed using base triethylamine. Consequently, triethylamine was chosen for further process development. In this study, the reaction temperature and stoichiometries of triethylamine and **7** were studied (Table 1 entries 1–9). Low equivalents of both triethylamine and **7** at 85 °C did not lead to desired target level of **3** (<3%; entry 1). A combination of high equivalents of **7** and low equivalent of triethylamine allowed the reaction to reach completion within three hours (entry 2). However, as expected, the level of **14** quickly increased to unacceptably high level. Use of 1.5 equivalents of **7** provided intermediate results in regard to conversion and levels of bis-alkylation. Doubling the charge of triethylamine (entry 5) not only slowed the reaction rate, but also led to a reduction in **14**. Use of high equivalence of triethylamine was



Scheme 4 Synthesis of **8**

excessive, thus co-solvents and addition rate of **7** were examined. CPME (cyclopentyl methyl ether) and toluene were both tested as co-solvents in the synthesis of **8** (Table 2). As the yield and quality profile of **8** was observed to be comparable, toluene was selected as co-solvent for further exploration. Entries 7 and 8 in Table 2 compare the impact of an up-front charge of **7** to the reaction versus a 16-hour charge of **7**. Both reactions gave similar conversions and product profiles. Thus, we preferred the up-front charge of **7** in the reaction along with the use of toluene as a co-solvent in the synthesis of **8**. A toluene solution of product **8** containing **14** and unreacted **3** obtained after an aqueous work up was used as such without any purification for the synthesis of **9**.

Table 1 N-Alkylation Data of Compound **8**

Entry	Et_3N (equiv)	Compound **7** (equiv)	Temp (°C)	Time (h)	GC area%		
					3	**8**	**14**
1	3.4	1.25	85	3	5.5	87.5	5.0
2	3.4	1.75	85	3	0.3	85.5	12.5
3	6.8	1.25	85	13	1.4	87.7	8.9
4	3.4	1.50	85	3	3.2	88.6	6.0
5	6.8	1.50	85	7	2.1	90.1	3.5
6	3.4	1.50	75	7	2.1	89.0	7.6
7	3.4	1.75	75	5	5.0	89.1	5.9
8	3.4	1.50	65	7	4.9	88.7	6.4
9	3.4	1.75	65	7	9.8	83.9	6.3

Carbamoylation of **8** to give **9** was achieved in toluene using methyl chloroformate and sodium carbonate. Subsequently, hydrolysis of **9** using sodium hydroxide followed by workup allowed the rejection of the bis-hydrolysis impurity originating from **14** to obtain **10** of high purity. The resulting solution of **10** in dichloromethane was used without further purification for the formation of **15**.

Synthesis of **2** via cyclization of **8** under acidic conditions was unsuccessful as it resulted in the formation of undesired impurities and 1-(2,4-dimethylphenyl)pyrrolidin-2-one. Based upon the literature,[13,14] attempts to cyclize **9** or **10** to **1** using trifluroacetic anhydride, methanesulfonic anhydride, methanesulfonic acid, trifluoromethanesulfonic acid, or polyphosphoric acid were also unsuccessful and resulted in the formation of undesired impurities. Thus, it was planned to carry out the synthesis of **1** via cyclization of an activated form of **10** such as acid chloride **15** using Lewis acids.

Preparation of acid chloride **15** from **10** was accomplished using either thionyl chloride or oxalyl chloride in the presence of either *N*,*N*-dimethylformamide or 2,6-lutidine catalyst and solvent dichloromethane or 1,2-dichloroethane (DCE). Use of $SOCl_2$ was preferred over oxalyl chloride due to its lower cost. Among the commonly employed Lewis acids such as BCl_3, $FeCl_3$, $SnCl_4$, $ZnCl_2$, $TiCl_4$, and aluminum trichloride for the Friedel–Crafts reaction,[14] only aluminum trichloride successfully provided **1** from **15**. As indicated by HPLC data, unreacted starting material and a few impurities were observed with the use of Lewis acids other than aluminum trichloride. Among the solvents (CH_2Cl_2, DCE, heptanes, nitromethane, and sulfolane) tested for conversion of **15** into **1** by aluminum trichloride, the best result was obtained using dichloromethane.

Following the literature precedent for catalytic Friedel–Crafts acylation reactions,[15,16] the use of other catalysts such as silica-bound aluminum trichloride or bromopentacarbonylrhenium or $AlPW_{12}O_{40}$ or $Ga(ONf)_3$ was explored in the synthesis of **1** from **15** under various

Table 2 Impact of Cosolvent, Stoichiometry, and Addition Time of **7** on the Synthesis of **8**

Entry	Et_3N (equiv)	Cosolvent (vol, mL)	Compound **7** (equiv)	Compound **7** addition time (h)	Reaction time (h)[a]	GC area%		
						3	**8**	**14**
1	3.4	CPME (6.0)	1.43	16	20	2.9	90.3	6.4
2	3.4	toluene (6.0)	1.40	16	20	1.8	91.1	6.7
3	5.8	CPME (3.3)	1.43	16	19	2.4	91.7	5.3
4	5.8	CPME (3.3)	1.26	16	21	4.2	90.8	5.3
5	5.8	toluene (3.3)	1.26	16	21	3.5	91.1	4.8
6	5.8	toluene (3.3)	1.26	16	22	2.5	92.1	5.4
7	5.8	toluene (3.3)	1.26	–	17	3.1	91.2	5.0
8	5.8	toluene (3.3)	1.30	16	18	2.4	92.6	5.0
9	5.8	CPME (3.3)	1.26	–	17	2.8	90.9	5.5

[a] The reactions were complete after 5 h, but were held at 100 °C for the indicated time to ensure product stability.

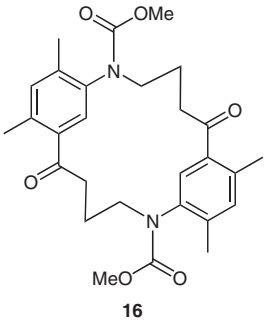
conditions. Synthesis of **1** from **15** under catalytic Friedel–Crafts reaction conditions was unsuccessful.

As mentioned previously, the Friedel–Crafts cyclization was successfully completed using **15** and aluminum trichloride as the Lewis acid, thus efforts were focused to optimize this approach. The use of **15** prepared using catalyst 2,6-lutidine led to the formation of more impurities in the synthesis of **1**. Further, the isolated product quality and yield were low. Therefore, we decided to use *N*,*N*-dimethylformamide as a catalyst for acid chloride formation. Impacts of solvent 1,2-dichloroethane and temperature were evaluated in the synthesis of **1** from **15** (Table 3, entries 1–4). In 1,2-dichloroethane, at high temperature and under dilute conditions a low yield of **1** was obtained and product quality was also poor. The conversion of **15** into **1** in dichloromethane under reflux conditions was better as compared to the reaction performed in 1,2-dichloroethane. Thus, we preferred dichloromethane to 1,2-dichloroethane for the synthesis of **1** using aluminum trichloride. In the process optimization study, the impact of reaction concentration and Lewis acid stoichiometry were studied in dichloromethane (entries 5–13). As indicated from the data (entry 10), low yield of **1** was obtained under dilute reaction conditions with 1.5 equivalents of Lewis acid. Similarly, high reaction concentration and Lewis acid equivalents (entries 5 and 7) also provided low yield. The best transformation was observed under dilute reaction conditions with 3.22 equivalents of aluminum trichloride (entries 12 and 13).

Table 3 Impact of Aluminum Trichloride Stoichiometery, Solvent Concentration, and Temperature on the Synthesis of **1** from **15**

Entry	$AlCl_3$ (equiv)	Solvent (vol, mL)	Temp (°C)	Time (h)	Compound **1** formation by HPLC assay (%)
1	3.22	DCE (12)	70–75	2	54.6
2	3.22	DCE (12)	50–55	2	61.9
3	3.22	DCE (12)	43–45	3	64.0
4	3.22	DCE (7)	36–38	3	57.3
5	3.22	CH_2Cl_2 (7)	35–40	3	72.4
6	3.22	CH_2Cl_2 (9)	35–40	3	75.0
7	3.22	CH_2Cl_2 (10)	35–40	2	77.0
8	3.22	CH_2Cl_2 (12)	35–40	2	88.0
9	3.22	CH_2Cl_2 (14)	35–40	2	88.5
10	1.5	CH_2Cl_2 (12)	35–40	2	70.2
11	2.5	CH_2Cl_2 (12)	35–40	2	77.0
12	3.22	CH_2Cl_2 (14)	35–40	3	87.5
13	3.22	CH_2Cl_2 (12)	35–40	2	88.2

An LCMS analysis of the Friedel–Crafts reaction performed under concentrated conditions indicated the presence of multiple peaks due to dimer, trimer, and polymers of **10**. The formation of dimer **16** was also observed under dilute reaction conditions. This impurity, shown in Figure 2, was isolated and identified by NMR spectroscopy.

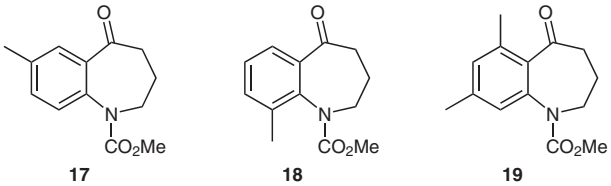


16

Figure 2 Structure of impurity **16**

Finally, we were able to achieve the synthesis of **1** from **3** without the isolation of intermediates by developing a streamlined process as shown in Scheme 5. This streamlined process involved i) preparation of a toluene solution of **8**, ii) carbamoylation of **8** followed by hydrolysis of **9** to obtain **10**, and iii) activation of **10** using thionyl chloride followed by intramolecular Friedel–Crafts reaction with aluminum trichloride, workup and crystallization from ethanol–water to obtain **1** in 67% isolated yield starting from **3**.

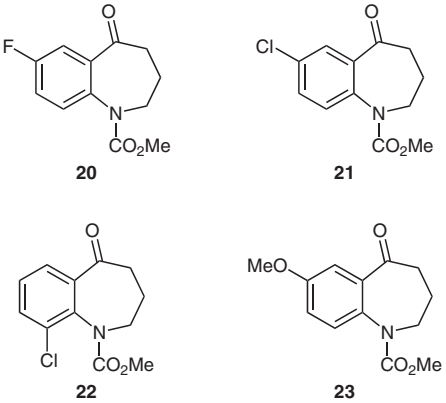
In a similar manner, analogues **17**–**19** of **1** were prepared successfully (Figure 3).



17 **18** **19**

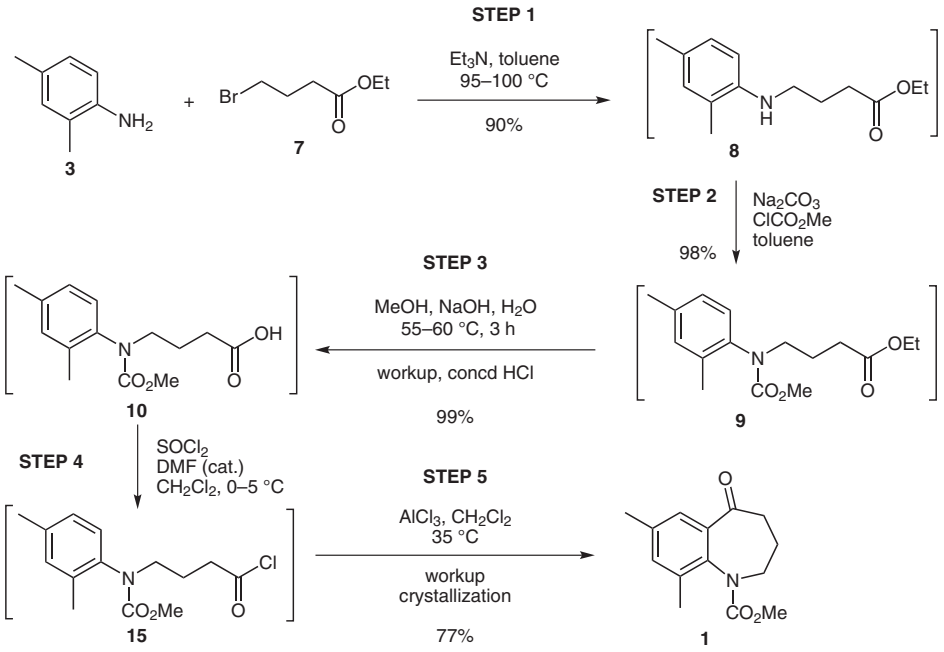
Figure 3 Synthesis of **17**–**19**

However, attempted synthesis of **20**–**22** under the same conditions was unsuccessful, potentially as a result of the reduced electron density of the aromatic ring bearing flu-



20 **21** **22** **23**

Figure 4 Attempted synthesis of **20**–**23**



Scheme 5 Synthesis of **1**

orine or chlorine relative to methyl substituted substrates (Figure 4). Attempted synthesis of **23** via an intramolecular Friedel–Crafts reaction resulted in a complex mixture. An analysis of this reaction mixture by LCMS indicated the presence of **23** to be less than 3%.

In conclusion, we have developed a high-yielding and practical synthesis of benzazepinone **1** starting from 2,4-dimethylaniline (**3**).

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 400, 500, and 600 MHz spectrometers. Chemical shifts (δ) are expressed in ppm and coupling constants (*J*) are given in Hz. Standard abbreviations are used to describe the signal patterns. HRMS recordings were obtained using a Waters GCT Premier TOF mass spectrometer with EI source. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, particle size 0.035–0.070 mm).

Methyl 7,9-Dimethyl-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxylate (1) (Scheme 5)

Step 1: Ethyl 4-[(2,4-Dimethylphenyl)amino]butanoate (8)
To a 3-necked round-bottomed flask equipped with a mechanical stirrer, thermocouple, reflux condenser, and N_2 purge was charged 2,4-dimethylaniline (**3**; 100.6 g, 830.2 mmol), toluene (330 mL, 3.3 vol), and Et_3N (485 g, 4793 mmol). The reaction contents were heated to 95–100 °C. Ethyl 4-bromobutyrate (**7**; 209.7 g, 1075.1 mmol) was added dropwise to the reaction mixture over 1 h. The reaction contents were stirred at 95–100 °C for 6 h. The reaction progress was monitored by HPLC (**3** = 3.0%, **8** = 90.3%; **14** = 5.1%). The reaction contents were cooled to 15–25 °C. H_2O (400 mL) was added by maintaining a reaction temperature of 15–25 °C. The reaction contents were stirred at 15–25 °C for 30–40 min. The organic layer was separated and washed with H_2O (300 mL). The organic layer was concentrated to 200–300 mL at a temperature below 50 °C under vacuum (25–30 Torr). Thus, 261.9 g toluene solution of **8** (89.3% purity and 66.1% potency assay) was obtained. This solution was used as such in the next step; yield: 173.1 g (89%). A pure sample of **8** was obtained by purification by column chromatography using a mixture of EtOAc and hexane as eluent (70:30); off-white solid; mp 202–213 °C.

IR (KBr): 3412 (sharp), 1720 (sharp), 1618 cm^{-1} (sharp).

^{1}H NMR (DMSO-d_6): δ = 1.17 (t, *J* = 5.50 Hz, 3 H), 1.81 (m, 2 H), 2.02 (s, 3 H), 2.12 (s, 3 H), 2.36 (d, *J* = 4.30 Hz, 2 H), 3.05 (m, 2 H), 4.06 (q, *J* = 4.50 Hz, 2 H), 4.59 (br, 1 H), 6.42 (d, *J* = 3.80 Hz, 1 H), 6.75 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 173.5, 144.6, 131.0, 127.4, 124.3, 122.30, 109.6, 60.2, 42.9, 31.8, 24.4, 20.5, 18.1, 14.6.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{14}H_{21}NO_2$: 235.1572; found: 235.1575.

Step 2: Ethyl 4-[(2,4-Dimethylphenyl)(methoxycarbonyl)]aminobutanoate (9)
To the above prepared toluene solution containing **8** (173.1 g, 735.6 mmol) was added toluene (540 mL) under N_2. Na_2CO_3 (78.5 g, 740.6 mmol) was added and the reaction contents were cooled to 0–10 °C. Methyl chloroformate (97.9 g, 1036 mmol) was charged to the reaction mixture dropwise below 10 °C. The contents were warmed to 10–20 °C and stirred for 1 h. The reaction progress was monitored by HPLC (**8** = not detected; **9** = 87.3%). H_2O (540 mL) was added to the mixture at 15–25 °C and the organic layer was separated. H_2O (200 mL) was added to the mixture at 15–25 °C and the contents were stirred for 30 min. The organic layer was separated and analyzed by HPLC for **9**. A toluene solution containing 776 g of **9** (87.7% purity and 27.3% assay) was obtained. This solution was used as such in the next step; yield 211.8 g (98%). A sample was concentrated and purified by column chromatography; viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 5.50 Hz, 3 H), 1.85 (m, 2 H), 2.15 (s, 3 H), 2.31 (s, 3 H), 2.32 (m, 2 H), 3.37 (m, 1 H), 3.62 (s, 3 H), 3.78 (m, 1 H), 4.09 (q, *J* = 4.50 Hz, 2 H), 6.95 (m, 2 H), 7.26 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 172.9, 156.4, 137.6, 137.4, 135.5, 131.7, 128.0, 127.4, 60.4, 52.9, 49.6, 31.6, 23.5, 21.0, 17.5, 14.2.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{16}H_{23}NO_4$: 293.1627; found: 293.1629.

Step 3: 4-[(2,4-Dimethylphenyl)(methoxycarbonyl)amino]butanoic Acid (10)

To a 3-necked round-bottomed flask equipped with a mechanical stirrer, thermocouple, N_2 purge was charged the toluene solution prepared above containing **9** (211.8 g, 0.722 mol) and MeOH (300 mL). A solution of NaOH (59.2 g, 1.48 mol) in H_2O (450 mL) was added dropwise to the reaction mixture below 60 °C. The contents were heated to 55–60 °C and this temperature was maintained for 3 h. The reaction progress was monitored by HPLC (**9** = not detected; **10** = 89.9%). The reaction contents were cooled to 15–25 °C and stirred for 20–30 min. The contents were allowed to stand for 30–35 min. The aqueous layer was separated and washed with toluene (175 mL). The aqueous layer was concentrated to 2–3 volumes on a rotary evaporator at reduced pressure (27.4 Torr) at a maximum temperature of ≤45 °C. After the addition of CH_2Cl_2 (475 mL), the pH of the contents was adjusted to 1–2 with concd HCl (148 g) below 5 °C. The contents were warmed to 15–25 °C and stirred for 30 min. The organic layer was separated, mixed with aq 5% HCl (320 mL), and the contents were stirred for 30 min at 15–25 °C. The organic layer was separated and concentrated at atmospheric pressure at a maximum pot temperature of 58–60 °C to obtain an oil (348.3 g). HPLC data indicated 97.6% purity of **10** with 55.0% potency assay; yield 191.5 g (quant.). A sample (10 mL) was further concentrated to obtain a viscous oil. *n*-Heptane (20 mL) was added slowly over 1 h to obtain a slurry. The solid was filtered to obtain the pure compound **10**; white solid; mp 60–61 °C.

^{1}H NMR ($CDCl_3$): δ = 1.86 (t, *J* = 5.50 Hz, 3 H), 2.15 (s, 3 H), 2.32 (s, 3 H), 2.40 (m, 2 H), 3.40 (m, 1 H), 3.62 (s, 3 H), 3.82 (m, 4 H), 6.97 (m, 2 H), 7.06 (s, 1 H), 10.96 (br, 1 H).

^{13}C NMR ($CDCl_3$): δ = 178.5, 156.7, 137.6, 137.4, 135.5, 131.8, 128.0, 127.5, 53.1, 49.4, 31.9, 23.3, 21.0, 17.5.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{19}NO_4$: 265.1314; found: 265.1317.

Step 4: Methyl (4-Chloro-4-oxobutyl)(2,4-dimethylphenyl)carbamate (15)

To a 3-necked round-bottomed flask equipped with a mechanical stirrer, thermocouple, and N_2 purge was charged **10** (191.5 g, 722 mmol) and anhydrous CH_2Cl_2 (820 mL). DMF (2.163 g, 29.59 mmol) was added and the reaction contents were cooled to 0–5 °C. $SOCl_2$ (96.72 g, 813 mmol) was added dropwise to the solution keeping the temperature below 5 °C. After the addition of $SOCl_2$, the reaction temperature was adjusted to 10–20 °C. The reaction contents were stirred for 1–2 h. A sample was drawn and quenched with MeOH for HPLC analysis. The reaction mixture was concentrated to an oil under vacuum at 25–35 °C. Anhydrous CH_2Cl_2 (500 mL) was added to dissolve the oil. The solution of **15** thus obtained was used as such in the synthesis of **1**.

Cyclization of 15 to Methyl 7,9-Dimethyl-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxylate (1)

To a 3-necked round-bottomed flask equipped with a mechanical stirrer, thermocouple, reflux condenser and N_2 purge was added anhydrous CH_2Cl_2 (1.96 L). $AlCl_3$ (319 g, 2.36 mol) was added and the contents were heated to 35–40 °C. The CH_2Cl_2 solution of **15** prepared above was added dropwise into the mixture at 35–40 °C over 3 h. The reaction contents were stirred for 2–3 h at 35–40 °C. A sample was drawn and quenched with aq 5% HCl for HPLC analysis. The reaction contents were cooled to 10–20 °C and added with stirring to a precooled aq 5% HCl (805 mL) by maintaining a temperature of 0–10 °C. The reaction contents were allowed to stand for 30 min. The organic layer was separated and washed with aq 5% HCl (445 mL) and the mixture was allowed to settle for 35 min. The organic layer was separated and concentrated to 2–3 volumes under reduced pressure. *i*-PrOAc (1.56 L) was added to the reaction flask and the contents were concentrated to ~8 volumes on a rotary evaporator at reduced pressure (27.4 Torr) at a temperature below 30 °C. *i*-PrOAc layer was washed with aq 0.5 M NaOH (980 mL) at 15–25 °C and separated. The *i*-PrOAc layer was washed again with aq 0.5 M NaOH (490 mL) at 15–25 °C and then with H_2O (490 mL). The *i*-PrOAc layer was separated and treated with activated carbon (40 g) for 2 h at 15–25 °C. The contents were filtered via diatomite (20 g) and the cake was washed with *i*-PrOAc (400 mL). The filtrate was transferred to a flask and concentrated to 1–1.5 volume. EtOH (400 mL) was added and the reaction mixture was concentrated to 1–2 volume. EtOH (352 mL) was added and the contents were concentrated to 2.5–2.8 volume. The contents were heated to 45–50 °C to obtain a clear solution. H_2O (392 mL) was added dropwise to the solution at 45–50 °C over 30 min. A sample was drawn to determine the ratio of EtOH–H_2O (H_2O–EtOH, 1.38). H_2O (23 g) was charged to the flask and the contents were cooled to 35 °C slowly. After seeding the contents with solid **1** (2.0 g) at 35 °C, the contents were stirred for 2 h at 35 °C. The mixture was cooled to 10 °C and stirred for 2 h. The slurry was cooled to 0 °C and stirred for 16 h. Filtration and washing of the cake with EtOH–H_2O (1:2; 200 mL) provided an off-white to a white solid. The product was dried under vacuum at 45–50 °C; yield: 138 g (76%); purity 99.3%; mp 79–81 °C.

^{1}H NMR (DMSO-d_6): δ = 1.51 and 1.67 (m, 1 H), 1.97 and 2.09 (m, 1 H), 2.10 and 2.17 (m, 3 H), 2.33 and 2.35 (s, 3 H), 2.15 and 2.10 (m, 3 H), 2.34 and 2.28 (m, 1 H), 2.38 (br s, 1 H), 2.53 and 2.67 (m, 1 H), 3.16 and 3.19 (m, 1 H), 3.51 and 3.70 (m, 3 H), 4.16 and 4.24 (m, 1 H), 7.22–7.26 (s, 1 H), 7.34 and 7.30 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 202.4, 155.0, 136.8, 136.7, 135.7, 134.7, 125.8, 52.2, 45.0, 20.9, 19.9, 19.8, 16.0.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{17}NO_3$: 247.1208; found: 247.1211.

Dimethyl 1^4,1^6,7^4,7^6-Tetramethyl-6,12-dioxo-2,8-diaza-1,7(1,3)-dibenzenacyclododecaphane-2,8-dicarboxylate (16)

Compound **1** (13 g) enriched with **16** was treated with MeOH (50 mL) at r.t. to obtain a slurry. The insoluble solids were collected by filtration and washed with MeOH (25 mL). The pale yellow solid was dried in vacuum oven at 40 °C to give 0.2 g of **16**; mp 297–302 °C.

^{1}H NMR ($CDCl_3$): δ = 1.81 (d, *J* = 5.50 Hz, 2 H), 1.91(d, *J* = 6.11 Hz, 2 H), 2.01 (s, 4 H), 2.02–2.04 (m, 2 H), 2.04 (s, 4 H), 2.12 (br s, 1 H), 2.24 (s, 5 H), 2.35 (s, 3 H), 2.63–2.68 (m, 1 H), 2.81 (br s, 2 H), 2.85 (d, *J* = 5.99 Hz, 2 H), 3.09 (dd, *J* =15.53, 5.62 Hz, 2 H), 3.14 (br s, 1 H), 3.40 (s, 3 H), 3.48 (br s, 3 H), 4.13 (d, *J* = 6.24 Hz, 1 H), 4.15 (d, *J* = 4.89 Hz, 1 H), 6.94 (s, 2 H), 7.02 (s, 1 H), 7.36 (s, 1 H), 7.44 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 202.5, 202.1, 157.3, 157.0, 140.8, 139.8, 139.6, 139.3, 139.1, 138.9, 138.7, 138.6, 136.3, 135.3, 130.9, 130.8, 54.2, 54.0, 50.5, 50.3, 39.5, 39.2, 26.2, 25.5, 24.7, 22.1, 18.6.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{28}H_{34}N_2O_6$: 494.2417; found: 494.2422.

Alternate Procedure for the Synthesis of 4-[(2,4-Dimethylphenyl)(methoxycarbonyl)amino]butanoic Acid (10) Starting from 4 (Scheme 2)

Ethyl 4-[(2,4-Dimethylphenyl)(methoxycarbonyl)]aminobutanoate (9)

To a dried 3-necked round-bottomed flask equipped with a condenser, thermometer, and N_2 purge was added $Pd(dba)_2$ (3.80 g, 6.61 mmol), KOH (37.5 g, 568.12 mmol), and 4-aminobutanoic acid (**5**; 23.0 g, 223 mmol), and the ligand di-*tert*-butyl(2′-isopropoxy-1,1′-binaphthyl-2-yl)phosphine (**13**; 3.25 g, 6.41 mmol). The mixture was degassed with N_2. Compound **4** (40.0 g, 216.14 mmol) and *t*-BuOH (1.50 L) were added to the brown mixture. The mixture was degassed with N_2 and heated to 90 °C for 18 h. The reaction progress was monitored by LCMS. After the completion of the reaction, majority of *t*-BuOH was removed under vacuum. A brown residue was obtained. H_2O (100 mL) and CH_2Cl_2 (500 ml) were added to the reaction mixture. The pH of the aqueous layer was adjusted to 3–4 by aq 4 M HCl. The contents were filtered through a pad of Celite and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (500 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to half of the volume and

petroleum ether (bp 40–60 °C) (200 mL) was added. The brown solution was cooled to 5–10 °C for 2 h to obtain a slurry, which upon filtration and drying provided a brownish solid; yield: 36 g (78%); purity: 96.5%; mp 107–114 °C.

^{1}H NMR ($DMSO_6$): δ = 1.77 (m, 2 H), 2.0 (s, 3 H), 2.13 (s, 3 H), 2.33 (m, 2 H), 3.02 (m, 2 H), 6.42 (d, *J* = 4.4 Hz, 1 H), 6.7 (m, 2 H), 11.97 (br, 1 H).

^{13}C NMR ($CDCl_3$): δ = 175.1, 144.9, 131.0, 127.4, 124.2, 122.3, 108.6, 43.1, 31.9, 24.5, 20.6, 18.1;

HRMS: *m*/*z* $[M]^+$ calcd $C_{12}H_{17}NO_2$: 207.1259; found: 207.1256.

Conversion of 6 into 10

To a dried 1 L round-bottomed flask was added **6** (35.0 g, 168.9 mmol), THF (300 mL), K_2CO_3 (50.0 g, 361.8 mmol), and methyl chloroformate (20 mL, 1.59 equiv). The brown heterogeneous mixture was stirred at 25–30 °C for 14 h. LCMS data indicated the formation of the desired product **10**. The reaction mixture was filtered and the cake was washed with CH_2Cl_2 (200 mL). The product was extracted into aqueous phase by treating the CH_2Cl_2 layer with 2 M NaOH (200 mL). The aqueous layer was extracted by CH_2Cl_2 (50 mL) and the combined organic phases were discarded. The pH of the aqueous layer was adjusted to 1–2 by aq 6 M HCl. The product was extracted with CH_2Cl_2 (2 × 100 mL). The brownish organic layer was separated, dried ($MgSO_4$), and concentrated to give a brown viscous oil; yield: 40 g (88%); purity: 95.7%.

Compounds 17–19

Compounds **17**–**19** were synthesized following procedure described for compound **1** starting from the corresponding aniline (85 mmol).

Compound 17

Yield: 5 g (62%); viscous oil.

^{1}H NMR (DMSO-d_6): δ = 7.49–7.48 (m, 1 H), 7.38–7.29 (m, 1 H), 7.30–7.28 (m, 1 H), 3.70 (t, *J* = 6.5 Hz, 2 H), 3.64 (s, 3 H), 2.61–2.48 (m, 2 H), 2.33 (s, 3 H), 1.98–1.94 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 200.6, 154.7, 139.1, 135.8, 133.4, 133.0, 128.0, 127.9, 52.4, 52.4, 47.5, 22.6, 19.9.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}NO_3$ + Na: 256.0941; found: 256.0944.

Compound 18

Yield: 4 g (60%); mp 79–81 °C; purity: 96.2%.

^{1}H NMR (DMSO-d_6): δ = 7.51 (d, *J* = 7.5 Hz, 1 H), 7.47–7.38 (m, 1 H), 7.38–7.28 (m, 1 H), 4.24 (ddd, *J* = 6.6, 10.1, 13.2 Hz, 1 H), 3.51 (s, 2 H), 3.19 (ddd, *J* = 2.9, 6.8, 13.2 Hz, 1 H), 2.68–2.55 (m, 1 H), 2.46–2.29 (m, 1 H), 2.21–2.12 (m, 3 H), 2.03 (br s, 1 H), 2.11–1.95 (m, 1 H), 1.74–1.45 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 203.8, 155.8, 137.8, 136.8, 136.7, 135.2, 128.5, 126.6, 53.4, 53.4, 45.6, 21.7, 17.1.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}NO_3$ + Na: 256.0941; found: 256.0946.

Compound 19

Yield: 7 g (65%); mp 123–125 °C.

^{1}H NMR (DMSO-d_6): δ = 7.05 (s, 1 H), 6.91 (s, 1 H), 3.65 (br s, 2 H), 3.56 (s, 3 H), 2.55–2.43 (m, 3 H), 2.29 (s, 3 H), 2.23 (s, 3 H), 1.87–1.71 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 205.9, 155.4, 140.6, 138.1, 136.3, 133.8, 130.7, 126.3, 52.6, 46.9, 40.7, 22.5, 20.6, 19.0.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}NO_3$: 248.1208; found: 248.1206.

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