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Highly Stereoselective, One-Pot Synthesis of Azetidines and 2,4-Dioxo-1,3-diazabicyclo[3.2.0] Compounds Mediated by I_2

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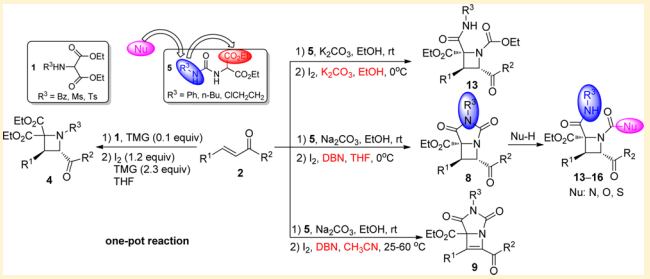
Supporting Information

ABSTRACT: We report here a convenient method to construct polysubstituted azetidines and 2,4-dioxo-1,3-diazabicyclo[3.2.0] compounds with high stereoselectivities in a one-pot reaction mediated by I_2. The tetramethylguanidine (TMG)/I_2-mediated formal [2 + 2] cycloaddition reaction of α-amidomalonate **1** with enones **2** affords functionalized azetidine derivatives **4** in moderate to good yields with high diastereoselectivity. When the α-ureidomalonate **5** is used instead of **1**, 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptanes **8** and 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptenes **9** can be prepared selectively through the control of solvent and temperature. 2,4-Dioxo-1,3-diazabicyclo[3.2.0]heptanes **8** can further undergo ring-opening reactions with different nucleophilic reagents to afford the corresponding polyfunctionalized azetidine derivatives **13**−**16** with high steroselectivities.



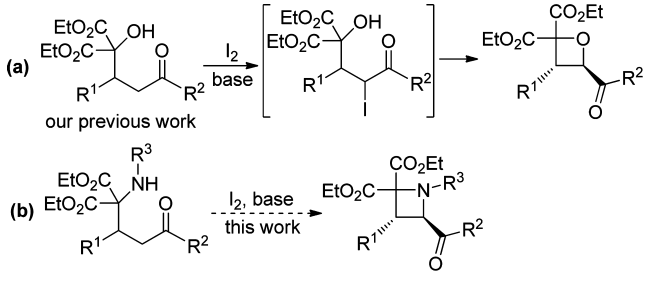
INTRODUCTION

Azetidines are an important class of four-membered constrained heterocyclic compounds and can be found as an important building block in a number of drugs and bioactive compounds,[1] which makes them an interesting synthetic topic. Azetidines can also undergo various transformations to generate a variety of compounds with new molecular skeletons.[2] However, the strain associated with the azetidine ring system leads to difficulties in its synthesis, functionalizations, and modifications.

Among the various general procedures available for the synthesis of azetidines,[2a,b,3] intramolecular nucleophilic substitution of 1,3-amino halides or 1,3-amino alcohol derivatives[4] and reduction of β-lactams[5] are the classical and commonly used approaches. Over the past few years, numerous new methods have been explored to synthesize azetidine derivatives such as intramolecular nucleophilic reactions of carbanions[6] and ring-opening reactions of epoxides and aziridines.[7] The Yadav group applied diethyl *N*-arylphosphoramidates as the nitrogen source in the preparation of azetidines starting from Morita−Baylis−Hillman adducts or chalcones.[8] The metal-catalyzed intramolecular NH insertion of diazo compounds has also received considerable attention.[9] Pd-catalyzed coupling−cyclization of β-sulfonylamino allenes has been reported.[10] Azetidines were also prepared from α- or β-aminoalkenes through intramolecular opening of bromonium, iodonium, and seleniranium intermediates.[11] Their unique reactivity and structural properties have prompted chemists to develop more efficient methodologies for the preparation of such strained cycles.

I_2 as an inexpensive and efficient reagent has been used extensively in organic transformations.[12] Most recently, we reported an interesting base-controlled selective conversion of Michael adducts of malonates with enones to cyclopropane, oxetane, and α-hydroxymalonate derivatives, respectively, in the presence of I_2.[13] During the investigation of the reaction mechanism, we established that α-hydroxymalonate derivatives could be converted to oxetane derivatives in the presence of I_2 and base. Owing to the structural similarity of α-amidomalonate and α-hydroxymalonate derivatives (Scheme 1), we questioned whether the α-amidomalonate derivatives could follow a similar reaction pathway to generate azetidines. Not long ago, Fan and co-workers reported the PhIO/Bu_4NI-mediated oxidative cyclization of the Michael adducts of α-amidomalonates with chalcones to afford azetidines.[14] Although in their research the I_2/Bu_4NOH system could not realize the

Scheme 1



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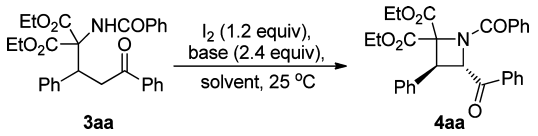
cyclization of Michael adducts to azetidines, we still wanted to attempt such a transformation in the presence of I_2 and other bases because I_2 is far cheaper and more readily available than hypervalent iodine reagents.

RESULTS AND DISCUSSION

The cyclization of the Michael adduct α-benzamidomalonate **3aa** was then selected as a model reaction (Table 1). Although

Table 1. I_2-Mediated Cyclization of Michael Adduct 3aa to 4aa[a]



3aa **4aa**

entry	base	solvent	time (h)	yield (%)
1	Na_2CO_3	DMF	24	0
2	DBU	EtOH	6	49
3	Na_2CO_3	EtOH	6	0
4	piperidine	EtOH	6	20
5	DMAP	EtOH	6	0
6	TEA	EtOH	6	0
7	DABCO	EtOH	6	0
8	$NaOBu^t$	EtOH	6	0
9	KOH	EtOH	6	0
10	NaOH	EtOH	6	0
11	TMG	EtOH	6	50
12	NaOAc	EtOH	6	0
13	DBU	toluene	6	40
14	DBU	CH_2Cl_2	4	74
15	DBU	THF	4	61
16	DBU	dioxane	4	54
17	DBU	CH_3CN	4	73
18	DBU	DMSO	6	40
19	DBU	DMF	6	45
20	TMG	toluene	4	58
21	TMG	CH_2Cl_2	4	55
22	**TMG**	**THF**	**4**	**88**
23	TMG	dioxane	4	86
24	TMG	CH_3CN	4	62
25	TMG	DMSO	4	50
26	TMG	DMF	4	73

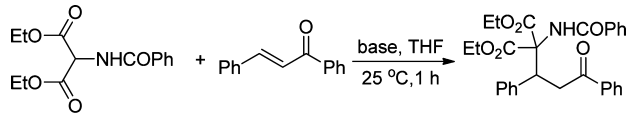
[a]All the reactions were performed with 0.5 mmol of **3aa** in 6 mL of solvent for the designated time. [b]Isolated yield based on substrate **3aa**.

the α-hydroxymalonates could be transformed to oxetanes under I_2/Na_2CO_3/DMF conditions quantitatively,[13] no reaction occurred with **3aa** under similar conditions (Table 1, entry 1). Thus, we attempted the use of a strong organic base. Under I_2/DBU/EtOH conditions the desired azetidine **4aa** was obtained in 49% yield after 6 h (Table 1, entry 2). Nevertheless, the reaction seemed to achieve an equilibrium, because there was no further increase in the yield by prolonging the reaction time. The yield is not satisfactory, and so we tried the use of various bases in this conversion using EtOH as the solvent (Table 1, entries 3−12). The results summarized in Table 1 showed that only strong organic bases such as TMG (tetramethylguanidine) and DBU were more efficient (Table 1, entries 2 and 11). When piperidine was used, the yield of **4aa** was only 20% (Table 1, entry 4). All of the inorganic bases and other weak organic bases could not initiate the reaction. We therefore shifted our further optimization efforts to the examination of the range of solvents compatible with the reactions (Table 1, entries 13−26). Although the 86% yield of **4aa** in TMG/dioxane is adequate, THF has a lower boiling point than dioxane and is easier to remove. Finally, I_2/TMG/THF was chosen as the optimal system for the conversion of **3aa** to **4aa** in 88% yield (Table 1, entry 22).

The Michael reaction is generally regarded as one of the most efficient carbon−carbon bond forming reactions, which can be catalyzed by various bases. Assuming that the Michael addition reaction of 2-aminomalonate **1a** with enone **2a** could be catalyzed by a base in THF, the final azetidines would be constructed easily in one pot via a formal [2 + 2] cycloaddition process involving a Michael addition and subsequent I_2-mediated cyclization. The Michael reaction of 2-aminomalonate **1a** with enone **2a** has been realized by a grind-promoted solvent-free method.[14] Nevertheless, 2 equiv of enone **2a**, 1 equiv of K_2CO_3, and 1 equiv of $PhEt_3NCl$ were required. It was not an atom-economical reaction. Moreover, before the next step of cyclization with $PhIO/Bu_4NI$ the Michael adducts must be preprocessed to remove the solid base. Therefore, we thought about exploring a better method to realize the one-pot synthesis of azetidines.

The Michael addition reaction of enone **2a** with α-benzamidomalonate **1a** was performed with different bases in THF (Table 2). Several bases could catalyze the Michael

Table 2. Michael Addition of 2-Benzamidomalonate with Chalcone[a]



1a **2a** **3aa**

	base	yield (%)[b]	entry	base	yield (%)[b]
1	Na_2CO_3	80	8	$NaHCO_3$	30
2	DMAP	nr	9	NaOH	80
3	DBU	81	10	$NaOBu^t$	70
4	piperidine	trace	11	NaOAc	35
5	TEA	nr	**12**	**TMG**	**82**
6	TEA, $LiClO_4$	75	13[c]	TMG	80
7	DABCO	trace	14[d]	TMG	36

[a]Unless otherwise noted, all the reactions were performed with 0.5 mmol of **1a**, 0.5 mmol of **2a**, and 0.05 mmol of base in 0.2 mL of THF at 25 °C for 1 h. [b]Isolated yield based on substrate **1a**; nr = no reaction. [c]2.4 equiv of TMG was used. [d]Reacted for 24 h in 6 mL of THF.

addition reaction and gave good yields of **3aa**. Fortunately, TMG was also an efficient base to catalyze the addition reaction. It was worth noting that the concentration of reactants had a great influence on the yield. When the enone **2a** was treated with α-benzamidomalonate **1a** using 10% mol TMG as the base in 6 mL of THF for 24 h, **3aa** was obtained in only 36% yield. Decreasing the amount of THF to 0.2 mL dramatically improved the yield of Michael adduct **3aa** to 82% after stirring for only 1 h (Table 2, entry 12). The small amount of THF plays a crucial role in keeping the reactants in high concentration and being well stirred. If there is no solvent, the mixture of the reactants cannot be well mixed and stirred sufficiently.

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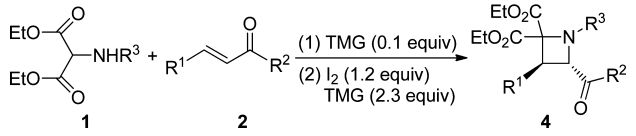
Next, we tested the one-pot formal [2 + 2] cycloaddition. A mixture of **1a** (0.5 mmol), **2a** (0.5 mmol), and TMG (0.05 mmol) was stirred in 0.2 mL of THF for 1 h. Without any workup procedure, 6 mL of THF, I_2 (0.6 mmol), and TMG (1.15 mmol) were added and the mixture was stirred for another 4 h. The azetidine **4aa** could be obtained in 76% yield. We also attempted to use 2.4 equiv of TMG directly in the first addition step. It also gave a similarly good yield of **4aa**. However, for some substrates, these conditions were unfavorable. For example, when R was a tosyl or mesyl group, the Michael adduct would transform quickly to other byproducts under high concentration of base in neat conditions and the next step of cyclization could not be realized.

Under the optimal reaction conditions, the scope and the generality of one-pot synthesis of polysubstituted azetidines were explored (Table 3). The reactions proceeded well when

Table 3. One-Pot Synthesis of Highly Functionalized Azetidines[a]



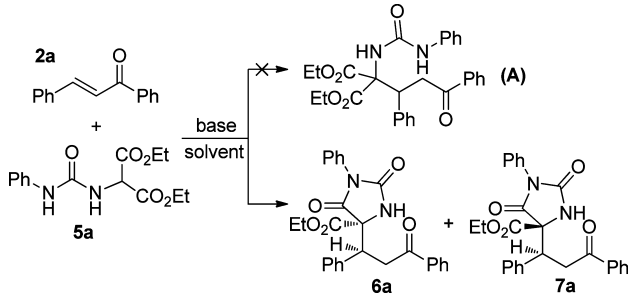
entry	R	R^1	R^2	product	yield (%)
1	PhCO	Ph	Ph	**4aa**	76
2	PhCO	4-$MeOC_6H_4$	Ph	**4ab**	55
3	PhCO	4-MeC_6H_4	Ph	**4ac**	63
4	PhCO	4-ClC_6H_4	Ph	**4ad**	54
5	PhCO	4-$NO_2C_6H_4$	Ph	**4ae**	63
6	PhCO	3-$NO_2C_6H_4$	Ph	**4af**	66
7	PhCO	Ph	4-$MeOC_6H_4$	**4ag**	66
8	PhCO	Ph	4-MeC_6H_4	**4ah**	78
9	PhCO	Ph	4-ClC_6H_4	**4ai**	69
10	PhCO	Ph	4-$NO_2C_6H_4$	**4aj**	62
11	PhCO	4-ClC_6H_4	4-MeC_6H_4	**4ak**	70
12	PhCO	furyl	4-MeC_6H_4	**4al**	59
13	PhCO	4-$MeOC_6H_4$	pyridyl	**4am**	47
14	PhCO	4-$NO_2C_6H_4$	pyridyl	**4an**	62
15	PhCO	Ph	PhCH=CH	**4ao**	61
16	PhCO	Ph	CH_3	**4ap**	0
17	PhCO	Bu^t	Ph	**4aq**	0
18	Ts (**1b**)	Ph	Ph	**4ba**	33
19	Ms(**1c**)	Ph	Ph	**4ca**	55

[a]The reactions were carried out in THF (0.2 mL) with **1** (0.5 mmol), **2** (0.5 mmol), and TMG (0.05 mmol) at 25 °C for 1 h. Then 6 mL of THF, I_2 (0.6 mmol), and TMG (1.15 mmol) were added and the mixture was stirred for another 4−6 h.

R^1 and R^2 were both aryl groups and gave gratifying yields of azetidines (Table 3, entries 1−11). The electronic effect of the substituent groups on the phenyl ring had no significant impact on the reaction. Heterocyclic substituted azetidines **4al**, **4am**, and **4an** could also be obtained in moderate yields (Table 3, entries 12−14). When R^1 was the phenyl group and R^2 was the styryl group, **4ao** was constructed in 61% yield (Table 3, entry 15). Notably, **4aj**, which could not be isolated using Fan's procedure,[14] also was obtained in 62% yield (Table 3, entry 10). Unfortunately, this method has some limitations. If R^1 or R^2 was an alkyl group, no azetidine was obtained (Table 3, entries 16 and 17). When R^1 was a phenyl group and R^2 was a methyl group, the second-step cyclization could not occur. When Bu^t was employed as the substrate of R^1, the Michael addition reaction failed, perhaps due to the large steric hindrance. It was fortunate that *N*-mesylazetidines **4ca** and *N*-tosylazetidines **4ba** were also obtained in 55% and 33% yields, respectively (Table 3, entries 18 and 19). The lower yield of **4ba** was mainly due to the lower reactivity in the Michael addition step. All azetidines were formed with a *trans* orientation of both R^1 and R^2 groups, because in this conformation, the two groups are both in equatorial positions.

In the above cyclization reaction only one nucleophilic atom existed in the Michael adducts **3**; thus, only the azetidine products **4** were formed. Presuming that two nucleophilic atoms existed in the Michael addition adducts, the reaction would yield two possible cyclization products. Therefore, diethyl 2-(3-phenylureido)malonate (**5a**) was chosen as a substrate to react with chalcone **2a**. Contrary to our expectations, no Michael adduct (**A**) was observed (Table 4).

Table 4. Addition Reaction of 2a with 5a[a]



entry	solvent	base	time (h)	**6a**/**7a**[b]	yield (%)[c]
1	THF	TMG	1	85/15	56
2	THF	DBU	1	67/33	54
3	THF	DBN	1	67/33	52
4	THF	piperidine	5		nr
5	THF	TEA	5		nr
6	**EtOH**	**Na_2CO_3**	**3**	**96/4**	**99**
7	THF	Na_2CO_3	43	80/20	20
8	CH_2Cl_2	Na_2CO_3	43	78/22	39
9	CH_3CN	Na_2CO_3	43	72/28	93
10	acetone	Na_2CO_3	43	70/30	86
11	DMF	Na_2CO_3	43	82/18	90
12	EtOH	$KHCO_3$	4	95/5	99
13	EtOH	Cs_2CO_3	3	96/4	99
14	EtOH	K_2CO_3	1	96/4	99

[a]The reactions were carried out with **5** (1 mmol), **2a** (1.05 mmol), and base (0.05 mmol) in 5 mL of solvent at 25 °C. [b]The ratio of **6a** and **7a** was determined by a ^1H NMR analysis. [c]Isolated yield of the mixture of **6a** and **7a**; nr = no reaction.

Instead, the follow-up intramolecular S_N reaction gave the mixed stereoisomers **6a** and **7a** (Table 4). Interestingly, the base and solvent had a great influence on the yield and diastereoselectivity. Under the same conditions (THF/TMG) as Michael addition of **2a** with **1a**, only 56% of the products (**6a** + **7a**) were isolated with a modest diastereoselectivity (**6a**/**7a** = 85/15; Table 4, entry 1). To optimize the reaction, we investigated the use of more bases and solvents. DBU and DBN gave lower yields and worse diastereoselectivities (Table 4, entries 2 and 3). No reaction took place in the presence of either Et_3N or piperidine (Table 4, entries 4 and 5). We were pleased to find that the reaction in EtOH using carbonate or bicarbonate as the basic catalyst afforded the corresponding

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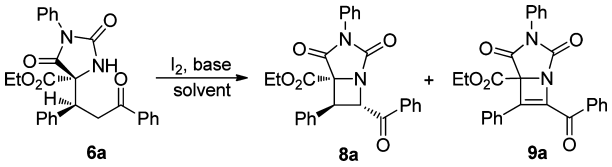
Table 5. I_2-Mediated Cyclization of Michael Adduct 6a to 8a or 9a



6a 8a 9a

							yield (%)[b]	
entry	conditions[a]	solvent	base (amt (equiv))	amt of I_2 (equiv)	T (°C)	time (h)	**8a**	**9a**
1	A	THF	TMG (2.4)	1.2	25	4	36	7
2	A	THF	TMG (2.4)	1.2	25	22	0	0
3	A	THF	DBU (2.4)	1.2	25	5	40	5
4	A	THF	DBN (2.4)	1.2	25	5	42	7
5	A	THF	piperidine (2.4)	1.2	25	5	trace	0
6	A	THF	TEA (2.4)	1.2	25	5	0	0
7	A	CH_3CN	DBN (2.4)	1.2	25	5	33	16
8	A	EtOH	DBN (2.4)	1.2	25	5	29	0
9	**B**	**THF**	**DBN (2.4)**	**1.2**	**0**	**4.5**	**55**	**5**
10	B	CH_3CN	DBN (6.0)	3.0	0	4.5	5	25
11	B	CH_3CN	DBN (6.0)	3.0	25	30	17	32
12[c]	**B**	**CH_3CN**	**DBN (6.0)**	**3.0**	**25−60**	**30**	**trace**	**48**

[a]Conditions A: a mixture of **6a** (0.5 mmol), I_2, and base was stirred in 7 mL of solvent at room temperature. Conditions B: a solution of base in 8 mL of solvent was added dropwise into a mixture of **6a** (0.5 mmol) and I_2 in 7 mL of solvent. [b]Isolated yield. [c]After addition of the base, the mixture was further stirred at 60 °C until only a trace of **8a** remained.

products (**6a** + **7a**) in nearly quantitative yield and excellent diastereoselectivity (**6a**/**7a** ≥ 95/5; Table 4, entries 6 and 12−14). Using THF or CH_2Cl_2 as the solvent resulted in a dramatic decrease in yield with no improvement on diastereoselectivity (Table 4, entries 7 and 8). Dipolar solvents such as CH_3CN, acetone, and DMF also gave high yields but with poor diastereoselectivities (Table 4, entries 9−11). Overall, an efficient method to construct high yield of imidazolidine **6a** with high diastereoselectivity using a catalytic amount of Na_2CO_3 in ethanol was developed (99% yield, dr = 96:4; Table 4, entry 6).

Since **6a** also contained a nucleophilic nitrogen atom similar to **3aa**, we next considered the possibility of I_2-mediated cyclization of **6a** to form a 1,3-diazabicyclic[3.2.0] heptane compound. The synthesis and character of compounds with a 1,3-diazabicyclic[3.2.0] heptane nucleus have seldom been reported in the literature.[15]

According to the previously developed conditions for synthesis of azetidines **4**, a mixture of **6a** (0.5 mmol), I_2 (1.2 equiv), and TMG (2.4 equiv) was stirred in 7 mL of THF. As expected, 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptane (**8a**) was isolated in 36% yield along with the minor product 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptene (**9a**) after 4 h (Table 5, entry 1). Surprisingly, by prolonging the reaction time, **8a** disappeared gradually on TLC (Table 5, entry 2). Afterward, we proved that the base TMG, which possessed an N−H, could further react with **8a** and generate a highly polar byproduct. Therefore, other strong organic bases such as DBU and DBN without N−H bonds were under consideration. Comparatively, DBN was superior to DBU and resulted in a better yield of **8a** (Table 5, entries 3 and 4). Furthermore, we observed that the low yields were due to the incomplete conversion of **6a** and notable decomposition of **6a** to chalcone **2a**. Neither TEA nor piperidine was effective in this conversion, probably due to their relatively weak basicity (Table 5, entries 5 and 6). Other solvents such as EtOH and CH_3CN were also tried. Interestingly, in CH_3CN more 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptene (**9a**) could be formed than in THF (Table 5, entry 7 vs 4). It reminded us that CH_3CN was a good solvent for the selective synthesis of **9a** and thus the solvent-controlled selective synthesis of 1,3-diazabicyclic[3.2.0] compounds **8a** and **9a** might be realized. Considering the decomposition of **6a** under these robust base conditions, we performed the reaction of **6a** with I_2 in THF by the dropwise addition of a solution of DBN in THF to decrease the basicity of the reaction mixture. However, part of **6a** inevitably decomposed to **2a**. Under similar conditions, decreasing the temperature to 0 °C partially suppressed the decomposition of **6a** and **8a** was selectively obtained in a moderate yield of 55% accompanied by 5% of **9a** (Table 5, entry 9). It is a pity that no further improvement in the yield was achieved by prolonging the reaction time. Pleasingly, under these conditions the main product **8a** was easily isolated as almost a single product. As for the formation of **9a**, it was assumed to be generated through iodination of **8a** and subsequent elimination of HI. Thus, the amounts of I_2 and DBN were increased to 3 and 6 equiv, respectively. When the reaction was performed in CH_3CN at 0 °C for 4.5 h, 25% of **9a** was produced with mostly unreacted **6a** (Table 5, entry 10). When the temperature was increased to 25 °C, the yield of **9a** was increased to 32% along with 17% of **8a** (Table 5, entry 11). Further increases in the reaction time did not lead to a noticeable transformation of **8a** to **9a**. When the mixture was stirred at 60 °C for another 24 h after the addition of the base, the yield of **9a** could be increased to 48% with a trace of **8a** remaining (Table 5, entry 12). In addition, it should be noted that the cyclization of **3aa** under the same conditions did not afford the azetine product at all.

Next, we attempted the one-pot selective preparation of **8a** and **9a** separately. A mixture of **2a** (1.05 mmol), **5a** (1 mmol), and Na_2CO_3 (0.05 mmol) was stirred in 5 mL of EtOH at 25 °C. Upon completion of the addition reaction, the solvent was removed in vacuo and I_2 and 7 mL of dry THF or CH_3CN were added. Subsequently, the same procedure as for the cyclization of **6a** produced **8a** and **9a** in 50% and 46% yields,

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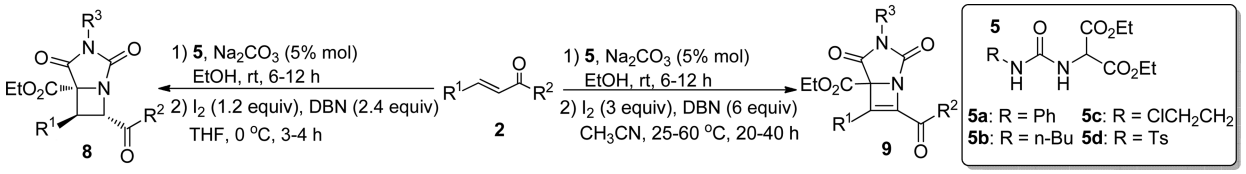
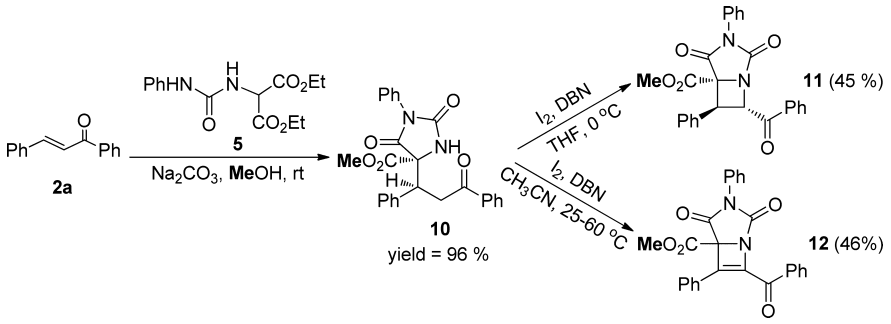
Table 6. One-Pot Construction of Highly Functionalized 1,3-Diazabicyclic[3.2.0] Azetidine Derivatives 8 and Azetine Derivatives 9



entry	R^1	R^2	R^3	product (yield (%)) 8	9
1	Ph	Ph	Ph	**8a** (50)	**9a** (46)
2	4-$MeOC_6H_4$	Ph	Ph	**8b** (56)	**9b** (33)
3	4-MeC_6H_4	Ph	Ph	**8c** (48)	**9c** (42)
4	4-ClC_6H_4	Ph	Ph	**8d** (51)	**9d** (45)
5	4-$NO_2C_6H_4$	Ph	Ph	**8e** (40)	**9e** (46)
6	Ph	4-$MeOC_6H_4$	Ph	**8f** (31)	**9f** (17)
7	Ph	4-MeC_6H_4	Ph	**8g** (36)	**9g** (31)
8	Ph	4-ClC_6H_4	Ph	**8h** (33)	**9h** (41)
9	Ph	4-$NO_2C_6H_4$	Ph	**8i** (0)	**9i** (24)
10	Ph	3-$NO_2C_6H_4$	Ph	**8j** (0)	**9j** (29)
11	4-$MeOC_6H_4$	pyridyl	Ph	**8k** (30)	**9k** (25)
12	2-furyl	4-MeC_6H_4	Ph	**8l** (27)	**9l** (25)
13	Ph	Ph	$ClCH_2CH_2$	**8m**(40)	**9m** (21)
14	Ph	Ph	*n*-Bu	**8n**(41)	**9n** (12)
15	Ph	Ph	Ts	0	0
16	Ph	CH_3	Ph	0	0

Scheme 2. Ester Exchange Reaction in MeOH and Further Cyclization



respectively (Table 6, entry 1). To study the generality of the current selective reaction, various α,β-unsaturated carbonyl compounds were investigated (Table 6). The reaction was found to tolerate a range of different groups with different electronic demands on the aromatic ring. Most of the substrates could give the 1,3-diazabicyclic[3.2.0] azetidine derivatives **8** and azetine derivatives **9** selectively (Table 6, entries 1−8). The substituent on the phenyl ring of the enone, especially on the benzoyl ring, had a great influence on the reaction. When a strong electron-withdrawing group was linked with the benzoyl ring, no azetidine derivatives **8i** and **8j** were generated (Table 6, entries 9 and 10). However, bicyclic heptenes **9i,j** could be obtained normally. Heterocycle-substituted bicyclic compounds **8k,l** and **9k,l** could also be selectively constructed (Table 6, entries 11 and 12). R^3 had no notable influence on the reaction. When R^3 was a phenyl or an alkyl group, 1,3-diazabicyclic[3.2.0] compounds **8** and **9** could be formed (Table 6, entries 13 and 14). The azetine derivatives **9m,n** were generated in lower yield than **8m,n**. However, if R^3 was a tosyl group, the first step of addition could not be realized (Table 6, entry 15). If the phenyl group of R^2 was replaced by a methyl group, no reaction occurred in the second cyclization step (Table 6, entry 16). We are not very clear why the oxetane could be obtained[13] but the azetidine could not be generated when R^2 was a methyl group.

When the first step of Michael addition was performed in methanol, a complete ester exchange reaction took place and gave the addition product **10**, which could be transformed to bicyclic compounds **11** and **12**, respectively, under those similar conditions (Scheme 2).

All of the known products were confirmed by comparison of their spectral data with those reported in the literature.[14] The identification of new compounds **4**, **6a**, **7a**, and **8**−**12** was fully confirmed by their HRMS, ^1H NMR, ^{13}C NMR, and FT-IR spectra. The relative stereochemistry of the first-step addition product **10** and the structure of 1,3-diazabicyclic[3.2.0] azetidine derivatives **8d** and azetine derivatives **9h** were unambiguously determined on the basis of their single-crystal X-ray diffraction analysis (see the Supporting Information).

In the process of screening the cyclization reaction conditions, an interesting phenomenon was observed. When the reaction of **6a** with I_2 was conducted in EtOH using K_2CO_3

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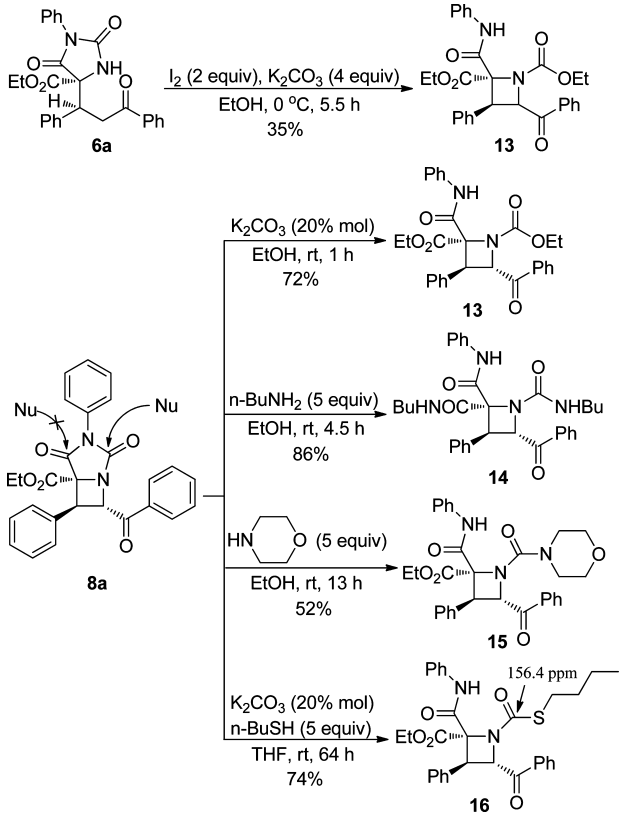
as the base, compound **13** was formed as the main product in 35% yield and neither **8a** nor **9a** was formed (Scheme 3).

Scheme 3. Cyclization of 6a under I_2/K_2CO_3 Conditions in EtOH and Ring-Opening Reaction of 8a Using Different Nucleophilic Reagents



Compounds **13** may be generated from the nucleophilic attack of ethanol at the carbonyl group of imidazolidine ring of **8a** under basic conditions. Further experiments confirmed this conjecture. The bicyclic compound **8a** could be converted to **13** in 72% yield using a catalytic amount of K_2CO_3 after stirring in EtOH for 1 h (Scheme 3). It should be mentioned that no ring-opening reaction took place for compound **6a** under the same conditions, even though it also contained a similar imidazolidine ring. These results led us to envision other nucleophilic reagents containing the nitrogen or sulfur atom (Scheme 3). When **8a** was treated with 5 equiv of *n*-butylamine in THF, **14** was isolated as the single product through the further ammonolysis of the ester group. Reducing the amount of *n*-butylamine to 1 equiv could not prevent the formation of the disubstituted product. Further reducing the temperature to −20 °C resulted in a very low conversion. When morpholine was used as the nucleophilic reagent, the monosubstituted product **15** was obtained in 52% yield. No disubstituted product was observed, due to the large steric hindrance. Using *n*-butyl mercaptan as the nucleophilic reagent and K_2CO_3 as the base produced **16** in 74% yield. The ring-opening reaction took place on the urea group but not the amide group, as confirmed by the ^{13}C NMR spectrum of **16**, which contained a clear signal at 156.4 ppm for the thiocarbamate group (N−(C═O)−S)[16], and the absence of a peak for the thioester group (C−(C═O)−S) at about 200 ppm.

This kind of ring-opening reaction realized the migration of the amine group from the carbonyl group of urea to the carbonyl group of the ester and provided an easy approach to construct azetidine derivatives containing various substituent groups with high stereoselectivities (Figure 1).

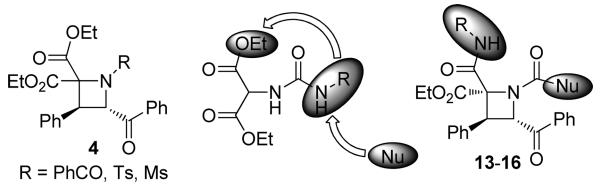


Figure 1. Comparison of the structure of azetidines **4** with those of azetidines **13**−**16**.

A plausible mechanism for the present reaction is described in Scheme 4. The Michael addition reaction of **2** with **1** or **5** affords **3** or intermediate **17**, respectively. Iodination of **3**[18] generates **18**, which undergoes an intramolecular S_N reaction to give the azetidine **4**. Cyclization of intermediate **17** affords adduct **6**. Iodination of **6** generates **20**, and a follow-up intramolecular S_N reaction produces 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptane **8**. Further iodination of **8** and subsequent elimination of HI forms the 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptene **9**. However, a similar reaction with azetidine **4** does not generate **19** in our hands. Nucleophilic attack at the carbonyl group of the imidazolidine ring of **8** leads to the formation of azetidines **13**−**16**. Perhaps the fused, highly strained four-membered ring in compound **8** leads to instability of the imidazolidine ring because **6** cannot transform to **22** under similar conditions.

In conclusion, we have explored a convenient one-pot TMG/I_2-mediated formal [2 + 2] cycloaddition reaction of *α*-amidomalonate with enones to efficiently synthesize azetidines. Highly functionalized azetidine derivatives **4** are divergently synthesized in moderate to good yields with high diastereoselectivity. We also explored an efficient method to construct imidazolidine derivatives with high yield and diastereoselectivity using a catalytic amount of Na_2CO_3 and realized the one-pot preparation of 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptanes and 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptenes with high stereoselectivities. The influence of the base and solvent on those reactions was investigated in detail. The ring-opening reaction of 2,4-dioxo-1,3-diazabicyclo[3.2.0]heptane with different nucleophilic reagents was also investigated. Our further investigations on the construction of thietanes under similar conditions are currently underway.

EXPERIMENTAL SECTION

Synthesis of Diethyl 2-(4-Methylphenylsulfonamido)-malonate (1b). *p*-Toluenesulfonyl chloride (1.9 g, 10 mmol) was added in portions to a stirred solution of the diethyl aminomalonate hydrochloride (2.11 g, 10 mmol) in 10 mL of pyridine at 0 °C. The mixture was stirred at room temperature until the completion of reaction (TLC analysis) and then was poured into 50 mL of ice-cold water with stirring. The precipitate was gathered and washed with water. Further recrystallization from ethyl acetate/petroleum ether afforded the white solid **1b** (2.7 g, 82%): mp 66−68 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.60 (d, J = 8.0 Hz, 1H), 4.65 (d, J = 8.3 Hz, 1H), 4.08−4.18 (m, 4H), 2.42 (s, 3H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.7, 144.1, 136.5, 129.8, 127.4, 63.0, 58.8, 21.7, 14.0; Q-

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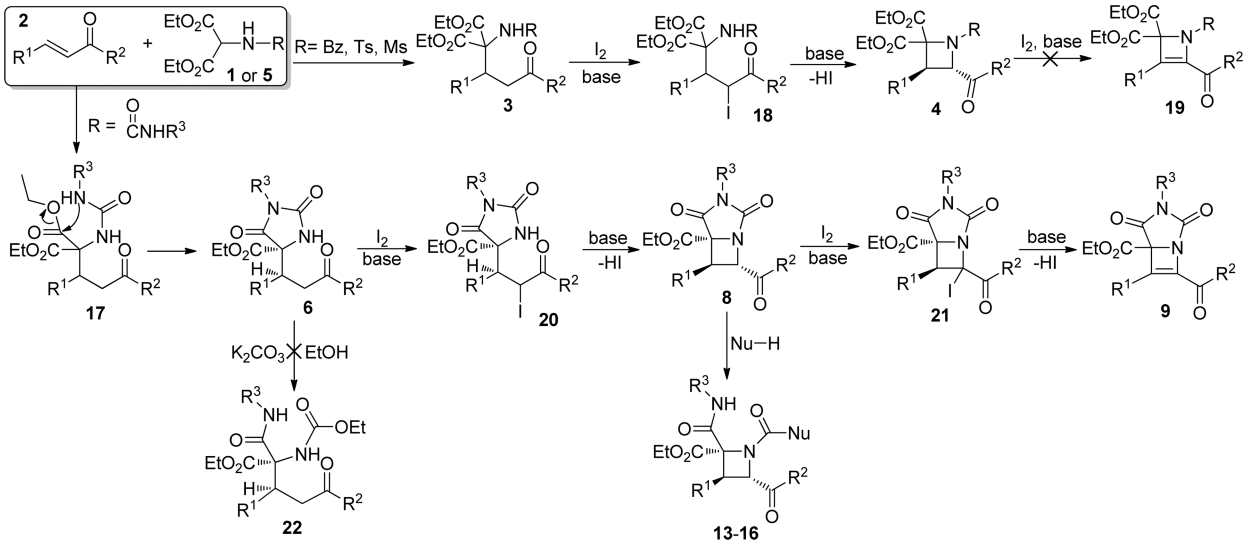
Scheme 4. Plausible Mechanism



TOF-MS (+ESI) calcd for $C_{14}H_{19}NNaO_6S$ $[M + Na]^+$ 352.0831, found 352.0816.

Synthesis of Diethyl 2-(Methylsulfonamido)malonate (1c). A solution of methanesulfonyl chloride (1.14g,10 mmol) in 15 mL of dichloromethane was added dropwise to a stirred solution of diethyl 2-aminomalonate hydrochloride (2.11 g, 10 mmol) and Et_3N (4.3 mL, 30 mmol) in 25 mL of dichloromethane at 0 °C. After completion of the addition the mixture was warmed to room temperature and stirred for another 1 h. The reaction mixture was diluted with CH_2Cl_2 and then washed with hydrochloric acid (1 N), saturated sodium bicarbonate, and water in turn. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was crystallized from ethyl acetate/petroleum ether to give the white solid **1c** (1.94 g, 77%): mp 74−75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (d, J = 8.0 Hz, 1H), 4.86 (d, J = 8.2 Hz, 1H), 4.25−4.35 (m, 4H), 3.06 (s, 3H), 1.32 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 63.1, 59.0, 42.3, 14.0; Q-TOF-MS (+ESI) calcd for $C_8H_{15}NNaO_6S$ $[M + Na]^+$ 276.0518, found 276.0531.

General Procedure for the Synthesis of Azetidines 4. A mixture of diethyl 2-aminomalonate **1** (0.5 mmol), enone **2** (0.5 mmol), and TMG (0.05 mmol) was stirred in 0.2 mL of THF at 25 °C for 1 h. Upon completion as shown by TLC, 6 mL of THF, I_2 (152 mg, 0.6 mmol), and TMG (132 mg, 1.15 mmol) were added and the mixture was stirred at 25 °C for 4−6 h. After completion of the reaction detected by TLC, 20 mL of water and saturated $Na_2S_2O_3$ were added until the disappearance of the umber color and the mixture was extracted with dichloromethane (15 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide azetidines **4**.

4af: colorless solid, 175 mg, 66%, mp 91−93 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 (br, 1 H), 8.28 (d, J = 7.9 Hz, 1 H), 8.11 (d, J = 7.6 Hz, 1 H), 7.72−7.86 (m, 3 H), 7.50−7.62 (m, 3 H), 7.47 (t, J = 7.4 Hz, 1 H), 7.33−7.44 (m, 4 H), 6.85 (br, 1 H), 4.53 (br, 1 H), 4.12−4.30 (m, 2 H), 3.77 (br, 1 H), 3.64 (br, 1 H), 1.23 (br, 3 H), 0.75 (br, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 191.6, 169.0, 166.2, 164.9, 147.9, 137.1, 135.3, 134.0, 133.6, 132.6, 131.1, 130.2, 128.8, 128.3, 128.0, 127.4, 123.9, 123.5, 73.8, 69.7, 61.7, 61.1, 45.9, 13.6, 13.2; IR (KBr) ν/cm^{-1} 3070, 2982, 1754, 1724, 1688, 1642, 1598, 1580, 1532, 1450, 1402, 1353, 1307, 1293, 1276, 1214, 1177, 1160, 1039, 992, 846, 827, 192, 770, 734, 717, 685, 574; Q-TOF-MS (+ESI) calcd for $C_{29}H_{26}N_2NaO_8$ $[M + Na]^+$ 553.1587, found 553.1571.

4aj: colorless solid, 164 mg, 62%, mp 133−135 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (br, 2 H), 7.79 (br, 3 H), 7.37−7.60 (m, 9 H), 6.81 (br, 1 H), 4.12−4.33 (m, 3 H), 3.76 (br, 1 H), 3.58 (br, 1 H), 1.23 (br, 3 H), 0.73 (br, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 191.5, 168.9, 166.6, 164.8, 150.3, 137.3, 134.3, 133.5, 131.1, 129.4, 128.7, 128.62, 128.57, 128.4, 127.3, 123.8, 73.9, 70.1, 61.7, 60.9, 46.8, 13.6, 13.3; IR (KBr) ν/cm^{-1} 3070, 2982, 1754, 1724, 1688, 1642, 1598, 1580, 1532, 1450, 1402, 1353, 1307, 1293, 1276, 1214, 1177, 1160, 1039, 992, 846, 827, 192, 770, 734, 717, 685, 574; Q-TOF-MS (+ESI) calcd for $C_{29}H_{26}N_2NaO_8$ $[M + Na]^+$ $C_{29}H_{26}N_2NaO_8$ $[M + Na]^+$ 553.1587, found 553.1542.

4am: colorless solid, 122 mg, 47%, mp 123−124 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (br, 1 H), 7.96 (br, 1 H), 7.88 (br, 1 H), 7.50−7.73 (m, 3 H), 7.32−7.50 (m, 5 H), 6.95 (d, J = 8.6 Hz, 2 H), 6.59 (d, J = 6.3 Hz, 1 H), 4.13−4.30 (m, 3 H), 3.60−3.81 (m, 5 H), 1.22 (br, 3 H), 0.80 (br, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 193.3, 169.5, 166.9, 165.0, 158.9, 150.0, 149.0, 137.8, 133.8, 130.8, 129.5, 128.4, 127.4, 127.1, 122.3, 113.5, 74.2, 69.8, 61.5, 60.9, 55.1, 46.8, 13.6, 13.3; IR (KBr) ν/cm^{-1} 3070, 2982, 1754, 1724, 1688, 1642, 1598, 1580, 1532, 1450, 1402, 1353, 1307, 1293, 1276, 1214, 1177, 1160, 1039, 992, 846, 827, 192, 770, 734, 717, 685, 574; Q-TOF-MS (+ESI) calcd for $C_{29}H_{28}N_2NaO_7$ $[M + Na]^+$ 539.1794, found 539.1789.

4an: colorless solid, 165 mg, 62%, mp 117−119 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26−8.32 (m, 3H), 7.97 (t, J = 7.4 Hz, 1 H), 7.83−7.93 (m, 3 H), 7.72 (br, 2 H), 7.58 (t, J = 5.7 Hz, 1 H), 7.46 (t, J = 7.2 Hz, 1 H), 7.40 (t, J = 7.4 Hz, 2 H), 6.66 (d, J = 6.0 Hz, 1 H), 4.54 (br, 1 H), 4.16−4.31 (m, 2 H), 3.77 (br, 1 H), 3.67 (br, 1 H), 1.22 (t, J = 6.5 Hz, 2 H), 0.76 (br, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.5, 169.6, 166.6, 164.8, 149.7, 148.9, 147.0, 143.9, 137.9, 133.5, 131.0, 129.9, 128.5, 128.3, 127.3, 123.1, 122.3, 73.9, 70.0, 61.8, 61.2, 46.4, 13.6, 13.2; IR (KBr) ν/cm^{-1} 3070, 2982, 1754, 1724, 1688, 1642, 1598, 1580, 1532, 1450, 1402, 1353, 1307, 1293, 1276, 1214, 1177, 1160, 1039, 992, 846, 827, 192, 770, 734, 717, 685, 574; Q-TOF-MS (+ESI) calcd for $C_{28}H_{26}N_3O_8$ $[M + H]^+$ 532.1714, found 532.1718.

4ba: colorless solid, 88 mg, 33%, mp 108−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.44 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.28−7.33 (m, 3H), 7.23 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 8.4 Hz, 1H), 4.26−4.39 (m, 3H), 4.05 (dq, J = 10.7, 7.2 Hz, 1H), 3.98 (dq, J = 10.7, 7.2 Hz, 1H), 2.40 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 167.8, 166.2, 143.5, 138.5, 134.8, 134.1, 132.7, 129.1, 128.94, 128.89, 128.6, 128.4, 128.0, 64.4, 62.6, 62.5, 45.3, 21.7, 14.1, 13.7; IR (KBr) ν/cm^{-1} 2989, 1749, 1732, 1695, 1599, 1497, 1450, 1372, 1338, 1299, 1278, 1211, 1165, 1152, 1092, 1054, 984, 946, 869, 813, 738, 697, 676; Q-TOF-MS (+ESI) calcd for $C_{29}H_{29}NNaO_7S$ $[M + Na]^+$ 558.1562, found 558.1594.

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4ca: colorless solid, 127 mg, 55%, mp 129−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 2H), 7.49−7.55 (m, 3H), 7.31−7.40 (m, 5H), 6.36 (d, J = 8.4 Hz, 1H), 4.35−4.48 (m, 2H), 4.23 (d, J = 8.4 Hz, 1H), 3.92 (dq, J = 10.7, 7.2 Hz, 1H), 3.98 (dq, J = 10.7, 7.2 Hz, 1H), 3.40 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 168.2, 165.9, 134.3, 133.7, 131.9, 129.3, 129.0, 128.9, 128.7, 66.0, 62.7, 62.6, 46.2, 44.0, 14.2, 13.7; IR(KBr) ν/cm^{-1} 2979, 1750, 1735, 1595, 1452, 1373, 1331, 1293, 1224, 1173, 1145, 1050, 970, 862, 818, 798, 780, 737, 699, 567, 519; Q-TOF-MS (+ESI) calcd for $C_{23}H_{25}NNaO_7S$ [M + Na]$^+$ 482.1249, found 482.1205.

General Procedure for the Synthesis of Ureidomalonates 5. Triethylamine (2.42 g, 24 mmol) was added dropwise to diethyl 2-aminomalonate hydrochloride (4.45 g, 21 mmol) in 30 mL of CH_2Cl_2 within 20 min. Then, a solution of phenyl isocyanate (2.38 g, 20 mmol) in 10 mL of CH_2Cl_2 was added dropwise to the mixture at 0 °C within 20 min. After that, the mixture was stirred at room temperature for 2.5 h. Upon completion as shown by TLC, the mixture was washed with 10% hydrochloride twice, saturated Na_2CO_3, and NaCl solution. After drying with anhydrous Na_2SO_4 the solvent was removed in vacuo. The residue was recrystallized from ethyl acetate to give pure **5a** (4.88 g, 83%).

5a: colorless solid, 83%, mp 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 6.8 Hz, 2H), 7.27 (d, J = 6.5 Hz, 2H), 7.08 (s, 1H, NH), 7.06 (t, J = 7.1 Hz, 1H), 6.17 (d, J = 7.2 Hz, 1H, NH), 5.22 (d, J = 7.2 Hz, 1H), 4.21−4.34 (m, 4H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 154.7, 138.2, 129.3, 124.0, 120.8, 62.8, 57.4, 14.1; IR (KBr) ν/cm^{-1} 3336, 2985, 2940, 1746, 1736, 1645, 1598, 1566, 1444, 1374, 1346, 1281, 1223, 1182, 1025, 734, 694, 636, 590, 517; Q-TOF-MS (+ESI) calcd for $C_{14}H_{18}N_2NaO_5$ [M + Na]$^+$ 317.1113, found 317.1127.

5b: colorless solid, 88%, mp 83−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (br, 1H, NH), 5.15 (d, J = 7.5 Hz, 1H), 5.04 (br, 1H, NH), 4.18−4.34 (m, 4H), 3.18 (q, J = 6.5 Hz, 2H), 1.43−1.52 (m, 2H), 1.26−1.40 (m, 8H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 157.0, 62.5, 57.4, 40.4, 32.2, 20.1, 14.1, 13.9; IR (KBr) ν/cm^{-1} 3335, 2957, 2935, 2873, 1747, 1736, 1633, 1581, 1371, 1343, 1282, 1225, 1179, 1162, 1117, 1105, 1024, 867, 672, 633, 601, 585; Q-TOF-MS (+ESI) calcd for $C_{12}H_{22}N_2NaO_5$ [M + Na]$^+$ 297.1426, found 297.1432.

5c: colorless solid, 85%, mp 120−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (d, J = 7.5 Hz, 1H, NH), 5.72 (t, J = 5.5 Hz, 1H, NH), 5.16 (d, J = 7.5 Hz, 1H), 4.19−4.35 (m, 4H), 3.52−3.63 (m, 4H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 156.9, 62.6, 57.4, 44.8, 42.3, 14.1; IR (KBr) ν/cm^{-1} 3360, 2984, 2950, 1748, 1731, 1629, 1581, 1372, 1348, 1282, 1226, 1180, 1118, 1025, 944, 865, 780, 731, 661, 606; Q-TOF-MS (+ESI) calcd for $C_{10}H_{17}ClN_2NaO_5$ [M + Na]$^+$ 303.0724, found 303.0741.

5d: colorless solid, 89%, mp 92−93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H, NH), 7.87 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 6.9 Hz, 1H, NH), 7.33 (d, J = 8.1 Hz, 2H), 5.04 (d, J = 6.9 Hz, 1H), 4.20−4.36 (m, 4H), 2.44 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 151.2, 145.0, 136.5, 130.0, 127.5, 63.0, 57.1, 21.8, 14.1; IR (KBr) ν/cm^{-1} 3328, 3279, 2979, 2944, 2872, 1758, 1737, 1536, 1448, 1372, 1343, 1292, 1265, 1222, 1180, 1093, 1056, 1021, 982, 891, 868, 816, 670, 604, 590, 551, 521; Q-TOF-MS (+ESI) calcd for $C_{15}H_{20}N_2NaO_7S$ [M + Na]$^+$ 395.0889, found 395.0897.

General Procedure for the One-Pot Synthesis of 1,3-Diazabicyclic[3.2.0] Compounds 8 and 9. A mixture of chalcone **2** (0.525 mmol), **5** (0.5 mmol), and Na_2CO_3 (2.7 mg, 0.025 mmol) was stirred in 3−5 mL of absolute EtOH at room temperature for 3−12 h until the disappearance of **5a**. The solvent was removed in vacuo, and the adducts obtained were directly used for the next step rof the eaction without further purification.

Synthesis of ***8***. I_2 (152.4 mg, 0.6 mmol) and 7 mL of dry THF were added. To the mixture was added dropwise a solution of DBN (148.8 mg, 1.2 mmol) in 8 mL of dry THF within 2.5 h at 0 °C. After that the mixture was stirred for another 2 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 10/1) to afford the desired products **8**.

Synthesis of ***9***. I_2 (381 mg, 1.5 mmol) and 7 mL of CH_3CN were added. To the mixture was added dropwise a solution of DBN (372 mg, 3.0 mmol) in 8 mL of CH_3CN within 2 h at 25 °C. After that the mixture was stirred at 60 °C for another 20−40 h until only a trace of **8** remained on TLC. The solvent was removed in vacuo, and the residue was purified by flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 10/1) to afford the desired products **9**.

8a: colorless solid, 113 mg, 50%, mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 7.1 Hz, 2H), 7.63 (tt, J = 7.4, 1.3 Hz, 1H), 7.38−7.52 (m, 10H), 7.11−7.14 (m, 2H), 5.70 (d, J = 4.4 Hz, 1H), 5.06 (d, J = 4.4 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 167.1, 165.6, 163.5, 134.5, 133.4, 132.9, 131.3, 129.7, 129.4, 129.3, 129.1, 129.0, 127.6, 125.6, 75.0, 68.9, 63.7, 50.3, 14.1; IR (KBr) ν/cm^{-1} 3063, 2985, 2937, 1790, 1736, 1715, 1697, 1597, 1495, 1451, 1385, 1371, 1300, 1285, 1238, 1223, 1175, 1155, 1128, 1115, 1098, 1052, 1036, 1022, 1001, 954, 852, 842, 772, 751, 730, 698, 689, 644, 637, 510, 494; Q-TOF-MS (+ESI) calcd for $C_{27}H_{22}N_2NaO_5$ [M + Na]$^+$ 477.1426, found 477.1423.

8b: colorless solid, 136 mg, 56%, mp 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.45 (t, J = 7.7 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 7.7 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 5.63 (d, J = 4.4 Hz, 1H), 4.97 (d, J = 4.4 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 167.3, 165.7, 163.5, 160.2, 134.4, 133.5, 131.4, 129.4, 129.1, 129.0, 128.8, 125.7, 124.8, 115.0, 75.2, 69.6, 63.6, 55.5, 49.9, 14.1; IR (KBr) ν/cm^{-1} 3056, 2987, 2939, 2829, 1789, 1736, 1713, 1694, 1612, 1597, 1583, 1512, 1494, 1463, 1450, 1385, 1371, 1302, 1286, 1247, 1223, 1183, 1172, 1156, 1116, 1042, 853, 844, 814, 770, 744, 699, 688, 644, 637, 553, 519; Q-TOF-MS (+ESI) calcd for $C_{28}H_{24}N_2NaO_6$ [M + Na]$^+$ 507.1532, found 507.1526.

8c: colorless solid, 112 mg, 48%, mp 136−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.2 Hz, 2H), 7.61 (tt, J = 7.4, 1.3 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 7.7 Hz, 2H), 7.41 (tt, J = 7.0, 1.6 Hz, 1H) 7.30 (d, J = 9.2 Hz, 2H), 7.26 (d, J = 9.2 Hz, 2H), 7.14−7.18 (m, 2H), 5.67 (d, J = 4.5 Hz, 1H), 4.98 (d, J = 4.4 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 167.3, 165.7, 163.5, 139.3, 134.4, 133.4, 131.4, 130.4, 129.9, 129.4, 129.1, 129.0, 127.5, 125.7, 75.1, 69.3, 63.6, 50.0, 21.3, 14.1; IR (KBr) ν/cm^{-1} 3069, 2984, 2923, 1790, 1739, 1721, 1680, 1596, 1498, 1450, 1386, 1289, 1239, 1168, 1123, 1050, 1021, 842, 784, 738, 722, 687, 654, 628, 549, 497; Q-TOF-MS (+ESI) calcd for $C_{28}H_{24}N_2NaO_5$ [M + Na]$^+$ 491.1583, found 491.1577.

8d: colorless solid, 125 mg, 51%, mp 136−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 7.3 Hz, 2H), 7.64 (tt, J = 7.4, 1.3 Hz, 1H), 7.40−7.53 (m, 7H), 7.34 (d, J = 8.5 Hz, 2H), 7.13−7.18 (m, 2H), 5.62 (d, J = 4.5 Hz, 1H), 5.07 (d, J = 4.4 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 167.0, 165.4, 163.4, 135.3, 134.5, 133.4, 131.5, 131.2, 129.9, 129.5, 129.2, 129.1, 128.9, 125.5, 74.7, 68.8, 63.7, 49.3, 14.1; IR (KBr) ν/cm^{-1} 3066, 2996, 2982, 2936, 1790, 1739, 1713, 1700, 1596, 1495, 1449, 1386, 1369, 1306, 1289, 1233, 1175, 1160, 1097, 854, 849, 767, 690, 644, 514; Q-TOF-MS (+ESI) calcd for $C_{27}H_{21}ClN_2NaO_5$ [M + Na]$^+$ 511.1037, found 511.1042.

8e: colorless solid, 100 mg, 40%, mp 158−159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8, 2H), 8.21 (d, J = 7.2 Hz, 2H), 7.66 (tt, J = 7.4, 1.3 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H), 7.38−7.50 (m, 3H), 7.13−7.17 (m, 2H), 5.67 (d, J = 4.6 Hz, 1H), 5.31 (d, J = 4.6 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 166.8, 165.2, 163.3, 148.2, 140.2, 134.7, 133.3, 131.0, 129.6, 129.4, 129.3, 129.2, 128.7, 125.4, 124.7, 74.4, 68.1, 64.0, 48.8, 14.1; IR (KBr) ν/cm^{-1} 3075, 2987, 2947, 2926, 1791, 1744, 1720, 1676, 1597, 1518, 1495, 1387, 1347, 1285, 1264, 1240, 1181, 1166, 1126, 1111, 1056, 1019, 869, 825, 752, 742, 694, 672, 737, 622, 544; Q-TOF-MS (+ESI) calcd for $C_{27}H_{21}N_3NaO_7$ [M + Na]$^+$ 522.1277, found 522.1284.

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8f: colorless solid, 75 mg, 31%, mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 2H), 7.35−7.51 (m, 8H), 7.10−7.14 (m, 2H), 6.96 (d, J = 9.0 Hz, 2H), 5.65 (d, J = 4.4 Hz, 1H), 5.07 (d, J = 4.4 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 167.2, 165.6, 164.5, 163.6, 133.1, 131.6, 131.4, 129.7, 129.4, 129.2, 129.0, 127.6, 126.5, 125.6, 114.3, 75.1, 68.7, 63.6, 55.7, 50.2, 14.1; IR (KBr) ν/cm^{-1} 3060, 2988, 2937, 2840, 1790, 1736, 1715, 1683, 1598, 1574, 1515, 1494, 1385, 1301, 1243, 1224, 1171, 1157, 1035, 847, 782, 749, 694, 602, 581, 510; Q-TOF-MS (+ESI) calcd for $C_{28}H_{24}N_2NaO_6$ $[M + Na]^+$ 507.1532, found 507.1525.

8g: colorless solid, 84 mg, 36%, mp 145−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.35−7.51 (m, 8H), 7.28 (d, J = 8.4 Hz, 2H), 7.10−7.14 (m, 2H), 5.68 (d, J = 4.4 Hz, 1H), 5.04 (d, J = 4.4 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 167.2, 165.6, 163.5, 145.5, 133.0, 131.4, 130.9, 129.8, 129.7, 129.4, 129.24, 129.21, 129.0, 127.6, 125.6, 75.0, 68.9, 63.6, 50.3, 21.9, 14.1; IR (KBr) ν/cm^{-1} 3059, 2987, 2938, 1790, 1741, 1716, 1687, 1606, 1495, 1384, 1300, 1243, 1224, 1174, 1157, 1126, 1051, 853, 749, 727, 692, 605, 511; Q-TOF-MS (+ESI) calcd for $C_{28}H_{24}N_2NaO_5$ $[M + Na]^+$ 491.1583, found 491.1575.

8h: colorless solid, 80.5 mg, 33%, mp 104−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.8, 2H), 7.36−7.51 (m, 10H), 7.10−7.14 (m, 2H), 5.62 (d, J = 4.4 Hz, 1H), 5.09 (d, J = 4.4 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 166.9, 165.5, 163.5, 141.0, 132.8, 131.8, 131.3, 130.7, 129.7, 129.5, 129.3, 129.1, 127.5, 125.6, 74.9, 68.8, 63.7, 50.0, 14.1; IR (KBr) ν/cm^{-1} 3059, 2988, 2939, 1791, 1744, 1716, 1691, 1589, 1494, 1386, 1282, 1239, 1225, 1173, 1159, 1092, 1013, 851, 771, 752, 735, 697, 690, 537, 501; Q-TOF-MS (+ESI) calcd for $C_{27}H_{21}ClN_2NaO_5$ $[M + Na]^+$ 511.1037, found 511.1042.

8k: yellow oil, 73 mg, 30%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.17 (dt, J = 7.8, 1.1 Hz, 1H), 7.88 (td, J = 7.8, 1.7 Hz, 1H), 7.46 (ddd, J = 7.7, 4.8, 1.2 Hz, 1H), 7.34−7.46 (m, 5H), 7.11−7.15 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.27 (d, J = 4.8 Hz, 1H), 4.73 (d, J = 4.8 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 167.9, 166.2, 163.4, 159.7, 150.6, 149.3, 137.3, 131.5, 129.3, 128.9, 128.7, 128.2, 125.7, 125.3, 122.9, 114.5, 75.2, 69.8, 63.5, 55.4, 50.7, 14.1; IR (KBr) ν/cm^{-1} 3061, 2982, 2936, 2839, 1790, 1728, 1612, 1516, 1496, 1384, 1254, 1228, 1182, 1161, 1125, 1034, 995, 843, 743, 691, 650, 617; Q-TOF-MS (+ESI) calcd for $C_{27}H_{23}N_3NaO_6$ $[M + Na]^+$ 508.1485, found 508.1491.

8l: yellow oil, 62 mg, 27%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.41−7.55 (m, 4H), 7.35−7.39 (m, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.49 (dd, J = 3.3, 0.6 Hz, 1H), 6.44 (dd, J = 3.2, 1.9 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.06 (d, J = 4.4 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 167.7, 165.3, 163.5, 147.0, 145.6, 143.9, 131.8, 130.9, 129.8, 129.5, 129.4, 129.0, 125.8, 111.5, 111.1, 73.9, 69.7, 63.6, 42.4, 21.9, 14.0; IR (KBr) ν/cm^{-1} 3067, 2983, 2924, 1793, 1728, 1684, 1607, 1501, 1387, 1271, 1225, 1173, 1125, 1044, 1015, 841, 778, 747, 690, 597, 504; Q-TOF-MS (+ESI) calcd for $C_{26}H_{22}N_2NaO_6$ $[M + Na]^+$ 481.1376, found 481.1368.

8m: colorless oil, 88 mg, 40%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.3 Hz, 2H)), 7.61 (tt, J = 7.4, 1.3 Hz, 1H), 7.38−7.50 (m, 5H), 7.31−7.34 (m, 2H), 5.59 (d, J = 4.7 Hz, 1H), 4.99 (d, J = 4.7 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.85 (dt, J = 14.0, 6.5 Hz, 1H), 3.79 (dt, J = 14.0, 6.2 Hz, 1H), 3.58 (dt, J = 11.3, 6.2 Hz, 1H), 3.54 (dt, J = 11.3, 6.5 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 168.2, 165.6, 163.9, 134.4, 133.4, 132.8, 129.6, 129.13, 129.08, 129.06, 127.4, 74.9, 68.4, 63.6, 49.2, 41.7, 39.4, 14.0; IR (KBr) ν/cm^{-1} 3064, 2983, 2938, 1790, 1747, 1724, 1597, 1498, 1397, 1231, 1169, 1100, 1025, 854, 756, 698, 658, 568; Q-TOF-MS (+ESI) calcd for $C_{23}H_{21}ClN_2NaO_5$ $[M + Na]^+$ 463.1037, found 463.1044.

8n: colorless oil, 89 mg, 41%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.36−7.42 (m, 3H), 7.30 (d, J = 7.3 Hz, 2H), 5.56 (d, J = 4.7 Hz, 1H), 4.98 (d, J = 4.7 Hz, 1H), 4.26−4.41 (m, 2H), 3.39−3.54 (m, 2H), 1.38−1.58 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.12−1.26 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 168.5, 166.0, 164.7, 134.4, 133.6, 133.0, 129.5, 129.2, 129.1, 129.0, 127.5, 74.8, 68.2, 63.4, 49.1, 40.2, 29.6, 19.9, 14.0, 13.6; IR (KBr) ν/cm^{-1} 3064, 2960, 2936, 2873, 1786, 1747, 1720, 1597, 1449, 1399, 1369, 1272, 1231, 1181, 1071, 1038, 947, 757, 698, 659, 639, 570; Q-TOF-MS (+ESI) calcd for $C_{25}H_{26}N_2NaO_5$ $[M + Na]^+$ 457.1739, found 457.1731.

9a: yellow solid, 104 mg, 46%, mp 153−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28−8.32 (m, 2H), 8.00−8.04 (m, 2H), 7.65 (tt, J = 7.4, 1.3 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.39−7.48 (m, 6H), 7.33−7.38 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 164.6, 163.3, 158.9, 144.5, 140.0, 135.9, 134.3, 131.9, 131.1, 130.3, 129.34, 129.32, 129.1, 128.9, 128.7, 127.9, 126.0, 75.6, 63.9, 14.1; IR (KBr) ν/cm^{-1} 3068, 2977, 2937, 1799, 1750, 1647, 1598, 1568, 1493, 1448, 1379, 1340, 1265, 1232, 1185, 1148, 1094, 1052, 962, 907, 752, 712, 690, 700, 631, 618, 595, 473; Q-TOF-MS (+ESI) calcd for $C_{27}H_{20}N_2NaO_5$ $[M + Na]^+$ 475.1270, found 475.1263.

9b: yellow solid, 80 mg, 33%, mp 189−190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27−8.31 (m, 2H), 8.08 (d, J = 9.0, 2H), 7.63 (tt, J = 7.4, 1.3 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.38−7.47 (m, 3H), 7.33−7.37 (m, 2H), 6.96 (d, J = 9.1 Hz, 2H), 4.42 (q, J = 7.0 Hz, 2H), 3.87 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 164.9, 163.5, 162.6, 159.4, 142.2, 140.7, 136.3, 134.0, 131.5, 131.1, 130.2, 129.30, 129.25, 128.5, 126.0, 120.8, 114.4, 75.6, 63.8, 55.6, 14.1; IR (KBr) ν/cm^{-1} 3069, 2962, 2930, 2838, 1798, 1752, 1736, 1643, 1599, 1583, 1505, 1386, 1261, 1230, 1183, 1151, 1093, 1047, 1024, 965, 912, 843, 750, 706, 695, 631, 591, 513; Q-TOF-MS (+ESI) calcd for $C_{28}H_{22}N_2NaO_6$ $[M + Na]^+$ 505.1376, found 505.1381.

9c: yellow solid, 98 mg, 42%, mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27−8.31 (m, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.64 (tt, J = 7.4, 1.3 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.38−7.47 (m, 3H), 7.33−7.37 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 4.34−4.48 (m, 2H), 2.40 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 164.7, 163.4, 159.1, 143.6, 142.8, 140.5, 136.1, 134.1, 131.1, 130.3, 129.7, 129.3, 129.32, 129.27, 129.2, 128.6, 126.0, 125.2, 75.6, 63.8, 22.0, 14.1; IR (KBr) ν/cm^{-1} 3058, 2978, 2928, 1798, 1737, 1637, 1598, 1584, 1504, 1381, 1341, 1269, 1230, 1181, 1152, 1092, 960, 910, 751, 702, 480; Q-TOF-MS (+ESI) calcd for $C_{28}H_{22}N_2NaO_5$ $[M + Na]^+$ 489.1426, found 489.1434.

9d: yellow solid, 109 mg, 45%, mp 172−173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28−8.32 (m, 2H), 8.00 (d, J = 8.7 Hz, 2H), 7.64 (tt, J = 7.4, 1.3 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.39−7.49 (m, 5H), 7.33−7.37 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 164.5, 163.1, 158.6, 144.7, 138.9, 138.0, 135.8, 134.4, 131.0, 130.5, 130.4, 129.39, 129.37, 129.2, 128.7, 126.3, 126.0, 75.5, 64.0, 14.1; IR (KBr) ν/cm^{-1} 3096, 2984, 2938, 1799, 1748, 1727, 1651, 1599, 1488, 1373, 1333, 1263, 1230, 1175, 1136, 1087, 1012, 962, 914, 835, 755, 725, 705, 689, 621, 503, 469; Q-TOF-MS (+ESI) calcd for $C_{27}H_{19}ClN_2NaO_5$ $[M + Na]^+$ 509.0880, found 509.0889.

9e: yellow solid, 114 mg, 46%, mp 207−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31−8.34 (m, 2H), 8.29 (d, J = 9.1 Hz, 2H), 8.18 (d, J = 9.1 Hz, 2H), 7.69 (tt, J = 7.4, 1.3 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.40−7.50 (m, 3H), 7.34−7.38 (m, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 164.2, 162.8, 157.9, 148.8, 147.4, 136.8, 135.4, 134.9, 133.3, 130.9, 130.5, 129.9, 129.6, 129.5, 128.8, 125.9, 124.0, 75.6, 64.3, 14.1; IR (KBr) ν/cm^{-1} 3110, 3057, 2991, 2933, 1801, 1761, 1737, 1644, 1597, 1583, 1520, 1492, 1384, 1346, 1336, 1263, 1229, 1184, 1168, 1151, 1092, 966, 909, 860, 853, 751, 711, 697; Q-TOF-MS (+ESI) calcd for $C_{27}H_{19}N_3NaO_7$ $[M + Na]^+$ 520.1121, found 520.1117.

9f: yellow solid, 41 mg, 17%, mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 9.0 Hz, 2H), 7.98−8.03 (m, 2H), 7.38−7.48 (m, 6H), 7.34−7.38 (m, 2H), 7.00 (d, J = 9.0 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 164.8, 164.7, 163.4, 158.9, 145.0, 139.1, 133.0, 131.5, 131.1, 129.32, 129.28, 129.0, 128.9, 128.8, 127.9, 126.0, 114.0, 75.6, 63.8, 55.7, 14.1; IR (KBr) ν/cm^{-1} 3065, 2960, 2931, 2835, 1797, 1740, 1648, 1601, 1491, 1378, 1339, 1263, 1239, 1170, 1143, 1093,

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1025, 962, 907, 829, 756, 750, 692, 611, 591, 571, 508; Q-TOF-MS (+ESI) calcd for $C_{28}H_{22}N_2NaO_6$ $[M + Na]^+$ 505.1376, found 505.1368.

9g: yellow solid, 72 mg, 31%, mp 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.3 Hz, 2H), 7.98−8.04 (m, 2H), 7.38−7.48 (m, 6H), 7.34−7.38 (m, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 164.7, 163.3, 158.9, 145.5, 144.8, 139.5, 133.4, 131.7, 131.1, 130.5, 129.4, 129.30, 129.27, 129.0, 128.9, 127.9, 126.0, 75.6, 63.8, 22.1, 14.1; IR (KBr) ν/cm^{-1} 3068, 2984, 1799, 1750, 1724, 1645, 1607, 1491, 1381, 1337, 1299, 1273, 1234, 1182, 1145, 1093, 907, 751, 743, 689, 609, 480; Q-TOF-MS (+ESI) calcd for $C_{28}H_{22}N_2NaO_5$ $[M + Na]^+$ 489.1426, found 489.1433.

9h: yellow solid, 100 mg, 41%, mp 151−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.6 Hz, 2H), 8.03−8.07 (m, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.38−7.48 (m, 6H), 7.33−7.37 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.2, 164.4, 163.2, 158.9, 144.0, 140.9, 140.7, 134.3, 132.1, 131.8, 131.0, 129.4, 129.2, 129.0, 128.9, 127.7, 125.9, 75.7, 64.0, 14.1; IR (KBr) ν/cm^{-1} 3068, 2984, 1798, 1751, 1649, 1590, 1569, 1491, 1379, 1336, 1267, 1234, 1186, 1145, 1094, 1014, 964, 908, 758, 744, 689, 619, 510, 477; Q-TOF-MS (+ESI) calcd for $C_{27}H_{19}ClN_2NaO_5$ $[M + Na]^+$ 509.0880, found 509.0876.

9i: yellow solid, 60 mg, 24%, mp 93−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 9.1 Hz, 2H), 8.36 (d, J = 9.1 Hz, 2H), 8.11−8.15 (m, 2H), 7.40−7.54 (m, 6H), 7.31−7.35 (m, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 164.1, 163.0, 159.1, 150.6, 143.2, 142.5, 140.7, 132.7, 131.3, 130.9, 129.5, 129.43, 129.42, 129.1, 127.5, 125.9, 123.7, 75.9, 64.2, 14.1; IR (KBr) ν/cm^{-1} 3067, 2985, 2938, 1797, 1735, 1663, 1603, 1526, 1495, 1375, 1345, 1265, 1229, 1142, 1093, 1049, 964, 850, 775, 748, 717, 688, 505; Q-TOF-MS (+ESI) calcd for $C_{27}H_{19}N_3NaO_7$ $[M + Na]^+$ 520.1121, found 520.1113.

9j: yellow solid, 72 mg, 29%, mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (t, J = 1.8 Hz, 1H), 8.63 (dt, J = 7.8, 1.4 Hz, 1H), 8.50 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 8.11−8.15 (m, 2H), 7.74 (t, J = 8.0 Hz, 1H), 7.38−7.55 (m, 6H), 7.32−7.37 (m, 2H), 4.38−4.53 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.3, 164.0, 162.9, 159.1, 148.2, 143.1, 142.4, 137.3, 135.7, 132.7, 130.9, 129.8, 129.5, 129.43, 129.37, 129.1, 128.2, 127.5, 125.9, 125.4, 75.9, 64.2, 14.1; IR (KBr) ν/cm^{-1} 3130, 3093, 2987, 1798, 1739, 1642, 1613, 1585, 1562, 1532, 1491, 1382, 1352, 1339, 1267, 1230, 1186, 1167, 1097, 1050, 975, 906, 848, 764, 745, 714, 689, 620; Q-TOF-MS (+ESI) calcd for $C_{27}H_{19}N_3NaO_7$ $[M + Na]^+$ 520.1121, found 520.1130.

9k: yellow solid, 61 mg, 25%, mp 211−212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (ddd, J = 4.7, 1.6, 0.9 Hz, 1H), 8.14 (dt, J = 7.8, 1.0 Hz, 1H), 7.97 (d, J = 9.1 Hz, 2H), 7.90 (td, J = 7.2, 1.7 Hz, 1H), 7.50 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.38−7.48 (m, 3H), 7.33−7.37 (m, 2H), 6.93 (d, J = 9.1, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 165.1, 163.2, 162.6, 159.5, 153.4, 149.5, 142.0, 141.1, 137.0, 131.8, 131.2, 129.3, 129.2, 127.3, 126.0, 124.7, 121.1, 114.3, 75.8, 63.8, 55.6, 14.0; IR (KBr) ν/cm^{-1} 3069, 2982, 2937, 1793, 1753, 1724, 1651, 1600, 1510, 1384, 1266, 1187, 1144, 1097, 1050, 1018, 940, 844, 746, 717, 695, 666, 630, 500; Q-TOF-MS (+ESI) calcd for $C_{27}H_{21}N_3NaO_6$ $[M + Na]^+$ 506.1328, found 506.1319.

9l: yellow solid, 57 mg, 25%, mp 171−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.3 Hz, 2H), 7.65 (dd, J = 1.8, 0.7 Hz, 1H), 7.56 (dd, J = 3.6, 0.7 Hz, 1H), 7.38−7.48 (m, 3H), 7.34−7.38 (m, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.60 (dd, J = 3.6, 1.7 Hz, 1H), 4.36−4.51 (m, 2H), 2.43 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 164.1, 162.9, 159.2, 146.8, 145.3, 144.2, 140.6, 133.1, 131.1, 130.4, 129.31, 129.30, 128.5, 126.0, 118.8, 113.2, 74.5, 63.9, 22.1, 14.1; IR (KBr) ν/cm^{-1} 3148, 3070, 2980, 2925, 1795, 1758, 1733, 1651, 1609, 1499, 1375, 1323, 1271, 1183, 1140, 1051, 961, 754, 746, 691, 590, 553, 477; Q-TOF-MS (+ESI) calcd for $C_{26}H_{20}N_2NaO_6$ $[M + Na]^+$ 479.1219, found 479.1226.

9m: yellow solid, 46 mg, 21%, mp 100−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23−8.27 (m, 2H), 7.90−7.94 (m, 2H), 7.65 (tt, J = 7.4, 1.3 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.38−7.48 (m, 3H), 4.38 (q, J = 7.1 Hz, 2H), 3.80−3.99 (m, 2H), 3.65−3.78 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 165.5, 163.1, 159.7, 144.6, 139.6, 135.8, 134.4, 131.8, 130.3, 129.0, 128.9, 128.7, 127.7, 75.7, 63.8, 41.8, 39.5, 14.0; IR (KBr) ν/cm^{-1} 3064, 2982, 2937, 1798, 1751, 1731, 1653, 1598, 1494, 1448, 1391, 1336, 1265, 1229, 1179, 1123, 959, 760, 711, 687, 595; Q-TOF-MS (+ESI) calcd for $C_{23}H_{19}ClN_2NaO_5$ $[M + Na]^+$ 461.0880, found 461.0877.

9n: colorless oil, 26 mg, 12%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25−8.30 (m, 2H), 7.92−7.96 (m, 2H), 7.65 (tt, J = 7.4, 1.3 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.38−7.46 (m, 3H), 4.37 (q, J = 7.1 Hz, 2H), 3.59 (dt, J = 13.5, 7.3 Hz, 1H), 3.47 (dt, J = 13.5, 7.0 Hz, 1H), 1.55−1.65 (m, 2H), 1.26−1.36 (m, 5H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 165.8, 163.4, 160.2, 144.6, 139.7, 135.9, 134.3, 131.7, 130.3, 129.0, 128.8, 128.7, 127.9, 75.6, 63.7, 40.4, 29.3, 19.8, 14.0, 13.6; IR (KBr) ν/cm^{-1} 3066, 2960, 2934, 2874, 1794, 1751, 1728, 1654, 1599, 1494, 1448, 1393, 1338, 1265, 1229, 1180, 1113, 1071, 955, 762, 712, 688, 596; Q-TOF-MS (+ESI) calcd for $C_{25}H_{24}N_2NaO_5$ $[M + Na]^+$ 455.1583, found 455.1591.

Ester Exchange Reaction for the Preparation of 10−12. The operation was the same as that of the one-pot reaction for the preparation of **8** and **9**, except for changing the solvent from EtOH to MeOH in the first addition step.

10: colorless solid, 212 mg, 96%, mp 202−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.42 (dd, J = 8.0, 1.7 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.28−7.33 (m, 6H), 7.21 (s, 1H, NH), 6.71−6.76 (m, 2H), 4.57 (dd, J = 8.9, 5.2 Hz, 1H), 3.88 (s, 3H), 3.78 (dd, J = 16.8, 8.9 Hz, 1H), 3.32 (dd, J = 16.8, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.1, 167.3, 166.9, 156.6, 136.5, 136.3, 133.6, 130.8, 129.4, 129.2, 128.80, 128.77, 128.5, 128.3, 126.5, 72.1, 54.3, 45.8, 39.1; IR (KBr) ν/cm^{-1} 3316, 3060, 2960, 2898, 2359, 2337, 1798, 1787, 1748, 1727, 1686, 1596, 1496, 1453, 1405, 1376, 1349, 1265, 1224, 1191, 1149, 1108, 1088, 1073, 1041, 1000, 983, 945, 839, 808, 792, 772, 705, 669, 610; Q-TOF-MS (+ESI) calcd for $C_{26}H_{22}N_2NaO_5$ $[M + Na]^+$ 465.1426, found 465.1433.

11: colorless solid, 99 mg, 45%, mp 127−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.6 Hz, 2H), 7.63 (tt, J = 7.4, 1.3 Hz, 1H), 7.35−7.52 (m, 10H), 7.10−7.1414 (m, 2H), 5.71 (d, J = 4.4 Hz, 1H), 5.06 (d, J = 4.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 167.0, 166.1, 163.4, 134.5, 133.4, 132.8, 131.3, 129.7, 129.44, 129.36, 129.13, 129.06, 127.6, 125.6, 74.9, 68.9, 54.3, 50.2; IR (KBr) ν/cm^{-1} 3064, 2960, 1791, 1743, 1722, 1594, 1494, 1449, 1385, 1290, 1234, 1166, 1118, 1050, 1019, 928, 832, 769, 721, 705, 687, 665, 640, 581, 542 485; Q-TOF-MS (+ESI) calcd for $C_{26}H_{20}N_2NaO_5$ $[M + Na]^+$ 463.1270, found 463.1264.

12: yellow solid, 101 mg, 46%, mp 196−197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.3 Hz, 2H), 7.99−8.04 (m, 2H), 7.65 (tt, J = 7.4, 1.3 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.39−7.49 (m, 6H), 7.33−7.38 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 164.5, 163.8, 158.8, 144.6, 140.0, 135.9, 134.3, 131.9, 131.0, 130.3, 129.3, 129.1, 129.0, 128.8, 128.7, 127.8, 126.0, 75.5, 54.4; IR (KBr) ν/cm^{-1} 3066, 2956, 1797, 1756, 1736, 1642, 1598, 1569, 1491, 1448, 1380, 1342, 1272, 1230, 1185, 1148, 1094, 1043, 971, 898, 784, 751, 708, 687, 630, 595, 468; Q-TOF-MS (+ESI) calcd for $C_{26}H_{18}N_2NaO_5$ $[M + Na]^+$ 461.1113, found 461.1120.

Ring-Opening Reaction of 8a with EtOH. A mixture of **8a** (45.4 mg, 0.1 mmol) and K_2CO_3 (2.8 mg, 0.02 mmol) was stirred in 2 mL of EtOH until the disappearance of **8a**. A 15 mL portion of water was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. The residue was purified on a silica gel column (petroleum ether/ethyl acetate, 10/1) to afford the desired product **13** (36 mg, 72%): white solid, mp 86−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H, NH), 7.97 (d, J = 7.3 Hz, 2H), 7.53 (tt, J = 7.4, 1.3 Hz, 1H), 7.32−7.46 (m, 9H), 7.27 (t, J = 7.5 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 6.16 (d, J = 7.9 Hz, 1H), 4.43−4.59 (m, 3H), 3.82 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 170.0, 165.9, 155.8, 138.6, 134.9, 133.9, 133.1, 129.0, 128.92, 128.89, 128.84, 128.78, 123.1, 119.4, 77.0, 63.7, 62.8, 61.4, 46.3, 14.2, 13.7; IR (KBr) ν/cm^{-1} 3328, 3064, 2972, 2938, 2869, 1750,

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1718, 1700, 1690, 1598, 1549, 1499, 1447, 1369, 1330, 1317, 1302, 1255, 1219, 1181, 1166, 1048, 1013, 849, 760, 696, 663, 632, 522, 504; Q-TOF-MS (+ESI) calcd for $C_{29}H_{28}N_2NaO_6$ $[M + Na]^+$ 523.1845, found 523.1836.

Ring-Opening Reaction of 8a with *n*-Butylamine. A mixture of **8a** (45.4 mg, 0.1 mmol) and Bu^nNH_2 (36.5 mg, 0.5 mmol) was stirred in 1 mL of dry THF for 4.5 h. The solvent was removed in vacuo, and the residue was purified on a silica gel column (petroleum ether/ethyl acetate, 6/1) to afford the desired product **14** (48 mg, 86%): white solid, mp 64−65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (br, 1H, NH), 8.42 (t, J = 5.6 Hz, 1H, NH), 7.72 (d, J = 7.8 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.47 (d, J = 7.0 Hz, 2H), 7.20−7.31 (m, 5H), 7.14 (t, J = 7.7 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 5.93 (d, J = 8.3 Hz, 1H), 4.82 (br, 1H, NH), 4.00 (d, J = 8.2 Hz, 1H), 3.21−3.46 (m, 4H), 1.48−1.66 (m, 4H), 1.30−1.44 (m, 4H), 0.95 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 171.5, 162.5, 158.9, 136.7, 134.3, 133.3, 132.7, 129.1, 128.9, 128.8, 128.7, 128.5, 124.5, 120.5, 76.1, 65.5, 50.2, 40.5, 39.6, 32.1, 31.3, 20.10, 20.06, 13.9, 13.8; IR (KBr) ν/cm^{-1} 3344, 3062, 2958, 2931, 2872, 1697, 1654, 1597, 1539, 1499, 1447, 1368, 1313, 1223, 1178, 1079, 970, 754, 692, 506; Q-TOF-MS (+ESI) calcd for $C_{33}H_{38}N_4NaO_4$ $[M + Na]^+$ 577.2791, found 577.2785.

Ring-Opening Reaction of 8a with Morpholine. A mixture of **8a** (45.4 mg, 0.1 mmol) and morpholine (43.5 mg, 0.5 mmol) was stirred in 1 mL of dry THF at room temperature for 13 h. The solvent was removed in vacuo, and the residue was purified on a silica gel column (petroleum ether/ethyl acetate, 3/1) to afford the desired product **15** (28 mg, 52%): white solid, mp 85−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (br, 1H, NH), 7.80 (d, J = 7.3 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.30−7.45 (m, 7H), 7.20 (t, J = 7.8 Hz, 2H), 7.06 (d, J = 7.4 Hz, 2H), 6.99 (t, J = 7.2 Hz, 1H), 6.00 (d, J = 6.2 Hz, 1H), 4.32−4.48 (m, 2H), 4.07 (d, J = 6.3 Hz, 1H), 3.62−3.74 (m, 4H), 3.45−3.52 (m, 2H), 3.34−3.42 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 171.4, 163.3, 158.6, 137.0, 134.6, 134.0, 133.7, 129.0, 129.02, 128.97, 128.91, 128.8, 128.7, 128.6, 124.7, 120.6, 76.0, 69.5, 66.5, 63.1, 49.9, 44.6, 14.0; IR (KBr) ν/cm^{-1} 3327, 3060, 2964, 2922, 2857, 1738, 1698, 1634, 1597, 1541, 1499, 1445, 1430, 1304, 1282, 1226, 1116, 1050, 968, 851, 756, 694, 560, 507; Q-TOF-MS (+ESI) calcd for $C_{31}H_{31}N_3NaO_6$ $[M + Na]^+$ 564.2111, found 564.2120.

Ring-Opening Reaction of 8a with n-BuSH. A mixture of **8a** (45.4 mg, 0.1 mmol), Bu^nSH (45 mg, 0.5 mmol), and K_2CO_3 (2.8 mg, 0.02 mmol) was stirred in 1 mL of dry THF at room temperature for 64 h. A 15 mL portion of water was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. Purification on a silica gel column (petroleum ether/ethyl acetate, 6/1) afforded the desired product **16** (40 mg, 74%): white solid, mp 179−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.32−7.49 (m, 7H), 7.26−7.31 (m, 3H), 6.73 (br, 1H, NH), 6.67−6.70 (m, 2H), 4.88 (d, J = 10.0 Hz, 1H), 4.60 (d, J = 10.0 Hz, 1H), 4.11−4.26 (m, 2H), 2.25 (t, J = 7.1 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.07−1.26 (m, 4H), 0.73 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 166.8, 166.0, 156.4, 135.7, 134.6, 133.2, 130.8, 130.7, 129.1, 128.8, 128.7, 128.6, 128.4, 126.5, 70.9, 63.9, 50.3, 47.8, 30.3, 29.3, 21.9, 13.8, 13.6; IR (KBr) ν/cm^{-1} 3235, 3120, 2960, 2928, 2856, 1790, 1724, 1673, 1596, 1495, 1421, 1262, 1250, 1224, 1195, 1113, 1041, 977, 881, 754, 694, 660, 573, 511; Q-TOF-MS (+ESI) calcd for $C_{31}H_{32}N_2NaO_5S$ $[M + Na]^+$ 567.1930, found 567.1937.

Cyclization of 6a with I_2/K_2CO_3 in EtOH for the Preparation of 13. A mixture of chalcone **2a** (218.4 mg, 1.05 mmol), **5a** (294 mg, 1.0 mmol), and K_2CO_3 (6.9 mg, 0.05 mmol) was stirred in 6 mL of absolute EtOH at room temperature until the disappearance of **5a**. Then K_2CO_3 (552 mg, 4 mmol) and 10 mL of EtOH were added. The mixture was cooled to 0 °C, and a solution of I_2 (508 mg, 2 mmol) in 10 mL of EtOH was added dropwise over 1 h. After that, the mixture was stirred for another 5.5 h. Most of the solvent was removed in vacuo, and 20 mL of water was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried with anhydrous Na_2SO_4. Removing the solvent and then purifying on a silica gel column gave the product **13** (175 mg, 35%).

■ ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra of the products and figures and CIF files giving the structures and crystallgraphic data for **8d**, **9h**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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