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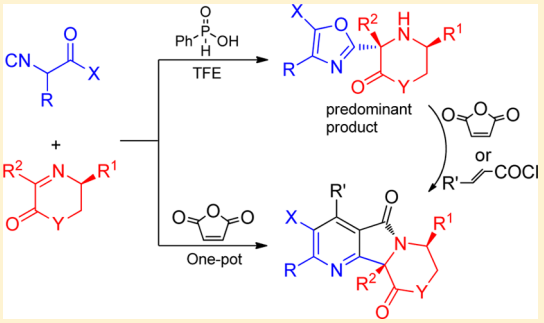
Catalytic Ugi-Type Condensation of α-Isocyanoacetamide and Chiral Cyclic Imine: Access to Asymmetric Construction of Several Heterocycles

Liang Xia,† Sheng Li,† Ruijiao Chen, Kai Liu, and Xiaochuan Chen*

Key Laboratory of Green Chemistry & Technology of the Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China

Supporting Information

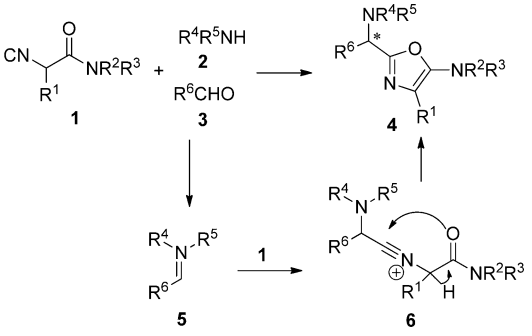
ABSTRACT: Several novel heterocycles have been constructed asymmetrically on the basis of a catalytic Ugi-type condensation of α-isocyanoacetamide and chiral cyclic imine. The combination of phenylphosphilic acid and trifluoroethanol is exploited to promote an Ugi-type reaction with α-isocyanoacetamide for the first time. By means of this reaction, chiral 3-oxazolyl morpholin-2-one/piperazin-2-one derivatives are synthesized with high yields and excellent stereoselectivities. As electron-rich azadienes, these condensation products are further transformed to fused tricyclic frameworks by treatment with appropriate dienophiles such as maleic anhydride and unsaturated acyl chlorides via domino processes. Moreover, a one-pot, three-component synthesis of the chiral tricyclic frameworks from isocyanoacetamide, imine, and maleic anhydride is also feasible.



INTRODUCTION

Polyfunctionalized heterocyclic compounds, particularly nitrogen-containing heterocycles, have assumed important roles in the structural identification of biological macromolecules and in the discovery of drugs via their special interaction with biological macromolecules or therapeutic targets.[1] With the rapid progress on biologically active macromolecule studies by means of genomics and proteomics,[2] the design and synthesis of novel heterocycle libraries is becoming more and more urgent to meet the growing demands of biological and medical research.[3] The classical four-component Ugi reaction and its variants have shown great potential in the generation of molecular complexity and diversity and have served as an efficient and versatile synthetic toolbox to quickly build a range of pharmacological compounds, including heterocycles.[4] Among them, Ugi-type reactions of α-isocyanoacetamide **1**, amine **2**, and carbonyl compound **3** open a highly efficient access to the synthesis of substituted oxazole derivatives **4**.[5] The proposed mechanism is shown in Scheme 1. The imine or iminium **5**, formed via condensation of amine **2** with carbonyl compound **3**, would react with isonitrile **1** to produce the nitrilium intermediate **6**, where the oxygen originally in the isocyanoacetamide component attacked the nitrilium moiety instead of carboxylic acid in the classical Ugi reaction, leading to cyclization. When secondary amines were employed as inputs, the yield of the reaction is usually better than for primary amines due to the higher activity of iminium.[5a,d,e] The oxazole unit is found in many bioactive natural products and pharmaceutically relevant molecules,[5a,6] and structure **4** has been applied to the design of important peptidomimetic platforms.[7] Moreover, by means of various chemical transformations involving oxazole frameworks,[8] the Ugi products containing oxazole are probably converted to more kinds of complex heterocyclic scaffolds.

Scheme 1. Representative Ugi-Type Reaction of an α-Isocyanoacetamide, an Amine, and an Aldehyde



Although one chiral center is generated in the condensation process, very little attention has been paid to the stereoselectivity of this Ugi-type condensation in previous studies. Until now, only one enantioselective version has been achieved in a chiral acid-catalyzed reaction of aldehydes, anilines, and α-isocyanoacetamides with 56−90% ee.[9] Examples employing chiral substrates in the condensation are very limited and have shown low or no diastereoselectivity.[5d,e,10] Few studies have

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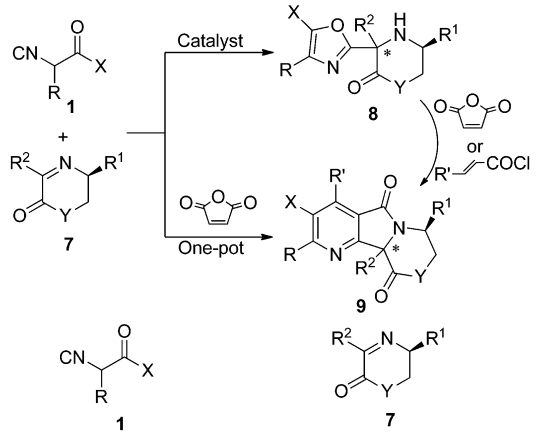
been carried out on the stereochemistry of the reactions employing chiral substrates. Therefore, although Ugi reactions as well as their combination with the appropriate postfunctionalizations have been applied widely to synthesize various heterocycles,[11] the synthesis of chiral heterocycles with high stereoselectivity has seldom been achieved by this strategy. The development of asymmetric Ugi reactions will provide some short cuts to chiral molecule libraries with potential applicability in medicine and agriculture. After all, optically pure compounds are of uttermost importance during the development of most drugs because of the possible different activities of various stereoisomers.[12] Recently we reported an asymmetric Ugi reaction of isocyanide, carboxylic acid, and chiral cyclic imine **7** in 2,2,2-trifluoroethanol (TFE).[13] As a continuation of our study on developing asymmetric Ugi reactions using imine **7**, herein we report the asymmetric syntheses of new 3-oxazolyl morpholin-2-one/piperazin-2-one species **8** by a catalytic Ugi-type reaction of **1** and **7** with excellent stereoselectivity.[14] Moreover, the post-transformation of **8** to novel fused tricyclic systems **9** by treatment with the appropriate dienophiles has been achieved (Scheme 2). Phenylphosphilic acid (**10**) is used to catalyze an Ugi-type reaction of isocyanoacetamide for the first time.

Scheme 2. Syntheses of 8 and 9 Starting from 1 and 7



1a: R = H, X = morpholinyl
1b: R = Bn, X = morpholinyl
1c: R = Ph, X = morpholinyl
1d: R = *i*Pr, X = morpholinyl
1e: R = Me, X = morpholinyl
1f: R = Ph, X = piperidinyl
1g: R = Ph, X = pyrrolidinyl
1h: R = Bn, X = piperidinyl
1i: R = Bn, X = diethylamino

7a: R^1 = Bn, R^2 = Me, Y= O
7b: R^1 = Ph, R^2 = Me, Y = O
7c: R^1 = *i*Pr, R^2 = Me, Y = O
7d: R^1 = Bn, R^2 = Et, Y = O
7e: R^1 = *i*Pr, R^2 = Et, Y = O
7f: R^1 = Bn, R^2 = Me, Y = NMe
7g: R^1 = Bn, R^2 = Me, Y = N^{n}Bu

RESULTS AND DISCUSSION

Similar to the classical Ugi reation, the favorable solvent for the Ugi-type condensation of α-isocyanoacetamide **1** with **2** and **3** is MeOH, in which the reactions usually proceed quite smoothly at heating or room temperature. Some additives, such as NH_4Cl, LiBr, $Et_3N{\cdot}HCl$, $Sc(OTf)_3$, and sulfoic acid, could promote the Ugi-type condensation in toluene, benzene, or MeOH,[5b−d,10,15] and satisfactory results are obtained. However, it is noteworthy that aldehydes, due to the minor steric hindrance around their carbonyl group, are employed rather than ketones in most cases. Furthermore, the unsubstituted α-isocyanoacetamides have rarely been investigated, despite their prospective utility, because their inherent instability and the side reactions caused by the competing nucleophilic methylene carbon lead to more complexity and uncertainty.[15b,16] Thus, in our initial experiments, unsubstituted and substituted isocyanoacetamides **1a**,**b** were chosen to react with **7a** for the screening of suitable conditions for both type of isocyanoacetamides. However, none of the existing conditions could achieve the condensation of the special substrate **7** and **1** to produce **8** with acceptable results. In the absence of additive, the reaction of **1** and **7** did not take place at all in various solvents (MeOH, toluene, CH_2Cl_2, THF, TFE) and temperatures. Under the previous conditions for similar Ugi-type reactions (NH_4Cl (**11**), $Et_3N{\cdot}HCl$ (**12**) or LiBr (**13**) as promoter, MeOH or toluene as solvent, from room to reflux temperature), our reaction ran sluggishly and gave poor yields or failed to give results.[14] Simply prolonging the reaction time resulted in serious decomposition of imines **7** and increased the tautomerization of **1**, particularly **1a**, to 2*H*-oxazole **14**. This means that the Ugi-type reactions based on **7** proceed with much more difficulty than all the precedents. **7**, imines derived from the condensation of primary amines and ketones, are probably less reactive than their iminium counterparts from secondary amines or imines from aldehydes. Therefore, a new efficient reaction system is required to promote the slow reactions of **1** and **7**.

In 2008 an Ugi reaction of aldehydes, amines, and isonitriles in toluene promoted by phenylphosphilic acid (**10**) was described.[17] However, the potential of **10** in the development of new catalytic Ugi reactions has not been further investigated and extended. To our delight, the reactions of **1** and **7** could be activated effectively by **10** after solvent screening. In the presence of 0.25 equiv of **10**, 3-oxazolylmorpholin-2-one **8a** was obtained in 52% yield at −40 °C in TFE (Table 1, entry 2). In other solvents including toluene,[17] the catalytic effect of **10** decreased dramatically (entries 3, 4, 13, and 14). As far as we know, TFE has never before been utilized as a solvent in the Ugi-type reactions of α-isocyanoacetamides. On the other hand, employment of those additives commonly used, such as $Et_3N{\cdot}HCl$ (**11**), NH_4Cl (**12**), LiBr (**13**), TsOH (**15**), $ZnCl_2$ (**16**), and $Sc(OTf)_3$ (**17**), to promote the reaction in TFE also gave inferior results (entries 6−10, 15, and 16). It is thus clear that phenylphosphilic acid and TFE are both necessary to facilitate this reaction. By further optimization of various parameters (temperature, concentration, amount of **10**, etc.), the desired products **8a**,**b** were obtained in high yields whenever unsubstituted isocyanoacetamide **1a** or substituted isocyanoacetamide **1b** was employed (entries 11 and 17). It is noteworthy that the tautomerization of **1** to **14** could not be inhibited entirely; therefore, the addition of **1** at the midway point is essential for thorough conversion of **7** and high yields of **8**.

With the optimal conditions in hand, the generality of this new catalytic Ugi-type reaction was next examined (Table 2). Gratifyingly, under the mild conditions the reactions of various **1** species and 5,6-dihydro-1,4-oxazin-2-one substrates **7a**−**e** proceeded quickly to give the desired products **8** in good to excellent yields, no matterwhether R on the oxazole is a hydrogen, alkyl, or aryl group. When the amino function (X) in **1** is morpholinyl, the reactions usually were complete in around 1 h with high yields. For some isocyanoacetamide inputs with other amino groups, the reaction process seemed somewhat slow, and more catalyst was needed to accelerate it (entries 15−19). Furthermore, 5,6-dihydropyrazin-2(1H)-ones **7f**,**g** (Y = NR) as imine inputs also react well with **1** to yield the 3-

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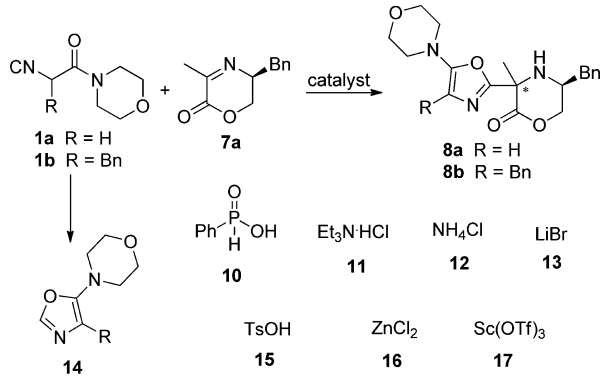
Table 1. Optimization of the Ugi-Type Reaction with 7a and 1a,b[a]



entry	R	solvent	t (h)	catalyst	x (mol %)	T (°C)	yield of **8** (%)
1	H	TFE	2	**10**	25	room temp	40 (16[d])
2	H	TFE	3	**10**	25	−40	52 (27[d])
3	H	MeOH	6	**10**	25	−30	trace (41[d])
4	H	CH_2Cl_2	11	**10**	25	room temp	10 (68[d])
5	H	TFE	1.5	**10**	10	room temp	51 (26[d])
6	H	TFE	120	**11**	150	room temp	trace (47[d])
7	H	TFE	1	**12**	100	room temp	8 (trace[d])
8	H	TFE	1	**13**	100	room temp	12
9	H	TFE	2.5	**15**	25	−40	10 (18[d])
10	H	TFE	2.5	**16**	100	room temp	6 (39[d])
11[b,c]	H	TFE	1.5	**10**	10	room temp	86
12[b,c]	Bn	TFE	3	**10**	25	−40	62 (24[d])
13[b,c]	Bn	Toluene	10	**10**	100	70	trace (69[d])
14[b,c]	Bn	MeOH	5	**10**	10	70	38 (trace[d])
15[b,c]	Bn	TFE	4	**17**	10	70	38 (trace[d])
16[b,c]	Bn	TFE	18	**12**	100	room temp	12 (57[d])
17[b,c]	Bn	TFE	1.25	**10**	10	room temp	93

[a]General conditions: **7a**/**1** = 1:/1, c = 0.2 M. [b]c = 0.4 M. [c]Additional **1** was supplemented at the midway point (0.8 equiv for **1a**, 0.4 equiv for **1b**). [d]Recovered **7a**.

oxazolylpiperazin-2-one scaffolds (entries 9−11). In this Ugi-type reaction all cyclic imines **7** showed excellent stereoinduction for the new chiral quaternary carbon, and quite a few products were obtained as single stereoisomers. In a few cases another diastereoisomer was detected in a trace amount (entries 1, 2, 4, 12, 13, and 15); nevertheless, dr values were all at least 10:1, as determined by NMR spectra or chromatography.

The diastereoselectivity in this reaction is better than that in our previous three-component Ugi reaction.[13] The NOESY ^{1}H NMR spectra of **8d,h,j** were analyzed to determine the stereochemistry of the products (Figure 1). The lack of an NOE correlation between Me-3 and H-5 signals but a correlation between Me-3 and aromatic or benzylic hydrogen illustrates the trans relationship of the C-3 oxazolyl and C-5 alkyl (R^1) group, namely an *S* configuration at C-3. It is reasonable that isocyanoacetamide **1** as nucleophile preferentially approaches imine **7** from the side opposite to the R^1 group to generate predominantlt the trans product.[13,18] The Ugi-type condensation allows access to chiral heterocycles **8** with five points of diversity derived from the isocyanoacetamide and imine inputs. Structurally, **8** also may be regarded as varied derivatives of chiral α,α-disubstitued oxazole-containing amino acids, which are of importance for the design and synthesis of various conformationally restricted and biologically active pseudopeptides, including galmic.[19]

Taking advantage of reactivity of 5-aminooxazoles as electron-rich azadienes with dienophiles,[20] several ingenious strategies for the combination of the Ugi-type reaction and Diels−Alder (D-A) cycloaddition have been devised to construct interesting and complex heterocycle scaffolds.[5d,15d,21]

However, an asymmetric tandem methodology to gain rapid access to chiral heterocycles has not been reported. Thus, the reactions of chiral oxazole **8** and several dienophiles were examined. After the conditions and dienophiles were screened, the desired cycloaddition could take place when maleic anhydride (**18**) was used. Stirring a mixture of **8d** and **18** (2 equiv) in toluene at 110 °C provided the novel tricyclic framework **9**, which incorporates a pyrrolopyridine unit with a morpholine or piperazine ring in modest yield (40%). It is envisaged that **9** is produced via sequential decarboxylation and dehydration of cycloaddition intermediate **19**. Addition of acid (AcOH) or base (DBU) to promote conversion of **19** to **9** led to deteriorative results. To our delight, 4 Å molecular sieves showed a beneficial effect on improving the yield of **9** by removal of water produced in the dehydration process (Scheme 3). Under similar conditions, several chain dienophiles, including maleic acid, diethyl maleate, fumaric acid, and diethyl fumarate, did not react with oxazole **8**, and no cycloaddition products were detected. Presumably cyclic dienophiles with inherent ring strain, such as maleic anhydride, have adequate activity and could react with the relatively inert oxazoles **8**, which are hindered by bulky substituents.

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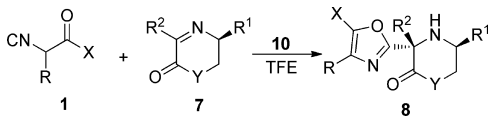
Table 2. Synthesis of 3-Oxazolyl Morpholin-2-one/Piperazin-2-one Derivatives 8a–s[a]



entry	R	R^1	R^2	Y	X	*t* (h)	**10** (*x* mol %)	product	yield (%)	dr
1	H	Bn	Me	O	morpholinyl	1	10	**8a**	86	14:1[b]
2	Bn	Bn	Me	O	morpholinyl	1	10	**8b**	93	19:1[b]
3	H	Ph	Me	O	morpholinyl	1	10	**8c**	85	single
4	*i*-Pr	Bn	Me	O	morpholinyl	1.25	10	**8d**	93	12:1[b]
5	Me	Bn	Me	O	morpholinyl	1	10	**8e**	92	single
6	Bn	Ph	Me	O	morpholinyl	1.25	10	**8f**	91	single
7	Bn	*i*-Pr	Me	O	morpholinyl	1.25	10	**8g**	87	single
8	*i*-Pr	Ph	Me	O	morpholinyl	1.25	10	**8h**	84	single
9	*i*-Pr	Bn	Me	NMe	morpholinyl	1	10	**8i**	64	single
10	*i*-Pr	Ph	Me	NMe	morpholinyl	1.25	10	**8j**	75	single
11	*i*-Pr	Bn	Me	N*n*-Bu	morpholinyl	1	10	**8k**	81	single
12	*i*-Pr	*i*-Pr	Et	O	morpholinyl	1.25	10	**8l**	88	14:1[b]
13	*i*-Pr	Bn	Et	O	morpholinyl	1.25	10	**8m**	78	10:1[b]
14	Bn	Bn	Et	O	piperidinyl	1	10	**8n**	72	single
15	Ph	Bn	Me	O	piperidinyl	4	25	**8o**	90	13:1[c]
16	Bn	Bn	Me	O	piperidinyl	4	25	**8p**	73	single
17	Bn	*i*-Pr	Me	O	piperidinyl	1.25	25	**8q**	54	single
18	Ph	Bn	Me	O	pyrrolidiny	1.5	25	**8r**	85	single
19	Bn	Bn	Me	O	diethylamino	2	50	**8s**	78	single

[a]General conditions: reactions were performed in TFE° (*c* = 0.4 M of **7**) at room temperature, 1 + 0.8 equiv of **1a** or 1 + 0.4 equiv of **1b–i**. [b]Determined by ^{1}H NMR spectra. [c]Determined by column chromatography.

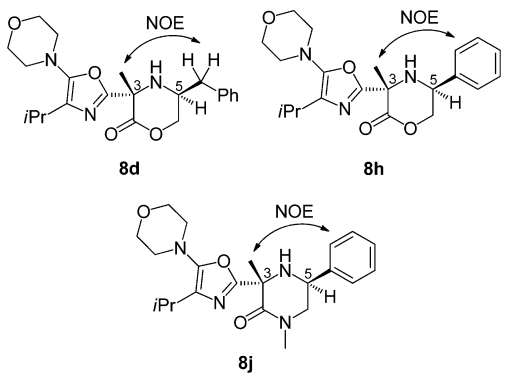
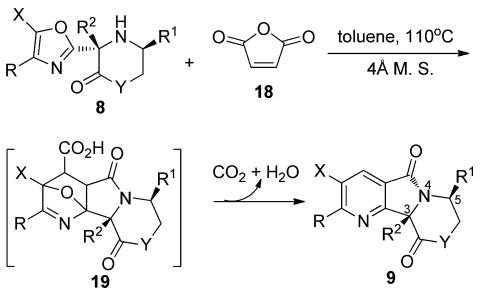


Figure 1. Configuration determination of Ugi products by NOESY analysis.

Scheme 3. Synthesis of Fused Tricyclic System 9 by the Reaction of 8 with Maleic Anhydride via a Multiple Domino Process



Next, the cycloadditions of various **8** species with **18** were performed under the optimized conditions (Table 3). Most reactions were complete within 12 h and gave satisfactory results. In comparison with other oxazoles **8**, **8a** (R = H) from unsubstituted isocyanoacetamide **1a** gave a relatively low yield (entry 1). In a few cases, the conversion of **8** proceeded a bit slowly, and a small amount of oxzaoles was recovered even when the heating time was prolonged (entries 3, 6, 7, and 11). All products **9** were obtained as single isomers, and other isomers were not detected. Analysis of the X-ray diffraction data of **9e** established the three-dimensional structure of the tricyclic systems (see the Supporting Information): planar pyrrolopyridine fused with the morpholine adopting a twist-boat conformation, where the methyl and isopropyl in a pseudoaxial orientation are on the same side of the morpholine ring as the lone pair electrons of nitrogen.[22] Absolute configurations at the three chiral centers are *S* (C-3), *R* (N-4), and *S* (C-5). The pyrrolopyridine, with a structure analogous to that of isoindolinones, nicotinamide, etc., is a potential pharmacophore and synthetic intermediate.[23] Heterocycles **9**, which incorporate pyrrolopyridine with the medically relevant morpholinone[24] or ketopiperazine[25] unit, possibly possess interesting bioactivity.

To further enrich the structural diversity of **9**, D-A cycloadditions of **8** with substituted maleic anhydrides were tried to prepare heterocycle **9** with a substituent at C-4 on the pyridine ring. Unfortunately, even the simplest substituted anhydride, **20** (R′ = Me), did not react with **8d** under the same conditions, and no product was observed (Scheme 4). The reactions of **8** with unsaturated acyl chlorides **21** were then investigated. Unsubstituted acryloyl chloride **21a** (R′ = H) instead of **18** was employed to react with **8** first. After preliminary attempts, heating a mixture of **8d** (or **8b**) and **21a** in toluene in the presence of DIPEA also furnished the same product, **9c** (or **9b**), as from **18** (Table 4, entries 1 and 2). However, in contrast with the reaction of **18**, the reactions of acyl chlorides with **8** became sluggish and complicated. The yields of **9** decreased to a great extent due to the formation of

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Table 3. Synthesis of Fused Tricyclic Frameworks 9a–n from 8 and 18[a]

entry	R	R^1	R^2	Y	X	t (h)	product	yield (%)
1	H	Bn	Me	O	morpholinyl	2.5	**9a**	47
2	Bn	Bn	Me	O	morpholinyl	8	**9b**	93
3	*i*-Pr	Bn	Me	O	morpholinyl	12	**9c**	76 (8[b])
4	Me	Bn	Me	O	morpholinyl	6	**9d**	78
5	Bn	*i*-Pr	Me	O	morpholinyl	6	**9e**	77
6	*i*-Pr	Ph	Me	O	morpholinyl	12	**9f**	84 (11[b])
7	*i*-Pr	*i*-Pr	Et	O	morpholinyl	18	**9g**	65 (22[b])
8	*i*-Pr	Bn	Et	O	morpholinyl	12	**9h**	83
9	*i*-Pr	Bn	Me	NMe	morpholinyl	12	**9i**	70
10	*i*-Pr	Bn	Me	N-*n*-Bu	morpholinyl	11	**9j**	90
11	Ph	Bn	Me	O	piperidinyl	13	**9k**	51 (24[b])
12	Bn	Bn	Me	O	piperidinyl	5	**9l**	65
13	Ph	Bn	Me	O	pyrrolidiny	5	**9m**	63
14	Bn	Bn	Me	O	diethylamino	5	**9n**	72

[a]General conditions: unless otherwise noted, all reactions were carried out with **8** (1 equiv), maleic anhydride (2 equiv), and molecular sieves (4 Å, powder, 50 mg) in toluene° (c = 0.04 M) at 110 °C. [b]Recovered **8**.

Scheme 4. Attempt To React 8d with Substituted Maleic Anhydride 20

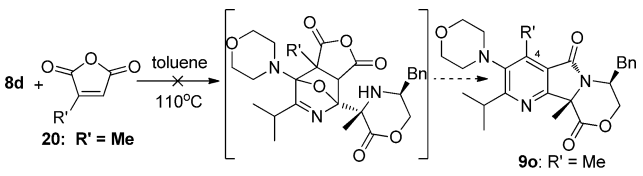
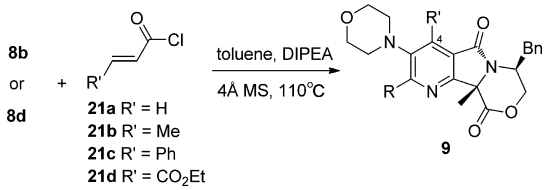


Table 4. Synthesis of Fused Tricyclic System 9 by the Reaction of 8 with Unsaturated Acyl Chlorides 21[a]



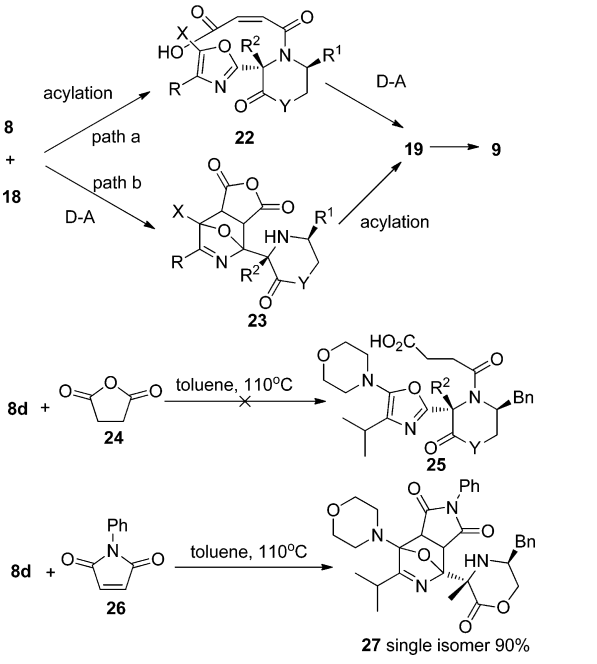
entry	R	R′	t (h)	product	yield (%)
1	Bn	H	2.5	**9b**	27
2	*i*-Pr	H	8	**9c**	32
3	*i*-Pr	Me	36	**9o**	31 (38[b])
4	*i*-Pr	Ph	20	**9p**	60
5	*i*-Pr	CO_2Et	20	**9q**	33

[a]General conditions: unless otherwise noted, all reactions were carried out with **8b**/**8d** (1 equiv), DIPEA (5 equiv), unsaturated acyl chlorides **21** (2.5 equiv), and molecular sieves (4 Å, powder, 50 mg) in toluene° (c = 0.04 M) at 110 °C. [b]Recovered **8**.

some indeterminable species. Under similar conditions, several substituted acryloyl chlorides **21b–d** could also react with **8** to produce new heterocycles **9o–q** with z fully substituted pyridine ring. The R′ group in **21** appears to have some effect on the yield of **9**, and cinnamoyl chloride (**21c**) gave better results than other acyl chlorides in the domino transformation (entry 4). The employment of the unsaturated acyl chlorides **21** instead of **18** allows us to introduce more variable points on **9**. However, for our oxazoles **8**, **18** has a great advantage over the unsaturated acyl chloride **21a** in the syntheses of heterocycles without a substituent at C-4, such as **9a–n** (R′ = H).

The formation of **9** from **8** and **18** is proposed to occur via the bridged tetracyclic intermediate **19**, which is produced by a domino process involving D-A addition and acylation in two possible sequences (path a or b, Scheme 5). Any intermediate

Scheme 5. Bridged Tetracyclic Intermediate 19 Produced by a D-A Addition/Acylation Process in Two Possible Sequences



such as **19**, **22**, or **23** in the course of the reaction could not be separated. Therefore, the exact reaction sequence is not clear. In previous reports on the reactions of 5-aminooxazoles and exotic dienophiles, such as unsaturated acyl chlorides or pentafluorophenyl esters, the sequence of acylation prior to the intramolecular D-A reaction is accepted (path a).[5d,e,21b,26] However, we found that the acylation of **8** is quite difficult, and the acylated product was not observed by heating a toluene solution of **8d** and succinic anhydride (**24**) or acetyl chloride. However, under similar conditions the intermolecular D-A reaction of **8d** and *N*-phenylmaleimide (**26**) occurred readily to

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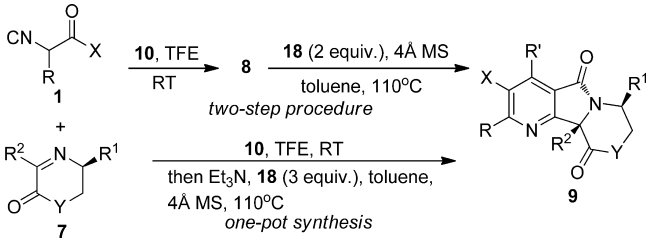
give the resulting oxa-bridged heterocycle **27** with excellent yield (92%) and stereoselectivity (single diastereoisomer). It seems as if **8** reacts with **18** in a reverse sequence (D-A reaction/acylation, path b).

One-pot protocols combining two or more reaction steps show higher efficiency because of simpler operation, lower costs, and shorter time.[27] Therefore, a one-pot, three-component synthesis of **9** from **1**, **7**, and **18** was then investigated by combining Ugi-type condensation and cycloaddition. In primary tests, TFE and toluene, as ideal solvents in the respective steps, do not fit for the other step. Therefore, when the one-pot operation was performed throughout in a single solvent including toluene and TFE, the desirable **9** was produced in low yield (<20%) or was not produced at all. We noticed that the D-A addition could work well even at a low concentrations. Thus, a one-pot synthesis of **9** from **1** and **7** was devised. A solution of **1** and **7** in TFE at high concentration (0.4 M for **7**) was stirred at room temperature. Once **7** was consumed completely, 1 equiv of Et_3N with respect to **10** was added to neutralize the acid. The resulting mixture was diluted with a large amount of toluene, and then **18** and molecular sieves were added. Refluxing the reaction mixture gave **9** in satisfactory yield. A small quantity of TFE in the mixture did not have an obviously negative effect on the reaction. Just the amount of **18** needs to be properly increased (3 equiv), because 2*H*-oxazoles **14** isomerized from **1** itself would partially consume **18** by possibly a similar cycloaddition. Moreover, the addition of Et_3N after completion of the Ugi reaction could reduce the harm of **10** to a subsequent cycloaddition step and favor the final yield of **9**. Particularly for those cases in which more **10** (0.25 equiv) was used, addition of Et_3N was essential and promoted the yield drastically. Under the optimized conditions, the one-pot yields are nearly equal to or slightly higher than the two-step method (Table 5), indicating higher efficiency in the synthesis of complex heterocycles **9** with five points of diversity.

CONCLUSION

Herein we have reported a new asymmetric Ugi-type reaction of α-isocyanoacetamides **1** and chiral imines **7** catalyzed by phenylphosphilic acid leading to 3-oxazolyl morpholin-2-one or piperazin-2-one derivatives **8**, in which excellent stereoselectivity of the new chiral center was achieved. The combination of phenylphosphilic acid and TFE efficiently promoted the condensation of **7** with **1** and showed potential to exploit more Ugi reactions. Whereas, under the previous conditions for Ugi reactions of α-isocyanoacetamides, imines **7**, as relatively inert substrates, react with **1** very sluggishly. The subsequent reaction of aminooxazoles **8** with maleic anhydride led to the novel fused heterocycles **9** in good yield via a multiple domino sequence involving cycloaddition. acylation, decarboxylation, and dehydration. The absolute stereochemistry of **9** was determined. The reactions of the unsaturated acyl chlorides **21** with **8** were also carried out to produce **9** with more substituents. Furthermore, a one-pot, three-component synthesis of **9** from **1**, **7**, and **18** was performed via combination of an Ugi-type condensation and cycloaddition. This methodology opens a shortcut to various interesting chiral hereocycles with potential activity such as **8** and **9**, which are not easily synthesized by other approaches.

Table 5. Comparison of Yield of 9 from 1 and 7 by One-Pot Synthesis with the Two-Step Procedure



		yield (%)	
entry	product	one-pot synthesis	two-step procedure
1	**9c**	68 (9[a])	70 (8[a])
2	**9d**	71	71
3	**9e**	70	67
4	**9k**	47 (26[a])	42 (24[a])
5	**9l**	55	47
6	**9m**	56	53

[a]Recovered **8**.

EXPERIMENTAL SECTION

General Considerations. IR spectra were recorded on a commercial spectrophotometer. Optical rotations were reported as follows: $[\alpha]_D^{T\circ}$ (*c* in units of g/100 mL, in solvent). ^1H and ^{13}C NMR were recorded on were recorded on commercial instruments (400 or 600 MHz) with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^1H NMR, 7.26 ppm; ^{13}C NMR, 77.16 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) are reported in hertz (Hz). HRMS spectra were recorded using a commercial apparatus, and methanol or dichloromethane was used to dissolve the sample. Solvents for reaction were distilled prior to use: toluene from CaH_2, methanol from magnesium turnings. Trifluoroethanol (TFE), phenylphosphilic acid, and other reagents were obtained from commercial suppliers unless otherwise stated. Molecular sieves (4 Å) was powdered <50 μm, was activated at 120 °C for 5 h, and was stored under nitrogen.

General Procedure for the Synthesis of 8 by the Ugi-Type Condensation of α-Isocyanoacetamides 1 and Cyclic Imines 7. To a solution of imine **7** (0.20 mmol) in TFE (0.5 mL) were added successively α-isocyanoacetamides **1** (0.20 mmol) and phenylphosphilic acid (**10**; 0.020 mmol generally, 0.050 mmol for **1f–h**, 0.10 mmol for **1i**) at room temperature. After the mixture was stirred at room temperature for 20 min, additional **1** (0.16 mmol for **1a**, 0.080 mmol for **1b–i**) was added. The resulting mixture was stirred for 1–4 h, quenched with 0.1% aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to afford the desired product **8**.

*(3S,5S)-5-Benzyl-3-methyl-3-(5-morpholinooxazol-2-yl)-morpholin-2-one (**8a**).* After the mixture was stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (5/1 to 3/2) as eluent: yield 63 mg, 86%; yellow gel; $[\alpha]_D^{20} = -51^\circ$ (*c* 0.9, CH_2Cl_2); IR (neat) 3311, 2968, 2856, 1744, 1609, 1452, 1240, 1117, 898, 752, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.12–7.36 (m, 5H), 5.97 (s, 1H), 4.31 (dd, *J* = 3.2, 10.5 Hz, 1H), 4.18 (t, *J* = 10.3 Hz, 1H), 3.72–3.85 (m, 4H), 3.48–3.58 (m, 1H), 2.93–3.02 (m, 4H), 2.75 (dd, *J* = 5.4, 13.6 Hz, 1H), 2.62 (dd, *J* = 8.4, 13.5 Hz, 1H), 2.51 (br s, 1H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.7, 157.5, 155.5, 136.3, 129.0, 128.8, 127.0, 102.8, 74.3, 66.0, 60.6, 49.5, 48.1, 37.8, 26.1; HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{23}N_3O_4Na$ $[M + Na]^+$ 380.1586, found 380.1589.

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*(3S,5S)-5-Benzyl-3-(4-benzyl-5-morpholinooxazol-2-yl)-3-methylmorpholin-2-one (**8b**).* After the mixture was stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (5:1 to 3:1) as eluent: yield 84 mg, 93%; Colorless gel; $[\alpha]_D^{20}$ = = −12°° (*c* 1.5, CH_2Cl_2); IR (neat) 3314, 2960, 2915, 2854, 1744, 1453, 1233, 1116, 755, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.05−7.34 (m, 10H), 4.30 (dd, *J* = 3.4, 10.5 Hz, 1H), 4.18 (t, *J* = 10.4 Hz, 1H), 3.80 (d, *J* = 15.4 Hz, 1H), 3.75 (d, *J* = 15.7 Hz, 1H), 3.64−3.70 (m, 4H), 3.52−3.61 (m, 1H), 2.81−2.89 (m, 4H), 2.73 (dd, *J* = 5.2, 13.7 Hz, 1H), 2.55 (dd, *J* = 8.7, 13.7 Hz, 1H), 2.27 (br s, 1H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 157.5, 152.3, 139.5, 136.3, 128.9, 128.8, 128.5, 128.4, 127.0, 126.3, 124.8, 74.4, 66.8, 60.9, 50.8, 49.5, 37.6, 31.8, 26.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{30}N_3O_4$ $[M + H]^+$ 448.2236, found 448.2229.

*(3S,5S)-3-Methyl-3-(5-morpholinooxazol-2-yl)-5-phenylmorpholin-2-one (**8c**).* After the mixture was stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (5/1 to 3/2) as eluent: yield 58 mg, 85%; yellow gel; $[\alpha]_D^{20}$ = −36° (*c* 0.14, CH_2Cl_2); IR (neat) 3422, 2923, 1743, 1609, 1454, 1222, 1153, 1115, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34−7.43 (m, 5H), 6.03 (s, 1H), 4.46−4.52 (m, 1H), 4.31−4.38 (m, 2H), 3.79−3.83 (m, 4H), 3.07−3.12 (m, 4H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 157.8, 155.8, 137.6, 129.0, 128.9, 127.4, 103.0, 74.5, 66.0, 61.0, 53.7, 48.3, 26.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{22}N_3O_4$ $[M + H]^+$ 344.1610, found 344.1614.

*(3S,5S)-5-Benzyl-3-(4-isopropyl-5-morpholinooxazol-2-yl)-3-methylmorpholin-2-one (**8d**).* After the mixture was stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (4/1 to 2/1) as eluent: yield 75 mg, 93%; yellow gel; $[\alpha]_D^{20}$ = −22° (*c* 2, CH_2Cl_2); IR (neat) 3314, 2964, 2855, 1747, 1656, 1452, 1200, 1115, 918, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.15−7.36 (m, 5H), 4.30−4.36 (m, 1H), 4.23 (t, *J* = 10.7 Hz, 1H), 3.71−3.77 (m, 4H), 3.62−3.71 (m, 1H), 2.88−2.94 (m, 4H), 2.75−2.87 (m, 2H), 2.51−2.61 (m, 1H), 2.34 (br s, 1H), 1.78 (s, 3H), 1.17 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 157.6, 150.4, 136.3, 132.3, 128.9, 128.8, 127.0, 74.4, 66.9, 60.8, 51.3, 49.3, 37.6, 26.3, 25.3, 21.9, 21.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{29}N_3O_4Na$ $[M + Na]^+$ 422.2056, found 422.2057.

*(3S,5S)-5-Benzyl-3-methyl-3-(4-methyl-5-morpholinooxazol-2-yl)morpholin-2-one (**8e**).* After the mixture was stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (2/1 to 1/2) as eluent: yield 68 mg, 92%; colorless gel; $[\alpha]_D^{20}$ −31° (*c* 0.7, CH_2Cl_2); IR (neat) 3312, 2922, 2854, 1744, 1213, 1116, 753, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22−7.33 (m, 5H), 4.33 (dd, *J* = 3.5, 10.5 Hz, 1H), 4.19 (t, *J* = 10.4 Hz, 1H), 3.72−3.78 (m, 4H), 3.46−3.55 (m, 1H), 2.88−2.93 (m, 4H), 2.76 (dd, *J* = 5.1, 13.7 Hz, 1H), 2.59 (dd, *J* = 8.7, 13.7 Hz, 1H), 2.06 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 157.1, 151.7, 136.3, 128.9, 128.8, 127.0, 121.3, 74.3, 66.8, 60.8, 50.7, 49.6, 37.7, 25.9, 11.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{25}N_3O_4Na$ $[M + Na]^+$ 394.1743, found 394.1749.

*(3S,5S)-3-(4-Benzyl-5-morpholinooxazol-2-yl)-3-methyl-5-phenylmorpholin-2-one (**8f**).* After the mixture was stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (2/1 to 1/2) as eluent: yield 79 mg, 91%; colorless gel; $[\alpha]_D^{20}$ = −31° (*c* 1.2, CH_2Cl_2); IR (neat) 3292, 3060, 3030, 2963, 2915, 2856, 1744, 1633, 1546, 1495, 1454, 1400, 1330, 1266, 1121, 1153, 1116, 1028, 921, 734, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.38 (m, 5H), 7.20−7.31 (m, 5H), 4.46 (t, *J* = 7.2 Hz, 1H), 4.35−4.37 (m, 2H), 3.82 (s, 2H), 3.70−3.73 (m, 4H), 2.98−3.10 (m, 4H), 2.59 (br s, 1H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 157.8, 152.4, 139.4, 137.5, 128.9, 128.8, 128.5, 128.4, 127.4, 126.2, 124.8, 75.2, 66.8, 61.1, 53.7, 50.8, 31.8, 26.5; HRMS (ESI-TOF): *m*/*z* calculated for $C_{25}H_{28}N_3O_4$ $[M + H]^+$ 434.2080, found 434.2075.

*(3S,5S)-3-(4-Benzyl-5-morpholinooxazol-2-yl)-5-isopropyl-3-methylmorpholin-2-one (**8g**).* After the mixture was stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 2/3) as eluent: yield 70 mg, 87%; yellow gel; $[\alpha]_D^{20}$ = −23° (*c* 4.1, CH_2Cl_2); IR (neat) 3314, 2960, 2854, 1744, 1233, 1116, 755, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.16−7.31 (m, 5H), 4.34 (dd, *J* = 3.4, 10.4 Hz, 1H), 4.18 (t, *J* = 10.4 Hz, 1H), 3.81 (s, 2H), 3.65−3.74 (m, 4H), 2.94−3.01 (m, 4H), 2.86−2.94 (m, 1H), 2.34 (br s, 1H), 1.76 (s, 3H), 1.57−1.67 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.1, 158.1, 152.3, 139.4, 128.5, 128.4, 126.2, 124.9, 73.4, 66.8, 60.8, 54.2, 50.9, 31.8, 29.8, 26.4, 18.7, 18.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{29}N_3O_4Na$ $[M + Na]^+$ 422.2056, found 422.2062.

*(3S,5S)-3-(4-Isopropyl-5-morpholinooxazol-2-yl)-3-methyl-5-phenylmorpholin-2-one (**8h**).* After the mixture was stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether/acetone (12/1 to 8/1) as eluent: yield 65 mg, 84%; yellow gel; $[\alpha]_D^{20}$ = −45° (*c* 0.1, CH_2Cl_2); IR (neat) 3353, 2935, 2854, 1741, 1631, 1448, 1198, 754, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31−7.45 (m, 5H), 4.54 (dd, *J* = 6.0, 8.4 Hz, 1H), 4.38 (s, 1H), 4.35−4.39 (m, 2H), 3.74−3.82 (m, 4H), 2.98−3.06 (m, 4H), 2.82−2.93 (m, 1H), 1.85 (s, 3H), 1.22 (d, *J* = 5.4 Hz, 3H), 1.20 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.7, 157.7, 150.5, 137.7, 132.5, 128.9, 128.7, 127.4, 75.2, 66.9, 61.1, 53.7, 51.4, 26.5, 25.5, 21.9; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{28}N_3O_4$ $[M + H]^+$ 386.2080, found 386.2072.

*(3S,5S)-5-Benzyl-3-(4-isopropyl-5-morpholinooxazol-2-yl)-1,3-dimethylpiperazin-2-one (**8i**).* After the mixture was stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (2/3 to 1/3) as eluent: yield 55 mg, 64%; colorless gel; $[\alpha]_D^{20}$ = −1° (*c* 0.7, CH_2Cl_2); IR (neat) 3299, 2964, 2856, 1656, 1499, 1452, 1200, 1115, 754, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.12−7.32 (m, 5H), 3.55−3.64 (m, 1H), 3.28 (t, *J* = 11.1 Hz, 1H), 3.15 (dd, *J* = 3.7, 11.3 Hz, 1H), 3.00 (s, 3H), 2.86−2.91 (m, 4H), 2.77−2.86 (m, 2H), 2.63 (dd, *J* = 8.8, 13.7 Hz, 1H), 2.20 (br s, 1H), 1.66 (s, 3H), 1.14−1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 159.4, 149.8, 137.1, 132.2, 128.9, 128.7, 126.8, 66.9, 60.7, 55.5, 51.4, 49.3, 39.6, 35.2, 26.0, 25.5, 22.0, 21.9; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{32}N_4O_3Na$ $[M + Na]^+$ 435.2372, found 435.2368.

*(3S,5S)-3-(4-Isopropyl-5-morpholinooxazol-2-yl)-1,3-dimethyl-5-phenylpiperazin-2-one (**8j**).* After the mixture was stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (2/3 to 1/3) as eluent: yield 61 mg, 75%; colorless gel; $[\alpha]_D^{20}$ = +26° (*c* 1.11, CH_2Cl_2); IR (neat) 3291, 2962, 2856, 1727, 1660, 1545, 1497, 1452, 1400, 1267, 1200, 1115, 920, 841, 758, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30−7.44 (m, 5H), 4.47 (dd, *J* = 3.8, 11.1 Hz, 1H), 3.76−3.78 (m, 4H), 3.52 (t, *J* = 11.3 Hz, 1H), 3.27 (dd, *J* = 3.8, 11.6 Hz, 1H), 3.03 (s, 3H), 3.00−3.02 (m, 4H), 2.82−2.92 (m, 1H), 2.40 (s, 1H), 1.77 (s, 3H), 1.21 (d, *J* = 4.4 Hz, 3H), 1.20 (d, *J* = 4.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 159.7, 150.0, 140.2, 132.5, 128.9, 128.4, 127.3, 67.1, 61.2, 57.0, 53.7, 51.6, 35.3, 26.4, 25.7, 22.1, 22.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{31}N_4O_3$ $[M + H]^+$ 399.2396, found 399.2399.

*(3S,5S)-5-Benzyl-1-butyl-3-(4-isopropyl-5-morpholinooxazol-2-yl)-3-methylpiperazin-2-one (**8k**).* After the mixture was stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (2/1 to 1/1) as eluent: yield 75 mg, 81%; yellow gel; $[\alpha]_D^{20}$ = +2° (*c* 3.3, CH_2Cl_2); IR (neat) 3300, 2962, 2859, 1656, 1452, 1115, 735, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.12−7.30 (m, 5H), 3.73−3.75 (m, 4H), 7.44−7.55 (m, 2H), 3.32−3.39 (m, 1H), 3.26 (dd, *J* = 11.1, 21.9 Hz, 1H), 3.16 (dd, *J* = 3.8, 11.2 Hz, 1H), 2.87−2.89 (m, 4H), 2.78−2.85 (m, 2H), 2.61 (dd, *J* = 9.0, 13.8 Hz, 1H), 2.16 (br s, 1H), 1.66 (s, 3H), 1.54−1.60 (m, 2H), 1.35−1.40 (m, 2H), 1.17 (d, *J* = 2.1 Hz, 3H), 1.15 (d, *J* = 2.1 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.3, 156.0, 150.0, 137.1, 132.2, 128.8, 128.7, 126.8, 67.0, 60.7, 53.2, 51.5, 49.4, 47.1, 39.6, 29.0, 25.7, 25.4, 22.0, 21.9, 20.0, 13.9; HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{39}N_4O_3$ $[M + H]^+$ 455.3022, found 455.3024.

*(3S,5S)-3-Ethyl-5-isopropyl-3-(4-isopropyl-5-morpholinooxazol-2-yl)morpholin-2-one (**8l**).* After the mixture was stirred for 1.25 h,

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the product was isolated by flash column chromatography using petroleum ether/acetone (20/1 to 10/1) as eluent: yield 66 mg, 88%; colorless gel; $[\alpha]_D^{20} = -9°$ (c 0.5, CH_2Cl_2); IR (neat) 3334, 2964, 1747, 1656, 1459, 1201, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.30 (dd, J = 3.0, 10.2 Hz, 1H), 4.17 (t, J = 10.4 Hz, 1H), 3.73−3.81 (m, 4H), 2.98−3.05 (m, 5H), 2.80−2.92 (m, 1H), 2.40 (br s, 1H), 2.16−2.30 (m, 1H), 1.97 (dq, J = 7.6, 21.4 Hz, 1H), 1.69 (dq, J = 7.0, 20.6 Hz, 1H), 1.19 (d, J = 1.2 Hz, 3H), 1.18 (d, J = 1.2 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H), 0.93−1.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 157.6, 150.7, 132.1, 73.3, 66.9, 64.9, 54.3, 51.4, 33.2, 29.7, 25.3, 22.0, 21.9, 18.7, 18.6, 8.2; HRMS (ESI-TOF) m/z calcd for $C_{19}H_{31}N_3O_4Na$ $[M + Na]^+$ 388.2212, found 388.2219.

*(3S,5S)-5-Benzyl-3-ethyl-3-(4-isopropyl-5-morpholinooxazol-2-yl)morpholin-2-one (**8m**).* After the mixture was stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether/ethyl ether (2/1 to 1/1) as eluent: yield 85 mg, 98%; colorless gel; $[\alpha]_D^{20} = -21°$ (c 1.6, CH_2Cl_2); IR (neat) 3316, 2965, 2854, 1745, 1654, 1456, 1199, 1116, 977, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.13−7.54 (m, 5H), 4.28 (dd, J = 3.2, 10.3 Hz, 1H), 4.16 (t, J = 10.3 Hz, 1H), 3.67−3.83 (m, 5H), 2.89−2.95 (m, 4H), 2.76−2.87 (m, 2H), 2.61 (dd, J = 8.9, 13.8 Hz, 1H), 2.30 (br s, 1H), 2.24 (dq, J = 7.4, 21.3 Hz, 1H), 1.92 (dq, J = 7.4, 21.3 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 157.3, 150.6, 136.5, 132.1, 129.0, 128.8, 126.9, 74.3, 66.9, 64.9, 51.3, 49.4, 37.7, 32.8, 25.3, 21.9, 21.8, 8.2; HRMS (ESI-TOF) m/z calcd for $C_{23}H_{32}N_3O_4$ $[M + H]^+$ 414.2393, found 414.2387.

*(3S,5S)-5-Benzyl-3-(4-benzyl-5-(piperidin-1-yl)oxazol-2-yl)-3-ethylmorpholin-2-one (**8n**).* After the mixture was stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether/ethyl ether (2/1 to 1/1) as eluent: yield 66 mg, 72%; colorless gel; $[\alpha]_D^{20} = -9°$ (c 0.95, CH_2Cl_2); IR (neat) 3317, 2936, 2855, 1745, 1637, 1495, 1451, 1156, 730, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25−7.32 (m, 3H), 7.17−7.24 (m, 5H), 7.09−7.15 (m, 2H), 4.22 (dd, J = 3.3, 10.3 Hz, 1H), 4.13 (t, J = 10.3 Hz, 1H), 3.78 (d, J = 15.6 Hz, 1H), 3.73 (d, J = 15.5 Hz, 1H), 3.59−3.66 (m, 1H), 2.84−2.86 (m, 4H), 2.73 (dd, J = 5.7, 13.7 Hz, 1H), 2.62 (dd, J = 8.2, 13.7 Hz, 1H), 2.18−2.27 (m, 2H), 1.90−1.99 (m, 1H), 1.64 (s, 1H), 1.56−1.60 (m, 4H), 1.50−1.52 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 156.7, 154.0, 139.9, 136.4, 129.0, 128.7, 128.5, 128.3, 126.9, 126.0, 123.5, 74.2, 64.9, 51.9, 49.5, 37.9, 32.7, 31.8, 25.8, 23.8, 8.2; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{34}N_3O_3$ $[M + H]^+$ 460.2600, found 460.2604.

*(3S,5S)-5-Benzyl-3-methyl-3-(4-phenyl-5-(piperidin-1-yl)oxazol-2-yl)morpholin-2-one (**8o**) (Major Isomer).* After the mixture was stirred for 4 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (4/1 to 3/1) as eluent: yield 73 mg, 84%; colorless gel; $[\alpha]_D^{20} = -12°$ (c 0.6, CH_2Cl_2); IR (neat) 3315, 2938, 2851, 1744, 1629, 1448, 1235, 1197, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80−7.86 (m, 2H), 7.20−7.42 (m, 8H), 4.35 (dd, J = 3.5, 10.4 Hz, 1H), 4.22 (t, J = 10.4 Hz, 1H), 3.67−3.78 (m, 1H), 2.92−3.00 (m, 4H), 2.81 (dd, J = 4.6, 13.7 Hz, 1H), 2.58 (dd, J = 9.2, 13.7 Hz, 1H), 2.51 (br s, 1H), 1.75 (s, 3H), 1.54−1.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 156.8, 153.1, 136.4, 132.0, 129.1, 128.9, 128.3, 127.0, 126.7, 125.8, 122.6, 74.5, 60.9, 51.2, 49.6, 37.7, 26.6, 25.8, 23.8; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{30}N_3O_3$ $[M + H]^+$ 432.2287, found 432.2290.

*(3R,5S)-5-Benzyl-3-methyl-3-(4-phenyl-5-(piperidin-1-yl)oxazol-2-yl)morpholin-2-one (**8o′**) (Minor Isomer).* After the mixture was stirred for 4 h, the product was isolated by flash column chromatography using dichloromethane as eluent: yield 5.6 mg, 6.5%; colorless gel; $[\alpha]_D^{20} = -73°$ (c 0.4, CH_2Cl_2); IR (neat) 3305, 2938, 2852, 1743, 1631, 1448, 1221, 755, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77−8.00 (m, 2H), 7.19−7.42 (m, 8H), 4.28−4.34 (m, 2H), 3.51−3.67 (m, 1H), 3.00−3.13 (m, 4H), 2.88 (dd, J = 6.9, 13.6 Hz, 1H), 2.88 (dd, J = 6.7, 13.6 Hz, 1H), 2.42 (br s, 1H), 1.82 (s, 3H), 1.55−1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.1, 156.6, 153.2, 136.7, 132.0, 129.1, 128.9, 128.3, 127.0, 126.7, 125.9, 122.6, 73.4, 59.7, 51.2, 50.5, 38.5, 25.9, 25.0, 23.9; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{30}N_3O_3$ $[M + H]^+$ 432.2287, found 432.2279.

*(3S,5S)-5-Benzyl-3-(4-benzyl-5-(piperidin-1-yl)oxazol-2-yl)-3-methylmorpholin-2-one (**8p**).* After the mixture was stirred for 4 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (6/1 to 3/2) as eluent: yield 66 mg, 73%; colorless gel; $[\alpha]_D^{20} = -7°$ (c 0.6, CH_2Cl_2); IR (neat) 3313, 2937, 2852, 1746, 1451, 1232, 1156, 1119, 728, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.05−7.35 (m, 10H), 4.28 (dd, J = 3.5, 10.4 Hz, 1H), 4.17 (t, J = 10.4 Hz, 1H), 3.79 (d, J = 15.6 Hz, 1H), 3.73 (d, J = 15.6 Hz, 1H), 3.52−3.61 (m, 1H), 2.80−2.88 (m, 4H), 2.73 (dd, J = 5.4, 13.7 Hz, 1H), 2.56 (dd, J = 8.6, 13.7 Hz, 1H), 2.29 (br s, 1H), 1.72 (s, 3H), 1.46−1.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 156.9, 153.8, 139.8, 136.3, 128.9, 128.8, 128.5, 128.3, 126.9, 126.1, 123.6, 74.3, 60.8, 51.9, 49.4, 37.7, 31.8, 26.1, 25.8, 23.8; HRMS (ESI-TOF) m/z calcd for $C_{27}H_{31}N_3O_3Na$ $[M + Na]^+$ 468.2263, found 468.2268.

*(3S,5S)-3-(4-Benzyl-5-(piperidin-1-yl)oxazol-2-yl)-5-isopropyl-3-methylmorpholin-2-one (**8q**).* After the mixture was stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (6/1 to 3/2) as eluent: yield 43 mg, 54%; colorless gel; $[\alpha]_D^{20} = -10°$ (c 1.24, CH_2Cl_2); IR (neat) 3329, 2937, 1735, 1639, 1450, 1375, 1283, 1171, 1072, 730, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.14−7.30 (m, 5H), 4.32 (dd, J = 3.7, 10.5 Hz, 1H), 4.17 (t, J = 10.4 Hz, 1H), 3.81 (d, J = 15.6 Hz, 1H), 3.75 (d, J = 15.6 Hz, 1H), 2.92−2.94 (m, 4H), 2.84−2.90 (m, 1H), 2.33 (s, 1H), 1.75 (s, 3H), 1.56−1.64 (m, 5H), 1.47−1.55 (m, 2H), 0.93 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.2, 157.5, 153.8, 139.8, 128.5, 128.3, 126.0, 123.7, 73.3, 60.8, 54.1, 52.0, 31.8, 29.8, 26.4, 25.9, 23.8, 18.6, 18.6; HRMS (ESI-TOF) m/z calcd for $C_{23}H_{32}N_3O_3$ $[M + H]^+$ 398.2444, found 398.2449.

*(3S,5S)-5-Benzyl-3-methyl-3-(4-phenyl-5-(pyrrolidin-1-yl)oxazol-2-yl)morpholin-2-one (**8r**).* After the mixture was stirred for 1.5 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 3/2) as eluent: yield 72 mg, 85%; yellow gel; $[\alpha]_D^{20} = -3°$ (c 0.7, CH_2Cl_2); IR (neat) 3312, 2973, 2873, 1743, 1621, 1449, 1234, 1156, 751, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58−7.63 (m, 2H), 7.18−7.40 (m, 8H), 4.34 (dd, J = 3.5, 10.5 Hz, 1H), 4.22 (t, J = 10.4 Hz, 1H), 3.75−3.82 (m, 1H), 3.13−3.26 (m, 4H), 2.80 (dd, J = 4.9, 13.7 Hz, 1H), 2.61 (dd, J = 8.9, 13.7 Hz, 1H), 1.88−1.97 (m, 4H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 154.7, 151.0, 136.4, 132.5, 129.1, 128.8, 128.1, 127.0, 126.5, 126.1, 119.2, 74.4, 60.8, 50.2, 49.5, 37.8, 26.8, 25.4; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{28}N_3O_3$ $[M + H]^+$ 418.2131, found 418.2137.

*(3S,5S)-5-Benzyl-3-(4-benzyl-5-(diethylamino)oxazol-2-yl)-3-methylmorpholin-2-one (**8s**).* After the mixture was stirred for 2 h, the product was isolated by flash column chromatography using dichloromethane/ethyl ether (100/1 to 40/1) as eluent: yield 68 mg, 78%; white gel; $[\alpha]_D^{20} = -13°$ (c 0.4, CH_2Cl_2); IR (neat) 3297, 2975, 2932, 2850, 1734, 1449, 1230, 729, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.04−7.32 (m, 10H), 4.30 (dd, J = 3.1, 10.4 Hz, 1H), 4.18 (t, J = 10.4 Hz, 1H), 3.68−3.80 (m, 2H), 3.53−3.63 (m, 1H), 2.88 (q, J = 7.2 Hz, 4H), 2.74 (dd, J = 5.2, 13.7 Hz, 1H), 2.55 (dd, J = 8.7, 13.5 Hz, 1H), 2.24 (br s, 1H), 1.73 (s, 3H), 0.90 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.1, 158.5, 151.3, 139.7, 136.3, 129.0, 128.9, 128.8, 128.7, 128.3, 127.1, 126.1, 74.4, 60.9, 49.5, 48.0, 38.0, 31.6, 26.1, 13.4; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{32}N_3O_3$ $[M + H]^+$ 434.2444, found 434.2449.

General Procedure for the Synthesis of 9 by the Reaction of 8 with Maleic Anhydride (18). To a solution of the compound **8** (0.10 mmol) in toluene (2.5 mL) were added successively maleic anhydride (**18**; 0.20 mmol) and molecular sieves (4 Å, powder, 50 mg) at room temperature. The resulting mixture was heated to 110 °C until **8** was no longer detected by TLC analysis. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product **9**.

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*(7S,10aS)-7-Benzyl-10a-methyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9a**).* After the mixture was heated for 2.5 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (5/3 to 1/3) as eluent: yield 21 mg, 47%; white gel; $[\alpha]_D^{20}$ = +130° (*c* 0.3, CH_2Cl_2); IR (neat) 2923, 2856, 1760, 1699, 1499, 1373, 1114, 1037, 909, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.55 (d, *J* = 2.8 Hz, 1H), 7.50 (d, *J* = 2.8 Hz, 1H), 7.22−7.36 (m, 5H), 4.61−4.71 (m, 1H), 4.43−4.55 (m, 2H), 3.86−3.92 (m, 4H), 3.18−3.35 (m, 6H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 167.4, 153.6, 148.0, 143.0, 135.6, 129.7, 128.8, 127.4, 123.9, 115.9, 67.8, 66.5, 63.9, 50.8, 48.4, 37.5, 23.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{23}N_3O_4Na$ $[M + Na]^+$ 416.1586, found 416.1580.

*(7S,10aS)-2,7-Dibenzyl-10a-methyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9b**).* After the mixture was heated for 8 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 1/1) as eluent: yield 40 mg, 80%; colorless gel; $[\alpha]_D^{20}$ = +76° (*c* 0.4, CH_2Cl_2); IR (neat) 2962, 2924, 2855, 1765, 1702, 1446, 1355, 1112, 902, 754, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80 (s, 1H), 7.13−7.37 (m, 10H), 4.60−4.69 (m, 1H), 4.33−4.57 (m, 4H), 3.76−3.91 (m, 4H), 3.30 (dd, *J* = 3.6, 13.8 Hz, 1H), 3.22 (dd, *J* = 7.9, 13.7 Hz, 1H), 2.83−2.90 (m, 2H), 2.73−2.80 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.2, 166.9, 163.2, 157.9, 148.7, 138.9, 135.6, 129.8, 128.9, 128.8, 128.3, 127.4, 126.3, 123.5, 122.5, 67.7, 67.1, 64.2, 52.9, 50.8, 40.5, 37.5, 23.4; HRMS (ESI-TOF) *m*/*z* calcd for $C_{29}H_{30}N_3O_4$ $[M + H]^+$ 484.2236, found 484.2230.

*(7S,10aS)-7-Benzyl-2-isopropyl-10a-methyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9c**).* After the mixture was heated for 12 h, the product was isolated by flash column chromatography using petroleum ether/ethyl ether (1/1 to 1/4) as eluent: yield 35 mg, 76% (recovered **8d**: 3.3 mg, 8%); white gel; $[\alpha]_D^{20}$ = +82° (*c* 0.3, CH_2Cl_2); IR (neat) 2960, 2926, 2856, 1768, 1703, 1440, 1352, 1114, 908, 751, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (s, 1H), 7.22−7.36 (m, 5H), 4.60−4.69 (m, 1H), 4.41−4.55 (m, 2H), 3.85−3.93 (m, 4H), 3.61−3.70 (m, 1H), 3.30 (dd, *J* = 3.6, 13.8 Hz, 1H), 3.21 (dd, *J* = 8.2, 13.8 Hz, 1H), 2.86−2.99 (m, 4H), 1.58 (s, 3H), 1.34 (d, *J* = 6.7 Hz, 3H),1.29 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.5, 168.6, 166.8, 157.7, 147.3, 135.7, 129.8, 128.8, 127.3, 121.9, 121.4, 67.7, 67.2, 64.3, 53.3, 50.8, 37.6, 30.1, 23.5, 22.5, 22.4; HRMS (ESI-TOF) *m*/*z* calcd for $C_{25}H_{30}N_3O_4$ $[M + H]^+$ 436.2236, found 436.2229.

*(7S,10aS)-7-Benzyl-2,10a-dimethyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9d**).* After the mixture was heated for 6 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 2/3) as eluent: yield 33 mg, 78%; colorless gel; $[\alpha]_D^{20}$ = +105° (*c* 0.6, CH_2Cl_2); IR (neat) 2923, 2853, 1760, 1700, 1452, 1369, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66 (s, 1H), 7.21−7.36 (m, 5H), 4.61−4.70 (m, 1H), 4.43−4.56 (m, 2H), 3.86−3.91 (m, 4H), 3.30 (dd, *J* = 3.6, 13.8 Hz, 1H), 3.22 (dd, *J* = 8.1, 13.8 Hz, 1H), 2.88−3.04 (m, 4H), 2.71 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.4, 167.1, 160.6, 156.9, 148.5, 135.6, 129.8, 128.8, 127.3, 122.0, 120.7, 67.7, 67.0, 64.1, 52.0, 50.7, 37.5, 23.5, 22.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{25}N_3O_4Na$ $[M + Na]^+$ 430.1743, found 430.1749.

*(7S,10aS)-2-Benzyl-7-isopropyl-10a-methyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9e**).* After the mixture was heated for 6 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 3/2) as eluent: yield 34 mg, 77%; white crystal; mp 198−200 °C; $[\alpha]_D^{20}$ = +50° (*c* 1.2, CH_2Cl_2); IR (neat) 2962, 2893, 2851, 1755, 1707, 1444, 1346, 1346, 1226, 1109, 894, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (s, 1H), 7.13−7.39 (m, 5H), 4.62 (dd, *J* = 6.8, 12.3 Hz, 1H), 4.35−4.57 (m, 3H), 4.21−4.30 (m, 1H), 3.76−3.88 (m, 4H), 2.81−2.90 (m, 2H), 2.71−2.80 (m, 2H), 2.20−2.32 (m, 1H), 2.00 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 167.0, 163.2, 157.5, 148.8, 139.1, 128.9, 128.3, 126.3, 123.6, 122.5, 67.3, 67.1, 64.7, 54.6, 52.9, 40.5, 31.0, 23.7, 19.6, 18.3; HRMS (ESI-TOF) *m*/*z* calcd for $C_{25}H_{30}N_3O_4$ $[M + H]^+$ 436.2236, found 436.2240.

*(7S,10aS)-2-Isopropyl-10a-methyl-3-morpholino-7-phenyl-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9f**).* After the mixture was heated for 12 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (8/1 to 3/2) as eluent: yield 36 mg, 84% (recovered **8h**: 4.2 mg, 11%); colorless gel; $[\alpha]_D^{20}$ = +68° (*c* 0.4, CH_2Cl_2); IR (neat) 2963, 2927, 2856, 1767, 1707, 1438, 1344, 1114, 908, 756, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (s, 1H), 7.32−7.46 (m, 5H), 5.48 (dd, *J* = 6.6, 10.7 Hz, 1H), 4.74 (dd, *J* = 6.6, 12.5 Hz, 1H), 4.61−4.69 (m, 1H), 3.84−3.93 (m, 4H), 3.62−3.72 (m, 1H), 2.86−2.98 (m, 4H), 2.00 (s, 3H), 1.38 (d, *J* = 7.6 Hz, 3H), 1.32 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.8, 168.4, 166.7, 157.8, 147.5, 136.2, 129.2, 128.5, 126.3, 122.1, 121.3, 69.0, 67.1, 64.6, 53.8, 53.3, 30.1, 24.4, 22.5; HRMS (ESI-TOF) *m*/*z* calcd for $C_{24}H_{27}N_3O_4Na$ $[M + Na]^+$ 444.1899, found 444.1898.

*(7S,10aS)-10a-Ethyl-2,7-diisopropyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9g**).* After the mixture was heated for 18 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (4/1 to 3/2) as eluent: yield 30 mg, 65% (recovered **8l**: 8.1 mg, 22%); white gel; $[\alpha]_D^{20}$ = +17° (*c* 0.3, CH_2Cl_2); IR (neat) 2964, 2857, 1762, 1702, 1437, 1358, 1116, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (s, 1H), 4.63 (dd, *J* = 7.0, 12.2 Hz, 1H), 4.44 (dd, *J* = 10.2, 12.0 Hz, 1H), 4.17−4.27 (m, 1H), 3.83−3.94 (m, 4H), 3.60−3.70 (m, 1H), 2.84−3.00 (m, 4H), 2.78 (dq, *J* = 7.4, 21.6 Hz, 1H), 2.14 (dq, *J* = 7.1, 21.2 Hz, 1H), 1.98−2.08 (m, 1H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.65 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.6, 169.5, 167.7, 155.9, 147.1, 122.5, 121.7, 69.0, 67.7, 67.2, 54.4, 53.3, 32.3, 30.0, 27.6, 22.7, 22.4, 20.4, 18.5, 6.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{32}N_3O_4$ $[M + H]^+$ 402.2393, found 402.2397.

*(7S,10aS)-7-Benzyl-10a-ethyl-2-isopropyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9h**).* After the mixture was heated for 12 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (8/1 to 5/2) as eluent: yield 39 mg, 83%; colorless gel; $[\alpha]_D^{20}$ = +24° (*c* 0.6, CH_2Cl_2); IR (neat) 2964, 2963, 2854, 1764, 1700, 1438, 1357, 1111, 1081, 927, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (s, 1H), 7.28−7.38 (m, 5H), 4.60−4.70(m, 1H), 4.42−4.50 (m, 1H), 4.36 (dd, *J* = 6.3, 12.2 Hz, 1H), 3.83−3.96 (m, 4H), 3.61−3.70 (m, 1H), 3.57 (dd, *J* = 4.0, 13.6 Hz, 1H), 2.84−3.01 (m, 5H), 2.67 (dq, *J* = 7.4, 21.6 Hz, 1H), 2.09 (dq, *J* = 7.2, 21.3 Hz, 1H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 0.59 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.6, 169.2, 166.9, 156.2, 147.1, 135.9, 129.1, 128.9, 127.3, 122.6, 121.5, 68.4, 68.2, 67.1, 53.3, 51.0, 38.5, 30.1, 28.8, 22.7, 22.4, 6.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{32}N_3O_4$ $[M + H]^+$ 450.2393, found 450.2397.

*(7S,10aS)-7-Benzyl-2-isopropyl-9,10a-dimethyl-3-morpholino-8,9-dihydropyrido[2′,3′:3,4]pyrrolo[1,2-a]pyrazine-5,10(7H,10aH)-dione (**9i**).* After the mixture was heated for 12 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (2/1 to 2/3) as eluent: yield 33 mg, 70%; white crystal; mp 205−206 °C; $[\alpha]_D^{20}$ = +76° (*c* 0.6, CH_2Cl_2); IR (KBr): 2965, 2853, 1701, 1663, 1430, 1362, 1114, 960, 904, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (s, 1H), 7.22−7.39 (m, 5H), 4.67−4.77 (m, 1H), 3.83−3.93 (m, 4H), 3.56−3.70 (m, 2H), 3.32−3.44 (m, 2H), 3.07 (dd, *J* = 9.5, 13.5 Hz, 1H), 2.95 (s, 3H), 2.83−2.99 (m, 4H), 1.70 (s, 3H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.0, 168.3, 167.9, 158.8, 146.9, 136.7, 129.5, 128.8, 127.0, 121.8, 121.7, 67.2, 66.0, 53.3, 50.6, 50.5, 39.2, 35.0, 30.0, 23.5, 22.6, 22.5; HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{32}N_4O_3Na$ $[M + Na]^+$ 471.2372, found 471.2368.

*(7S,10aS)-7-Benzyl-9-butyl-2-isopropyl-10a-methyl-3-morpholino-8,9-dihydropyrido[2′,3′:3,4]pyrrolo[1,2-a]pyrazine-5,10-(7H,10aH)-dione (**9j**).* After the mixture was heated for 11 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 3/2) as eluent: yield 46 mg, 90%; colorless gel; $[\alpha]_D^{20}$ = +8° (*c* 0.4, CH_2Cl_2); IR (neat) 2959, 2958, 2857, 1673, 1430, 1356, 1112, 1111, 902, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (s, 1H), 7.24−7.38 (m, 5H), 4.58−4.68 (m, 1H), 3.83−3.94 (m, 4H), 3.58−3.72 (m, 2H), 3.40−3.50 (m, 1H), 3.32−3.40 (m,

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2H), 3.14−3.23 (m, 1H), 3.07 (dd, J = 9.2, 13.6 Hz, 1H), 2.84−2.98 (m, 4H), 1.64 (s, 3H), 1.40−1.55 (m, 2H), 1.37 (d, J = 6.7 Hz, 3H), 1.29 (d, J = 6.6 Hz, 3H), 1.20−1.27 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.9, 168.3, 167.5, 158.9, 146.9, 136.7, 129.6, 128.7, 127.0, 121.7, 67.2, 66.1, 53.3, 51.1, 48.4, 47.2, 39.3, 30.0, 29.6, 23.1, 22.6, 22.5, 20.1, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{38}N_4O_3Na$ $[M + Na]^+$ 513.2842, found 513.2838.

*(7S,10aS)-7-Benzyl-10a-methyl-2-phenyl-3-(piperidin-1-yl)-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9k**).* After the mixture was heated for 13 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (4/1 to 3/2) as eluent: yield 24 mg, 51% (recovered **8o**: 11 mg, 24%); pale green gel; $[\alpha]_D^{20}$ = +97° (c 0.3, CH_2Cl_2); IR (neat) 2925, 2852, 1761, 1696, 1423, 1349, 1105, 777, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.06−8.13 (m, 2H), 7.67 (s, 1H), 7.22−7.47 (m, 8H), 4.61−4.72 (m, 1H), 4.41−4.56 (m, 2H), 3.32 (dd, J = 3.5, 13.8 Hz, 1H), 3.22 (dd, J = 8.3, 13.8 Hz, 1H), 2.74−2.91 (m, 4H), 1.60 (s, 3H), 1.44−1.59 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.7, 167.1, 157.1, 155.7, 149.5, 139.7, 135.7, 132.0, 129.8, 128.9, 128.8, 128.1, 127.3, 122.3, 120.4, 67.7, 64.3, 52.5, 50.8, 37.6, 25.7, 23.7, 23.6; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{29}N_3O_3Na$ $[M + Na]^+$ 490.2107, found 490.2110.

*(7S,10aS)-2,7-Dibenzyl-10a-methyl-3-(piperidin-1-yl)-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9l**).* After the mixture was heated for 5 h, the product was isolated by flash column chromatography using petroleum ether/acetone (7/1 to 4/1) as eluent: yield 32 mg, 65%; yellow gel; $[\alpha]_D^{20}$ = −25° (c 0.4, CH_2Cl_2); IR (neat) 2934, 2859, 1730, 1449, 1217, 1166, 755, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73 (s, 1H), 7.12−7.43 (m, 10H), 4.59−4.68 (m, 1H), 4.30−4.55 (m, 4H), 3.29 (dd, J = 3.6, 13.8 Hz, 1H), 3.22 (dd, J = 8.0, 13.7 Hz, 1H), 2.80−2.88 (m, 2H), 2.68−2.77 (m, 2H), 1.66−1.78 (m, 4H), 1.54−1.62 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.6, 167.1, 163.3, 156.9, 150.3, 139.3, 135.6, 129.8, 129.0, 128.8, 128.2, 127.3, 126.1, 122.9, 122.2, 67.7, 64.2, 54.1, 50.8, 40.2, 37.5, 26.3, 23.9, 23.5; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{32}N_3O_3$ $[M + H]^+$ 482.2444, found 482.2449.

*(7S,10aS)-7-Benzyl-10a-methyl-2-phenyl-3-(pyrrolidin-1-yl)-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9m**).* After the mixture was heated for 5 h, the product was isolated by flash column chromatography using petroleum ether/ethyl ether (3/4 to 1/4) as eluent: yield 29 mg, 63%; pale green gel; $[\alpha]_D^{20}$ = +62° (c 0.3, CH_2Cl_2); IR (neat) 2927, 1764, 1699, 1456, 1435, 1353, 1253, 753, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71−7.75 (m, 2H), 7.46 (s, 1H), 7.23−7.44 (m, 8H), 4.62−4.71 (m, 1H), 4.41−4.55 (m, 2H), 3.32 (dd, J = 3.5, 13.8 Hz, 1H), 3.21 (dd, J = 8.2, 13.7 Hz, 1H), 2.96−3.04 (m, 2H), 2.88−2.96 (m, 2H), 1.72−1.92 (m, 4H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.1, 167.5, 152.0, 151.8, 145.6, 141.3, 135.8, 129.8, 129.0, 128.8, 128.1, 128.0, 127.3, 122.0, 114.7, 67.8, 64.2, 51.4, 50.9, 37.7, 25.6, 23.3; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{28}N_3O_3$ $[M + H]^+$ 454.2131, found 454.2137.

*(7S,10aS)-2,7-Dibenzyl-3-(diethylamino)-10a-methyl-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10(10aH)-dione (**9n**).* After the mixture was heated for 5 h, the product was isolated by flash column chromatography using dichloromethane/ethyl ether (80/1 to 40/1) as eluent: yield 35 mg, 72%; yellow gel; $[\alpha]_D^{20}$ = +114° (c 0.5, CH_2Cl_2); IR (neat) 2972, 2929, 1766, 1703, 1447, 1352, 1205, 746, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 (s, 1H), 7.11−7.37 (m, 10H), 4.60−4.69 (m, 1H), 4.29−4.56 (m, 4H), 3.31 (dd, J = 3.5, 13.8 Hz, 1H), 3.21 (dd, J = 8.2, 13.8 Hz, 1H), 2.91−3.04 (m, 4H), 1.61 (s, 3H), 0.91 (t, J = 7.04 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.6, 167.1, 164.6, 157.1, 147.4, 139.3, 135.7, 129.8, 129.1, 128.8, 128.1, 127.3, 126.0, 125.0, 121.9, 67.8, 64.2, 50.8, 47.5, 40.4, 37.7, 23.6, 12.0; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{31}N_3O_3Na$ $[M + Na]^+$ 492.2263, found 492.2257.

*(4S)-4-((3S,5S)-5-Benzyl-3-methyl-2-oxomorpholin-3-yl)-6-isopropyl-7-morpholino-2-phenyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxypyrrolo[3,4-c]pyridine-1,3(2H)-dione (**27**).* After the mixture was heated for 11 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (4/1 to 3/2) as eluent: yield 52 mg, 90%; colorless gel; $[\alpha]_D^{20}$ = −48° (c 0.3, CH_2Cl_2); IR (neat) 3318, 2967, 2854, 1716, 1497, 1454, 1369, 1116, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.08−7.43 (m, 10H), 4.55 (d, J = 8.1 Hz, 1H), 4.33 (dd, J = 3.0, 10.2 Hz, 1H), 4.20 (t, J = 10.5 Hz, 1H), 3.73−3.80 (m, 4H), 3.71 (d, J = 8.2 Hz, 1H), 3.52−3.62 (m, 1H), 2.97−3.08 (m, 2H), 2.66 (dd, J = 2.9, 13.2 Hz, 1H), 2.53−2.62 (m, 2H), 2.29−2.42 (m, 2H), 1.95 (s, 3H), 1.63 (br s, 1H), 0.85 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 186.3, 170.9, 170.8, 170.5, 137.5, 131.2, 129.0, 128.9, 128.7, 128.5, 127.0, 125.9, 108.0, 104.0, 74.8, 66.8, 60.8, 51.1, 50.0, 48.6, 44.9, 38.1, 29.5, 26.5, 20.4, 20.0; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{37}N_4O_6$ $[M + H]^+$ 573.2713, found 573.2709.

General Procedure for the Synthesis of 9 by the Reaction of 8 with Unsaturated Acyl Chlorides 21. To a solution of the compound **8** (0.12 mmol) in toluene (3 mL) were added successively DIPEA (0.60 mmol), **21** (0.30 mmol), and molecular sieves (4 Å, powder, 60 mg) under an argon atmosphere at room temperature. The resulting mixture was heated to reflux for 20−36 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product **9**.

*(7S,10aS)-7-Benzyl-2-isopropyl-4,10a-dimethyl-3-morpholino-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10-(10aH)-dione (**9o**).* After the mixture was heated for 36 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 1/1) as eluent: yield 14 mg, 31% (recovered **8d**: 15 mg, 38%); yellow gel; $[\alpha]_D^{20}$ = +73° (c 0.21, CH_2Cl_2); IR (neat) 2960, 2925, 2853, 1767, 1697, 1578, 1448, 1346, 1261, 1112, 1036, 921, 737, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22−7.36 (m, 5H), 4.56−4.60 (m, 1H), 4.40−4.54 (m, 2H), 3.84 (m, 4H), 3.33 (dd, J = 3.4, 13.8 Hz, 1H), 3.00−3.23 (m, 5H), 2.73 (s, 3H), 1.60 (s, 3H), 1.31 (d, J = 6.7, 3H), 1.28 (d, J = 6.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 169.6, 167.0, 159.9, 146.4, 143.6, 136.0, 129.8, 128.9, 127.4, 120.0, 68.1, 68.0, 67.8, 63.5, 50.9, 50.5, 50.4, 38.0, 31.5, 23.8, 22.8, 22.4, 13.4; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{32}N_3O_4$ $[M + H]^+$ 450.2393, found 450.2396.

*(7S,10aS)-7-Benzyl-2-isopropyl-10a-methyl-3-morpholino-4-phenyl-7,8-dihydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c][1,4]oxazine-5,10-(10aH)-dione (**9p**).* After the mixture was heated for 20 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 1/1) as eluent: yield 37 mg, 60%; yellow gel; $[\alpha]_D^{20}$ = +88° (c 0.65, CH_2Cl_2); IR (neat) 2960, 2853, 1766, 1704, 1560, 1437, 1348, 1263, 1208, 1110, 912, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48−7.53 (m, 3H), 7.27−7.33 (m, 4H), 7.16−7.26 (m, 3H), 4.45−4.50 (m, 2H), 4.34−4.40 (m, 1H), 3.63−3.71 (m, 1H), 3.43−3.63 (m, 4H), 3.31 (dd, J = 2.6, 13.9 Hz, 1H), 3.00 (dd, J = 8, 13.6 Hz, 1H), 2.51−2.94 (m, 4H), 1.70 (s, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.35 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 167.9, 167.1, 159.0, 146.5, 143.4, 135.8, 134.0, 129.6, 129.4, 128.8, 128.7, 128.5, 127.9, 127.2, 119.2, 67.8, 67.4, 36.3, 52.2, 51.9, 50.8, 38.0, 31.2, 23.6, 22.7, 22.4; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{34}N_3O_4$ $[M + H]^+$ 512.2549, found 512.2545.

*(7S,10aS)-Ethyl 7-Benzyl-2-isopropyl-10a-methyl-3-morpholino-5,10-dioxo-7,8,10,10a-tetrahydro-5H-pyrido[2′,3′:3,4]pyrrolo[2,1-c]-[1,4]oxazine-4-carboxylate (**9q**).* After the mixture was heated for 20 h, the product was isolated by flash column chromatography using petroleum ether/ethyl acetate (3/1 to 1/1) as eluent: yield 21 mg, 33%; yellow gel; $[\alpha]_D^{20}$ = +61° (c 0.25, CH_2Cl_2); IR (neat) 2926, 2855, 1763, 1636, 1600, 1567, 1469, 1395, 1321, 1114, 1078, 1024, 903, 753, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31−7.34 (m, 2H), 7.22−7.28 (m, 3H), 4.35−4.65 (m, 5H), 3.75−3.82 (m, 4H), 3.55−3.66 (m, 1H), 3.31−3.35 (dd, J = 4.0, 12.0 Hz, 1H), 3.12−3.15 (m, 1H), 3.08−3.09 (m, 4H), 1.61 (s, 3H), 1.46−1.49 (t, J = 7.2 Hz, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.4, 166.5, 166.3, 165.6, 159.2, 140.9, 136.7, 135.5, 129.7, 128.8, 127.3, 117.9, 67.7, 67.7, 64.2, 62.6, 51.4, 51.3, 50.8, 37.6, 31.3, 23.3, 22.4, 22.3, 14.2; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{33}N_3O_6Na$ $[M + Na]^+$ 530.2267, found 530.2270.

General Procedure for the One-Pot Synthesis of 9 from α-Isocyanoacetamides 1, Cyclic Imines 7, and Maleic Anhydride (18). To a solution of the imine **7** (0.20 mmol) in TFE (0.5 mL) were added successively α-isocyanoacetamides **1** (0.20 mmol) and phenyl-

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phosphinic acid (**10**; 0.020 mmol for **1b,d**, 0.050 mmol for **1f,h**) at room temperature. After the mixture was stirred at room temperature for 20 min, additional **1** (0.080 mmol) was added. The resulting mixture was stirred until **7** was converted thoroughly (monitored by TLC), and then 1 equiv of Et_3N with respect to **10** was added. After this mixture was stirred for 5 min, toluene (5 mL), maleic anhydride **18** (0.60 mmol), and 4 Å molecular sieves (powder, 100 mg) were added. The mixture was refluxed until **8** was no longer detected by TLC analysis and filtered. The filtrate was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product **9**.

■ ASSOCIATED CONTENT

Supporting Information

Text giving a description of the general experimental procedures, figures giving NMR spectra of the compounds, and a table, figure, and CIF file giving crystallographic data for **9e**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*X.C.: fax, (+)(+86) 28-8541-2095; e-mail, chenxc@scu.edu.cn.

Author Contributions

[†]These individuals contributed equally to this work.

Notes

The authors declare no competing financial interest.

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