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An Efficient and Diastereoselective Intramolecular 1,3-Dipolar Cycloaddition of Cyclic Azomethine Ylides and Nitrones

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Nitrones and azomethine ylides formed by condensation of chiral 2-formyl-perhydro benzoxazines and *N*-substituted hydroxylamines or cyclic α-amino acids cyclize intramolecularly yielding polycyclic isoxazolidine or pyrrolidine derivatives, respectively, with total diastereoselectivity. On the contrary, stabilized azomethine ylides derived from methyl prolinate undergo the cyclization products in very low yields.

Introduction

Polycyclic nitrogen-containing heterocycles form the basic skeleton of numerous alkaloids[1] and pharmacologically important compounds; therefore their efficient construction in a regio- and stereocontrolled way is an important challenge. In this context, the intramolecular 1,3-dipolar cycloaddition reaction[2] has emerged as an important synthetic tool for the preparation of structurally complex, fused, heterocyclic ring systems with simultaneous generation of several stereogenic centers. Among them, those involving azomethine ylides[3] and nitrones[4] constitute an efficient and versatile entry to fused or bridged polycyclic pyrrolidines and isoxazolidines. For instance, several polycyclic, fused pyrrolidine ring systems are synthesized by intramolecular cycloadditions of cyclic azomethine ylides with tethered dipolarophiles.[5] The stereocontrol in these reactions can be achieved by the use of chiral catalysts or stoichiometric chiral auxiliaries that are attached either to the dipole or dipolarophile. The asymmetric intermolecular 1,3-dipolar cycloaddition is well known,[6–12] but the asymmetric intramolecular version of this powerful reaction, which employs a removable chiral auxiliary or catalyst has not been extensively explored.[13,14]

Recently, it has been shown[15–17] that chiral cyclic N,O-acetals are useful templates in asymmetric 1,3-dipolar cycloadditions. We herein report on a facile diastereoselective synthesis of heteropolycyclic derivatives following this methodology. To this end, azomethine ylides were prepared by the reaction of cyclic α-amino acids with 2-formyl-3-alkenyl perhydrobenzoxazines derived from (–)-8-aminomenthol. These compounds cyclized intramolecularly with the inactivated double bond placed on the nitrogen atom of the heterocycle.

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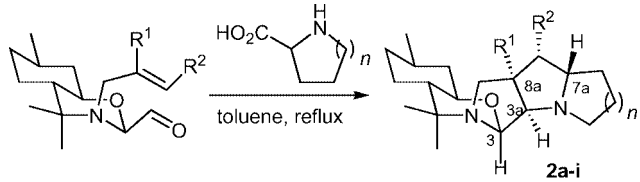
Results and Discussion

The starting aldehydes **1a**–**f** were prepared, as single diastereoisomers in good yields, by condensation of (–)-8-aminomenthol with glycolaldehyde dimer followed by *N*-allylation and Swern oxidation of the 3-allyl-2-(hydroxymethyl) intermediates.[16] Azomethine ylides, generated by a decarboxylative route,[18,19] were formed by condensation of the aldehydes **1a**–**f** with L-proline or D,L-pipecolinic acid as secondary amino acids, and trapped by the dipolarophile to yield the corresponding adducts.

After extensive experimentation, we found that the cycloadducts were obtained in high yields and excellent stereoselection by adding 1.2 equiv. of the amino acid to a 0.1 M solution of the aldehydes **1a**–**f** in refluxing toluene (Scheme 1).



1a: $R^1 = R^2 = H$
1b: $R^1 = H$, $R^2 = Me$
1c: $R1 = Me$, $R^2 = H$
1d: $R^1 = H$, $R^2 = Ph$
1e: $R^1 = Me$, $R^2 = Ph$
1f: R^1 , $R^2 = -(CH_2)_4-$

Scheme 1.

The scope of the dipolar cycloaddition described above is summarized in Table 1, and some trends can be generalized. First of all, the cyclization is totally regio- and diastereoselective, and the formation of only one diastereoisomer was observed in all the cases. The reaction occurs with high yield with mono-, di- (1,1- or 1,2-), and trisubstituted dipolarophiles except for the cyclohexenyl derivative (Entry 9), which yielded **2i** in a moderate 63% after chromatographic purification. This fact is probably due to steric factors because the endocyclic character of the double bond or the alkyl nature of all the substituents at the double bond.

Table 1. Intramolecular 1,3-dipolar cycloaddition of azomethine ylides.

Entry	R^1	R^2	*n*	Time [h]	Product (yield, %)[a]
1	H	H	1	0.5	**2a** (83)
2	H	H	2	5.0	**2b** (84)
3	H	CH_3	1	1.5	**2c** (88)
4	CH_3	H	1	0.5	**2d** (91)
5	CH_3	H	2	4.0	**2e** (82)
6	H	Ph	2	1.0	**2f** (90)
7	CH_3	Ph	1	0.5	**2g** (82)
8	CH_3	Ph	2	4.0	**2h** (87)
9	$-(CH_2)_4-$		2	6.0	**2i** (63)

[a] Yield refers to isolated and pure compounds after flash chromatography.

These results contrast with those previously reported for other dipolar cycloaddition reactions. For instance, the yields of the reaction are highly dependent on the substitution of the olefinic bond that operates as dipolarophile in the cycloaddition of azomethine imines.[15b]

The reactions of the proline derivatives are much faster than that of the pipecolinic acid (compare Entries 2, 5 and 8 vs. 1, 4 and 7 in Table 1), but no significant differences in chemical yield and diastereoselectivity were observed in our reactions. This fact is very interesting because it is known that the replacement of proline by pipecolinic acid highly decreases the yield,[20] or make the reaction to be unsuccessful.[21]

As expected, the change of L-proline to D-proline or D,L-proline did not affect the chemical yield and stereoselectivity of these reactions.

The stereochemistry of **2a**–**i** was determined on the basis of NMR experiments. The signal for the hydrogen H-3, attached to the N,O-acetal carbon atom, appears as a singlet in the ^{1}H NMR spectra, indicating that it does not couple with the vicinal H-3a because the dihedral angle between H-3 and H-3a is near 90°. This means that the substituent attached to the nitrogen atom of the oxazine moiety is in axial arrangement. The values of the coupling constants between H-3a and H-8a for **2a**–**c** and **2f** ($J_{3a,8a}$ = 8.0–8.5 Hz) are consistent with a *cis* fusion between the pyrrolidine rings.[22] Whereas the coupling constants between H-7a and H-8 for **2c**, **2g** and **2h**, ($J_{7a,8}$ = 6.0 Hz, 6.3 Hz and 5.3 Hz, respectively) indicates a *cis* arrangement of these protons.[23] This stereochemical assignment was confirmed by NOESY experiments for compounds **2b**, **2c**, **2e**, **2h** and **2i**. The NOESY contacts point to *cis*-fused bicyclic systems with *cis* relationship between the substituents R^1, R^2 and H-3a and *trans* for H-3 and H-7a. As an example, Figure 1 summarizes the observed effects for compound **2h**.

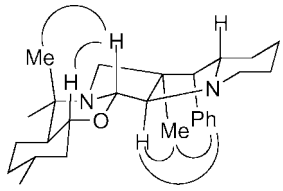
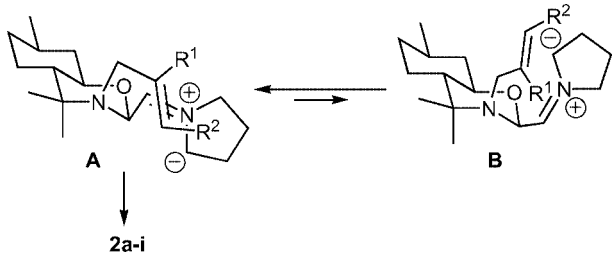


Figure 1. Observed NOE for compound **2h**.

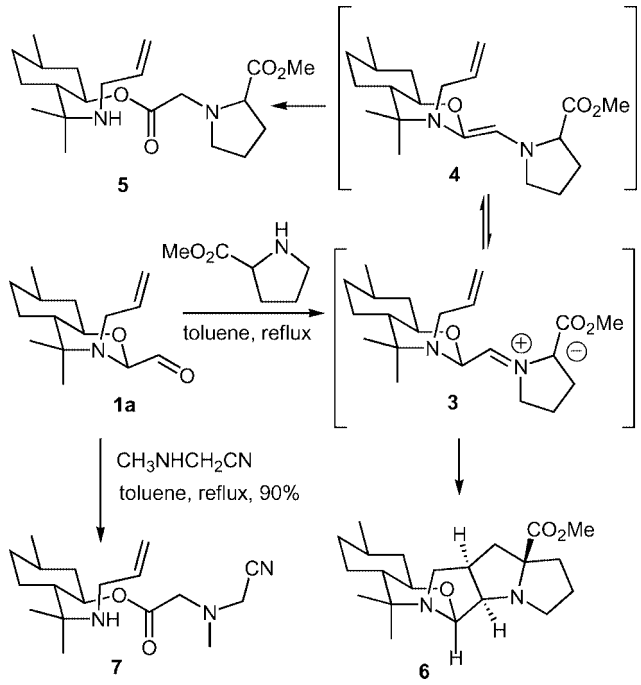
The stereochemistry observed can be explained by accepting that the decarboxilative condensation of proline or picolinic acid with the aldehydes **1** generates an azomethine ylide with an *anti* dipole geometry,[24] which approach to the dipolarophile in an *exo* mode with respect to the linking chain with the oxazine nitrogen atom. The stereochemistry observed is also consistent with a reactive conformation, where the allylic substituent at the nitrogen atom of the oxazine moiety is in axial arrangement. Although two different transition states **A** and **B** are possible (Scheme 2), transition state **B** would be less favorable due to electronic repulsions between the lone pair on the oxygen atom at the oxazine ring and the dipole, and products are not formed from this conformation.



Scheme 2.

The extension of the method led us to consider the cycloaddition of ester-stabilized azomethine ylides generated in situ by condensation of α-amino esters with carbonyl compounds. These substrates do not participate in intermolecular dipolar cycloaddition with unactivated dipolarophiles such as simple alkenes,[3b] but easily react intramolecularly.[25] However, when a mixture of aldehyde **1a**, L-proline methyl ester hydrochloride and pyridine was refluxed for one hour in toluene, the only isolated product was the diester **5** (Scheme 3 and Table 2). This product will be formed by hydrolysis of the transient N,O-ketene ketal **4**, formed by tautomerization of the initial iminium intermediate **3**.[26]

The heating of L-proline methyl ester with the aldehyde **1a** in toluene for one hour led to a mixture of the ester **5** (58%) and the cycloadduct **6** but only in 18% (Entry 2). The yield of the desired cycloaddition product was increased to only 26% when the water formed in the condensation was continuously removed with the aid of a Dean–Stark trap to prevent the hydrolysis of the enamine (Entry 3). Addition of a drying agent such as anhydrous magne-



Scheme 3.

Table 2. Generation of stabilized azomethine ylides and intramolecular 1,3-dipolar cycloaddition.

Entry	Amino derivative	Additive	Time [min]	Products (%)[a]
1	methyl prolinate·HCl	pyridine	60	**5** (75)
2	methyl prolinate	–	240	**5** (58), **6** (18)
3	Methyl prolinate	–	210	**5** (40), **6** (26)[b]
4	Methyl prolinate	$MgSO_4$	240	**5** (36), **6** (30)
5	(methylamino)acetonitrile	$MgSO_4$	210	**7** (88)

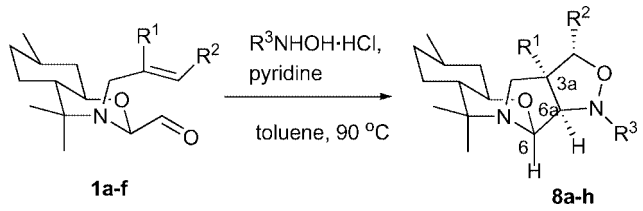
[a] Yields in parentheses refer to isolated and pure compounds after flash chromatography. [b] The reflux was carried out under Dean–Stark conditions.

sium sulfate to the reaction only improved the yield lightly (Entry 4). In the same conditions, condensation of **1a** with (methylamino)acetonitrile provided **7** in an excellent 88% yield. The cycloadduct derived from a cyano-stabilized ylide was not detected on the ^{1}H NMR of the reaction mixture.

Our interest in the preparation of different chiral nitrogen heterocyclic derivatives[27] led us to consider the preparation of fused isoxazolidines[28] by the use of nitrones as 1,3-dipoles.

The aldehydes **1a**–**f** were treated with *N*-methylhydroxylamine- and *N*-benzylhydroxylamine hydrochlorides in the presence of a base leading to the isoxazolidine derivatives **8a**–**h** with total regio- and diastereoselectivity via the unisolated nitrone intermediate.[29] The results are summarized in Scheme 4 and Table 3.

Different reaction conditions were initially explored on the formyl derivative **1a** (Entries 1–7 in Table 3). The reaction of **1a** and *N*-methylhydroxylamine hydrochloride does not work efficiently in toluene at room temperature in the presence of Et_3N, and only 5% of isoxazolidine **8a** was isolated after 5 h. An increase of temperature to 90 °C greatly improved the yield. Nevertheless, the reaction was not completed by heating in DMF at 90 °C in the presence of Et_3N or K_2CO_3, or in toluene in the presence of Et_3N or $NaHCO_3$. On the contrary, the aldehyde **1a** gave a clean conversion in the presence of K_2CO_3 and toluene as solvent. The best results were obtained when the reaction of **1a** and *N*-methylhydroxylamine hydrochloride was carried out in toluene at 90 °C for 45 minutes in the presence of pyridine. In these reaction conditions the isoxazolidine derivative **8a** was isolated in an excellent 98% yield. Under the same experimental conditions the aldehydes **1b**–**f** also were transformed in the *N*-methylisoxazolidine derivatives **8b**–**f** in very good yield. Finally, when *N*-methylhydroxylamine was changed to the *N*-benzyl derivative, it was necessary to increase the reaction time to obtain the cyclization products in excellent yields (Entries 13 and 14 in Table 3).



Scheme 4.

Table 3. Intramolecular 1,3-dipolar cycloaddition of nitrones.

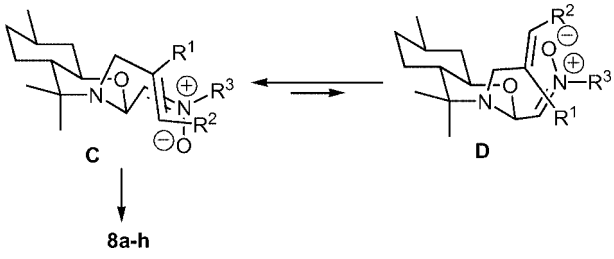
Entry	R^1	R^2	R^3	Base	Solvent	Time [min]	Product (yield, %)[a]
1	H	H	CH_3	Et_3N	toluene (23 °C)	300	**8a** (5)
2	H	H	CH_3	Et_3N	DMF (90 °C)	60	**8a** (40)
3	H	H	CH_3	K_2CO_3	DMF (90 °C)	60	**8a** (48)
4	H	H	CH_3	Et_3N	toluene (90 °C)	60	**8a** (66)
5	H	H	CH_3	$NaHCO_3$	toluene (90 °C)	60	**8a** (78)
6	H	H	CH_3	K_2CO_3	toluene (90 °C)	60	**8a** (89)
7	H	H	CH_3	pyridine	toluene (90 °C)	45	**8a** (98)
8	H	CH_3	CH_3	pyridine	toluene (90 °C)	70	**8b** (95)
9	CH_3	H	CH_3	pyridine	toluene (90 °C)	70	**8c** (93)
10	H	Ph	CH_3	pyridine	toluene (90 °C)	60	**8d** (94)
11	CH_3	Ph	CH_3	pyridine	toluene (90 °C)	80	**8e** (90)
12	$-(CH_2)_4-$		CH_3	pyridine	toluene (90 °C)	80	**8f** (94)
13	H	H	Bn	pyridine	toluene (90 °C)	75	**8g** (92)
14	H	CH_3	Bn	pyridine	toluene (90 °C)	100	**8h** (84)

[a] Yield refers to isolated and pure compounds after flash chromatography.

The intramolecular cycloaddition of nitrones just like the cycloaddition of unstabilized azomethine ylides occurred with complete facial selectivity providing the isoxazolidine derivatives as single diastereoisomers. The stereochemistry of these adducts was determined on the basis of their ^{1}H NMR spectroscopic data. The signal for the hydrogen H-6,

attached to the N,O-acetal carbon atom, appears as a singlet in the ^{1}H NMR spectra, indicating that the dihedral angle between H-6 and H-6a is near 90°, and therefore the substituent attached to the nitrogen atom of the oxazine moiety would be in axial arrangement. On the other hand, the values of the coupling constants between H-3a and H-6a for **8b**, **8d**, **8g**, and **8h** ($J_{3a–6a}$ = 9.2, 9.1, 9.4 and 8.7 Hz, respectively) are consistent with a *cis* fusion between the pyrrolidine and isoxazolidine rings.

The observed stereochemistry in the cycloadducts can be explained in the same way as previously proposed for the cyclization of azomethine ylides. Condensation of the aldehydes **1a**–**f** with hydroxylamines generated a (*Z*)-nitrone that approach to the dipolarophile in an *exo* mode, in a conformation where the allylic substituent at the nitrogen atom of the oxazine moiety is in axial arrangement. Two different transition states **C** and **D** are possible (Scheme 5), but cycloadducts are formed only from the transition state **C** because the transition state **D** is electrostatically destabilized by repulsive interaction between the lone pair on the oxygen atom at the oxazine ring and the partial negative charge on the dipole oxygen atom.



Scheme 5.

In summary, nitrones and cyclic azomethine ylides derived from proline or pipecolic acid underwent intramolecular dipolar cycloaddition reaction with unactivated alkenes leading exclusively to fused cycloadducts. Only one diastereoisomer, resulting from an *exo* approach was formed. The generation of stabilized azomethine ylides from amino esters or amino nitriles was unsuccessful and the cyclization products were obtained in low yields. The major products in these reactions were esters derived from hydrolysis of the tautomeric N,O-ketene ketals of the initial iminium derivatives formed by condensation of the amino esters with the aldehyde.

Experimental Section

General Methods: All reactions were carried out in anhydrous solvents, under argon, in oven-dried glassware. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ as solvent and chemical shifts are given relative to TMS as internal reference. Specific rotations were determined on a digital polarimeter using a Na lamp and concentration is given in g per 100 mL. The preparation of the starting compounds **1a**–**d**[15a] and **1e**–**f**[15b] has been previously reported.

General Procedure for 1,3-Dipolar Cycloaddition of Unstabilized Azomethine Ylides: A mixture of 3.0 mmol of the appropriate aldehyde **1** and 3.6 mmol of the amino acid in 50 mL of toluene was refluxed for the time given in Table 1. The mixture was poured into H_2O (50 mL) and extracted with Et_2O (3 × 30 mL). The combined organic fractions were washed with H_2O and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel with hexane/EtOAc as eluent.

Pyridazino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2a: Yield 758 mg, 83%. Colorless oil. $[a]_D^{25}$ = –29.8 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.82–1.07 (m, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 1.08 (s 3 H), 1.11 (s, 3 H), 1.31–1.54 (m, 3 H), 1.59 (m, 1 H), 1.63–1.81 (m, 4 H), 1.82–1.98 (m, 3 H), 2.54 (dd, J_1 = 8.3 Hz, J_2 = 2.7 Hz, 1 H), 2.70 (dt, J_1 = 10.5 Hz, J_2 = 7.3 Hz, 1 H), 2.87 (m, 1 H), 3.04 (ddd, J_1 = 10.5 Hz, J_2 = 7.6 Hz, J_3 = 5.2 Hz, 1 H), 3.19 (d, *J* = 8.3 Hz, 1 H), 3.20 (dd, J_1 = 8.3 Hz, J_2 = 8.3 Hz, 1 H), 3.40 (td, J_1 = 10.6 Hz, J_2 = 4.2 Hz, 1 H), 3.50 (m, 1 H), 4.54 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.5, 22.2, 24.2, 24.8, 26.8, 29.4, 31.2, 34.9, 38.3, 39.0, 41.4, 44.1, 50.4, 52.8, 54.2, 66.0, 74.7, 75.6, 92.3 ppm. IR (film): ṽ = 2950, 2870, 1455, 730, 640 cm^{-1}. $C_{19}H_{32}N_2O$ (304.47): calcd. C 74.95, H 10.59, N 9.20; found C 75.03, H 10.47, N 9.33.

Indolizino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2b: Yield 803 mg, 84%. Colorless oil. $[a]_D^{25}$ = –11.5 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.84–1.09 (m, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 1.08 (s, 3 H), 1.11 (s, 3 H), 1.19–1.52 (m, 5 H), 1.53–1.78 (m, 7 H), 1.92 (m, 1 H), 2.49 (dd, J_1 = 8.3 Hz, J_2 = 2.6 Hz, 1 H), 2.51–2.64 (m, 2 H), 2.74 (m, 1 H), 3.05 (m, 1 H), 3.22 (dd, J_1 = 8,3 Hz, J_2 = 7.8 Hz, 1 H), 3.39 (td, J_1 = 10.6 Hz, J_2 = 4.1 Hz, 1 H), 3.51 (d, *J* = 8.0 Hz, 1 H), 4.69 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.0, 22.1, 24.2, 24.3, 24.7, 26.9, 30.6, 31.2, 34.9, 36.3, 39.7, 41.4, 44.3, 48.0, 50.7, 53.0, 60.1, 71.7, 74.8, 84.8 ppm. IR (film, cm^{-1}): ṽ = 2925, 2865, 1450, 730, 705. $C_{20}H_{34}N_2O$ (318.50): calcd. C 75.42, H 10.76, N 8.80; found C 75.46, H 10.89, N 8.66.

Pyridazino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2c: Yield 840 mg, 88%. Colorless oil. $[a]_D^{25}$ = –73.5 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.84–1.08 (m, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 1.02 (d, *J* = 6.5 Hz, 3 H), 1.09 (s, 3 H), 1.18 (s, 3 H), 1.24–1.47 (m, 3 H), 1.48–1.61 (m, 2 H), 1.62–1.73 (m, 2 H), 1.82 (m, 1 H), 1.96 (m, 1 H), 2.22–2.37 (m, 2 H), 2.63 (d, *J* = 8.3 Hz, 1 H), 2.93 (d, *J* = 8.3 Hz, 1 H), 2.94–3.09 (m, 2 H), 3.12 (dd, J_1 = 8.3 Hz, J_2 = 6.6 Hz, 1 H), 3,25 (dt, J_1 = 10.2 Hz, J_2 = 6.0 Hz, 1 H), 3.40 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 4.65 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.6, 21.4, 22.2, 23.8, 24.8, 24.9, 27.1, 31.3, 35.1, 41.6, 41.8, 43.2, 45.8, 48.8, 52.6, 54.2, 72.3, 74.5, 76.6, 92.3 ppm. IR (film, cm^{-1}): ṽ = 2925, 2875, 1455, 893. $C_{20}H_{34}N_2O$ (318.50): calcd. C 75.42, H 10.76, N 8.80; found C 75.30, H 10.89, N 8.91.

Pyridazino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2d: Yield 867 mg, 91%. Colorless oil. $[a]_D^{25}$ = –15.8 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.82–1.22 (m, 4 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 1.05 (s, 3 H), 1.11 (s, 3 H), 1.35 (s, 3 H), 1.39 (m, 1 H), 1.48–1.61 (m, 3 H), 1.65 (m, 1 H), 1.72–2.08 (m, 5 H), 2.73 (d, *J* = 8.3 Hz, 1 H), 2.76 (dt, J_1 = 10.2 Hz, J_2 = 7.6 Hz, 1 H), 2.88 (s, 1 H), 2.90 (d, *J* = 8.3 Hz, 1 H), 3.12 (ddd, J_1 = 10.2 Hz, J_2 = 7.6 Hz, J_3 = 5.0 Hz, 1 H), 3.38 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 3.66 (m, 1 H), 4.62 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.7, 22.2, 24.3, 24.8, 26.8, 28.8, 29.8, 31.2, 35.0, 41.4, 43.8, 47.0, 48.6, 52.8, 54.5, 58.7, 65.7, 74.7, 81.6, 92.9 ppm. IR (film, cm^{-1}): ṽ = 2930, 2865, 1450, 730. $C_{20}H_{34}N_2O$ (318.50): calcd. C 75.42, H 10.76, N 8.80; found C 75.53, H 10.66, N 8.69.

Indolizino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2e: Yield 815 mg, 82%. Colorless oil. $[a]_D^{25}$ = –11.8 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.83–1.21 (m, 4 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 1.05 (s, 3 H), 1.09 (s, 3 H), 1.23–1.1.53 (m, 4 H), 1.29 (s, 3 H), 1.54–

1.63 (m, 3 H), 1.65–1.79 (m, 4 H), 1.87 (m, 1 H), 2.45 (td, J_1 = 11.1 Hz, J_2 = 3.6 Hz, 1 H), 2.64 (m, 1 H), 2.63 (d, J = 8.2 Hz, 1 H), 2.94 (d, N–CH, J = 8.2 Hz, 1 H), 2.97 (m, 1 H), 3.06 (s, 1 H), 3.37 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 4.77 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 22.2, 24.2, 24.7, 25.3, 27.0, 27.4, 31.2, 31.6, 34.9, 41.4, 43.9, 44.0, 48.0, 48.1, 52.9, 58.4, 61.1, 74.8, 78.2, 84.7 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 2925, 2875, 1450, 1381. $C_{21}H_{36}N_2O$ (332.52): calcd. C 75.85, H 10.91, N 8.42; found C 75.96, H 11.03, N 8.51.

Indolizino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2f: Yield 1.06 g, 90%. Colorless oil. $[\alpha]_D^{25}$ = –54.3 (c = 1.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.73–114 (m, 5 H), 0.92 (d, J = 6.5 Hz, 3 H), 1.07 (s, 3 H), 1.18–1.34 (m, 2 H), 1.20 (s, 3 H), 1.36–1.62 (m, 4 H), 1.63–1.75 (m, 2 H), 1.90 (m, 1 H), 2.68 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1 H), 2.83 (td, J_1 = 12.8 Hz, J_2 = 2.9 Hz, 1 H), 3.00–3.25 (m, 4 H), 3.30 (dd, J_1 = 8.3 Hz, J_2 = 7.4 Hz, 1 H), 3.44 (td, J_1 = 10.5 Hz, 1 H, J_2 = 4.1), 3.60 (d, 1 H J = 8.3 Hz), 5.27 (s, 1 H), 7.15–7.25 (m, 3 H), 7.26–7.31 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.8, 21.2, 22.2, 24.1, 24.8 (2 C), 27.1, 31.3, 35.0, 41.5, 42,7, 43.3, 47.8, 49.9, 52.8, 55.0, 64.7, 70.1, 74.6, 88.2, 125.9, 127.9 (2 C), 128.5 (2 C), 141.1 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3060, 3040, 3025, 2930, 2860, 1600, 1450, 760, 730, 700, 645. $C_{26}H_{38}N_2O$ (394.59): calcd. C 79.14, H 9.71, N 7.10; found C 79.25, H 9.80, N 6.99.

Pyridazino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2g: Yield 968 mg, 82%. Colorless oil. $[\alpha]_D^{25}$ = –67.3 (c = 2.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.77–1.10 (m, 3 H), 0.91 (d, J = 6.5 Hz, 3 H), 1.10 (s, 3 H), 1.11 (s, 3 H), 1.24 (s, 3 H), 1.38–1.53 (m, 2 H), 1.58 (m, 1 H), 1.71 (m, 1 H), 1.80 (m, 1 H), 1.82–1.95 (m, 3 H), 2.06 (m, 1 H), 2.75 (s, 1 H), 2.77 (d, J = 8.4 Hz, 1 H), 2.96 (m, 1 H), 2.98 (d, J = 8.4 Hz, 1 H), 3.10 (ddd, J_1 = 11.8 Hz, J_2 = 8.3 Hz, J_3 = 6.8 Hz, 1 H), 3.44 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 3.67 (dt, J_1 = 9.2 Hz, J_2 = 6.8 Hz, 1 H), 3.80 (d, J = 6.3 Hz, 1 H), 4.75 (s, 1 H), 7.15–7.32 (m, 5 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5, 22.2, 24.9, 25.0, 25.2, 27.1, 28.2, 31.2, 35.0, 41.4, 42.9, 49.8, 52.6, 53.5, 55.2, 58.8, 71.5, 74.4, 83.6, 92.8, 126.2, 127.8 (2 C), 129.6 (2 C), 139.2 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3060, 3040, 3025, 2924, 2870, 1605, 1455, 1094, 730, 705, 640. $C_{26}H_{38}N_2O$ (394.59): calcd. C 79.14, H 9.71, N 7.10; found C 79.27, H 9.84, N 7.19.

Indolizino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2h: 1.07 g, 87%. Colorless oil. $[\alpha]_D^{25}$ = –18.5 (c = 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.75–1.11 (m, 4 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.93 (s, 3 H), 1.10 (s, 3 H), 1.13–1.28 (m, 2 H), 1.15 (s, 3 H), 1.31–1.50 (m, 3 H), 1.52–1.66 (m, 3 H), 1.71 (m, 1 H), 1.88 (m, 1 H), 2.45 (dt, J_1 = 11.8 Hz, J_2 = 2.7 Hz, 1 H), 2.79 (d, J = 8.5 Hz, 1 H), 2.80 (d, J = 5,3 Hz, 1 H), 3.02 (m, 1 H), 3.05 (d, J = 8.5 Hz, 1 H), 3.07 (m, 1 H), 3.17 (s, 1 H), 3.40 (td, J_1 = 10.4 Hz, J_2 = 4.2 Hz, 1 H), 4.90 (s, 1 H), 7.12–7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9, 22.3, 24.3, 24.8, 24.9, 25.7, 26.8, 28.0, 31.3, 35.0, 41.5, 43.4, 47.7 (CH_2), 49.1 (C), 53.0 (C), 61.0 (CH), 61.4 (CH_2), 63.7 (CH), 74.9 (CH), 76.2, 86.2, 125.7, 127.2 (2 C), 130.7 (2 C), 141.2 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3060, 3040, 3025, 2929, 2870, 1601, 1455, 770, 730, 710, 650, 620. $C_{27}H_{40}N_2O$ (408.62): calcd. C 79.36, H 9.87, N 6.86; found C 79.24, H 9.99, N 6.97.

Indolizino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 2i: Yield 702 mg, 63%. Colorless oil. $[\alpha]_D^{25}$ = –8.2 (c = 2.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.89–1.26 (m, 6 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.05 (s, 3 H), 1.14 (s, 3 H), 1.29–1.75 (m, 15 H), 1.86 (m, 1 H), 2.05 (m, 1 H), 2.46 (dt, J_1 = 11.8 Hz, J_2 = 2.7 Hz, 1 H), 2.64 (d, J = 8.5 Hz, 1 H), 2.80 (m, 1 H), 2.88 (m, 1 H), 2.89 (d, J = 8.5 Hz, 1 H), 3.14 (s, 1 H), 3.36 (td, J_1 = 10.4, J_2 = 4.2 Hz, 1 H), 4.92 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 22.3, 23.1, 24.2, 24.5, 24.8, 25.2, 26.0, 26.7, 26.9, 31.3, 35.1 (2 C), 41.6, 42.2, 47.4, 47.7, 48.5, 52.6, 61.7, 63.8, 71.2, 74.7, 87.0 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 2925, 2855, 1450, 735, 705. $C_{24}H_{40}N_2O$ (372.59): calcd. C 77.37, H 10.82, N 7.52; found C 77.24, H 10.91, N 7.60.

Reaction of 1a with Stabilized Azomethine Ylides: A mixture of **1a** (0.5 g, 2.0 mmol) and L-proline methyl ester (0.31 g, 2.4 mmol) or (methylamino)acetonitrile (0.17 g, 2.4 mmol) and anhydrous $MgSO_4$ (4.0 g) in toluene was refluxed for 3.5–4 hours. The solid was filtered, the solvent was removed under vacuum, and the residue was chromatographed on silica gel using hexane/EtOAc as eluent.

Methyl 1-[2-({2-[1-(Allylamino)-1-methylethyl]-5-methylcyclohexyl}-oxy)-2-oxoethyl]pyrrolidine-2-carboxylate (5): Yield 270 mg, 36%. Colorless oil. $[\alpha]_D^{25}$ = –52.6 (c = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.83–1.30 (m, 4 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.18 (s, 6 H), 1.53 (m, 1 H), 1.74 (m, 1 H), 1.80–2.12 (m, 5 H), 2.21 (m, 1 H), 2.75 (dt, J_1 = 8.3 Hz, J_2 = 7.6 Hz, 1 H), 3.16 (m, 1 H), 3.30 (dd, J_1 = 12.8 Hz, J_2 = 5.7 Hz, 1 H), 3.37 (dd, J_1 = 12.8 Hz, J_2 = 5.7 Hz, 1 H), 3.43 (d, J = 17.5 Hz, 1 H), 3.51 (d, J = 17.5 Hz, 1 H), 3.57 (dd, J_1 = 8.8 Hz, J_2 = 4.9 Hz, 1 H), 3.71 (s, 3 H), 4.65 (s, broad 1 H), 4.80 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 5.16 (d, J = 10.1 Hz, 1 H), 5.26 (d, J = 17.1 Hz, 1 H), 6.06 (ddt, J_1 = 17.1 Hz, J_2 = 10.1 Hz, J_3 = 5.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5, 23.3, 23.4, 24.5, 26.1, 29.3, 31.0, 34.1, 40.9, 44.5, 46.1, 51.7, 53.1, 54.5, 57.1, 63.9, 75.6, 117.2, 134.9, 169.5, 174.0 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3320, 3080, 2950, 1735, 1455, 730. $C_{21}H_{36}N_2O_4$ (380.52): calcd. C 66.28, H 9.54, N 7.36; found C 66.12, H 9.69, N 7.23.

Pyridazino[3′,2′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 6: Yield 215 mg, 30%. Colorless oil. $[\alpha]_D^{25}$ = –77.3 (c = 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.72–0.98 (m, 3 H), 0.83 (d, J = 6.5 Hz, 3 H), 1.01 (s, 3 H), 1.09 (s, 3 H), 1.27–1.57 (m, 4 H), 1.61 (m, 1 H), 1.73–1.90 (m, 4 H), 2.11 (m, 1 H), 2.44 (dd, J_1 = 12.6 Hz, J_2 = 8.8 Hz, 1 H), 2.54 (d, J = 8.3 Hz, 1 H), 2.78 (m, 1 H), 2.92 (m, 1 H), 3.01 (m, 1 H), 3.05 (dd, J_1 = 8.3 Hz, J_2 = 6.9 Hz, 1 H), 3.33 (td, J_1 = 10.3 Hz, J_2 = 4.1 Hz, 1 H), 3.58 (d, J = 8.3 Hz, 1 H), 3.62 (s, 3 H), 4.77 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4, 22.1, 24.8, 26.3, 27.3, 31.2, 34.4, 35.0, 41.3, 42.6, 42.7, 43.0, 47.9, 49.0, 52.1, 52.7, 71.7, 74.9, 78.7, 87.3, 176.5 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 2930, 2870, 1730, 1450, 730, 700. $C_{21}H_{34}N_2O_3$ (362.51): calcd. C 69.58, H 9.45, N 7.73; found C 69.52, H 9.60, N 7.58.

2-[1-(Allylamino)-1-methylethyl]-5-methylcyclohexyl [*N*-(Cyanomethyl)methylamino]acetate (7): Yield 560 mg, 88%. Colorless oil. $[\alpha]_D^{25}$ = +13.0 (c = 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.83–1.28 (m, 4 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.03 (s, 3 H), 1.06 (s, 3 H), 1.53 (m, 1 H), 1.67–1.78 (m, 2 H), 1.86 (m, 1 H), 1.98 (m, 1 H), 2.47 (s, 3 H), 3.12 (dd, J_1 = 12.9 Hz, J_2 = 5.8 Hz, 1 H), 3.24 (dd, J_1 = 12.9 Hz, J_2 = 5.8 Hz, 1 H), 3.25 (s, 2 H), 3.68 (d, J = 16.5 Hz, 1 H), 3.73 (d, J = 16.5 Hz, 1 H), 4.87 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 5.07 (dd, J_1 = 10.1 Hz, J_2 = 1.4 Hz, 1 H), 5.18 (dd, J_1 = 17.1 Hz, J_2 = 1.4 Hz, 1 H), 5.82–6.05 (ddt, J_1 = 17.1 Hz, J_2 = 10.1 Hz, J_3 = 5.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 24.8, 25.6, 26.4, 31.2, 34.3, 41.3, 42.4, 44.6, 44.9, 46.9, 54.8, 56.9, 76.0,114.4, 115.3, 137.6, 168.6 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3370, 3080, 2955, 1735, 1455, 1186, 995. $C_{18}H_{31}N_3O_2$ (321.46): calcd. C 67.25, H 9.72, N 13.07; found C 67.11, H 9.58, N 13.21.

General Procedure for 1,3-Dipolar Cycloaddition of Nitrones: A mixture of the appropriate aldehyde (3.0 mmol), *N*-methylhydroxylamine hydrochloride (0.3 g, 3.6 mmol) or *N*-benzylhydroxylamine hydrochloride (0.57 g, 3.6 mmol) and pyridine (0.6 mL, 7.5 mmol) in 50 mL of toluene was heated at 90 °C for the time given in Table 3. The mixture was poured into H_2O (100 mL) and extracted with Et_2O (3 × 30 mL). The combined organic fractions were washed with H_2O and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel with hexane/EtOAc as eluent.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8a: Yield 823 mg, 98%. Colorless oil. $[\alpha]_D^{25}$ = –25.1 (*c* = 1.8, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.85–1.09 (m, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 1.12 (s, 3 H), 1.14 (s, 3 H), 1.20–1.55 (m, 2 H), 1.59 (m, 1 H), 1.70 (m, 1 H), 1.87 (m, 1 H), 2.69 (m, 1 H), 2.72 (s, 3 H), 3.15–3.27 (m, 3 H), 3.42 (td, J_1 = 10.6 Hz, J_2 = 4.1 Hz, 1 H), 3.55 (dd, J_1 = 8.3 Hz, J_2 = 4.6 Hz, 1 H), 4.10 (dd, J_1 = 8.3 Hz, J_2 = 7.4 Hz, 1 H), 4.55 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 22.0, 24.8, 26.6, 31.2, 35.0, 41.4, 44.5, 44.6 (2 C), 48.2, 53.1, 71.4, 75.0, 78.0, 89.5 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 2925, 2870, 1455, 1055, 730, 705, 670. $C_{16}H_{28}N_2O_2$ (280.41): calcd. C 68.53, H 10.06, N 9.99; found C 68.41, H 9.91, N 10.09.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8b: Yield 838 mg, 95%. Colorless oil. $[\alpha]_D^{25}$ = –16.8 (*c* = 2.2, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.86–1.06 (m, 3 H), 0,91 (d, *J* = 6.5 Hz, 3 H), 1.11 (s, 3 H), 1.20 (s, 3 H), 1.28 (d, *J* = 6.2 Hz, 3 H), 1.39–1.47 (m, 2 H), 1.58 (m, 1 H), 1.70 (m, 1 H), 1.83 (m, 1 H), 2.60 (ddd, J_1 = 9.2 Hz, J_2 = 7.8 Hz, J_3 = 7.0 Hz, 1 H), 2.75 (d, *J* = 8.6 Hz, 1 H), 2.79 (s, 3 H), 3.03 (d, *J* = 9.2 Hz, 1 H), 3.16 (dd, J_1 = 8.6 Hz, J_2 = 7.0 Hz, 1 H), 3.42 (td, J_1 = 10.6 Hz, J_2 = 4.0 Hz, 1 H), 3.77 (dq, J_1 = 7.8 Hz, J_2 = 6.2 Hz, 1 H), 4.65 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.5, 21.5, 22.1, 24.7, 26.8, 31.1, 34.8, 41.2, 42.7, 45.0, 46.7, 52.5 (2 C), 74.5, 79.4 (2 C), 88.6 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 2925, 2770, 1455, 705, 670, 610. $C_{17}H_{30}N_2O_2$ (294.43): calcd. C 69.35, H 10.27, N 9.51; found C 69.42, H 10.24, N 9.64.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8c: Yield 818 mg, 93%. Colorless oil. $[\alpha]_D^{25}$ = –17.3 (*c* = 1.2, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.88–1.07 (m, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 1.09 (s, 3 H), 1.15 (s, 3 H), 1.34 (s, 3 H), 1.39–1.52 (m, 2 H), 1.58 (m, 1 H), 1.70 (m, 1 H), 1.87 (m, 1 H), 2.63 (s, 1 H), 2.78 (s, 3 H), 2.82 (d, *J* = 8.5 Hz, 1 H), 2.93 (d, *J* = 8.5 Hz, 1 H), 3.41 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 3.70 (s, 2 H), 4.59 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 333 K): δ = 19.9, 22.1, 24.8 (2C), 26.8, 31.3, 35.1, 41.5, 44.0, 45.0, 52.9, 53.3, 55.0, 74.9, 78.2, 84.8, 89.9 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 2925, 2870, 2775, 1460, 735, 705, 670. $C_{17}H_{30}N_2O_2$ (294.43): calcd. C 69.35, H 10.27, N 9.51; found C 69.26, H 10.18, N 9.64.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8d: 1.0 g, 94%. Colorless oil. $[\alpha]_D^{25}$ = –49.7 (*c* = 0.7, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.85–1.09 (m, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 1.15 (s, 3 H), 1.25 (s, 3 H), 1.40–1.56 (m, 2 H), 1.59 (m, 1 H), 1.70 (m, 1 H), 1.85 (m, 1 H), 2.87 (d, *J* = 8.7 Hz, 1 H), 2.88 (s, 3 H), 3.08 (ddd, J_1 = 9.1 Hz, J_2 = 7.9 Hz, J_3 = 6.8 Hz, 1 H), 3.20 (dd, J_1 = 8.7 Hz, J_2 = 6.8 Hz, 1 H), 3.22 (d, *J* = 9.1 Hz, 1 H), 3.45 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 4.65 (d, *J* = 7.9 Hz, 1 H), 4.73 (s, 1 H), 7.26–7.41 (m, 5) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.7, 22.2, 24.8, 27.0, 31.2, 34.9, 41.3, 42.8, 45.2, 47.0, 52.8, 53.2, 74.7, 79.7, 85.7, 88.9, 127.0 (2 C), 128.1, 128.4 (2C), 138.5 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3060, 3030, 2925, 2870, 2775, 1605, 1495, 1455, 755, 745, 700, 675. $C_{22}H_{32}N_2O_2$ (356.50): calcd. C 74.12, H 9.05, N 7.86; found C 74.01, H 8.92, N 7.97.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8e: Yield 998 mg, 90%. Colorless oil. $[\alpha]_D^{25}$ = –22.2 (*c* = 1.1, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.80 (s, 3 H), 0.90–1.10 (m, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 1.17 (s, 3 H), 1.24 (s, 3 H), 1.40–1.52 (m, 2 H), 1.59 (m, 1 H), 1.72 (m, 1 H), 1.87 (m, 1 H), 2.72 (s, 1 H), 2.89 (s, 3 H), 2.91 (d, *J* = 8.7 Hz, 1 H), 3.05 (d, *J* = 8.7 Hz, 1 H), 3.45 (dt, J_1 = 10.5 Hz, J_2 = 4.1 Hz, 1 H), 4.72 (s, 1 H), 4.88 (s, 1 H), 7.21–7.32 (m, 5) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 22.2 (2C), 24.9, 27.1, 31.2, 35.0, 41.3, 42.8, 45.7, 52.8, 55.1, 55.8, 76.6, 86.6, 87.0, 89.6, 126.3 (2C), 127.4, 127.8 (2C), 136.7 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3085, 3060, 3030, 2925, 2870, 2775, 1605, 1495, 1455, 745, 735, 705. $C_{23}H_{34}N_2O_2$ (370.53): C 74.55, H 9.25, N 7.56; found C 74.46, H 9.40, N 7.65.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8f: Yield 939 mg, 94%. Colorless oil. $[\alpha]_D^{25}$ = –1.82 (*c* = 6.0, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.85–1.07 (m, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 1.09 (s, 3 H), 1.16 (s, 3 H), 1.15 (m, 1 H), 1.38–1.53 (m, 4 H), 1.55–1.77 (m, 6 H), 1.85 (m, 1 H), 1.96 (m, 1 H), 2.67 (s, 1 H), 2.82 (d, *J* = 8.3 Hz, 1 H), 2.84 (s, 3 H), 2.88 (d, *J* = 8.3 Hz, 1 H), 3.41 (td, J_1 = 10.5, J_2 = 4.2 Hz, 1 H), 3.82 (dd, J_1 = 4.3 Hz, J_2 = 2.8 Hz, 1 H), 3.84 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.7, 21.2, 21.9, 22.2, 23.8, 24.8, 26.9, 31.2, 33.4, 35.0, 41.4, 43.1, 46.0, 52.7, 53.3, 54.1, 74.6, 79.7, 86.3, 89.3 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 2925, 2870, 1455, 740, 705. $C_{20}H_{34}N_2O_2$ (334.50): calcd. C 71.81, H 10.25, N 8.37; found C 71.92, H 10.35, N 8.24.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8g: Yield 980 mg, 92%. Colorless oil. $[\alpha]_D^{25}$ = –10.8 (*c* = 2.3, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.81–1.01 (m, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 1.06 (s, 3 H), 1.08 (s, 3 H), 1.40–1.50 (m, 2 H), 1.58 (m, 1 H), 1.69 (m, 1 H), 1.84 (m, 1 H), 2.66 (dd, J_1 = 8.2 Hz, J_2 = 1.9 Hz, 1 H), 3.15 (m, 1 H), 3.21 (dd, J_1 = 8.2 Hz, J_2 = 7.1 Hz, 1 H), 3.30 (td, J_1 = 10.5 Hz, J_2 = 4.1 Hz, 1 H), 3.37 (d, *J* = 8.7 Hz, 1 H), 3.56 (dd, J_1 = 8.1, Hz, J_2 = 5.0 Hz, 1 H), 3.85 (d, *J* = 13.1 Hz, 1 H), 4.04 (d, *J* = 13.1 Hz, 1 H), 4.09 (t, *J* = 8.1 Hz, 1 H), 4.39 (s, 1 H), 7.20–7.44 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.9, 22.0, 24.6, 26.6, 31.0, 34.8, 41.2, 44.1, 44.3, 48.1, 52.9, 61.2, 71.3, 74.7, 76.0, 89.7, 127.1, 128.0 (2C), 129.0 (2C), 136.8 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3085, 3060, 3030, 2925, 2865, 1605, 1495, 1455, 730, 700. $C_{22}H_{32}N_2O_2$ (356.50): calcd. C 74.12, H 9.05, N 7.86; found C 74.28, H 9.14, N 7.77.

Isoxazolo[3′,4′:3,4]pyrrolo[2,1-*b*][1,3]benzoxazine Derivative 8h: Yield 931 mg, 84%. Colorless oil. $[\alpha]_D^{25}$ = –16.4 (*c* = 2.3, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.80–1.01 (m, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.06 (s, 3 H), 1.07 (s, 3 H), 1.26 (d, *J* = 6.1 Hz, 3 H), 1.37 (m, 2 H), 1.53 (m, 1 H), 1.67 (m, 1 H), 1.75 (m, 1 H), 2.55 (ddd, J_1 = 9.4 Hz, J_2 = 7.8 Hz, J_3 = 6.9 Hz, 1 H), 2.67 (d, *J* = 8.6 Hz, 1 H), 3.10 (dd, J_1 = 8.6 Hz, J_2 = 6.9 Hz, 1 H), 3.14 (td, J_1 = 10.5 Hz, J_2 = 4.2 Hz, 1 H), 3.24 (d, *J* = 9.4 Hz, 1 H), 3.78 (dq, J_1 = 7.8 Hz, J_2 = 6.1 Hz, 1 H), 3.91 (d, *J* = 12.6 Hz, 1 H), 4.18 (s, 1 H), 4.20 (d, *J* = 12.6 Hz, 1 H), 7.20–7.34 (m, 3 H), 7.37–7.43 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.7, 21.3, 22.1, 24.7, 26.8, 31.1, 34.9, 41.3, 42.9, 46.4, 52.2, 52.6, 62.7, 74.5, 77.5, 79.0, 89.2, 127.2, 128.0 (2C), 129.5 (2C), 136.5 ppm. IR (film, cm^{-1}): $\tilde{\nu}$ = 3085, 3060, 3030, 2925, 2870, 1605, 1495, 1455, 750, 735, 700. $C_{23}H_{34}N_2O_2$ (370.53): calcd. C 74.55, H 9.25, N 7.56; found C 74.62, H 9.31, N 7.65.

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