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Generation of functionalized azomethine ylides and their application to stereoselective heterocycle synthesis: an equivalent process of *C*-unsubstituted nitrile ylide cycloaddition reaction

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Abstract—The synthetic process equivalent to *C*-unsubstituted (CH) nitrile ylides cycloaddition reaction is achieved via cycloaddition of NH-azomethine ylide and the following fission reaction of the cycloadducts under acidic conditions. Cycloaddition of NH-azomethine ylide generated by a thermal 1,2-prototropy in 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde system with maleimides provides proline derivatives under extremely mild conditions. Heating their adducts in AcOH at 85 °C causes a cleavage of C–C bond between the proline and heterocyclic moiety to give the parent heterocyclic system and dehydroproline derivatives, which is regarded as a cycloadduct of *C*-unsubstituted (CH) nitrile ylide. This cycloaddition–fission reaction sequences can be applied to one-pot three-component reaction.
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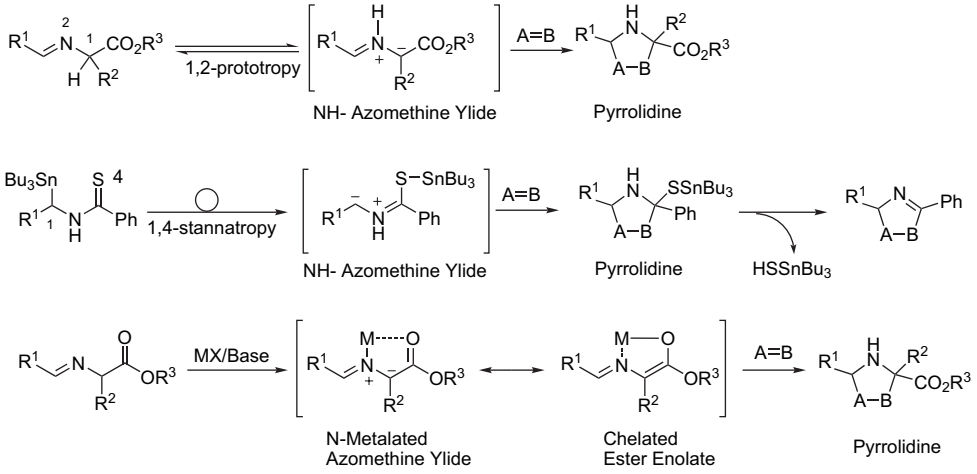
1. Introduction

The cycloaddition reaction of azomethine ylides with alkenes is a useful synthetic method for polysubstituted pyrrolidine derivatives, which are widely found in natural products and biologically active compounds.[1] Among them, the chemistry of *N*-unsubstituted (NH) azomethine ylides has been more attractive due to the biological and pharmacological aspects of *N*-unsubstituted (NH) pyrrolidines. Representative approaches for the generation of NH-azomethine ylides are constituted of three methodologies (Scheme 1). The first is thermal and uncatalyzed isomerization of α-iminoester to NH-azomethine ylide through a 1,2-prototropy, which was first reported by Grigg and Kemp at 1977.[2] They afterward systematized the imine-azomethine ylide isomerization as one of the general methodology of NH-1,3-dipole generation from X=Y–ZH system.[3] The highly acidic hydrogen adjacent to the imine migrates to the nitrogen to produce the



Scheme 1. Three representative methodologies for NH-azomethine ylide generation.

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NH-azomethine ylide under neutral conditions, which takes part in the cycloaddition reaction with various activated dipolarophiles. Formation of the NH-azomethine ylide is sensitive to the pK_a of α-hydrogen and the basicity of imine nitrogen, and the equilibrium between imine and NH-azomethine ylide leans to the imine side. Therefore, very harsh reaction conditions, i.e., benzene or toluene at reflux for longtime, are required for generation of the species, which lead to less-stereoselective cycloaddition reaction. The second method is generation from α-metalloimines and α-metalloamides by utilizing 1,2- and 1,4-metallotropic strategy reported by Komatsu and co-workers.[4] For example, in the reactions of α-stannylthioamides, the strong affinity between Sn and sulfur causes a 1,4-stannatropy to afford the NH-azomethine ylide. The reaction with dipolarophiles, such as electron-deficient alkenes and alkynes, provided the corresponding pyrrolidine and pyrrole derivatives in good to excellent yields. It should be noted that the cycloaddition reaction of NH-azomethine ylides generated by 1,4-stannatropy is regarded as nitrile ylide equivalents, because cycloadducts of the corresponding nitrile ylides are obtained as the results of cycloaddition of the azomethine ylide followed by the elimination of Bu_3SnSH. The production of highly toxic Sn compound is the weak point of this methodology. The third method is N-metalation of α-iminoesters.[5] Treatment of the α-iminoester possessing a coordinating group with MX/base provides *N*-metalated azomethine ylide in situ, which reacts with activated alkenes at a low temperature. Various Lewis acids such as Ag, Cu, and Li salts can be used for generation of the species in conjunction with various bases such as Et_3N, Hunig's base, and DBU. The cycloaddition reaction involving the *N*-metalated azomethine ylide can overcome the less stereoselectivity, which is the disadvantage point of 1,2-prototropic strategy, and recently the application of this strategy to a catalytic enantioselective version has been achieved by a number of research groups.[6]

As a part of our projects to develop 1,3-dipolar cycloadditions at the periphery of heterocyclic system, we reported a facile generation of NH-nitrones **C** and NH-azomethine imines **D** from oximes **A** and hydrazones **B** through the 1,2-prototropy under neutral conditions (Scheme 2).[7,8] The intermolecular cycloaddition reaction of the NH-azomethine imines **D** with olefinic dipolarophiles such as *N*-phenylmaleimide (NPMI), dimethyl maleate, and dimethyl fumarate in benzene at reflux provided the corresponding pyrazolidine derivatives **F** in moderate to good yields. Although the cycloaddition reaction of NH-nitrones **C** with dimethyl maleate and dimethyl fumarate did not proceed, we succeeded in proceeding the cycloaddition reaction with NPMI in benzene at reflux and offering the second example of intermolecular cycloaddition reaction of NH-nitrone. We proposed that the internal hydrogen bond formation between the NH of resulting dipoles and carbonyl oxygen in the heterocycles might facilitate the generation of the NH-dipoles. The fission reaction of the cycloadduct made synthetic utility of our chemistry more convenient, i.e., treatment of the pyrazolidines **F** obtained from cycloaddition of NH-azomethine imines **D** with pyridinium *p*-toluenesulfonate (PPTS) caused a cleavage of the C–C bond between the pyrazolidine and heterocyclic moiety to give 2-pyrazoline derivatives **G** in good yields, which can be useful synthetic building block.

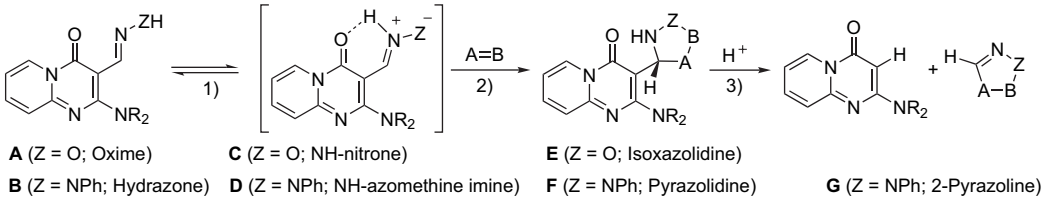
In this paper, we will report the generation of NH-azomethine ylide from aldimine in the same heterocyclic system under extremely mild conditions and their stereoselective cycloaddition reaction. Imines are derived from heterocyclic aldehydes and amino acid methyl esters, and we expect that the generated NH-azomethine ylides from the corresponding imines are fixed only one configuration by double internal hydrogen bond formations between the NH of resulting dipoles and the carbonyl oxygen in the heterocycle and ester carbonyl oxygen, which leads the stereoselective cycloaddition reaction with maleimides. Fission reaction of cycloadducts under acidic conditions accompanied by the stereoselective cycloaddition will provide various dehydroproline derivatives. The application of the cycloaddition–fission reaction sequences to a one-pot three-component process will also be discussed.

2. Results and discussion

2.1. Optimization of reaction conditions and substrates

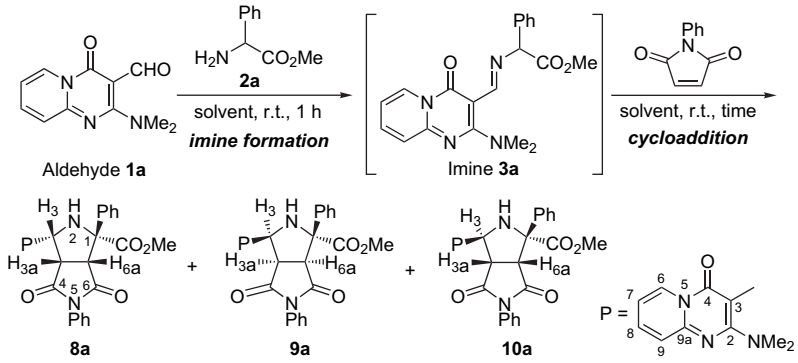
In order to elucidate the scope and features of the imine-azomethine ylide isomerization in pyrido[1,2-*a*]pyrimidine-4(4*H*)-one system, four aldehydes **1a**–**d**, which have *N*,*N*-dimethylamino (**1a**), *N*,*N*-dibenzylamino (**1b**), pyrrolidine-1-yl (**1c**), and morpholino (**1d**) groups at 2-position of heterocyclic moiety were prepared and thermal reaction was explored with NPMI.

At the outset, the cycloaddition reactions of imine **3a** with NPMI were carried out in various solvents at room temperature in order to determine the best reaction solvent (Table 1). In all cases, imine **3a** was generated only in situ and used for reaction without isolation. Typical experimental procedure was provided as following; aldehyde **1a** (1.0 equiv) and (DL)-phenylglycine methyl ester **2a** (1.1 equiv) were combined in solvent (0.5 M of **1a**) and the mixture was stirred for 1 h under an aerobic atmosphere, and then NPMI was added. The mixture was stirred at room temperature for the indicated time. Although the reaction in acetonitrile provided proline derivatives **8a** (93), **9a** (5), and **10a** (2) in a quantitative yield, it took about 30 h to complete the reaction (Table 1,



Scheme 2. Reaction modes: (1) 1,2-prototropy; (2) cycloaddition reaction; and (3) fission reaction.

Table 1. Optimization of reaction solvent



Entry	Solvent	Time (h)	Products	Yield[a] (%)	Isomer ratio[b] **8a**:**9a**:**10a**	*endo*:*exo*
1	MeCN	32		Quant.	93:5:2	98:2
2	DME	27	**8a**+**9a**+**10a**	Quant.	92:6:2	98:2
3	Toluene	1		Quant.	97:2:1	99:1
4	EtOH	45	**8a**	43	—	—

[a] The yield is isolated yield.
[b] Determined by ^{1}H NMR.

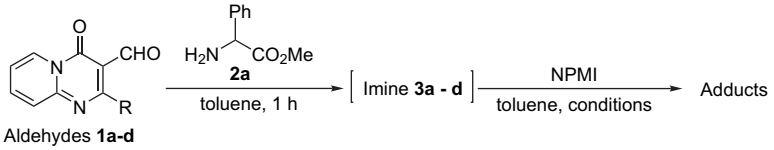
entry 1). From the inspection of their spectroscopic data it was found that, proline **8a** was formed through the *endo*-approach of NPMI to the kinetically favored (*E*,*E*)-dipole. On the other hand, prolines **9a** and **10a** were deduced to *endo*- and *exo*-approaches of NPMI to (*E*,*Z*)-dipole, respectively, as discussed later. The reaction in 1,2-dimethoxyethane (DME) also provided similar results (Table 1, entry 2). The reaction in ethanol was very sluggish and led to recovery of aldehyde **1a** even after 45 h (entry 4). In the case of toluene, the reaction proceeded on smoothly within 1 h together with a quantitative yield and high *endo*-selectivity. The reason why the reactions in acetonitrile, DME, and ethanol were sluggish in comparison with the reaction in toluene is that it would be hard to generate the imine **3a** in situ. In view of efficiency and selectivity, we chose toluene as the best reaction solvent.

Next, we focused on the effect of amino groups at 2-position of heterocyclic moiety on diastereoselectivity of the reaction (Table 2). The cycloaddition reaction of imines **3a–d** with NPMI was performed at 85 °C and room temperature, using toluene. In all cases, the cycloaddition reactions gave excellent yields and *endo*-selectivity. Although the reaction using aldehyde **1a** at 85 °C proceeded within 10 min, the diastereoselectivity of proline **8a** was moderate (entry 1). The reaction using aldehyde **1a** at room temperature provided the highest diastereoselectivity (94% de) of **8a** (entry 2). The reaction using the other aldehydes (entries 3–5) at room temperature afforded moderate diastereoselectivities (72–80% de) of the corresponding prolines **8**. It is worth noting that the corresponding prolines **10** were not formed when aldehydes **1b** and **1d** were used in the reaction. The bulky amino groups would suppress the formation of cycloadducts **10b** and **10d**. In view of selectivity, *N*,*N*-dimethylamino group was adopted as the best amino group of heterocyclic moiety.

2.2. Amino acid methyl ester scope

To investigate the scopes and limitations of imine-azomethine ylide isomerization and its intermolecular cycloaddition reaction, a variety of amino acid methyl esters were used to form imines **3e–i** and these imines were subjected

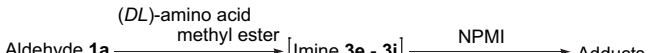
Table 2. Influence of amino groups R on reaction selectivity



Entry	Aldehyde	R	Cycloaddition conditions	Adducts	Yield[a] (%)	de (%) of **8**	*endo*:*exo*
1	**1a**	$N(Me)_2$	85 °C, <10 min	**8a**+**9a**+**10a**	Quant.	74	98:2
2			rt, 60 min		Quant.	94	99:1
3	**1b**	$N(Bn)_2$	rt, 90 min	**8b**+**9b**	Quant.	80	100:0
4	**1c**		rt, 60 min	**8c**+**9c**+**10c**	Quant.	72	97:3
5	**1d**		rt, 60 min	**8d**+**9d**	94	76	100:0

[a] The yield is isolated yield.

Table 3. Generality of amino acid esters



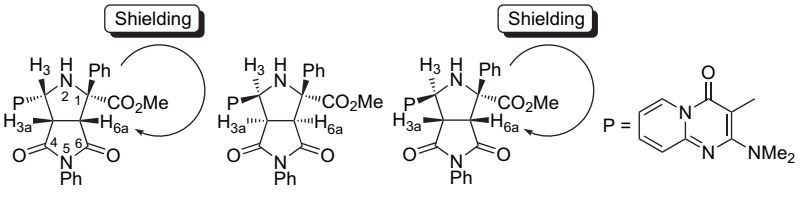
Entry	(DL)-amino acid methyl ester	Imine	Conditions	Products	Isomer ratio[a] **8**:**9**:**10**	Yield[b] (%)	*endo*:*exo*
1	Gly (R^1=H)	**3e**	85 °C, 21 h	**8e+10e**	82:0:18	67	82:18
2	Ala (R^1=Me)	**3f**	85 °C, 3 h	**8f+9f**	94:6:0	76	100:0
3	Val (R^1=*i*-Pr)	**3g**	85 °C, 2.5 h	**8g+9g**	43:57:0	72	100:0
4			rt, 22 h		38:62:0	98	100:0
5	Phe (R^1=Bn)	**3h**	85 °C, 0.5 h	**8h+9h**	90:10:0	85	100:0
6			rt, 1 h	**8h+9h**	97:3:0	88	100:0
7			−30 °C, 20 h	**8h**	100:0:0	88	100:0
8	Met	**3i**	85 °C, 1 h	**8i+9i**	86:14:0	94	100:0
9	(R^1=$(CH_2)_2$SMe)		rt, 24 h		94:6:0	77	100:0

[a] Determined by ^{1}H NMR.
[b] The yield is isolated yield.

to react with NPMI without isolation (Table 3). In entries 2–9, the cycloaddition reaction with NPMI yielded the corresponding proline derivatives in good to excellent yields (72–98%) and the perfect *endo*-selectivity was achieved. The simplest imine **3e** derived from glycine methyl ester reacted with NPMI at 85 °C for 21 h to give the proline derivatives **8e** and **10e** as a 82:18 ratio in 67% yield (entry 1). Why **10e** was obtained as a minor product is unclear yet. Imine **3f** derived from (DL)-alanine methyl ester also underwent the cycloaddition reaction with NPMI at 85 °C for 3 h to give the corresponding proline derivatives **8f** and **9f** as a 94:6 ratio in 76% yield (entry 2). Sterically hindered imine **3g** also reacted with NPMI at 85 °C for 2.5 h, and the corresponding proline derivatives **8g** and **9g** were isolated as a 43:57 ratio in 72% yield (entry 3). Although the prolonged reaction time was required to complete the reaction, the reaction of imine **3g** with NPMI at room temperature provided proline derivatives **8g** and **9g** as a 38:62 ratio in 98% yield (entry 4). We will discuss later in this paper why adducts **8g** and **9g** were obtained almost even ratio in the case of imine **3g**. Aromatic-substituted imine **3h** (R^1=Bn) and heteroalkyl-substituted imine **3i** (R^1=$(CH_2)_2$SMe) were also good substrates for this reaction at both 85 °C and room temperature, and the corresponding proline derivatives were isolated in 77–94% yields and good diastereoselectivities (entries 5, 6, 8, and 9). In order to elucidate the scope and features of the imine-azomethine ylide isomerization in this system, imine **3h** was subjected to react with NPMI at −30 °C. Surprisingly, the cycloaddition reaction of imine **3h** with NPMI proceeded even at −30 °C, although it took about 20 h to complete the reaction, and the proline **8h** was obtained as a sole product in 88% yield (entry 7).

2.3. Structural determination

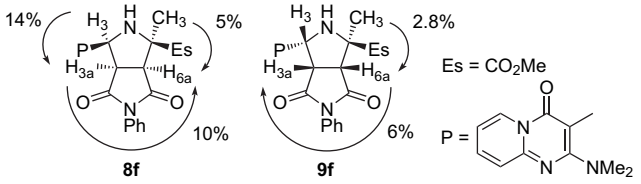
The structure of prolines **8a**, **9a**, and **10a** was fully characterized by ^{13}C NMR and COSY experiments as well as the coupling constants of ^{1}H NMR spectra. Since prolines **8a** and **9a** have large coupling constants between H_3 and H_{3a}, and H_{3a} and H_{6a} as shown in Figure 1, the relative configurations among the three methine protons (H_3, H_{3a}, and H_{6a}) in the proline ring were assigned to be all cis. In the proline **10a**, the relative configuration between H_{3a} and H_{6a} was assigned to be cis on the basis of large coupling constant ($J_{H3a–H6a}$=10.6 Hz), while between H_3 and H_{3a} was assigned to be trans on the basis of small coupling constant ($J_{H3–H3a}$=7.3 Hz) as showing in Figure 1. In view of the shielding effect of phenyl group on H_{6a}, the relative configurations between phenyl group and H_{6a} in prolines **8a**, **9a**, and **10a** were determined. Since prolines **8a** and **10a** have the chemical shift values of H_{6a} in higher field, relative configurations between phenyl group and H_{6a} were assigned to be cis. In the case of proline **9a**, its correlation was trans because it has the chemical shift value of H_{6a} in lower field.



cycloadduct	$J_{3\text{-}3a}$ (Hz)	$J_{3a\text{-}6a}$ (Hz)	6a-H (ppm)
8a	9.2 (*cis*)	8.3 (*cis*)	4.31 - 4.40
9a	9.2 (*cis*)	7.9 (*cis*)	4.76
10a	7.3 (*trans*)	10.6 (*cis*)	4.12

Figure 1. Selected ^{1}H NMR spectral data for prolines **8a**, **9a**, and **10a**.

Finally, the structure of proline **8a** was confirmed by its single-crystal X-ray analysis.[9] The structure of prolines **8b–d**, **9b–d**, and **10c** was determined by the same considerations as mentioned above. The structure of prolines **8e** and **10e** was also characterized by ^{13}C NMR, COSY and NOE experiments as well as the coupling constants of ^{1}H NMR spectra. It was predicted that the relative configurations among the four methine protons (H_1, H_3, H_{3a}, and H_{6a}) in proline **8e** were all cis on the basis of the coupling constants ($J_{H1–H6a}$=8.9 Hz, $J_{H3a–H6a}$=8.6 Hz, and $J_{H3–H3a}$=7.3 Hz). In the case of proline **10e**, the correlations among four methine protons (H_1, H_3, H_{3a}, and H_{6a}) predicted that H_1 and H_{6a}, and H_{3a} and H_{6a} were cis, while H_3 and H_{3a} was trans on the basis of the coupling constants ($J_{H1–H6a}$=8.9 Hz, $J_{H3a–H6a}$=8.6 Hz, and $J_{H3–H3a}$=1.0 Hz). NOE experiments of prolines **8e** and **10e** made our predictions mentioned above undoubted (Fig. 2). The structure of prolines **8f** and **9f** were deduced on the basis of the coupling constants in ^{1}H NMR spectra and NOE experiments. The details are summarized in Figure 3. The structure of the other prolines **8g–i** and **9g–i** was confirmed on comparison with ^{1}H NMR spectral data of prolines **8f** and **9f**. The structure of prolines **8f** and **8g** was confirmed by their single-crystal X-ray analysis.[9]

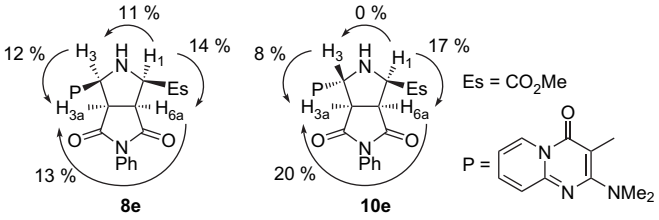


Cycloadduct	3-H (ppm)	3a-H (ppm)	6a-H (ppm)	J_{3-3a} (Hz)	J_{3a-6a} (Hz)
8f	4.75	3.66	3.54	9.2 (*cis*)	8.3 (*cis*)
9f	4.60	3.66	4.10	9.2 (*cis*)	8.3 (*cis*)

Figure 3. Selected ^{1}H NMR spectral data and NOE signal enhancements for prolines **8f** and **9f**.

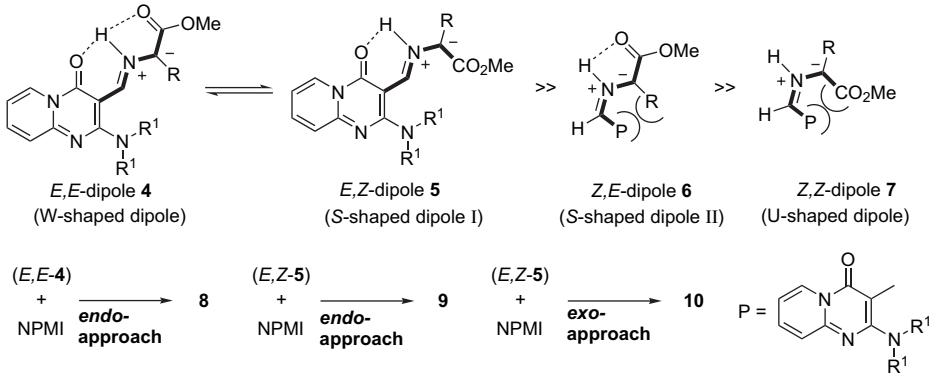
2.4. Reaction mechanism

Four geometrical isomers **4–7** are possible for the NH-azomethine ylides formed through the thermal 1,2-prototropy of imines **3a–i** and these ylides could be interconverted to each other under the reaction conditions (Scheme 3). Relative stability among them could be evaluated on the grounds of steric repulsion and intramolecular hydrogen bond formation between the NH and the carbonyl oxygen. The severe steric repulsion exists in both *Z*,*E*-dipole **6** and *Z*,*Z*-dipole **7** between heterocyclic moiety (P) and R groups (in the dipole **6**) or ester group (in the dipole **7**); accordingly, they would be excluded from reaction species involved in cycloaddition reaction. The *E*,*E*-dipole **4** is stabilized by double intramolecular hydrogen bonds, therefore, this is kinetically predominant dipole. The *E*,*Z*-dipole **5** having only one hydrogen bond is the second predominant dipole. Prolines **8** were formed through the *endo*-approach of NPMI to the kinetically favored *E*,*E*-dipole **4**. Likewise, the *endo*-approach of NPMI to the *E*,*Z*-dipole **5** would lead to prolines **9** and *exo*-approach of the one to the same dipole would lead to prolines **10**. The cycloaddition reaction of imine **3g**, which was derived from the condensation of (DL)-valine methyl ester and aldehyde **1a**, exceptionally gave the two diastereomers **8g** and **9g** in an almost 1:1 ratio. A likely account for this result is suggested as follows; the dipole **4g**



Cycloadduct	J_{1-6a} (Hz)	J_{3a-6a} (Hz)	J_{3-3a} (Hz)
8e	8.9 (*cis*)	8.6 (*cis*)	7.3 (*cis*)
10e	8.9 (*cis*)	8.6 (*cis*)	1.0 (*trans*)

Figure 2. Selected ^{1}H NMR spectral data and NOE signal enhancements for prolines **8e** and **10e**.

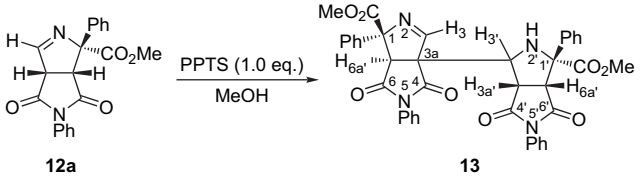


Scheme 3. Four possible isomers **4–7** for NH-azomethine ylide.

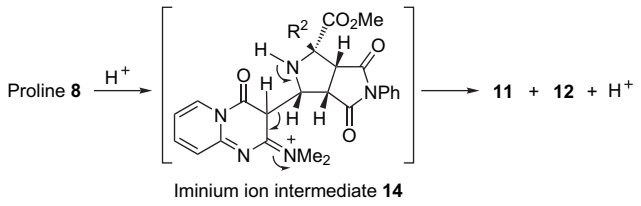
(R=*i*-Pr) would still be kinetically favored dipole, in which a severe steric repulsion between the isopropyl group and the azomethine proton is there. Therefore, dipole **4g** could be easily converted to dipole **5g** in order to release this steric repulsion and the concentration of dipole **4g** and **5g** in situ would become nearly even. Consequently, prolines **8g** and **9g** were obtained in an almost 1:1 ratio.

2.5. Fission reaction of cycloadducts and its application to one-pot three-component reaction

In the preceding paper,[8] we reported that the fission reaction of cycloadducts obtained from the cycloaddition reaction of NH-azomethine imines with NPMI took place in the presence of PPTS, where a cleavage of C–C bond between pyrazolidine and heterocyclic moiety occurred to give the parent heterocyclic system and 2-pyrazoline derivatives in high yields. We expected that the treatment of prolines **8** with acids would cause a similar fission reaction to give the parent heterocyclic system and dehydroproline derivatives. The treatment of proline **8a** with PPTS in acetonitrile provided 2-(*N*,*N*-dimethylamino)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one **11a** in 90% yield and inseparable mixture of dehydroproline **12a** and its dimer **13** as 4:1 ratio in 73% yield (Table 4, entry 1). It was found that the dehydroproline **12a** was easily dimerized under acidic conditions, i.e., the treatment of **12a** with PPTS in refluxing methanol for 15 h gave the dimer **13** in 92% yield (Scheme 4). The structure of dimer **13** was characterized by ^{1}H, ^{13}C NMR, and mass spectra. Especially mass spectra provided clear evidence of dimer **13** (FAB-mass: *m*/*z* 697 (MH^+), 637, 349 (1/2MH^+, base peak), 289). The dimer **13** existed as two isomeric mixture (1:1 ratio) in $CDCl_3$ solution. Although it is not clear in detail whether those isomers are related as diastereomers or rotamers, we suggest the latter on the basis of the sharp melting point and molecular model considerations. The dimerization of **12a** would proceed via acid-catalyzed Mannich type addition. Heating proline **8a** in acetic acid (AcOH) at 85 °C suppressed the formation of dimer **13** and provided **11a** in 67% yield and dehydroproline **12a** in 83% yield (Table 4, entry 2). The fission reaction of prolines **8b–d** under similar conditions was essentially independent of amino substituent at the 2-position of heterocyclic moiety and gave the corresponding heterocyclic moieties **11b–d** and dehydroproline **12a** in good yields (Table 4, entries 3–5). Prolines **8f–i** were also good substrates for this reaction to give the corresponding heterocyclic moiety **11a** and dehydroprolines **12f–i** in good yields (Table 4, entries 6–9). The fission reaction of proline **8e** (R^2=H) was also examined in AcOH solution at 50 °C. Four products were detected on TLC analysis after 9 h and they were identified as **8e**, aldehyde **1a**, NPMI, and **11a** by ^{1}H NMR analysis of the crude mixture. This result indicated that retro-cycloaddition reaction proceeded in this case. A likely mechanism for this conversion is suggested in Scheme 5. A reaction path similar to a retro-Mannich addition process catalyzed by proton was proposed for this conversion. A protonation at the 3-position of **8** affords an iminium ion intermediate **14**, which undergoes a retro-Mannich type reaction to give the parent heterocyclic moiety **11** and dehydroproline **12**.



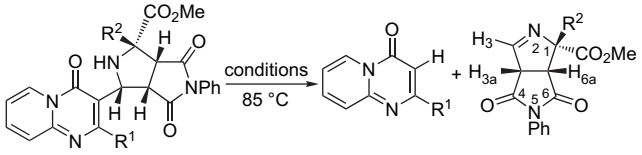
Scheme 4. Dimerization of dehydroproline **12a** in the presence of PPTS.



Scheme 5. Plausible pathway for fission reaction of proline **8**.

In order to make the cycloaddition–fission reaction sequences more efficient, these reaction sequences were

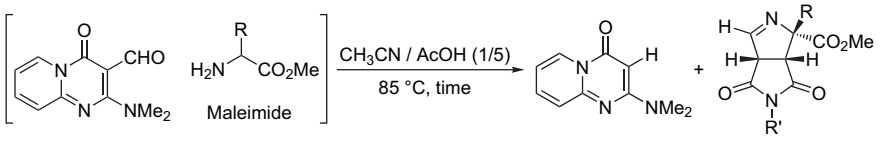
Table 4. Fission reaction of prolines **8**



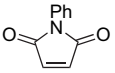
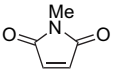
Entry	Cycloadduct	R^1	R^2	Reaction conditions			Product/yield (%)	
				Solv.	Additive (equiv)	Time (h)		
1	**8a**	NMe_2	Ph	CH_3CN	PPTS (1.0)	3.0	**11a**/90	**12a**/73[a]
2				AcOH	None	0.5	**11a**/67	**12a**/83
3	**8b**	NBn_2			None	4.5	**11b**/83	**12a**/81
4	**8c**	Pyrrolidin-1-yl	Ph	AcOH	None	0.75	**11c**/90	**12a**/82
5	**8d**	Morpholino			None	3.0	**11d**/73	**12a**/88
6	**8f**	NMe_2	Me	AcOH	None	1.5	**11a**/quant.	**12f**/quant.
7	**8g**		*i*-Pr			0.5	**11a**/84	**12g**/84
8	**8h**		Bn			1.0	**11a**/70	**12h**/84
9	**8i**		$(CH_2)_2SMe$			0.5	**11a**/89	**12i**/91

[a] The yield included 15% of dimer **13**.

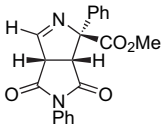
Table 5. Synthesis of dehydroprolines **12** via one-pot three-component reaction



11a **12a, h-k**

Entry	R	R′	Maleimide	Time (h)	Product/yield (%)	
1[a]	Ph	Ph		3	**11a**/83	**12a**/78
2	Bn	Ph		1	**11a**/89	**12h**/94
3	$(CH_2)_2SMe$	Ph		1.5	**11a**/96	**12i**/61
4	Ph	Me		5	**11a**/86	**12j**/85
5	Bn	Me		3	**11a**/94	**12k**/78

[a] Dehydroproline **12a′** was also obtained in 10% yield.



12a'

applied to one-pot three-component reaction. The results of our survey for the one-pot reaction are compiled in Table 5. The one-pot reaction of aldehyde **1**, (DL)-phenylglycine methyl ester, and NPMI in acetonitrile/acetic acid (=1/5) solution was examined at the outset, and dehydroproline **12a**, its isomer **12a′**, and the parent heterocyclic system **11a** was obtained in 78%, 10%, and 83% yields, respectively (Table 5, entry 1). The progress of the one-pot reaction could be traced out easily by TLC. On TLC, the formations of cycloadducts **8a** and its isomers were observed at first. When the cycloadducts disappeared, the formation of **11a** and **12a** was observed. Similar reactions of (DL)-phenylalanine methyl ester and (DL)-methionine methyl ester gave the corresponding dehydroproline **12h** in 94% yield and **12i** in 61% yield (Table 5, entries 2 and 3). The one-pot reaction of *N*-methylmaleimide (NMMI) used as the dipolarophile also provided the corresponding dehydroprolines **12j** and **12k** in good yields (Table 5, entries 4 and 5). The dehydroprolines **12** correspond to the cycloadducts of *C*-unsubstituted (CH) nitrile ylides **15** and the maleimides. The *C*-unsubstituted nitrile ylide chemistry as a synthetic tool has seldom been studied. Although some examples for functionalized azomethine ylides as synthetic equivalents of nitrile ylides are found in the literature,[10] there are few examples of *C*-unsubstituted nitrile ylides.[4g] Therefore, in the present reaction sequences, the cycloaddition of functionalized azomethine ylides **4** and an acid fission reaction of the prolines **8**, could be regarded as an equivalent process of *C*-unsubstituted nitrile ylide cycloaddition reaction. According to the procedure in the literature,[11] the parent heterocycle **11a** could be easily formylated to the starting aldehyde **1a** in 80% yield.

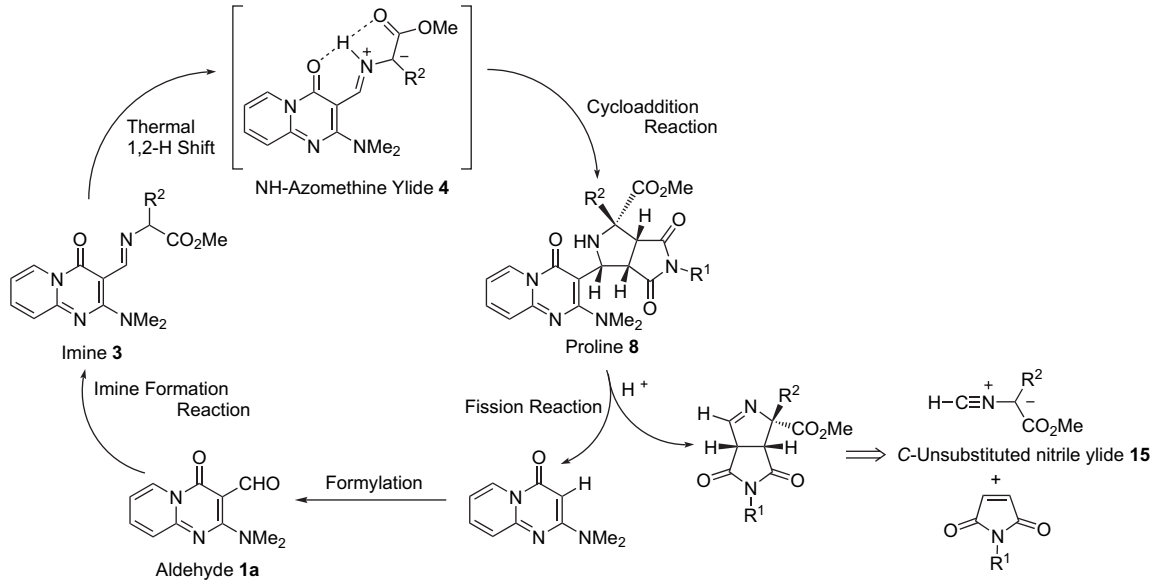
3. Conclusion

We have reported a facile isomerization of imine to NH-azomethine ylide under extremely mild conditions, e.g., at −30 °C to room temperature, and the resulting NH-azomethine ylide reacts with NPMI in high yield and *endo*-selectivity. Heating cycloadducts in AcOH at 85 °C provides dehydroproline derivatives, which are regarded as cycloadducts of *C*-unsubstituted (CH) nitrile ylides and maleimides. Our methodology is summarized in Scheme 6. Therein, the parent heterocyclic system plays an important role in the facile generation of azomethine ylide and the fission reaction of their cycloadducts. The cycloaddition–fission reaction sequences can be applied to one-pot three-component reaction. It is worth noting that all of these reaction processes described herein can be performed under an aerobic atmosphere, using wet solvents. Further investigation on the related chemistry is in progress and the results will be reported elsewhere.

4. Experimental

4.1. General

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a HORIBA FT-200 spectrophotometer from samples as pellets or NaCl discs. ^{1}H NMR spectra were measured on JEOL EX-270 and/or EX-400 spectrometers (270 and 400 MHz, respectively) and ^{13}C NMR spectra were measured on a JEOL EX-270 spectrometer (67.8 MHz) in deuteriochloroform ($CDCl_3$) solutions unless otherwise stated. Tetramethylsilane was used as an internal standard, and *J* values are given in hertz. Splitting patterns are indicated as: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad signals; and ov, overlapping signals. Mass spectra were determined on a JEOL 700QQ spectrometer. Elemental analyses were performed on a Yanagimoto MT-5 CHN analyzer. The progress of reactions was monitored by TLC (silica gel $60F_{254}$, Merck). Chromatographic purification was performed with Wakogel C-200 (100–200 mesh, Wako Pure Chemical Industries) and/or silica gel 60 (230–400 mesh, Merck).



Scheme 6. Functionalized NH-azomethine ylide **4** as *C*-unsubstituted nitrile ylide equivalent.

4.2. General procedure for the preparation of 2-amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehydes 1

A solution of 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carbaldehyde[11] (1.04 g, 5 mmol), dimethylamine (2.0 M solution in methanol, 5 mL, 10 mmol), and triethylamine (3.5 mL, 25 mmol) was stirred at room temperature for 5 h. The solvent was evaporated to dryness to give solid residue, which was extracted with dichloromethane (CH_2Cl_2)/5% aqueous sodium hydrogencarbonate. The organic layer was dried on anhydrous magnesium sulfate and the solvent was evaporated to give aldehyde **1a** (0.945 g, 87%). Aldehyde **1a** was used for the next procedure without further purification.

4.2.1. 2-(*N*,*N*-Dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (1a). Yellow prisms from hexane/benzene; mp 165.7–166.3 °C; ^{1}H NMR ($CDCl_3$): 3.12 (6H, s, $N(CH_3)_2$), 6.86 (1H, ddd, *J*=1.0, 6.9, 6.9 Hz, 7-H), 7.22 (1H, dd, *J*=1.0, 8.2 Hz, 9-H), 7.63 (1H, ddd, *J*=1.7, 6.9, 8.2 Hz, 8-H), 8.81 (1H, ddd, *J*=1.0, 1.7, 6.9 Hz, 6-H), 10.12 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): 41.2, 95.7, 112.5, 124.5, 127.8, 138.8, 150.6, 159.9, 161.7, 186.5. Anal. calcd for $C_{11}H_{11}N_3O_2$ (217.22): C, 60.82; H, 5.10; N, 19.34. Found: C, 60.63; H, 5.15; N, 19.20.

4.2.2. 2-(*N*,*N*-Dibenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (1b). Colorless prisms from hexane/benzene; mp 128.5–129.5 °C; ^{1}H NMR ($CDCl_3$): 4.80 (4H, s, $N(CH_2Ph)_2$), 6.93 (1H, ddd, *J*=1.0, 6.9, 6.9 Hz, 7-H), 7.16 (4H, m, Ph–H), 7.22–7.33 (7H, ov, Ph–H and 9-H), 7.68 (1H, ddd, *J*=1.3, 6.9, 8.6 Hz, 8-H), 8.87 (1H, dd, *J*=1.3, 6.9 Hz, 6-H), 10.20 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): 53.8, 96.9, 113.2, 124.9, 127.4, 127.8, 128.0, 128.6, 136.9, 139.2, 151.0, 160.6, 161.9, 186.7. Anal. calcd for $C_{23}H_{19}N_3O_2$ (369.42): C, 74.78; H, 5.18; N, 11.37. Found: C, 74.82; H, 5.15; N, 11.45.

4.2.3. 4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (1c). This compound has been already prepared and its physical and spectroscopic data are provided in the literature.[12]

4.2.4. 2-Morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (1d). Yellow crystals from benzene; mp 175.5–176.5 °C; ^{1}H NMR ($CDCl_3$): 3.74–3.77 (4H, m, $N(CH_2CH_2)_2O$), 3.81–3.85 (4H, m, $N(CH_2CH_2)_2O$), 6.93 (1H, ddd, *J*=1.3, 6.9, 6.9 Hz, 7-H), 7.25 (1H, dd, *J*=1.3, 8.6 Hz, 9-H), 7.71 (1H, ddd, *J*=1.3, 6.9, 8.6 Hz, 8-H), 8.85 (1H, ddd, *J*=1.3, 6.9, 6.9 Hz, 6-H), 10.13 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): 50.1, 67.6, 96.4, 113.7, 125.1, 128.4, 139.9, 151.6, 159.6, 162.5, 186.6. Anal. calcd for $C_{13}H_{13}N_3O_3$ (259.26): C, 60.22; H, 5.05; N, 16.21. Found: C, 60.11; H, 5.10; N, 16.13.

4.3. General procedure for reaction of imines 3a–d and 3g–i with NPMI

A solution of aldehyde **1a** (0.217 g, 1.0 mmol) and (DL)-phenylglycine methyl ester **2a** (0.182 g, 1.1 mmol) in toluene (2 mL) was stirred at room temperature for 1 h under an aerobic atmosphere. To the solution *N*-phenylmaleimide (0.19 g, 1.1 mmol) was added and the mixture was allowed to react at the same temperature for additional 1 h. The mixture was evaporated to dryness to give solid residue, which was crystallized from methanol to give proline **8a** (97%). The filtrate methanol solution was evaporated to dryness to give solid residue, which was subjected to a column chromatography on silica gel to give **9a** (2%) and **10a** (1%) with hexane/ethyl acetate (1:2) as an eluent.

4.4. General procedure for reaction of imines 3e–f with NPMI

A solution of aldehyde **1a** (0.217 g, 1.0 mmol), glycine methyl ester hydrochloride **2e** (0.188 g, 1.5 mmol), and triethylamine (0.21 mL, 1.5 mmol) in toluene (2 mL) was heated at 85 °C for 1 h under an aerobic atmosphere. To the solution *N*-phenylmaleimide (0.19 g, 1.1 mmol) was added and the mixture was allowed to react at the same temperature

for 21 h. The mixture was evaporated to dryness to give solid residue, which was extracted with dichloromethane (CH_2Cl_2)/5% aqueous sodium hydrogencarbonate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was crystallized from methanol to give proline **8e** (55%). The filtrate methanol solution was evaporated to dryness to give solid residue, which was subjected to a column chromatography on silica gel to give **10e** (12%) with ethyl acetate as an eluent.

4.4.1. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8a).** Colorless prisms from hexane/benzene; mp 211–212 °C; IR (KBr): 3280 (NH), 1745, 1709, 1655, 1632 (CO); ^{1}H NMR ($CDCl_3$): 2.98 (6H, s, $N(CH_3)_2$), 3.47 (1H, dd, *J*=8.3, 9.2 Hz, 3a-H), 3.78 (3H, s, CO_2CH_3), 4.31–4.4 (2H, ov, 3-H, 6a-H), 5.59 (1H, br d, *J*=13.2 Hz, exchanged with D_2O, NH), 6.86 (1H, ddd, *J*=1.0, 7.3, 7.3 Hz, 7′-H), 7.27–7.58 (10H, ov, 8′-H, 9′-H, Ph–H, and NPh–H), 7.78 (2H, dd, *J*=1.7, 6.6 Hz, Ph–H), 8.79 (1H, dd, *J*=1.0, 7.3 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 41.5, 49.8, 53.0, 56.5, 59.6, 74.0, 91.3, 113.1, 124.5, 126.9, 127.0, 127.3, 128.1, 128.3, 128.4, 128.8, 132.5, 136.2, 139.3, 148.3, 159.1, 164.5, 170.7, 175.0, 175.5. Anal. calcd for $C_{30}H_{27}N_5O_5$ (537.57): C, 67.03; H, 5.06; N, 13.03. Found: C, 67.01; H, 5.10; N, 12.89.

4.4.2. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9a).** White crystals from hexane/ethyl acetate; mp 229–230 °C; ^{1}H NMR ($CDCl_3$): 3.17 (6H, s, $N(CH_3)_2$), 3.71–3.79 (4H, ov, 3a-H and CO_2CH_3), 4.51 (1H, dd, *J*=9.2, 12.2 Hz, 3-H), 4.76 (1H, d, *J*=7.9 Hz, 6a-H), 5.55 (1H, br d, *J*=12.2 Hz, exchanged with D_2O, NH), 6.91 (1H, ddd, *J*=1.3, 6.9, 6.9 Hz, 7′-H), 7.28–7.40 (9H, ov, 9′-H, Ph–H, and NPh–H), 7.51–7.65 (3H, ov, 8′-H and Ph–H), 8.79 (1H, dd, *J*=1.0, 6.9 Hz, 6′–H); ^{13}C NMR ($CDCl_3$): 41.5, 49.9, 53.5, 53.9, 60.4, 76.4, 91.6, 113.2, 124.5, 126.1, 126.6, 126.7, 128.0, 128.1, 128.5, 132.3, 134.8, 136.2, 148.2, 159.1, 164.6, 173.9, 174.7. Anal. calcd for $C_{30}H_{27}N_5O_5$ (537.57): C, 67.03; H, 5.06; N, 13.03. Found: C, 67.01; H, 5.19; N, 12.89.

4.4.3. (1*R,3*S**,3a*S**,6a*R**)-(±)-Methyl 3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (10a).** Although this compound could not be isolated in a pure form, the structure was estimated on comparison with ^{1}H and ^{13}C NMR spectroscopic data of prolines **8a** and **9a**. Colorless prisms from hexane/benzene; mp 231–232 °C; ^{1}H NMR ($CDCl_3$): 3.23 (6H, s, $N(CH_3)_2$), 3.62 (3H, s, CO_2CH_3), 4.12 (1H, d, *J*=10.6 Hz, 6a-H), 4.23 (1H, br d, *J*=11.9 Hz, exchanged with D_2O, NH), 4.47 (1H, dd, *J*=7.3, 10.6 Hz, 3a-H), 4.85 (1H, dd, *J*=7.3, 11.9 Hz, 3-H), 6.88 (1H, ddd, *J*=1.0, 6.6, 7.9 Hz, 7′-H), 7.32–7.48 (9H, ov, 9′-H, Ph–H, and NPh–H), 7.57 (1H, ddd, *J*=1.2, 6.6, 8.9 Hz, 8′-H), 7.88 (2H, d, *J*=6.93 Hz, Ph–H), 8.74 (1H, dd, *J*=1.2, 7.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 41.3, 51.4, 53.1, 58.4, 59.9, 77.2, 92.7, 113.0, 124.8, 126.5, 126.7, 127.1, 128.1, 128.3, 128.5, 129.0, 132.5, 136.2, 140.3, 148.5, 158.6, 163.7, 172.4, 175.4, 177.2.

4.4.4. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 3-[2-(*N*,*N*-dibenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8b).** White powders from *i*-PrOH/benzene; mp 221–222 °C; IR (KBr): 3290 (NH), 1743, 1707, 1655, 1633 (CO); ^{1}H NMR ($CDCl_3$): 3.29 (1H, dd, *J*=7.9, 9.6 Hz, 3a-H), 3.76 (3H, s, CO_2CH_3), 4.25 (1H, d, *J*=7.9 Hz, 6a-H), 4.37 (1H, d, *J*=15.5 Hz, CH_2Ph), 4.60 (1H, d, *J*=15.5 Hz, CH_2Ph), 4.68 (1H, dd, *J*=9.6, 13.2 Hz, 3-H), 5.62 (1H, d, *J*=13.2 Hz, exchanged with D_2O, NH), 6.95 (1H, t, *J*=6.9 Hz, 7′-H), 7.08–7.18 (10H, ov, CH_2Ph–*H*, Ph–H, and NPh–H), 7.32–7.49 (9H, ov, CH_2Ph–*H*, Ph–H, NPh–H, and 9′-H), 7.60 (1H, ddd, *J*=1.7, 6.9, 8.6 Hz, 8′-H), 7.72 (2H, m, Ph–H), 8.89 (1H, br d, *J*=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 49.3, 53.0, 54.1, 56.7, 59.1, 73.8, 95.8, 113.9, 124.9, 127.0, 127.2, 127.24, 127.5, 128.1, 128.45, 128.5, 128.9, 132.5, 136.4, 137.5, 138.9, 148.4, 159.2, 165.2, 170.5, 175.1, 175.6. Anal. calcd for $C_{42}H_{35}N_5O_5$ (689.76): C, 73.13; H, 5.11; N, 10.15. Found: C, 72.95; H, 5.23; N, 9.98.

4.4.5. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 3-[2-(*N*,*N*-dibenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9b).** White powders from hexane/*i*-PrOH; mp 191–192 °C; ^{1}H NMR ($CDCl_3$): 3.54 (3H, s, CO_2CH_3), 3.55 (1H, dd, *J*=7.9, 9.2 Hz, 3a-H), 4.59–4.62 (2H, ov, 3-H and 6a-H), 4.68 (1H, d, *J*=16.2 Hz, CH_2Ph), 4.75 (1H, d, *J*=16.2 Hz, CH_2Ph), 5.60 (1H, br s, exchanged with D_2O, NH), 6.96 (1H, ddd, *J*=1.3, 6.9, 6.9 Hz, 7′-H), 7.24–7.37 (19H, ov, CH_2Ph–*H*, Ph–H, NPh–H, and 9′-H), 7.48 (2H, dd, *J*=1.3, 8.3 Hz, Ph–H), 7.63 (1H, ddd, *J*=2.0, 6.9, 8.6 Hz, 8′-H), 8.85 (1H, br d, *J*=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 49.9, 53.35, 53.44, 53.8, 59.9, 76.2, 93.7, 113.8, 124.7, 126.1, 126.7, 126.8, 127.3, 127.7, 128.1, 128.6, 132.3, 134.9, 136.4, 137.3, 148.1, 159.4, 164.6, 173.3, 174.0, 174.9. Anal. calcd for $C_{42}H_{35}N_5O_5$ (689.76): C, 73.13; H, 5.11; N, 10.15. Found: C, 72.84; H, 5.12; N, 10.10.

4.4.6. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 3-[2-(pyrrolidin-1-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8c).** This compound was obtained as a (1:1) molecular complex with ethyl acetate after recrystallization. White crystals from hexane/ethyl acetate; mp 223–224 °C; IR (KBr): 3296 (NH), 1740, 1709, 1655, 1630 (CO); ^{1}H NMR ($CDCl_3$): 1.26 (3H, t, *J*=7.3 Hz, $CH_3CO_2CH_2CH_3$), 1.77–1.85 (4H, br m, $N(CH_2CH_2)_2$), 2.04 (3H, s, $CH_3CO_2CH_2CH_3$), 3.42 (1H, dd, *J*=8.3, 9.2 Hz, 3a-H), 3.51–3.52 (4H, br m, $N(CH_2CH_2)_2$), 3.78 (3H, s, CO_2CH_3), 4.12 (2H, q, *J*=7.3 Hz, $CH_3CO_2CH_2CH_3$), 4.36 (1H, d, *J*=8.3 Hz, 6a-H), 4.48 (1H, dd, *J*=9.2, 12.9 Hz, 3-H), 5.76 (1H, br d, *J*=12.9 Hz, exchanged with D_2O, NH), 6.80 (1H, ddd, *J*=1.3, 6.9, 6.9 Hz, 7′-H), 7.21–7.54 (10H, ov, 8′-H, 9′-H, Ph–H, and NPh–H), 7.78 (2H, dd, *J*=1.0, 7.9 Hz, Ph–H), 8.78 (1H, dd, *J*=1.0, 6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 14.2, 21.1, 25.6, 50.28, 50.33, 53.0, 56.7, 59.1, 60.4, 74.0, 89.1, 112.4, 124.3, 127.0, 127.4, 128.1, 128.3, 128.4, 128.9, 132.6, 136.0, 139.5, 148.3, 158.8, 160.5, 170.7, 171.2, 175.1, 175.6. Anal. calcd for $C_{36}H_{37}N_5O_7$ (651.71): C, 66.35; H, 5.72; N, 10.75. Found: C, 66.30; H, 5.79; N, 10.67.

4.4.7. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 3-[2-(pyrrolidin-1-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9c).** Colorless crystals from *i*-PrOH/benzene; mp 223–224 °C; ^{1}H NMR ($CDCl_3$): 1.87–2.04 (4H, br m, $N(CH_2CH_2)_2$), 3.67–3.79 (8H, ov, CO_2CH_3, 3a-H, and $N(CH_2CH_2)_2$), 4.64 (1H, dd, *J*=9.2, 12.2 Hz, 3-H), 4.74 (1H, d, *J*=7.9 Hz, 6a-H), 5.76 (1H, br d, *J*=12.2 Hz, exchanged with D_2O, NH), 6.84 (1H, ddd, *J*=1.3, 6.9, 6.9 Hz, 7′-H), 7.24–7.40 (9H, ov, 9′-H, Ph–H, and NPh–H), 7.51–7.58 (3H, ov, 8′-H and Ph–H), 8.76 (1H, dd, *J*=1.0, 6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 25.8, 50.4, 50.7, 53.6, 54.1, 60.0, 89.3, 112.6, 124.4, 126.3, 126.8, 128.1, 128.2, 128.6, 132.5, 135.0, 136.0, 148.3, 158.9, 160.9, 174.0, 174.2, 174.9. Anal. calcd for $C_{32}H_{29}N_5O_5$ (563.60): C, 68.19; H, 5.19; N, 12.43. Found: C, 68.03; H, 5.33; N, 12.71.

4.4.8. (1*R,3*S**,3a*S**,6a*R**)-(±)-Methyl 3-[2-(pyrrolidin-1-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (10c).** Colorless crystals from *i*-PrOH/benzene; mp 217–218 °C; ^{1}H NMR ($CDCl_3$): 1.86–1.96 (4H, br m, $N(CH_2CH_2)_2$), 3.61 (3H, s, CO_2CH_3), 3.80–3.83 (4H, br m, $N(CH_2CH_2)_2$), 4.15 (1H, d, *J*=10.2 Hz, 6a-H), 4.37 (1H, br d, *J*=8.3 Hz, exchanged with D_2O, NH), 4.55 (1H, dd, *J*=6.9, 10.2 Hz, 3a-H), 5.15 (1H, br s, 3-H), 6.81 (1H, ddd, *J*=1.3, 7.3, 7.3 Hz, 7′-H), 7.25–7.57 (10H, ov, 8′-H, 9′-H, Ph–H, and NPh–H), 7.88 (2H, d, *J*=6.9 Hz, Ph–H), 8.70 (1H, br d, *J*=7.3 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 26.2, 50.8, 52.1, 53.5, 58.9, 59.3, 91.5, 112.8, 125.0, 126.2, 127.1, 127.6, 128.5, 128.8, 129.0, 129.5, 132.9, 136.4, 140.8, 148.9, 158.8, 160.0, 173.1, 175.9, 177.9. Anal. calcd for $C_{32}H_{29}N_5O_5$ (563.60): C, 68.19; H, 5.19; N, 12.43. Found: C, 68.09; H, 5.33; N, 12.24.

4.4.9. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 3-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8d).** This compound was obtained as a (2:1) molecular complex with benzene after recrystallization. White powders from hexane/benzene; mp 196–197 °C; IR (KBr): 3267 (NH), 1734, 1714, 1659, 1632 (CO); ^{1}H NMR ($CDCl_3$): 3.28–3.59 (9H, ov, $N(CH_2CH_2)_2O$ and 3a-H), 3.79 (3H, s, CO_2CH_3), 4.29 (1H, dd, *J*=9.2, 13.2 Hz, 3-H), 4.39 (1H, d, *J*=7.9 Hz, 6a-H), 5.36 (1H, d, *J*=13.2 Hz, exchanged with D_2O, NH), 6.98 (1H, ddd, *J*=1.0, 6.9, 6.9 Hz, 7′-H), 7.33–7.50 (12H, ov, 9′-H, NPh–H, Ph–H, and $1/2C_6H_6$), 7.64 (1H, ddd, *J*=1.7, 6.6, 6.6 Hz, 8′-H), 7.75 (2H, dd, *J*=1.3, 7.6 Hz, Ph–H), 8.82 (1H, br d, *J*=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 49.7, 50.4, 53.1, 55.9, 59.0, 66.7, 94.6, 114.3, 125.0, 126.9, 127.0, 127.1, 128.3, 128.46, 128.54, 128.9, 132.5, 136.5, 139.2, 149.0, 159.4, 164.7, 170.6, 175.0, 175.4. Anal. calcd for $C_{35}H_{32}N_5O_6$ (618.66): C, 67.95; H, 5.21; N, 11.32. Found: C, 67.98; H, 5.23; N, 11.23.

4.4.10. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 3-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9d).** Colorless crystals from *i*-PrOH/benzene; mp 213–214 °C; ^{1}H NMR ($CDCl_3$): 3.46–3.60 (4H, ov, $N(CH_2CH_2)_2O$), 3.67 (1H, dd, *J*=7.9, 8.9 Hz, 3a-H), 3.77–3.83 (7H, ov, CO_2CH_3 and $N(CH_2CH_2)_2O$), 4.53 (1H, dd, *J*=8.9, 12.2 Hz, 3-H), 4.76 (1H, d, *J*=7.9 Hz, 6a-H), 5.34 (1H, br d, *J*=12.2 Hz, exchanged with D_2O, NH), 7.01 (1H, ddd, *J*=1.0, 6.9, 7.1 Hz, 7′-H), 7.25–7.45 (9H, ov, 9′-H, NPh–H, and Ph–H), 7.53 (2H, dd, *J*=1.7, 7.9 Hz, Ph–H), 7.67 (1H, ddd, *J*=1.3, 7.1, 8.3 Hz, 8′-H), 8.83 (1H, dd, *J*=1.3, 6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 49.9, 50.4, 53.7, 53.9, 59.9, 66.9, 95.0, 114.4, 125.1, 126.2, 126.7, 128.2, 128.3, 128.34, 128.7, 132.3, 134.6, 136.6, 148.9, 159.5, 164.7, 173.8, 174.7. Anal. calcd for $C_{32}H_{29}N_5O_6$ (579.60): C, 66.31; H, 5.04; N, 12.08. Found: C, 66.32; H, 5.13; N, 11.95.

4.4.11. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]-pyrrole-1-carboxylate (8e).** White crystals from CH_2Cl_2/benzene; mp 246–247 °C; IR (KBr): 3298 (NH), 1740, 1701, 1651, 1630 (CO); ^{1}H NMR ($CDCl_3$): 3.14 (6H, s, $N(CH_3)_2$), 3.59 (1H, dd, *J*=8.6, 8.9 Hz, 6a-H), 3.83–3.89 (4H, ov, CO_2CH_3 and 3a-H), 4.08 (1H, dd, *J*=7.3, 13.2 Hz, 3-H), 4.57 (1H, dd, *J*=8.9, 13.2 Hz, 1-H), 4.79 (1H, dd, *J*=13.2, 13.2 Hz, exchanged with D_2O, NH), 6.89 (1H, ddd, *J*=1.3, 6.6, 6.6 Hz, 7′-H), 7.31–7.45 (6H, ov, 9′-H and NPh–H), 7.58 (1H, ddd, *J*=1.7, 6.6, 7.8 Hz, 8′-H), 8.79 (1H, br d, *J*=6.6 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 41.7, 49.3, 51.4, 52.4, 61.9, 63.1, 91.6, 113.2, 124.6, 126.9, 127.0, 128.4, 128.9, 132.5, 136.3, 148.4, 159.0, 164.7, 169.8, 175.0, 175.4. Anal. calcd for $C_{24}H_{23}N_5O_5$ (461.47): C, 62.46; H, 5.02; N, 15.18. Found: C, 62.35; H, 4.92; N, 15.16.

4.4.12. (1*R,3*R**,3a*R**,6a*S**)-(±)-Methyl 3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (10e).** Colorless crystals from benzene/*i*-PrOH; mp 226–227 °C; ^{1}H NMR ($CDCl_3$): 3.16 (6H, s, $N(CH_3)_2$), 3.65 (1H, dd, *J*=8.6, 8.9 Hz, 6a-H), 3.82 (3H, s, CO_2CH_3), 3.99 (1H, dd, *J*=1.0, 8.6 Hz, 3a-H), 4.63 (1H, br s, 3-H), 4.74–4.77 (2H, ov, NH and 1-H), 6.87 (1H, ddd, *J*=1.3, 6.9, 6.9 Hz, 7′-H), 7.30–7.48 (6H, ov, 9′-H and NPh–H), 7.57 (1H, ddd, *J*=1.7, 6.9, 6.9 Hz, 8′-H), 8.71 (1H, br d, *J*=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 41.6, 48.9, 52.1, 52.7, 62.0, 63.4, 90.9, 113.2, 124.6, 126.6, 126.8, 128.3, 128.9, 132.6, 136.2, 148.3, 159.0, 164.5, 172.7, 175.5, 177.1. Anal. calcd for $C_{24}H_{23}N_5O_5$ (461.47): C, 62.46; H, 5.02; N, 15.18. Found: C, 62.51; H, 4.96; N, 14.88.

4.4.13. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 1-methyl-3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8f).** Colorless crystals from *i*-PrOH/benzene; mp 245–246 °C; IR (KBr): 3286 (NH), 1736, 1705, 1655, 1630 (CO); ^{1}H NMR ($CDCl_3$): 1.62 (3H, s, CH_3), 3.12 (6H, s, $N(CH_3)_2$), 3.54 (1H, d, *J*=8.3 Hz, 6a-H), 3.66 (1H, dd, *J*=8.3, 9.2 Hz, 3a-H), 3.85 (3H, s, CO_2CH_3), 4.75 (1H, dd, *J*=9.2, 13.2 Hz, 3-H), 5.29 (1H, br d, *J*=13.2 Hz, exchanged with D_2O, NH), 6.86 (1H, ddd, *J*=1.3, 6.6, 6.9 Hz, 7′-H), 7.26–7.44 (7H, ov, 9′-H and NPh–H), 7.56 (1H, ddd, *J*=1.0, 6.9, 8.2 Hz, 8′-H), 8.78 (1H, dd, *J*=1.0, 6.6 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 24.2, 41.6, 49.3, 52.7, 57.9, 60.2, 68.3, 91.6, 113.1, 124.5, 126.9, 127.0, 128.3, 128.8, 132.5, 136.2, 148.3, 159.0, 164.7, 172.1, 175.0, 175.3. Anal. calcd for $C_{25}H_{25}N_5O_5$ (475.50): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.39; H, 5.32; N, 14.68.

4.4.14. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 1-methyl-3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9f).** Although this compound could not be isolated in a pure form, the structure was elucidated from its ^{1}H NMR spectroscopic data. ^{1}H NMR ($CDCl_3$): 1.78 (3H, s, CH_3), 3.14 (6H, s, $N(CH_3)_2$), 3.66 (1H, dd, J=8.3, 9.2 Hz, 3a-H), 3.83 (3H, s, CO_2CH_3), 4.10 (1H, d, J=8.3 Hz, 6a-H), 4.60 (1H, d, J=9.2 Hz, 3-H), 6.88 (1H, ddd, J=1.3, 6.9, 6.9 Hz, 7′-H), 7.30–7.47 (6H, ov, 9′-H and Ph–H), 7.57 (1H, ddd, J=1.3, 6.9, 8.6 Hz, 8′-H), 8.72 (1H, br d, J=6.9 Hz, 6′-H).

4.4.15. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 1-isopropyl-3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8g).** White powders from hexane/*i*-PrOH; mp 205–206 °C; IR (KBr): 3307 (NH), 1736, 1701, 1655, 1630 (CO); ^{1}H NMR ($CDCl_3$): 1.15 (6H, br d, J=6.6 Hz, $CH(CH_3)_2$), 2.38 (1H, br m, $CH(CH_3)_2$), 3.17 (6H, s, $N(CH_3)_2$), 3.70–3.79 (2H, ov, 3a-H and 6a-H), 3.86 (3H, s, CO_2CH_3), 4.82 (1H, dd, J=8.9, 12.2 Hz, 3-H), 4.99 (1H, br d, J=12.2 Hz, exchanged with D_2O, NH), 6.84 (1H, ddd, J=1.0, 6.9, 6.9 Hz, 7′-H), 7.23–7.41 (6H, ov, 9′-H and NPh–H), 7.55 (1H, ddd, J=1.7, 6.9, 8.6 Hz, 8′-H), 8.79 (1H, br d, J=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 17.9, 18.5, 35.0, 41.6, 50.7, 52.5, 55.2, 61.1, 75.6, 92.3, 113.0, 124.5, 127.0, 128.25, 128.28, 128.8, 132.5, 136.1, 148.3, 158.6, 164.6, 172.1, 175.1, 176.0. Anal. calcd for $C_{27}H_{29}N_5O_5$ (503.55): C, 64.40; H, 5.80; N, 13.91. Found: C, 64.09; H, 5.83; N, 13.86.

4.4.16. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 1-isopropyl-3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9g).** This compound was obtained as a (1:1) molecular complex with benzene after recrystallization. Colorless crystals from hexane/benzene; mp 122–123 °C; IR (KBr): 3278 (NH), 1747, 1704, 1650, 1625 (CO); ^{1}H NMR ($CDCl_3$): 1.13 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.20 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 2.68 (1H, m, $CH(CH_3)_2$), 3.13 (6H, s, $N(CH_3)_2$), 3.63 (1H, dd, J=8.6, 8.6 Hz, 3a-H), 3.84 (3H, s, CO_2CH_3), 4.37–4.44 (2H, ov, 3-H and 6a-H), 4.63 (1H, br s, exchanged with D_2O, NH), 6.85 (1H, dd, J=6.9, 6.9 Hz, 7′-H), 7.26–7.46 (12H, ov, 9′-H, NPh–H, and C_6H_6), 7.54 (1H, ddd, J=0.7, 6.9, 8.3 Hz, 8′-H), 8.73 (1H, br d, J=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 19.0, 20.0, 32.2, 41.5, 50.0, 52.6, 53.2, 60.6, 78.1, 91.9, 113.1, 124.5, 126.7, 126.9, 128.3, 128.8, 132.6, 136.1, 148.2, 158.9, 164.5, 173.6, 175.1, 175.3. Anal. calcd for $C_{33}H_{35}N_5O_5$ (581.66): C, 68.14; H, 6.07; N, 12.04. Found: C, 68.04; H, 6.00; N, 12.19.

4.4.17. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 1-benzyl-3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8h).** White crystals from benzene/*i*-PrOH; mp 215–216 °C; IR (KBr): 3298 (NH), 1741, 1701, 1649, 1630 (CO); ^{1}H NMR ($CDCl_3$): 3.09 (6H, s, $N(CH_3)_2$), 3.19 (1H, d, J=13.9 Hz, CH_2Ph), 3.36 (1H, d, J=13.9 Hz, CH_2Ph), 3.61 (1H, dd, J=8.6, 9.2 Hz, 3a-H), 3.74 (1H, d, J=8.6 Hz, 6a-H), 3.84 (3H, s, CO_2CH_3), 4.67 (1H, dd, J=9.2, 12.5 Hz, 3-H), 5.12 (1H, br d, J=12.5 Hz, exchanged with D_2O, NH), 6.83 (1H, ddd, J=1.3, 7.3, 7.3 Hz, 7′-H), 7.23–7.42 (11H, ov, 9′-H, NPh–H, and CH_2Ph–*H*), 7.54 (1H, ddd, J=1.3, 7.3, 8.6 Hz, 8′-H), 8.76 (1H, dd, J=1.3, 7.3 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 41.7, 42.4, 49.8, 52.6, 57.7, 60.3, 72.8, 92.4, 113.1, 124.5, 126.95, 127.0, 128.2, 128.3, 128.8, 130.3, 132.5, 136.2, 136.6, 148.4, 158.7, 165.0, 171.2, 175.0, 175.4. Anal. calcd for $C_{31}H_{29}N_5O_5$ (551.59): C, 67.50; H, 5.30; N, 12.70. Found: C, 67.49; H, 5.28; N, 12.72.

4.4.18. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 1-benzyl-3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9h).** Colorless crystals from *i*-PrOH/benzene; mp 229–230 °C; ^{1}H NMR ($CDCl_3$): 3.12 (7H, ov, $N(CH_3)_2$ and CH_2Ph), 3.59–3.67 (4H, ov, CO_2CH_3 and 3a-H), 3.93 (1H, d, J=14.2 Hz, CH_2Ph), 4.22 (1H, d, J=8.3 Hz, 6a-H), 4.56 (1H, dd, J=9.2, 12.2 Hz, 3-H), 4.78 (1H, br d, J=12.2 Hz, exchanged with D_2O, NH), 6.90 (1H, ddd, J=1.0, 7.3, 7.3 Hz, 7′-H), 7.18–7.62 (12H, ov, 8′-H, 9′-H, NPh–H, and CH_2Ph–*H*), 8.75 (1H, br d, J=7.3 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 40.7, 41.4, 49.9, 52.4, 53.9, 60.9, 74.5, 91.8, 113.1, 124.6, 126.7, 126.8, 126.9, 128.3, 128.4, 128.9, 129.8, 132.5, 136.1, 136.5, 148.1, 158.9, 164.4, 173.6, 175.1, 175.13. Anal. calcd for $C_{31}H_{29}N_5O_5$ (551.59): C, 67.50; H, 5.30; N, 12.70. Found: C, 67.33; H, 5.18; N, 12.60.

4.4.19. (1*R,3*S**,3a*R**,6a*S**)-(±)-Methyl 3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-1-(2-methylthio)ethyl-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (8i).** Colorless crystals from *i*-PrOH/benzene; mp 240–241 °C; IR (KBr): 3298 (NH), 1734, 1701, 1653, 1630 (CO); ^{1}H NMR ($CDCl_3$): 1.96 (1H, m, $CH_2CH_2SCH_3$), 2.14 (3H, s, SCH_3), 2.39 (1H, m, $CH_2CH_2SCH_3$), 2.54 (1H, m, $CH_2CH_2SCH_3$), 2.68 (1H, m, $CH_2CH_2SCH_3$), 3.16 (6H, s, $N(CH_3)_2$), 3.52 (1H, d, J=8.3 Hz, 6a-H), 3.63 (1H, dd, J=8.3, 8.9 Hz, 3a-H), 3.87 (3H, s, CO_2CH_3), 4.64 (1H, dd, J=8.9, 12.5 Hz, 3-H), 5.15 (1H, br d, J=12.5 Hz, exchanged with D_2O, NH), 6.87 (1H, ddd, J=1.0, 6.9, 6.9 Hz, 7′-H), 7.31–7.43 (6H, ov, 9′-H and NPh–H), 7.56 (1H, ddd, J=1.0, 6.9, 8.3 Hz, 8′-H), 8.78 (1H, dd, J=1.0, 6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 15.7, 29.0, 35.9, 41.7, 49.2, 52.9, 57.8, 60.0, 71.7, 91.6, 113.2, 124.6, 127.0, 128.4, 128.9, 132.5, 136.3, 148.4, 159.0, 164.9, 171.0, 174.9, 175.0. Anal. calcd for $C_{27}H_{29}N_5O_5S$ (535.62): C, 60.55; H, 5.46; N, 13.08. Found: C, 60.74; H, 5.39; N, 13.09.

4.4.20. (1*R,3*R**,3a*S**,6a*R**)-(±)-Methyl 3-[2-(*N*,*N*-dimethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-1-(2-methylthio)ethyl-4,6-dioxo-5-phenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (9i).** Colorless needle crystals from *i*-PrOH/benzene; mp 175–176 °C; ^{1}H NMR ($CDCl_3$): 2.12 (3H, s, SCH_3), 2.34 (1H, m, $CH_2CH_2SCH_3$), 2.46–2.66 (2H, ov, $CH_2CH_2SCH_3$), 2.88 (1H, m, $CH_2CH_2SCH_3$), 3.14 (6H, s, $N(CH_3)_2$), 3.67 (1H, dd, J=8.2, 9.2 Hz, 3a-H), 3.85 (3H, s, CO_2CH_3), 4.17 (1H, d, J=8.2 Hz, 6a-H), 4.53 (1H, d, J=9.2 Hz, 3-H), 4.65 (1H, br s, exchanged with D_2O, NH), 6.88 (1H, ddd, J=1.3, 6.6, 6.6 Hz, 7′-H), 7.30–7.46 (6H, ov, 9′-H and NPh–H), 7.57 (1H, ddd, J=2.0, 6.6, 8.6 Hz, 8′-H), 8.72 (1H, br d, J=6.6 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 15.4, 29.8, 34.5,

41.5, 50.0, 52.9, 53.1, 60.5, 73.1, 91.4, 113.2, 124.6, 126.6, 126.9, 128.4, 128.9, 132.5, 136.2, 148.2, 158.9, 164.5, 173.9, 174.9, 175.1. Anal. calcd for $C_{27}H_{29}N_5O_5S$ (535.62): C, 60.55; H, 5.46; N, 13.08. Found: C, 60.55; H, 5.50; N, 12.76.

4.5. General procedure for fission reaction of prolines 8a–d and 8f–i

A solution of proline **8a** (0.161 g, 0.3 mmol) in acetic acid (3 mL) was heated at 85 °C for 0.5 h under an aerobic atmosphere. After cooling to room temperature, the mixture was diluted with dichloromethane (10 mL) and pH was adjusted to 6–7 with 5% aqueous sodium hydrogencarbonate. The organic layer was dried on anhydrous magnesium sulfate and the solvent was evaporated. The residue was subjected to a column chromatography on silica gel to give **12a** (83%) with hexane/ethyl acetate (1:3) as an eluent and then **11a** (67%) with ethyl acetate as an eluent.

4.6. General procedure for one-pot three-component reaction

Aldehyde **1a** (0.109 g, 0.5 mmol), (DL)-phenylglycine methyl ester **2a** (0.107 g, 0.65 mmol), and *N*-phenylmaleimide (0.095 g, 0.55 mmol) were combined in acetic acid (5 mL)/acetonitrile (1 mL) and the mixture was heated at 85 °C for 3 h. The mixture was evaporated to dryness to give an oily residue, which was extracted with dichloromethane (CH_2Cl_2)/5% aqueous sodium hydrogencarbonate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was subjected to a column chromatography on silica gel to give **12a** (78%) and its diastereomer **12a′** (10%) with hexane/ethyl acetate (1:1) as an eluent, and then **11a** (83%) with ethyl acetate as an eluent.

4.6.1. (1*R,3a*S**,6a*R**)-(±)-Methyl 1,3a,4,5,6,6a-hexahydro-4,6-dioxo-1,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (12a).** Colorless needles from *i*-PrOH; mp 191–192 °C; IR (KBr): 1747, 1716, 1628 (CO), 1597 (CH=N–); ^{1}H NMR ($CDCl_3$): 3.54 (3H, s, CO_2CH_3), 3.77 (1H, d, J=9.2 Hz, 6a-H), 4.26 (1H, dd, J=1.3, 9.2 Hz, 3a-H), 7.17–7.42 (8H, ov, Ph–H and NPh–H), 7.52 (2H, dd, J=1.3, 7.9 Hz, Ph–H), 7.89 (1H, d, J=1.3 Hz, CH=N–); ^{13}C NMR ($CDCl_3$): 53.6, 54.0, 59.8, 90.3, 126.5, 126.9, 128.1, 128.4, 128.9, 129.2, 131.5, 140.6, 161.7, 170.0, 171.0, 174.3. Anal. calcd for $C_{20}H_{16}N_2O_4$ (348.35): C, 68.96; H, 4.63; N, 8.04. Found: C, 68.68; H, 4.60; N, 7.86.

4.6.2. (1*R,3a*R**,6a*S**)-(±)-Methyl 1,3a,4,5,6,6a-hexahydro-1-methyl-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (12f).** White powders from ether; mp 138–139 °C; IR (KBr): 1743, 1707, 1620 (CO), 1597 (CH=N–); ^{1}H NMR ($CDCl_3$): 1.68 (3H, s, CH_3), 3.39 (1H, d, J=8.6 Hz, 6a-H), 3.69 (3H, s, CO_2CH_3), 4.42 (1H, dd, J=1.3, 8.6 Hz, 3a-H), 7.21 (2H, m, NPh–H), 7.40–7.50 (3H, ov, NPh–H), 7.73 (1H, d, J=1.3 Hz, CH=N–); ^{13}C NMR ($CDCl_3$): 25.8, 51.9, 52.9, 59.3, 83.9, 126.3, 128.9, 129.2, 131.2, 160.1, 170.3, 171.0, 174.1. Anal. calcd for $C_{15}H_{14}N_2O_4$ (286.28): C, 62.93; H, 4.93; N, 9.79. Found: C, 63.12; H, 4.85; N, 9.88.

4.6.3. (1*R,3a*R**,6a*S**)-(±)-Methyl 1,3a,4,5,6,6a-hexahydro-1-isopropyl-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (12g).** Colorless crystals from hexane/benzene; mp 140–141 °C; IR (KBr): 1749, 1713, 1622 (CO), 1597 (CH=N–); ^{1}H NMR ($CDCl_3$): 0.97 (3H, d, J=6.3 Hz, $CH(CH_3)_2$), 0.99 (3H, d, J=5.9 Hz, $CH(CH_3)_2$), 2.75 (1H, m, $CH(CH_3)_2$), 3.48 (1H, d, J=8.9 Hz, 6a-H), 3.70 (3H, s, CO_2CH_3), 4.29 (1H, dd, J=0.7, 8.9 Hz, 3a-H), 7.24 (2H, m, NPh–H), 7.36–7.60 (3H, ov, NPh–H), 7.84 (1H, d, J=0.7 Hz, CH=N–); ^{13}C NMR ($CDCl_3$): 16.8, 17.7, 34.1, 47.6, 52.8, 59.8, 91.8, 126.4, 128.9, 129.3, 131.5, 160.7, 170.0, 171.1, 174.7. Anal. calcd for $C_{17}H_{18}N_2O_4$ (314.34): C, 64.96; H, 5.77; N, 8.91. Found: C, 64.99; H, 5.77; N, 8.98.

4.6.4. (1*R,3a*R**,6a*S**)-(±)-Methyl 1-benzyl-1,3a,4,5,6,6a-hexahydro-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (12h).** Colorless crystals from hexane/benzene; mp 186–187 °C; IR (KBr): 1745, 1716, 1624 (CO), 1597 (CH=N–); ^{1}H NMR ($CDCl_3$): 3.30 (1H, dd, J=1.3, 8.7 Hz, 3a-H), 3.51 (2H, s, CH_2Ph), 3.57 (1H, d, J=8.7 Hz, 6a-H), 3.76 (3H, s, CO_2CH_3), 7.13–7.50 (10H, ov, CH_2Ph–*H* and NPh–H), 7.65 (1H, d, J=1.3 Hz, CH=N–); ^{13}C NMR ($CDCl_3$): 42.3, 48.8, 53.1, 59.5, 86.9, 126.3, 127.4, 128.3, 129.0, 129.2, 131.1, 131.2, 134.3, 161.8, 170.1, 170.8, 174.5. Anal. calcd for $C_{21}H_{18}N_2O_4$ (302.38): C, 69.60; H, 5.01; N, 7.73. Found: C, 69.54; H, 4.98; N, 7.77.

4.6.5. (1*R,3a*R**,6a*S**)-(±)-Methyl 1,3a,4,5,6,6a-hexahydro-1-(2-methylthio)ethyl-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (12i).** Colorless needles from *i*-PrOH; mp 132–133 °C; IR (KBr): 1741, 1705, 1618 (CO), 1597 (CH=N–); ^{1}H NMR ($CDCl_3$): 2.04–2.17 (5H, ov, SCH_3 and CH_2CH_2SMe), 2.53–2.65 (2H, ov, CH_2CH_2SMe), 3.55 (1H, d, J=8.9 Hz, 6a-H), 3.70 (3H, s, CO_2CH_3), 4.43 (1H, dd, J=1.3, 8.9 Hz, 3a-H), 7.24 (2H, m, NPh–H), 7.40–7.58 (3H, ov, NPh–H), 7.82 (1H, d, J=1.3 Hz, CH=N–); ^{13}C NMR ($CDCl_3$): 15.6, 28.5, 38.7, 50.6, 53.0, 59.4, 86.8, 126.3, 129.0, 129.3, 131.2, 161.3, 169.5, 170.8, 173.9. Anal. calcd for $C_{17}H_{18}N_2O_4S$ (346.40): C, 58.94; H, 5.24; N, 8.09. Found: C, 58.93; H, 5.28; N, 8.08.

4.6.6. (1*R,3a*S**,6a*R**)-(±)-Methyl 1,3a,4,5,6,6a-hexahydro-5-methyl-4,6-dioxo-1-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (12j).** Colorless crystals from hexane/benzene; mp 186–187 °C; IR (KBr): 1738, 1697, 1630 (CO), 1603 (CH=N–); ^{1}H NMR ($CDCl_3$): 3.02 (3H, s, NCH_3), 3.64 (3H, s, CO_2CH_3), 3.79 (1H, d, J=8.9 Hz, 6a-H), 4.25 (1H, dd, J=1.3, 8.9 Hz, 3a-H), 7.34–7.41 (3H, ov, Ph–H), 7.56–7.59 (2H, m, Ph–H), 7.93 (1H, d, J=1.3 Hz, CH=N–); ^{13}C NMR ($CDCl_3$): 25.3, 53.5, 54.0, 59.8, 89.5, 127.0, 128.1, 128.4, 140.5, 161.7, 169.7, 172.0, 175.2. Anal. calcd for $C_{15}H_{14}N_2O_4$ (286.28): C, 62.93; H, 4.93; N, 9.79. Found: C, 62.89; H, 4.94; N, 9.76.

4.6.7. (1*R,3a*R**,6a*S**)-(±)-Methyl 1-benzyl-1,3a,4,5,6,6a-hexahydro-5-methyl-4,6-dioxopyrrolo[3,4-*c*]-pyrrole-1-carboxylate (12k).** Colorless needles from pentane/ethyl ether; mp 104–105 °C; IR (KBr): 1741, 1703, 1647 (CO), 1612 (CH=N–); ^{1}H NMR ($CDCl_3$): 2.89 (3H, s, NCH_3), 3.10 (1H, dd, J=1.3, 8.3 Hz, 3a-H), 3.41 (1H, d,

J=8.3 Hz, 6a-H), 3.42 (1H, d, J=13.9 Hz, CH_2Ph), 3.48 (1H, d, J=13.9 Hz, CH_2Ph), 3.75 (3H, s, CO_2CH_3), 7.12 (2H, m, CH_2Ph–*H*), 7.24–7.29 (3H, ov, CH_2Ph–*H*), 7.56 (1H, d, J=1.3 Hz, CH═N–); ^{13}C NMR ($CDCl_3$): 25.1, 42.4, 49.0, 52.9, 59.5, 86.0, 127.3, 128.3, 131.1, 134.2, 161.8, 170.1, 171.8, 175.3. Anal. calcd for $C_{16}H_{16}N_2O_4$ (300.31): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.89; H, 5.19; N, 9.45.

4.6.8. 2-(*N*,*N*-Dimethylamino)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (11a). This compound has been already prepared and its physical and spectroscopic data are provided in the literature.[13]

4.6.9. 2-(*N*,*N*-Dibenzylamino)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (11b). Colorless needles from hexane/*i*-PrOH; mp 152–153 °C; ^{1}H NMR ($CDCl_3$): 4.80 (4H, br s, CH_2Ph), 5.62 (1H, s, 3-H), 6.83 (1H, ddd, J=1.3, 6.9, 6.9 Hz, 7-H), 7.17–7.34 (11H, ov, 9-H and CH_2Ph–*H*), 7.54 (1H, ddd, J=1.7, 6.9, 8.6 Hz, 8-H), 8.88 (1H, br d, J=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 50.5, 81.2, 112.4, 124.5, 127.2, 127.4, 127.6, 128.7, 136.3, 137.3, 150.6, 158.6, 161.3. Anal. calcd for $C_{22}H_{19}N_3O$ (341.41): C, 77.40; H, 5.61; N, 12.31. Found: C, 77.52; H, 5.59; N, 12.34.

4.6.10. 2-(Pyrrolidin-1-yl)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (11c). This compound has already been prepared and its physical and spectroscopic data are provided in our previous paper.[8]

4.6.11. 2-Morpholinopyrido[1,2-*a*]pyrimidin-4(4*H*)-one (11d). Colorless needles from *i*-PrOH; mp 188–189 °C; ^{1}H NMR ($CDCl_3$): 3.65–3.68 (4H, ov, N(CH_2CH_2)$_2$O), 3.78–3.81 (4H, ov, N(CH_2CH_2)$_2$O), 5.62 (1H, s, 3-H), 6.89 (1H, ddd, J=1.3, 6.9, 6.9 Hz, 7-H), 7.28 (1H, m, 9-H), 7.59 (1H, ddd, J=2.0, 6.9, 8.9 Hz, 8-H), 8.90 (1H, br d, J=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 44.6, 66.6, 81.3, 112.7, 124.4, 127.6, 136.5, 150.6, 158.7, 161.1. Anal. calcd for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.13; H, 5.80; N, 18.06.

4.7. Procedure for dimerization of dehydroproline 12a

A solution of dehydroproline **12a** (0.174 g, 0.5 mmol) and pyridinium *p*-toluenesulfonate (0.126 g, 0.5 mmol) in methanol (5 mL) was heated under reflux for 15 h. The resulting precipitates were filtrated to give dimer **13** (0.165 g, 92%).

This compound existed in two isomeric mixture (1:1 ratio) in $CDCl_3$ solution. Their selected ^{1}H and ^{13}C NMR spectral data are provided as following.

4.7.1. Methyl 3a-(1-methoxycarbonyl-4,6-dioxo-1,5-diphenylperhydropyrrolo[3,4-*c*]pyrrol-3-yl)-1,3a,4,5,6,6a-hexahydro-4,6-dioxo-1,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (13). Colorless crystals from acetonitrile/MeOH; mp 284–285 °C; ^{1}H NMR ($CDCl_3$): 2.47 (1H, dd, J=6.6, 9.9 Hz, 3a′-H), 3.04–3.11 (2H, ov, NH and 3a′-H), 3.26–3.31 (2H, ov, NH and 6a-H), 3.38 (1H, d, J=10.9 Hz, 6a-H), 3.60 (1H, s, 6a-H), 3.62 (3H, s, CO_2CH_3), 3.63 (3H, s, CO_2CH_3), 3.64 (3H, s, CO_2CH_3), 3.66 (3H, s, CO_2CH_3), 4.09 (1H, dd, J=3.9, 6.6 Hz, 3′-H), 4.41 (1H, s, 6a-H), 4.62 (1H, t, J=6.6 Hz, 3′-H), 8.07 (1H, s, CH═N–), 8.26 (1H, s, CH═N–); ^{13}C NMR ($CDCl_3$): 47.26 (CH), 47.53 (CH), 53.48 (CO_2CH_3), 53.68 (CH), 53.71 (CO_2CH_3), 53.80 (CO_2CH_3), 53.93 (CO_2CH_3), 54.22 (CH), 56.34 (CH), 56.73 (CH), 59.89 (CH), 60.88 (CH), 72.38 (quaternary C), 73.59 (quaternary C), 73.87 (quaternary C), 75.10 (quaternary C), 89.78 (quaternary C), 90.89 (quaternary C), 163.58 (CH═N–), 163.77 (CH═N–), 169.65 (C═O), 169.88 (C═O), 171.81 (C═O), 172.18 (C═O), 173.10 (C═O), 173.31 (C═O), 173.37 (C═O), 173.60 (C═O), 173.66 (C═O), 174.23 (C═O), 174.54 (C═O). Anal. calcd for $C_{40}H_{32}N_4O_8$ (696.70): C, 68.96; H, 4.63; N, 8.04. Found: C, 68.90; H, 4.47; N, 7.91. MS (FAB): *m*/*z* 697 (MH^+), 637, 349 (1/2MH^+, base peak), 289.

References and notes

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