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A NEW ROUTE TO PAPAVERINE ANALOGS *VIA* PHOTOCYCLIZATION OF SUBSTITUTED *N*-ACYL-α-DEHYDRO-PHENYLALANINAMIDES

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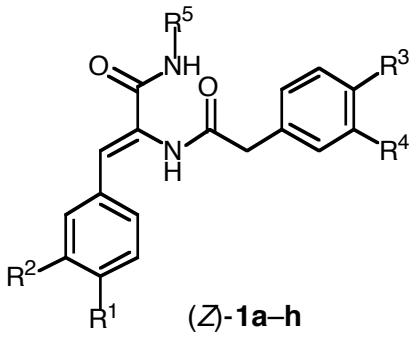
Abstract–(*Z*)-*N*-Phenylacetyl-α-dehydro(3,4-dimethoxyphenyl)alaninamide derivatives [(*Z*)-**1**] were prepared in satisfactory yields, starting from 3,4-dimethoxybenzaldehyde. On irradiation in methanol, regioselective photocyclization of these derivatives proceeded to give papaverine analogs in good yields. Substituents introduced into (*Z*)-**1** were found to exert only a minor effect on the conversion of the starting isomers (**1**) as well as on the selectivity of the analogs which were formed along with 1-azetines.

Photochemistry has continued to contribute to the development of efficient and selective transformations of organic materials into pharmaceutically important heterocyclic compounds.[1] It is well-known that numerous biomolecules and natural products contain various types of heterocyclic compounds as their principal constituents. We have been interested in exploring the excited-state reactivities of α-dehydroamino acid derivatives, one of the main constituents of some antibiotics,[2] as well as in demonstrating the synthetic utility of these photochemical reactions. Taking into account that α-dehydroamino acid-derived products may possess high biological activities, we embarked on a systematic study regarding photochemical reactivities of aryl-substituted α-dehydroalanine derivatives and discovered novel photocyclization reactions forming pharmaceutically useful products.[3,4] One of the important findings is that the photocyclization of substituted (*Z*)-*N*-acetyl-α-dehydrophenylalaninamides in methanol and acetonitrile constitutes a useful method for constructing the isoquinoline skeleton.[3] Very recently, we found that the introduction of a methoxy group at the *meta* position on the styryl benzene ring accomplishes regioselective photocyclization to give 6-methoxyisoquinoline derivative in a reasonable yield without forming any 8-methoxy derivative.[5] These findings stimulated us to photochemically synthesize analogs of papaverine, one of the isoquinoline alkaloids, as an extension of our study on the photocyclization of *N*-acyl-α-dehydroamino acid derivatives. To this end we designed and synthesized substituted (*Z*)-*N*-phenylacetyl-α-dehydrophenylalaninamides (**1a–h**), hoping to establish a new route to analogs of pharmaceutically important papaverine.

The starting (*Z*)-isomers (**1a–h**) were prepared in high yields (>80%) by the ring opening reactions of (*Z*)-

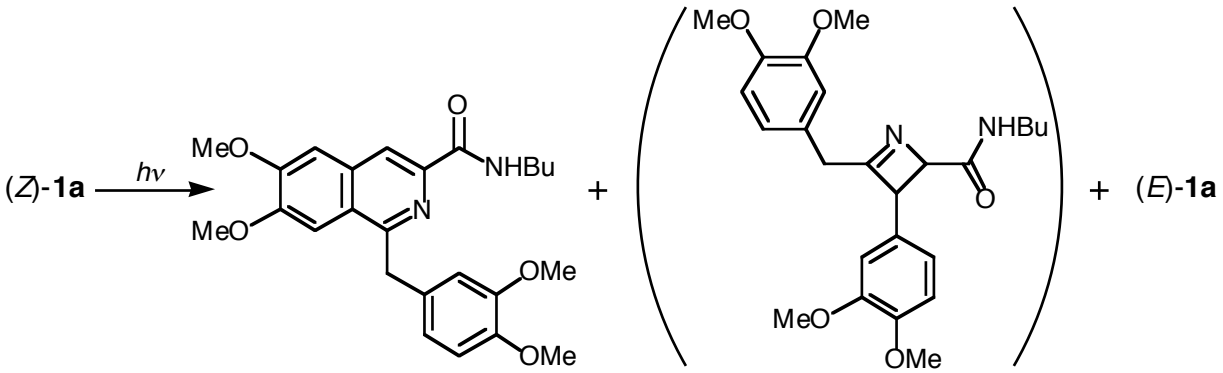
2-substituted benzyl-4-methoxy-substituted benzylidene-5(4*H*)-oxazolones with butylamine (**1a**,**c**–**h**)



(*Z*)-**1a–h**

	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**
R^1:	OMe	OMe	OMe	OMe	OMe	OMe	OMe	OMe
R^2:	OMe	OMe	OMe	OMe	H	OMe	OMe	OMe
R^3:	OMe	OMe	OMe	H	OMe	Cl	Cl	F
R^4:	OMe	OMe	H	H	OMe	Cl	H	H
R^5:	Bu	CH_2Ph	Bu	Bu	Bu	Bu	Bu	Bu

or benzylamine (**1b**) in the presence of triethylamine.[6] The synthesis of these oxazolones was achieved by the Knoevenagel-type condensation and ring closure reactions between methoxy-substituted benzaldehydes and *N*-substituted phenylacetylglycines,[6] though their yields were not so high (20–30%). After a nitrogen purged methanol solution of **1a** (1.0×10^{-3} mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 400 W high pressure Hg lamp for 360 min at room temperature, the product mixture obtained was subjected to column or preparative thin layer chromatography over silica gel (ethyl acetate-chloroform), which allowed us to isolate papaverine analog (**2a**, 46%). In addition, (*E*)-**1a** could be isolated in 33% yield from the mixture obtained by the 60 min irradiation of the same solution. The structures of 2-(3,4-dimethoxybenzyl)-substituted oxazolone, (*Z*)-**1a**, (*E*)-**1a**, and **2a** were determined based on their spectroscopic and physical properties.[7] A ^{1}H NMR spectral analysis of the product mixture showed that there is formation of *trans*-1-azetine [*trans*-**3a**; δ= 4.37 and 5.45 ppm, *J*= 6.7 Hz (azetine ring-proton signals)] and *cis*-**3a** [δ= 4.82 and 5.69 ppm, *J*= 10.4 Hz (azetine ring-proton signals)], as predicted from the previous studies (Scheme 1).[3,4] However, any attempts to isolate these azetine derivatives were unsuccessful, probably because of the more decreased stability of **3a** as compared to that of 1-azetines previously isolated.



2a **3a** (*trans* and *cis*)

Scheme 1

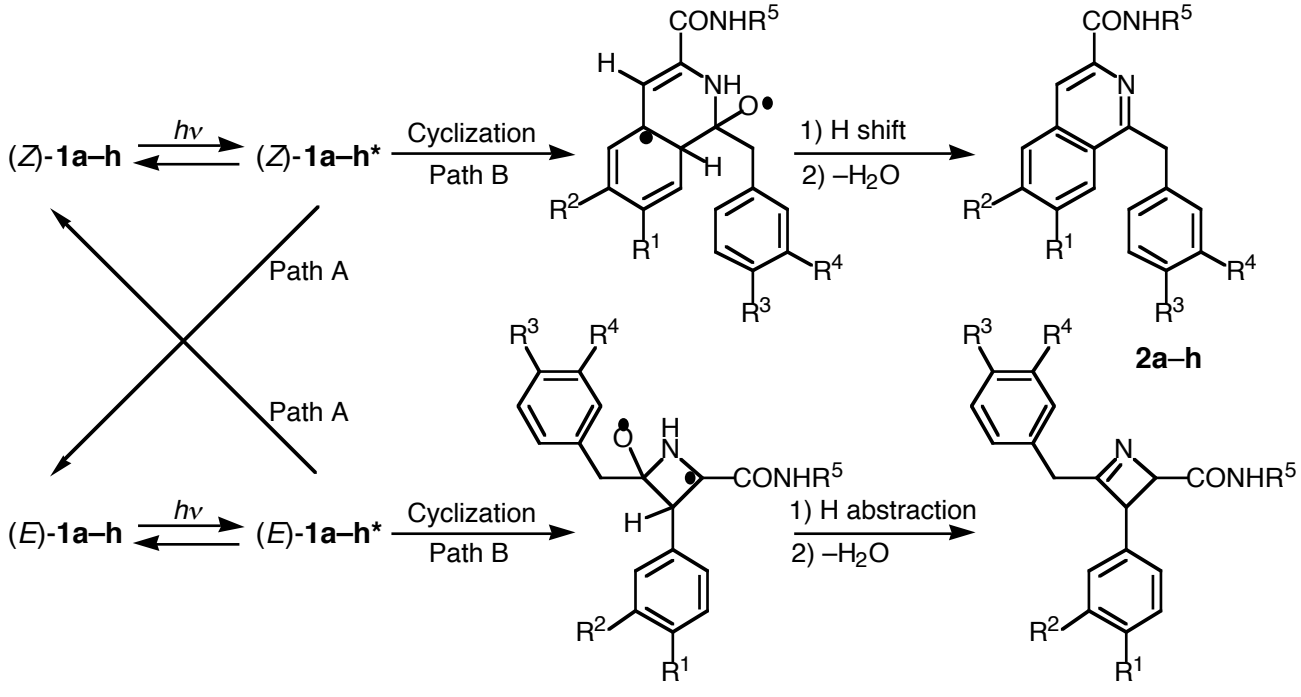
Since the photocyclization of (*Z*)-**1a** accompanies side reactions to some extent, the sum of composition for (*Z*)-**1a**, (*E*)-**1a**, **2a**, and **3a** was regarded as 100% for estimating the compositions of these compounds

based on the area ratio of given ^{1}H NMR signals (Table 1). The result obtained for (*Z*)-**1a** demonstrates the rapid production of (*E*)-**1a** and the subsequent increase in a composition for **2a** and **3a** with the decrease of (*Z*)- and (*E*)-isomer compositions. In addition, the use of (*E*)-**1a** (1.0×10^{-3} mol dm^{-3}) as the starting isomer gave almost the same isomer composition as that derived from (*Z*)-**1a** at the early stage of the reaction (Table 1), confirming that the rate of the photoisomerization (Path A in Scheme 2) is much faster than that

Table 1. Relation between irradiation time and composition (%) of each compound obtained by the irradiation of (*Z*)-**1a** and (*E*)-**1a** in methanol

Compound	Irradiation time (min)						
	0	30	60	90	120	240	360
(Z)-**1a**	100	39.6	38.6	36.2	34.1	18.4	3.5
	(0)[a]	(38.9)[a]	(38.0)[a]				
(E)-**1a**	0	57.3	53.5	50.2	46.4	25.9	4.3
	(100)[a]	(58.0)[a]	(54.5)[a]				
2a	0	1.8	4.6	8.0	12.5	38.0	63.9
	(0)[a]	(1.5)[a]	(4.0)[a]				
trans-**3a**	0	0.8	2.0	3.2	4.4	12.0	19.6
	(0)[a]	(1.0)[a]	(2.0)[a]				
cis-**3a**	0	0.5	1.3	2.4	2.6	5.7	8.7
	(0)[a]	(0.6)[a]	(1.5)[a]				

a) Composition obtained by the irradiation of (*E*)-**1a**.



Scheme 2

of the subsequent photocyclization process (Path B).[8] The data in Table 1 also show that selectivity for **2a** [defined as the product-composition ratio, namely, **2**/(**2** + **3**)] is in the range of 60–70% and comparable to that (69%) for isoquinoline derivative generated by the irradiation of *N*-acetyl-□-dehydro(4-methoxyphenyl)alaninamide in methanol.[3] This finding strongly suggests that the methoxy-substituted phenylacetyl carbonyl carbon in the excited-state (*Z*)- and (*E*)-isomers possesses the reactivity comparable to that of the acetyl carbonyl carbon. A careful analysis of the ^{1}H NMR spectrum recorded after 360 min irradiation revealed negligible formation of 7,8-dimethoxyisoquinoline derivative. In order to confirm whether the methoxy group introduced at the 3-position on the styryl benzene ring exerts a large steric effect on the cyclization proceeding at the 2-position, conformational energy of the (*Z*)-isomer was minimized by MM2 and PM5 calculations (Figure 1).[9] An examination of the energy-minimized conformation revealed that the 3-methoxy methyl group is directed toward the hydrogen atom attached to the 2-position and, hence, the cyclization process taking place at this position experiences a great steric hindrance of the methoxy group. Therefore, we were led to conclude that the 3-methoxy substituent plays a decisive role in constructing the papaverine skeleton.

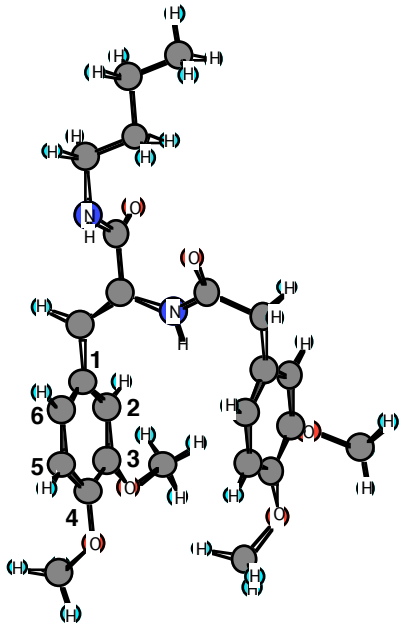


Figure 1. Energy-minimized conformation of (*Z*)-**1a**.

Table 2. Relation between irradiation time and composition (%) of each compound obtained by the irradiation of (*Z*)-**1a** in acetonitrile

Compound	Irradiation time (min)				
	0	30	60	90	120
(Z)-**1a**	100	69.7	66.0	62.5	57.3
(E)-**1a**	0	30.3	32.0	33.4	35.2
2a	0	0	2.0	3.5	6.3
trans-**3a**	0	0	0	0.6	1.2
cis-**3a**	0	0	0	0	0

In Table 2 are shown solvent effects on the photoreactivity of **1a** and the product composition. A comparison of the data given in Tables 1 and 2 clearly indicates that the use of aprotic polar solvent, acetonitrile, lowers the reactivity of each isomer in the excited state whereas the (*Z*)-isomer composition is increased by a factor of about 2 at photostationary state in this solvent. It was previously found that methanol is able to form a hydrogen bond to the amide carbonyl oxygen of *N*-acetyl-□-dehydronaphthylalaninamide derivative in the ground and excited states.[4] In addition to the fact that methanol and acetonitrile have comparable polarities,[10] this finding allowed us to propose that hydrogen-bonding solvation of (*Z*)- and (*E*)-isomers in the excited state greatly affects not only the relative rate for the isomerization but also the rate for the cyclization from a given isomer. Interestingly, the change in solvent

from methanol to acetonitrile resulted in an increase of the selectivity for **2a** (64→84% at 120 min irradiation) with a decrease of that for **3a** (36→16%). However, on prolonged irradiation (>240 min) in acetonitrile side reactions took place to an appreciable extent, making methanol better solvent for the reaction.

In order to shed light on the scope and limitations of the photoinduced cyclization of (*Z*)-**1a** that provides a new route to papaverine analog (**2a**), we investigated substituent effects on the composition of each compound obtained at a given irradiation time. As demonstrated in Table 3, the removal of the methoxy group from the 3-position on the styryl benzene ring (**1e**) had only a small effect on both the conversion of **1a** and the selectivity of **2a**. In addition, these conversion and selectivity were only sightly affected also by the replacement of two methoxy groups on the benzene ring of the phenylacetyl moiety (R^3 and R^4) by two chlorine atoms (**1f**), as well as by the introduction of benzyl group (R^5) instead of butyl one (**1b**). A comparison of the data for **1c** (R^3= OMe, R^4= H), **1d** (R^3= R^4= H), **1g** (R^3= Cl, R^4= H), and **1h** (R^3= F, R^4= H) confirmed that the electron-donating methoxy group has a clear tendency to increase the conversion of **1** at a given irradiation time. It is likely that the methoxy group as substituent R^3 (**1c**) results in an enhancement in the reactivity of the phenylacetyl carbonyl carbon in the excited state (Scheme 2). Thus, the observed substituent effects allow us to predict that the regioselective photocyclization of (*Z*)-**1** is applicable to the synthesis of various kinds of papaverine analogs.

Table 3. Substituent effects on the composition of each compound obtained by the irradiation of *(Z)*-**1a** in methanol and the selectivity of **2a**.

Compound	Irradiation time (min)	Composition (%)				Selectivity of **2** (%)
		(Z)-**1**	*(E)*-**1**	**2**	**3**[a)]	
1a	60	38.6	53.5	4.6	3.3	
	360	3.5	4.3	63.9 (46)[b)]	28.3	69
1b	60	39.9	55.5	2.6	2.0	
	360	4.3	5.7	60.7 (45)[b)]	29.3	67
1c	60	36.7	55.0	5.2	3.1	
	240	0.7	0.9	68.6 (43)[b)]	29.8	70
1d	60	36.9	56.1	3.7	3.3	
	360	3.0	4.0	61.5 (48)[b)]	31.5	66
1e	60	50.0	47.6	1.5	0.9	
	360	5.3	5.7	54.9 (40)[b)]	34.1	62
1f	60	34.8	59.7	3.8	1.7	
	360	2.7	3.6	75.6 (50)[b)]	18.1	81
1g	60	36.5	59.6	2.9	1.0	
	360	3.2	4.2	62.6 (42)[b)]	30.0	68
1h	60	36.1	57.8	4.2	1.9	
	360	2.5	3.7	70.4 (46)[b)]	23.4	75

a) The sum of *cis*- and *trans*-isomers. b) Isolated yield (%).

Although there are many synthetic routes to papaverine and its analogs,[11] no convenient photochemical route to the analogs is known. The procedure for preparing the starting **1** is very simple and easily applicable to its related compounds. In addition, column chromatography on silica gel enables rapid separation of **2**, the R_f value of which is much larger than that of (*Z*)-**1**, (*E*)-**1**, and **3**. The photocyclization of substituted (*Z*)-*N*-phenylacetyl-□-dehydrophenylalaninamides described above, therefore, provides a new synthetic route to papaverine analogs.

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7. Selected data for (*Z*)-2-(3,4-dimethoxybenzyl)-4-(3,4-dimethoxybenzylidene)-5(4*H*)-oxazolone: mp 157.0–158.0 °C ($CHCl_3$-hexane); IR (KBr): 1794, 1770, 1650, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): □3.85 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 3.91 (2H, s), 3.93 (3H, s), 6.84 (1H, d, *J*= 8.3 Hz), 6.88 (1H, d, *J*= 2.0 Hz), 6.92 (1H, dd, *J*= 2.0, 8.3 Hz), 7.10 (1H, s), 7.46 (1H, dd, *J*= 2.0, 8.3 Hz), 7.97 (1H, d, *J*= 2.0 Hz); ^{13}C NMR ($CDCl_3$): □35.7, 55.8, 56.0 (3C), 110.8, 111.3, 112.6, 113.9, 121.7, 125.4, 126.5, 127.5, 130.4, 132.3, 148.6, 149.1 (2C), 152.0, 166.2, 168.0.

   For (*Z*)-*N*-butyl-3-(3,4-dimethoxyphenyl)-2-(3,4-dimethoxyphenylacetylamino)-2-propenamide [(*Z*)-**1a**]: mp 140.0–141.0 °C (EtOH-hexane); IR (KBr): 3272, 2956, 2836, 1644, 1620 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): □0.87 (3H, t, *J*= 7.3 Hz), 1.27 (2H, tq, *J*= 7.3, 7.3 Hz), 1.40 (2H, tt, *J*= 7.3, 7.3 Hz), 3.11 (2H, dt, *J*= 5.5, 7.3 Hz), 3.55 (2H, s), 3.64 (3H, s), 3.71 (3H, s), 3.74 (3H, s), 3.75 (3H, s), 6.76 (1H, d, *J*= 8.5 Hz), 6.84 (1H, dd, *J*= 1.8, 7.9 Hz), 6.90 (1H, d, *J*= 7.9 Hz), 6.94 (1H, br s), 6.95 (1H, dd, *J*= 1.8, 8.5 Hz), 6.97 (1H, s), 7.12 (1H, d, *J*= 1.8 Hz), 7.71 (1H, t, *J*= 5.5 Hz), 9.43 (1H, s);

^{13}C NMR (DMSO-d_6): δ 13.7, 19.5, 31.2, 38.7, 41.9, 55.2, 55.3 (2C), 55.5, 111.2, 111.8, 113.0, 113.1, 121.2, 122.7, 126.7, 127.7, 128.0, 128.2, 147.6, 148.2, 148.5, 149.1, 164.9, 169.9. Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.91; H, 7.03; N, 6.35.

For (*E*)-*N*-butyl-3-(3,4-dimethoxyphenyl)-2-(3,4-dimethoxyphenylacetylamino)-2-propenamide [(*E*)-**1a**]: mp 139.0–140.0 °C (EtOH-hexane); IR (KBr): 3310, 2956, 1641 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.79 (3H, t, *J*= 7.3 Hz), 1.13 (2H, tq, *J*= 7.3, 7.3 Hz), 1.30 (2H, tt, *J*= 6.7, 7.3 Hz), 3.02 (2H, dt, *J*= 6.1, 6.7 Hz), 3.47 (2H, s), 3.69 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.75 (3H, s), 6.76 (1H, dd, *J*= 1.8, 8.5 Hz), 6.80 (1H, s), 6.81 (1H, dd, *J*= 1.8, 8.5 Hz), 6.84 (1H, d, *J*= 8.5 Hz), 6.86 (1H, d, *J*= 1.8 Hz), 6.88 (1H, d, *J*= 8.5 Hz), 6.92 (1H, d, *J*= 1.8 Hz), 7.99 (1H, t, *J*= 6.1 Hz), 9.63 (1H, s); ^{13}C NMR (DMSO-d_6): δ 13.6, 19.5, 30.4, 38.6, 42.2, 55.2, 55.4 (2C), 55.5, 111.5, 111.6, 111.8, 113.1, 115.5, 120.8, 121.1, 128.0, 128.3, 132.2, 147.6, 147.8, 148.2, 148.5, 164.8, 169.1. Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.46; H, 6.84; N, 5.99.

For 3-butylaminocarbonyl-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (**2a**): mp 140.0–140.5 °C (EtOAc); IR (KBr): 3388, 2932, 1743, 1665 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (3H, t, *J*= 7.3 Hz), 1.33 (2H, tq, *J*= 7.3, 7.3 Hz), 1.54 (2H, tt, *J*= 6.7, 7.3 Hz), 3.36 (2H, dt, *J*= 6.1, 6.7 Hz), 3.67 (3H, s), 3.69 (3H, s), 3.92 (6H, s), 4.56 (2H, s), 6.82 (1H, d, *J*= 7.9 Hz), 6.83–6.85 (1H, m), 7.12 (1H, br s), 7.56 (1H, s), 7.60 (1H, s), 8.25 (1H, s), 8.68 (1H, t, *J*= 6.1 Hz); ^{13}C NMR (DMSO-d_6): δ 13.7, 19.6, 31.5, 38.3, 40.4, 55.3, 55.4, 55.77, 55.82, 104.5, 107.1, 111.8, 112.9, 117.2, 120.7, 123.3, 131.6, 133.0, 141.4, 147.2, 148.6, 150.7, 152.5, 157.0, 164.3. Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.14; H, 6.82; N, 6.19.

8. The photocyclization of (*Z*)-**1a** in methanol gave the same product distribution as that derived from the cyclization of substituted *N*-acetyl-Δ-dehydrophenylalaninamides,[3] thus allowing us to discuss the rate of the isomerization relative to the rate of the cyclization on the basis of the same reaction scheme as that previously proposed.
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