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Synthesis of 2-Aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane Derivatives by the 1,3-Dipolar Cycloaddition Reaction of Homoadamantane-Incorporated Nitrones with Alkenes[1]

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Abstract: The 1,3-dipolar cycloaddition reaction of homoadamantane-incorporated nitrones, 4-azahomoadamant-4-ene *N*-oxide (**1**) and 5-methyl-4-azahomoadamant-4-ene *N*-oxide (**2**), with various alkenes afforded 2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane derivatives as the 1:1 cycloadduct. The reaction showed relatively low regio- and stereo-selectivities, however only the 5-*endo* adduct was not formed. This was rationalized by the steric effect in the course of reaction process on the basis of PM3 calculations of the transition state model. © 1997 Elsevier Science Ltd.

Introduction

The 1,3-dipolar cycloaddition reactions of nitrones provide a useful and effective method for synthesizing *N*-heterocyclic five-membered compounds[2]. We have reported the cycloaddition reaction of nitrones such as 4-azahomoadamant-4-ene *N*-oxide (**1**) and 5-methyl-4-azahomoadamant-4-ene *N*-oxide (**2**) with alkynes, nitriles, isocyanates, and isothiocyanates as a useful method for the synthesis of novel homoadamantane-fused nitrogen heterocycles[3-6]. For example, in the reaction with acetylenic compounds, the initial cycloadducts of **2** readily rearranged to give homoadamantane-fused pyrroles[3], and the 1,3-dipolar cycloaddition with nitrile compounds provided a general and efficient route to 2,3-dihydro-1,2,4-oxadiazole derivatives which are difficult to prepare by other routes[4,5]. Homoadamantane-incorporated nitrones also cycloadd across the C=N double bond of isocyanates and isothiocyanates affording oxadiazolidinone and oxadiazolidinethione derivatives[6]. From our continued interest in the synthetic

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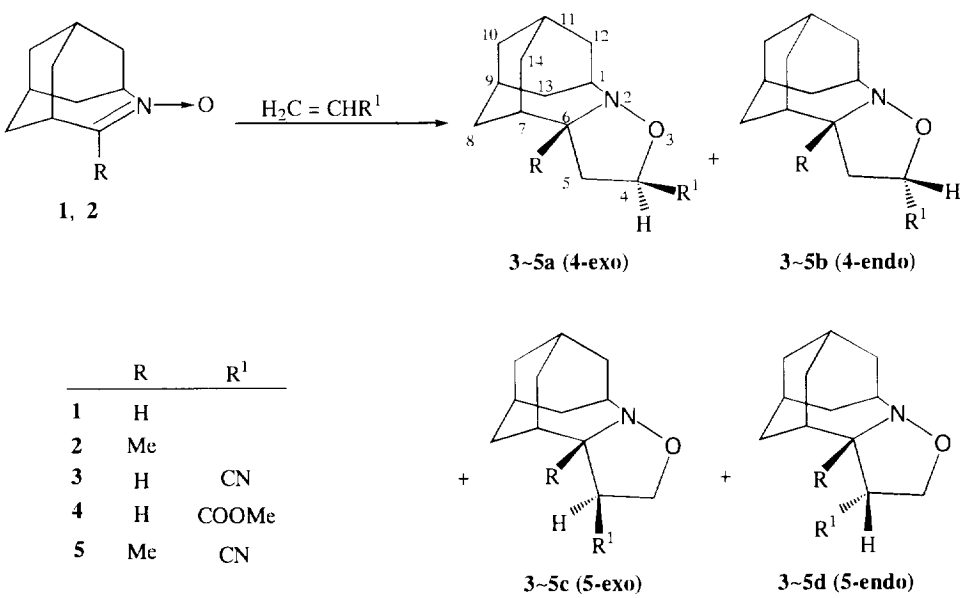
application of the unique nitrones **1** and **2**, we investigated the cycloaddition reaction of **1** and **2** with various alkenes. Our main interest involved the elucidation of the stereochemical nature of the addition reaction, since the understanding of the nature of the reaction is important for its use as a tool of synthesizing new adamantane heterocyclic compounds.

Results and Discussion

1,3-Dipolar Cycloaddition

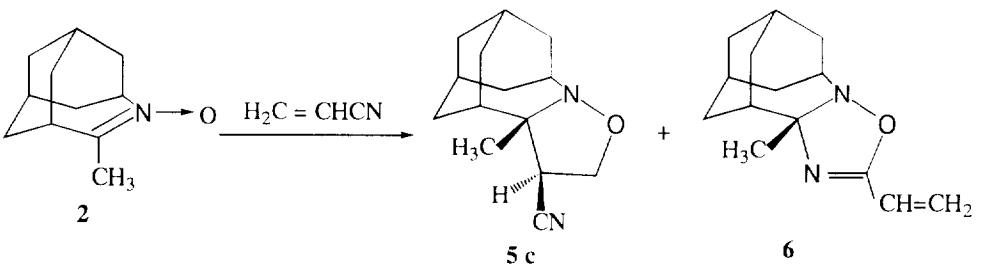
The 1,3-dipolar cycloadditions of nitrones **1** and **2** with olefinic compounds were found to be considerably different from those of the corresponding acetylenic ones. The reactions of nitrones **1** and **2** with substituted alkene analogs with the same activating groups such as cyano and methoxycarbonyl groups underwent at a much slower rate, and without high regioselectivity compared with those of alkynes[3]. The alkene case also has the possibility of forming a mixture of *endo* and *exo* stereoisomers.

The mono-substituted dipolarophiles used in this investigation were acrylonitrile and methyl acrylate. Between nitrones **1** and **2**, only aldonitrone **1** readily reacted with an excess amount of olefinic dipolarophiles at room temperature. However, the reaction showed poor regio- and stereo-selectivities. The reaction of aldonitrone **1** with acrylonitrile (2.0 equivalent) at room temperature gave 4- and 5-cyano-2-aza-3-oxatetracyclo[7.3.1.$1^{7,11}$.$0^{2,6}$]tetradecane derivatives as three regio- and stereoisomers **3a**, **3b**, and **3c** in the ratio of 10:11:9. These isomers could be easily separated by thin layer chromatography (silica gel; ethyl acetate/hexane in 1:3 ratio) (Scheme 1). Methyl acrylate also



	R	R^1
1	H	
2	Me	
3	H	CN
4	H	COOMe
5	Me	CN

Scheme 1

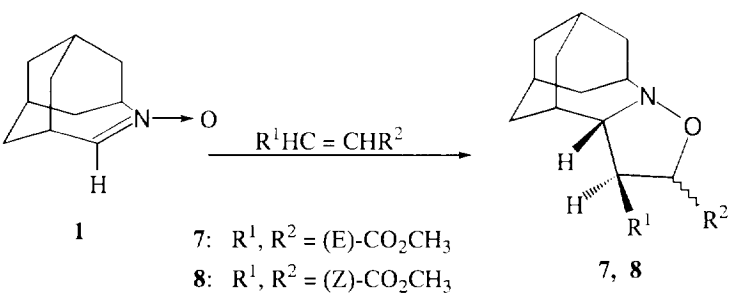


Scheme 2

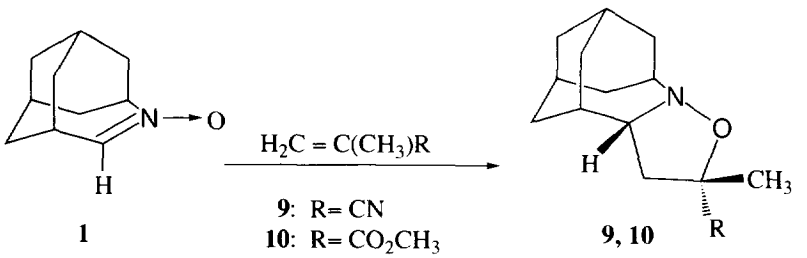
showed obvious reactivity toward **1** under the same conditions as for acrylonitrile: separation of the reaction products by TLC (silica gel; ethyl acetate/hexane in 1:1 ratio) gave two fractions. The ^{1}H NMR spectra showed that the second fraction referred to **4b** and the first fraction was still a mixture. Further separation of this mixture by TLC using a different elution system (silica gel; ether/hexane in 1:3 ratio) gave two isomers **4a** and **4c** (Scheme 1).

In contrast, ketonitrone **2** was much less reactive than aldonitrone **1**. Heating of ketonitrone **2** with acrylonitrile in a sealed tube at 110 °C for 8 h gave no cycloproduct. A prolonged reaction time to 10 days gave two products, a C=C cycloadduct **5c** and C≡N cycloaduct **6** in low isolated yields as reported previously (Scheme 2) [4].

The different reactivity between the two nitrones was also observed in the case of reaction of 1,2-disubstituted alkenes with electron-withdrawing groups. The cycloaddition of aldonitrone **1** with dimethyl fumarate carried out at room temperature for 1 h gave the corresponding 4,5-disubstituted isoxazolidine **7** in an excellent yield. The cycloaddition of **1** with dimethyl maleate underwent similarly with longer time to give **8** (Scheme 3 and Table 1). Similarly, 1,1-disubstituted dipolarophiles, methyl methacrylate and methacrylonitrile, reacted with nitrone **1** to afford regiospecifically 4-substituted isoxazolidines **9** and **10** (Scheme 4 and Table 1). However, ketonitrone **2** did not show any reactivity with these alkenes even under longer heating conditions. The above differences may be explained by the much higher steric hindrance encountered in the attack particularly on nitrone **2**.

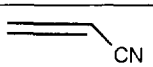
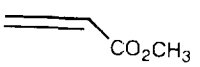
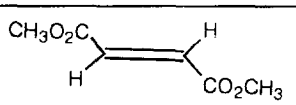
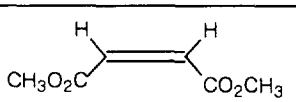
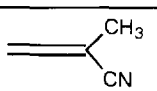
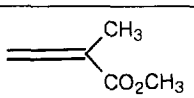
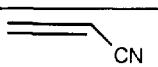


Scheme 3



Scheme 4

Table 1. Cycloaddition of nitrones **1** and **2** with alkenes.

Nitrones	Alkenes	Temperature	Reaction Time	Product	Yield (%)
1		r.t.	30 min	**3a**	23
				3b	26
				3c	20
1		r.t.	2 h	**4a**	20
				4b	33
				4c	15
1		r.t.	1 h	**7**	86
1		r.t.	15 h	**8**	89
1		r.t.	4 h	**9**	65
1		r.t.	2 h	**10**	74
2		110 °C	10 d	**5c**	23[a]
				6	19

a) See references 4 and 5.

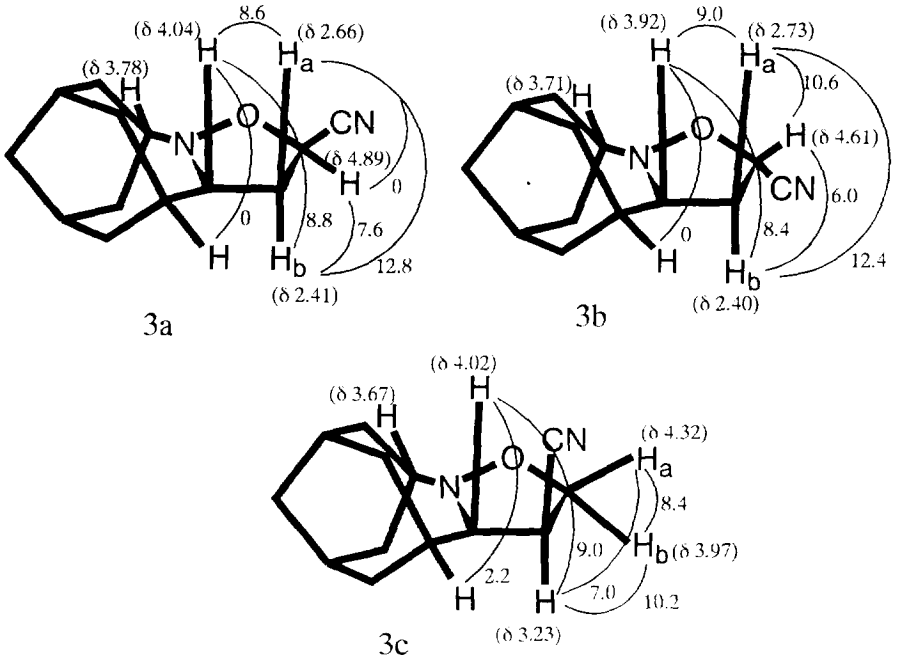


Figure 1. ^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) of the isoxazolidine protons of three isomers **3a-c**.

Structure Determination Based on Spectral Data.

The structural elucidation of the products was done as follows. Compound **3** is taken as an example. All three isomers (**3a**, **3b**, and **3c**) had the same molecular ion peak (m/z = 218) and parent nitrone peak (m/z = 165) in the MS spectra. These data indicated that all the isomers are 1:1 adducts of the nitrone and acrylonitrile. The IR absorption at ~2230 cm^{-1} for all three isomers showed that they have a C≡N moiety. From the ^{1}H NMR spectra, isomers **3a** and **3b** were assigned to be the 5'-substituted isoxazolidine isomers because three one-proton peaks were observed in the low magnetic field (δ > 3 ppm). The remaining isomer, **3c**, was assigned as the 4'-substituted isoxazolidine isomer because its ^{1}H NMR spectra gave five one-proton peaks in the low magnetic field (Figure 1). The stereochemistry of these isomers was determined by the NOESY spectra by assigning the proton pairs with the nearest distance. In the ^{1}H NMR spectrum of **3a**, the nearest proton pairs were observed between C_3-H (δ = 4.04) and C_4-H_a (δ = 2.66) as well as between C_4-H_b (δ = 2.41) and C_5-H (δ = 4.89), so that **3a** could be assigned to an *exo* adduct of the 5'-substituted isoxazolidine. The NOESY spectra of isomer **3b** indicated that the three protons (C_3-H, C_4-H_a, and C_5-H) should be on the same side of the isoxazolidine ring, and hence, **3b** was formed by the *endo* cycloaddition. As for **3c**, the NOESY spectra indicated that C_3-H and C_4-H are not on the same side of the isoxazolidine ring. Therefore, **3c** was assigned as an *exo* type adduct with the different regiochemistry. Other products were characterized similarly by spectral data (See experimental).

Stereochemical Consideration Using PM3 Calculations.

The 1,3-dipolar cycloaddition of a monosubstituted alkene to aldonitrone **1** yields, in principle, four regio- and stereo-isomers(cf. Scheme 1). As described above, by the reaction of **1** with acrylonitrile we obtained **3a**, **3b** and **3c** in approximately equal ratios, but we could not detect **3d**. Similarly, the 1,3-dipolar cycloaddition with methyl acrylate also

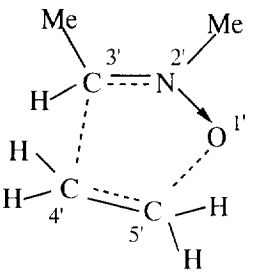


Figure 2. Transition state model of the 1,3-dipolar cycloaddition of ethylene to an aldonitrone.

gave only **4a**, **4b**, and **4c**. We wondered why the 5-*endo* products (**3d** and **4d**) were not produced. Therefore, the molecular orbital calculations of the four isomers of **3** were performed using the PM3 method of MOPAC 6.01[7]. As shown in Table 2, the heat of formation of **3d** was higher than the other three isomers, but the energy difference was not significant enough to explain the experimental results. From an inspection of a molecular model, it was suggested that an unfavorable steric interaction must occur during the reaction process, and not in the product structure.

Therefore, we tried to compare the stability of the transition state models related to the four cycloaddition products. We first considered the model system in which ethylene cycloadds to a simple aldonitrone as shown in Figure 2. An approximate structure of the transition state was searched by scanning the two bond distances between O_1 and C_5 as well as C_3 and C_4 in a step of 0.1 Å. The resulting structure was then optimized to reach the transition state by applying the TS key word in MOPAC. In the calculated transition state, the two bond lengths were 1.9374Å and 2.1094Å for O_1-C_5 and C_3-C_4, respectively. We then combined this transition structure into the homoadamantane skeleton to simulate the 1,3-dipolar cycloaddition of aldonitrone **1**. Finally, the four hydrogen atoms of the ethylene moiety in the model system were replaced with a nitrile group one by one to mimic the corresponding isomers(**3a**~**3d**)[8]. The heat of formation calculated for the four transition state models are listed in Table 2 and the calculated structures(**3at**~**3dt**) are shown in Figure 3. The model related to **3d** was especially unstable. In this structure, the nitrogen atom of the nitrile group is separated by only 1.5981 Å from a hydrogen atom (asterisked in **3dt**) on the homoadamantane ring. There were no such short contacts in the other three transition state models(**3at**~**3ct**). This is apparently the reason why **3d** and **4d** were not formed. During the addition reaction, the ethylene molecule perpendicularly approaches the O_1-N_2-C_3 plane, in contrast, the C_4-C_5 bond of the product exists in approximately the same plane. The regioselectivity observed in the reaction of 1,1-disubstituted alkenes is also explicable in the same way.

Our calculation procedure is much convenient comparing to the conventional way which exactly determines the transition structure of the individual isomer. Nevertheless our procedure unambiguously attributed the reaction specificity to the steric repulsion during the reaction process.

Table 2 The PM3 calculation results for the four isomers of compound **3**.

		Heat of Formatiom (kcal/mol)		Distance to the Nearest Adamantane H
Isomer	Yield (%)	Product	Transition State Model	from Nitrile N (Å)
3a	23	14.39591	96.70974	4.1563
3b	26	15.62129	96.07066	3.3584
3c	20	15.53508	95.30502	2.9437
3d	0	18.77163	118.00631	1.5981

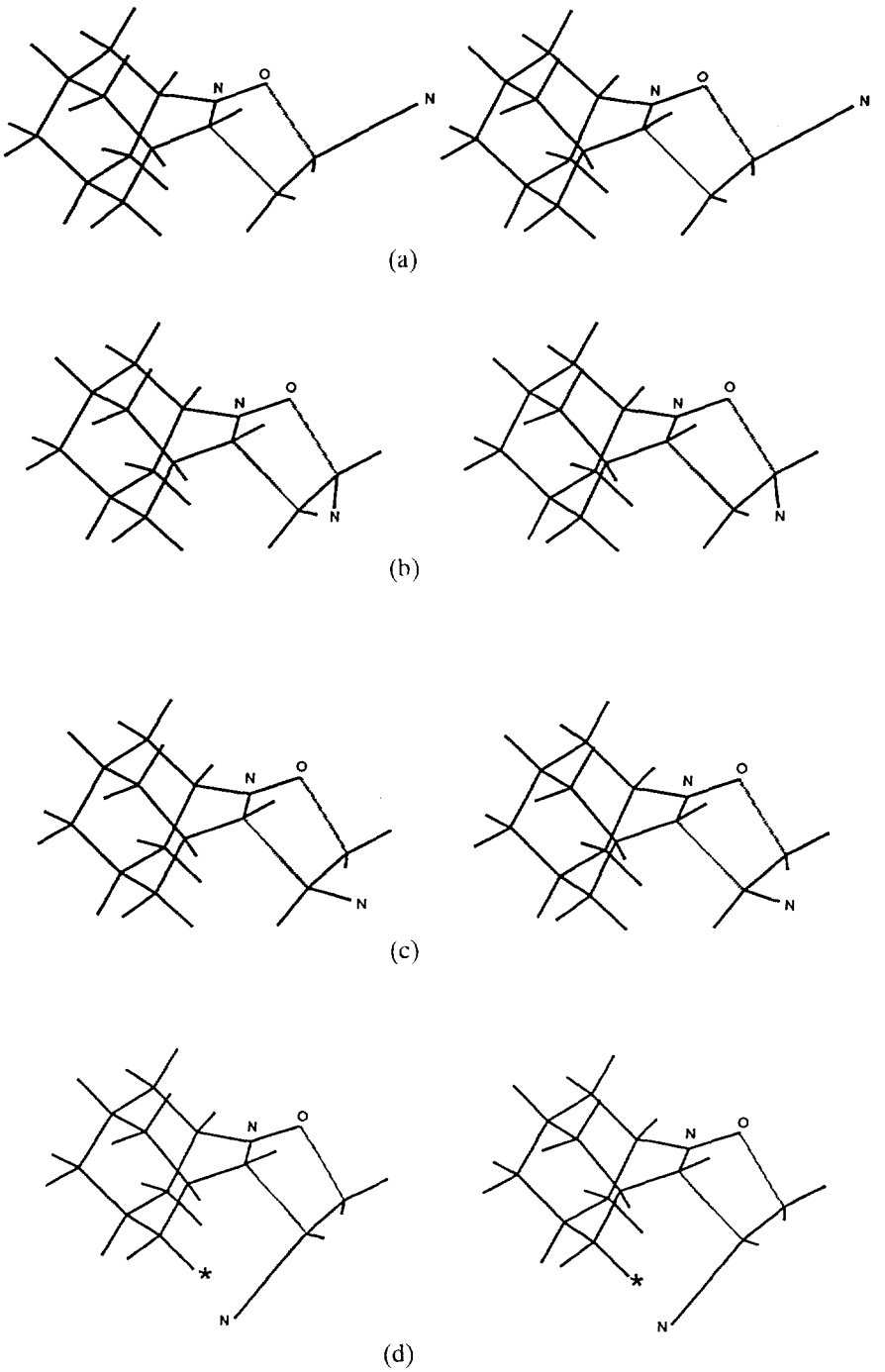


Figure 3. Stereo drawing of the transition state model. (a) **3at** , (b) **3bt** , (c) **3ct** , and (d) **3dt** .

Experimental

Melting points were measured using a Yanagimoto micro-melting point hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR 5300 spectrometer. ^{1}H NMR spectra were recorded with a Varian GEMINI 200 spectrometer at 200 MHz with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the δ scale (ppm). Coupling constants *J* are given in Hz. Micro-elemental analyses were performed on a Perkin-Elmer 2400S elemental analyser. Mass spectra (EI) were obtained using a JEOL-JMS-AX 505 HA mass spectrometer at 70eV. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} and/or Merck Aluminiumoxide F_{254}.

Cycloaddition reaction of aldonitrone 1 with acrylonitrile

To a solution of **1** (50 mg, 0.30 mmol) in toluene (1.0 ml), acrylonitrile (32 mg, 0.60 mmol) was added in one portion, and the mixture was stirred at room temperature for 30 min. Removal of the solvent *in vacuo* gave a residue which was separated by preparative TLC (silica gel, 20×20×0.25 cm; hexane/ ethyl acetate =1/1) to give three products: (4R*,6R*)-4-cyano-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane **3a** (15 mg, R_f=0.60, mp: 97.5-99.0°C); (5R*,6S*)-5-cyano-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane **3c** (13 mg, R_f=0.45, oil); (4S*,6R*)-4-cyano-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane **3b** (17 mg, R_f=0.24,mp: 84.0-86.5°C). The overall yield was 69%.

3a ; IR (KBr) ν_{max}(cm^{-1}): 2911, 2857, 2236, 1447, 1383, 1329, 1269, 1177, 1159, 1092, 1061, 1038, 1005, 949, 909, 837, 739; ^{1}H NMR ($CDCl_3$) δ: 4.89(1H,d, J=7.6Hz), 4.04(1H,dd, J=8.8, 8.6Hz), 3.78 (1H, br t, J = 8.8Hz), 2.66 (1H, dd, J=12.8, 8.6 Hz), 2.41 (1H, ddd, J=12.8, 8.8, 7.6 Hz), 2.33-1.46 (13H, m); MS m/z(%): 218 (M$^+$,93), 165(49), 163(50), 148(26), 135(100), 120(36), 107(16), 106(16). High resolution MS for $C_{13}H_{18}N_2O$: 218.1419; Found: 218.1418.

3b ; IR (KBr) ν_{max}(cm^{-1}): 2913, 2853, 2247, 1462, 1447, 1375, 1346, 1306, 1260, 1152, 1094, 1071, 1028, 947, 914, 845, 760; ^{1}H NMR ($CDCl_3$) δ: 4.61(1H,dd, J=10.6, 6.0Hz), 3.92(1H, dd, J=9.0, 8.4Hz), 3.71 (1H, br t, J = 8.6Hz), 2.73 (1H, ddd, J=12.4, 8.4, 6.0 Hz), 2.40 (1H, ddd, J=12.4, 10.6, 9.0 Hz), 2.37-1.50 (13H, m); MS m/z (%): 218 (M$^+$,86), 165(51), 163(51), 148(27), 135(100), 120(37), 107(17), 106(16). High resolution MS for $C_{13}H_{18}N_2O$: 218.1419; Found: 218.1420.

3c ; IR (neat) ν_{max}(cm^{-1}): 2913, 2855, 2243, 1447, 1159, 1061, 1028, 972, 752; ^{1}H NMR ($CDCl_3$) δ: 4.32(1H, dd, J=8.4, 7.0Hz), 4.02(1H, dd, J=9.0, 2.2Hz), 3.97 (1H, dd, J=10.2, 8.4Hz), 3.67 (1H, m), 3.23 (1H, ddd, J=10.2, 9.0, 7.0 Hz), 2.25-1.48 (13H,m); MS m/z (%): 218 (M$^+$,33), 188(3), 165(86), 148(19), 135(100). High resolution MS for $C_{13}H_{18}N_2O$: 218.1419; Found: 218.1415.

Cycloaddition reaction of nitrone 1 with methyl acrylate

A solution of **1** (100 mg, 0.60 mmol) and methyl acrylate (100 mg, 1.20 mmol) in toluene(2.0 ml) was stirred at room temperature for 12 h. The excess reagent and solvent were removed *in vacuo*. Separation of the residue by preparative TLC (silica gel, 20×20×0.2 cm; ether) gave two fractions with *Rf* value of 0.84 and 0.22. Further separation of the former fraction by TLC (silica gel, 20×20×0.25 cm; dichloromethane/ acetone =6/1) gave two adducts methyl (4R*,6R*)-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane-4-carboxylate **4a**, (30 mg, R_f=0.36, mp : 72.0-74.5°C) and methyl (5R*,6S*)-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane-5-carboxylate **4c**, (22 mg, R_f=0.27, m.p. 35.0-37.5°C). The latter fraction only gave a solid methyl (4S*,6R*)-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane-4-carboxylate **4b**, (50 mg, mp : 119.5-122.5°C). The overall yield was 68%.

4a ; IR (KBr) ν_{max}(cm^{-1}): 2951, 2907, 2847, 1726, 1460, 1431, 1345, 1233, 1100, 1073, 1030, 959, 829, 754, 702; ^{1}H NMR ($CDCl_3$) δ: 4.65(1H, dd, J=8.0, 2.4Hz), 3.85(1H, ddd, J=8.6, 8.0, 2.0Hz), 3.79(3H, s), 3.74(1H, m), 2.78 (1H, ddd,

J=12.6, 8.6, 2.4 Hz), 2.35 (1H, dt, J=12.6, 8.0 Hz), 2.30-1.50 (13H, m); MS m/z (%): 251 (M$^+$,75), 234(8), 218(7), 208(10), 192(100), 165(21), 135(32). High resolution MS for $C_{14}H_{21}NO_3$: 251.1521; Found: 251.1521.

4b ; IR (KBr) ν_{max}(cm^{-1}): 2911, 2865, 1755, 1439, 1364, 1262, 1209, 1194, 1111, 1080, 1020, 943, 918, 845, 812; ^{1}H NMR ($CDCl_3$) δ: 4.58(1H, dd, J=11.0, 5.8Hz), 3.95(1H, ddd, J=9.4, 8.4, 1.0Hz), 3.79 (3H, s), 3.74(1H, m), 2.59(1H, ddd, J=12.0, 8.4, 5.8 Hz), 2.25 (1H, ddd, J=12.0, 11.0, 9.4 Hz), 2.47-1.50 (13H, m); MS m/z (%): 251 (M$^+$, 75), 234(5), 221(4), 208(17), 192(100), 165(23), 164(17), 163(12), 148(11), 135(31). High resolution MS for $C_{14}H_{21}NO_3$: 251.1521; Found: 251.1521.

4c ; IR (KBr) ν_{max}(cm^{-1}): 2911, 2851, 1738, 1439, 1273, 1250, 1204, 1198, 1177, 1109, 1051, 1017, 978, 941, 839, 754; ^{1}H NMR ($CDCl_3$) δ: 4.24(1H, dd, J=8.6, 7.4Hz), 3.98(1H, dd, J=10.2, 8.6Hz), 3.97 (1H, dd, J=8.4, 2.2Hz), 3.72 (3H, s), 3.67(1H, m), 3.27 (1H, ddd, J=10.2, 8.4, 7.4 Hz), 2.32-1.48 (13H, m); MS m/z (%): 251 (M$^+$,78), 236(4), 221(50), 206(6), 192(30), 190(35), 178(16), 165(93), 149(50), 135(100). High resolution MS for $C_{14}H_{21}NO_3$: 251.1521; Found: 251.1508.

Dimethyl (4S*,5S*,6S*)-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane-4,5-dicarboxylate (7)

A solution of **1** (50 mg, 0.30 mmol) and dimethyl fumarate (87 mg, 0.60 mmol) in toluene (1.0 ml) was stirred at room temperature for 1 h. Then removal of the solvent *in vacuo* and separation of the residue on preparative TLC (silica gel, 20×20×0.2 cm; ethyl acetate /hexane=1 /1, R_f=0.34) gave only one oily product **7** (80 mg, 86%). IR (neat) ν_{max} (cm^{-1}): 2913, 2851, 1744, 1439, 1346, 1273, 1231, 1174, 1115, 1036, 1011, 961, 887, 851, 820, 787, 752; ^{1}H NMR ($CDCl_3$) δ: 4.80(1H, d, J=10.0Hz), 4.01(1H, dd, J=8.8, 1.8Hz), 3.08(3H,s), 3.76(3H, s), 3.74(1H, m), 3.40 (1H, dd, J=10.0, 8.8Hz), 2.45-1.45 (13H, m); MS *m/z*(%): 309 (M$^+$, 36), 190(40), 165(46),149(94), 135(39), 113(88), 80(100); Anal. Calcd. for $C_{16}H_{23}NO_5$ (309.36): C,62.12; H, 7.49; N, 4.53. Found: C,62.06; H, 7.57; N, 4.52.

Dimethyl (4R*,5S*,6S*)-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane-4,5-dicarboxylate (8)

A solution of **1** (50 mg, 0.30 mmol) and dimethyl maleate (87 mg, 0.60 mmol) in toluene(1.0 ml) was stirred at room temperature for about 15 h. Removal of the solvent *in vacuo*, and separation of the residue on preparative TLC (silica gel, 20×20×0.2 cm; ethyl acetate/hexane=1:1, R_f=0.40) gave only one oily product **8** (83 mg, 89%). IR (neat) ν_{max}(cm^{-1}): 2913, 2853, 1744, 1441, 1348, 1275, 1231, 1115, 1036; ^{1}H NMR ($CDCl_3$) δ: 4.87 (1H, d, J=7.4Hz), 4.17(1H, dd, J=9.2, 2.2Hz), 3.77 (3H,s), 3.72 (3H, s), 3.69(1H, m), 3.45 (1H, dd, J=9.2, 7.4Hz), 3.35-1.45 (13H, m); MS m/z (%): 309 (M$^+$, 56), 292(11), 278(9), 250(29), 222(27), 221(22), 218(15), 208(16), 190(100), 165(30); High resolution MS for $C_{16}H_{23}NO_5$ 309.1576. Found: 309.1572.

(4S*, 6R*)-4-Methyl-4-cyano-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane (9)

A solution of **1** (50 mg, 0.30 mmol) in methacrylonitrile (1.0 ml, 12 mmol) was stirred at room temperature for 4 h. The excess reagent was removed *in vacuo* and separation of the residue by preparative TLC (silica gel, 20×20×0.2 cm; ethyl acetate/hexane=1 /1) gave **9** (45 mg, 65%) as an oil, IR (KBr) ν_{max}(cm^{-1}): 2911, 2851, 2245, 1445, 1372, 1194, 1161, 1109, 1063, 1038, 980, 953, 928, 752; ^{1}H NMR ($CDCl_3$) δ: 3.96(1H, ddd, J=9.4, 8.4, 2.4Hz), 3.61(1H, br t, J=5.6Hz), 2.72 (1H, dd, J=12.6, 9.4 Hz), 2.45 (1H, dd, J=12.6, 8.4 Hz), 1.70(3H, s), 2.35-1.55 (13H, m); MS m/z (%): 232 (M$^+$, 65), 217(10), 165(74), 163(24), 149(40), 148(24), 135(100); High resolution MS for $C_{14}H_{20}N_2O$ 232.1576. Found: 232.1565.

Methyl (4S*,6S*)-4-methyl-2-aza-3-oxatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradecane-4-carboxylate (10)

A solution of **1** (50 mg, 0.30 mmol) in methyl methacrylate (1.0 ml) was stirred at room temperature for 2 h. The excess methyl methacrylate was removed under a reduced pressure. Separation of the residue by preparative TLC (silica gel, 20×20×0.2 cm; ethyl acetate) gave **10** (59 mg, 74%) as an oil, IR (KBr) ν_{max}(cm^{-1}): 2909, 2849, 1740, 1441, 1368,

1258, 1231, 1161, 1125, 1067, 1040, 988, 953, 849, 818, 745; ^{1}H NMR ($CDCl_3$) δ: 4.01(1H, ddd, J=9.8, 8.2, 1.6Hz), 3.79(3H, s), 3.65(1H, br t, J = 5.8Hz), 2.52(1H,dd,J=12.4, 9.8Hz), 2.33(1H, m), 2.26(1H, dd, J=12.4, 8.2Hz), 1.61(3H, s), 2.05-1.55 (12H, m); MS m/z (%): 265 (M^+, 65); 248 (9), 206(100), 165(32), 164(25), 148(14), 135(52); High resolution MS for $C_{15}H_{23}NO_3$ 265.1678. Found: 265.1674.

Calculation Method

Molecular orbital calculations were carried out using the PM3 method in the software package MOPAC Ver. 6.01[7]. The starting geometry was generated on a graphic display using the AVS/Chemistry Viewer[9] and all intramolecular flexibility was optimized by MOPAC. To search the transition state structure of the model system, the reaction coordinates connecting the product and the reactants were identified by scanning the two bond lengths, O_1-C_5 and C_3-C_4 (see Figure 2), by an increment of 0.1 Å. The saddle point was assigned on the potential energy surface. The transition state structure was then refined with the TS key word until the gradient of 0.266 kcal/mol Å was attained. The transition state structure thus obtained was confirmed as follows. The vibration analysis applying the FORCE key word exhibited only one imaginary vibration mode, furthermore, the reactants and the product were reproduced by the calculation with the IRC key word. All calculations were performed on a TITAN Vistra 800a workstation.

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8 The validity of our transition state models - **3at** and **4at**, for example, was ascertained by the whole optimization with the TS key word. There was essentially no difference between the models and the optimized structures in the geometry of assembling isoxazolidine ring and in the HOMO and LUMO electron distributions.

9 AVS/Chemistry Viewer, Molecular Simulations, Inc., Pasadena, USA.

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