Synthesis of Nucleosides and Related Compounds. XXVI.[1] The Difference in Effects between High Pressure and $LiClO_4$ for the Diels–Alder Reaction of Cyclopentadiene with Methylenemalonates or *O*-Acetylisonitrosomalonates[2]

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Diels–Alder reactions of cyclopentadiene with methylenemalonates or *O*-acetylisonitrosomalonates in the presence of $LiClO_4$ as the catalyst were examined and the results were compared with those obtained under high pressure without the catalyst. Diels–Alder reaction of cyclopentadiene with dimethyl acetoxymethylenemalonate (1) in the presence of $LiClO_4$ afforded the [4+2] adduct (2) as a mixture of *endo*- and *exo*-isomers, whose ratio was 2.0, irrespective of the solvent or the concentration of $LiClO_4$. Asymmetric Diels–Alder reaction of cyclopentadiene with di-*l*-methyl acetoxymethylenemalonate (3) was accelerated ramarkably by $LiClO_4$. The configurations of both *endo* and *exo* adducts corresponded to the natural form (D-form). These results suggested strongly that $LiClO_4$ would behave as a bidentate Lewis acid catalyst just like titanium tetrachloride. The hetero Diels–Alder reaction of cyclopentadiene with *O*-acetylisonitrosomalonate in $LiClO_4$–ether producted the adduct (5) in a higher yield than the reaction performed under high pressure.

Keywords lithium perchlorate; high pressure; Diels–Alder reaction; cyclopentadiene; methylenemalonate; *O*-acetylisonitrosomalonate; carbocyclic nucleoside; Lewis acid

The usefulness of the Diels–Alder reaction in organic synthesis arises from its versatility and its high regio- and stereoselectivities. During the past fifteen years, great efforts have been put into the detailed investigation of the reaction conditions with the intention of accelerating the reaction rate and improving the selectivity. These studies have led not only to the finding of novel Lewis acid catalysts but also to novel synthetic methods of enantiomerically pure compounds (EPC) by the use of either chiral catalysts or chiral components (dienophiles or dienes) in the Diels–Alder reaction.[3]

On the other hand, the acceleration of the Diels–Alder reaction either in water[4] or under high pressure[5] is attributed to the activation volume ($\Delta V^{\neq}$), the difference between the volume of transition state and that of the starting materials. The former is due to internal solvent pressure,[4,6] whereas the latter is effected by external solvent pressure.[5] As a result, Diels–Alder reactions having negative activation volume ($-\Delta V^{\neq}$) are accelerated under these conditions.

Quite recently, Grieco and his coworkers[7] have found that 5 M lithium perchlorate ($LiClO_4$)–ether solution remarkably facilitates Diels–Alder reaction. Using this methodology, they achieved the synthesis of cantharidine, which had been synthesized previously only by a high-pressure technique.[8] In order to clarify the limitations and mechanism of this remarkable acceleration of Diels–Alder reaction by $LiClO_4$, we have investigated the Diels–Alder reaction of cyclopentadiene with both methylenemalonates and *O*-acetylisonitrosomalonates in the presence of $LiClO_4$ and compared the result with that obtained under high-pressure conditions.

We initially chose dimethyl acetoxymethylenemalonate (**1**) as a dienophile, since it had been useful for the synthesis of C-nucleoside precursor.[9] Previously, we reported that **1** reacted with cyclopentadiene[10,11] or furan[12] to give the [4+2] adducts (B), which were transformed into C-nucleoside precursors (C) stereoselectively by means of reductive retrograde aldol reaction (RRA reaction).[9] Knowing that **1** did not react with cyclopentadiene under atmospheric pressure at room temperature,[10] we carried out the Diels–Alder reaction of cyclopentadiene with **1** in a variety of solvents containing $LiClO_4$.

The results are summarized in Table I. First, the reaction was carried out in the presence of various concentrations of $LiClO_4$ in ether. Though the reaction was accelerated remarkably, the concentration of $LiClO_4$ hardly affected the yield of the product (**2**). Though the use of acetonitrile[13] instead of ether did not affect the yield of the product, the use of methanol[14] as the solvent resulted in an appreciable decrease of the yield. It should be noted that, irrespective of the solvent or the concentration of $LiClO_4$, the ratio of the *endo* and *exo* adducts was 2.0. As shown in Table I, the ratios of the *endo*/*exo* adducts were 0.4 under high pressure, 1.5 in the presence of titanium tetrachloride, and 0.3 under heating, respectively. The similar *endo*/*exo* ratios between the reactions catalyzed by $TiCl_4$ and by $LiClO_4$ suggest that $LiClO_4$ acts just like $TiCl_4$, as a bidentate Lewis acid for **1**. Though the $LiClO_4$-promoted Diels–Alder reaction of **1** with cyclopentadiene was inferior to the reaction under high pressure in terms of the yield of the adduct, it remarkably changed the *endo*/*exo* selectivities [note that the ratio obtained under high-pressure reaction (13 kbar) was 0.4].

Di-*l*-menthyl acetoxymethylenemalonate (**3**), a chiral dienophile originally prepared in our loboratory, has been utilized for the enantioselective synthesis of C-nucleoside[15] and its carbocyclic analogue.[16] The dienophile **3** reacted with cyclopentadiene in the presence of titanium tetrachloride at −78 °C to give the [4+2] adduct (**4**) as a mixture of *endo*- and *exo*-isomers with high diastereoselectivity. Thus, both *endo*- and *exo*-acetonides (**5a** and **5b**) derived

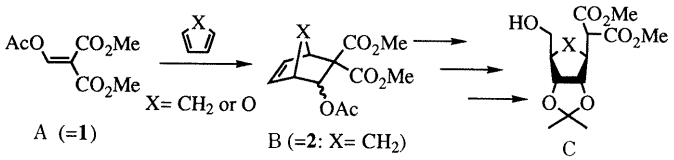
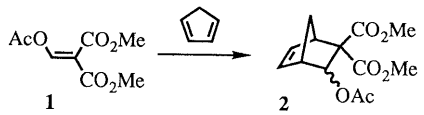


Chart I

from **4**, when subjected to RRA reaction, gave the carbocyclic C-nucleoside precursor (**6**) as a single product, whose absolute structure corresponded to the natural form (D-form).[14] On the contrary, the Diels–Alder reaction of **3** with cyclopentadiene under high pressure gave a mixture of *endo* adduct (**4a**) and *exo* adduct (**7**). The corresponding acetonides were separated by column chromatography and each adduct was subjected to RRA reaction. From the analysis of the structure of the precursors (**6** and **9**) thus obtained, it was found that, while the *endo* adduct had the natural form (**4a**), the *exo* adduct had the unnatural form (**7**).[15]

TABLE I. Diels–Alder Reaction of Dimethyl Acetoxymethylenemalonate with Cyclopentadiene

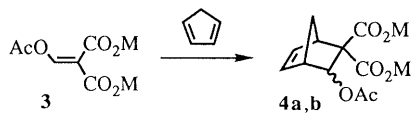


Reaction conditions			Yield (%)	*endo/exo*
Temp. (°C) (Pressure)	Solvent (Catalyst)	Time (h)		
r.t.	Ether	20	0	2.0
r.t.	Ether (1 M $LiClO_4$)	20	74	2.0
r.t.	Ether (3 M $LiClO_4$)	20	83	2.0
r.t.	Ether (5 M $LiClO_4$)	20	82	2.0
r.t.	CH_3CN (Sat. $LiClO_4$)	2	50	2.0
r.t.	CH_3CN (Sat. $LiClO_4$)	5	65	2.0
r.t.	CH_3CN (Sat. $LiClO_4$)	10	75	2.0
r.t.	CH_3CN (Sat. $LiClO_4$)	20	74	2.0
r.t.	MeOH (Sat. $LiClO_4$)	20	39	2.0
15 (13 kbar)	Toluene	60	95	0.4
−15	Toluene ($TiCl_4$)	4	74	1.5
70—80	Benzene	72	80	0.3

r.t. = room temperature.

On the basis of the above-mentioned results, we examined the asymmetric Diels–Alder reaction of **3** with cyclopentadiene in the presence of $LiClO_4$ catalyst in order to clarify its effect on the Diels–Alder reaction. The results are shown in Table II, together with the results obtained either under high pressure or in the presence of titanium tetrachloride. In contrast to the failure of the reaction with cyclopentadiene without catalyst or by mere heating, the reaction was accelerated by $LiClO_4$ and gave the expected adduct. For example, the reaction in the 5 M $LiClO_4$–ether solution at room temperature resulted in quantitative formation of a mixture of **4a** and **4b** having the natural configuration. The ratio of *endo*- and *exo*-isomers was again 2.0, and the diastereomeric excess (d.e.) values were 50% and 30%, respectively.[17] When this reaction was carried out at −25 °C,[18] the yield was decreased, but the d.e. was slightly improved. The acceleration of the reaction, as well as the fact that the major diastereomer of each adduct was the natural form, suggests that $LiClO_4$ acts as a bidentate Lewis acid catalyst and fixes **3** in the *s-trans*, *s-trans* conformation (Fig. 1),[19] just as in the reactions using $TiCl_4$ (note that, in the reaction under high pressure without any catalyst, **3**

TABLE II. Asymmetric Diels–Alder Reaction of Di-*l*-menthyl Acetoxymethylenemalonate with Cyclopentadiene



Reaction conditions			Yield (%)	*endo/exo*	d.e.	
Temp. (°C) (Pressure)	Solvent (Catalyst)	Time (h)			*endo*	*exo*
−25	Ether (1 M $LiClO_4$)	72	30	2.25	55	49
r.t.	Ether (5 M $LiClO_4$)	24	98	2.00	50	30
r.t.	CH_3CN (Sat. $LiClO_4$)	72	75	2.00	45	42
15 (13 kbar)	Toluene	48	96	0.56	54	60[a]
−25	Toluene ($TiCl_4$)	4	80	3.00	>99	65

a) Unnatural configuration.

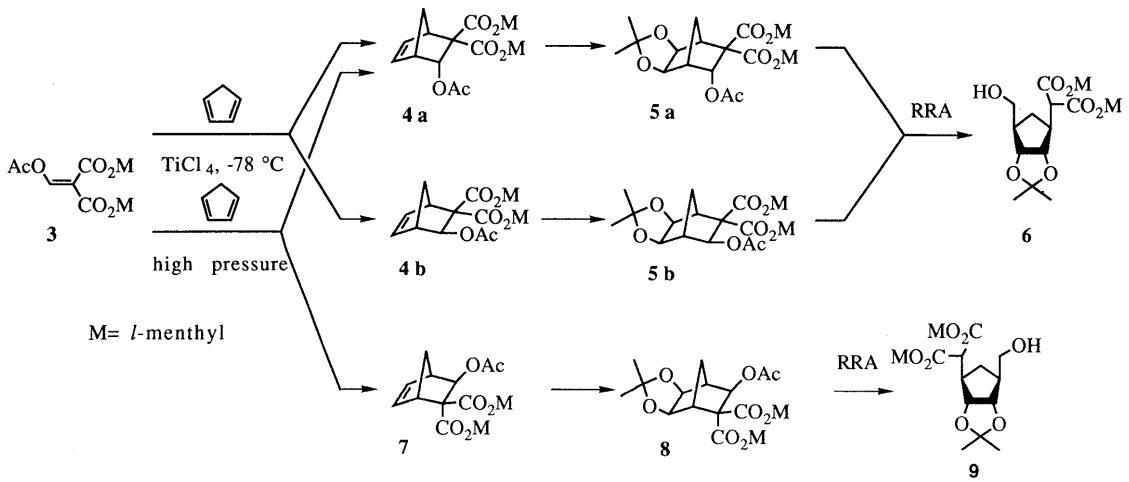


Chart 2

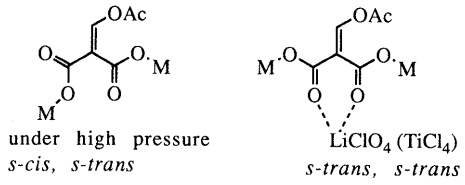
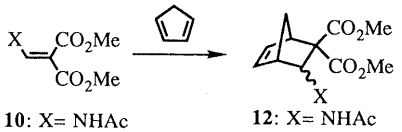


Fig. 1

TABLE III. Diels–Alder Reaction of Acetamino-(**10**) and Methoxymethylenemalonate (**11**) with Cyclopentadiene



10: X= NHAc
11: X= OMe

12: X= NHAc
13: X= OMe

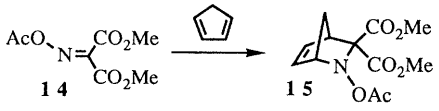
X	Reaction conditions			Yield (%)	*endo/exo*
	Temp. (°C) (Pressure)	Solvent (Catalyst)	Time (h)		
AcNH	r.t.	Ether (5 M $LiClO_4$)	72	21	3.07
AcNH	r.t. (11 kbar)	Toluene	72	22	0.29
AcNH	60 (11 kbar)	Toluene	72	38	0.36
AcNH	r.t. (11 kbar)	CH_2Cl_2 ($ZnCl_2$)	72	57	0.33
MeO	r.t.	Ether (5 M $LiClO_4$)	72	40	2.00
MeO	r.t. (11 kbar)	Toluene	72	0	—

takes *s-cis*, *s-trans* conformation[11]). In support of a bidentate Lewis acid character of lithium derivatives, Lappert and his coworkers reported that the lithium salt of hexamethyldisilasane chelated with ethers to form the bidentate complex.[20]

Finally, the reason for the difference of the *endo/exo* ratios depending on the reaction conditions employed might be as follows. For the predominant formation of the *endo* adduct over the *exo* adduct in the presence of bidentate Lewis acid catalyst (*e.g.* $TiCl_4$ or $LiClO_4$), the acetoxyl group plays the major role (the so-called secondary orbital interaction). The fact that, under high-pressure conditions, the *exo* adduct was the major product could be explained by assuming that the *s-cis* carbonyl (*trans* to the acetoxyl group) exerts the strongest secondary orbital interaction among the acetoxyl and *s-trans* carbonyl groups.[21]

In order to clarify the scope and limitations of the Diels–Alder reaction using $LiClO_4$ as a catalyst, we then examined the reaction of cyclopentadiene with acetamino-(**10**) and methoxymethylenemalonate (**11**),[22] both of which are less active than **1** as a dienphile and, hence, cannot react with cyclopentadiene without a suitable catalyst. The results are shown in Table III. Though **10** did not react with cyclopentadiene even in the presence of titanium tetrachloride, the reaction in the presence of $LiClO_4$ afforded the [4+2] adduct (**12**) in a low yield as a mixture of *endo*- and *exo*-isomers. The yield was improved when high pressure was used for the reaction. Especially, the use of high pressure in the presence of $ZnCl_2$ afforded the adduct (**12**) in 57% yield. Though the reaction under high pressure or in the presence of titanium tetrachloride resulted in the recovery of the starting material (**11**), methoxymethylenemalonate (**11**) reacted with cyclopentadiene in the presence of $LiClO_4$ to give the [4+2] adduct (**13**) in 40% yield. Therefore, $LiClO_4$ was the only catalyst to produce the [4+2] adduct from the reaction of **11** with cyclopentadiene.

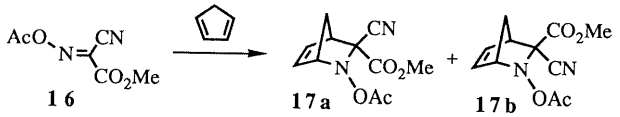
TABLE IV. Hetero Diels–Alder Reaction of Dimethyl *O*-Acetylisonitrosomalonate with Cyclopentadiene



14 **15**

Reaction conditions			Yield (%)
Temp. (°C) (Pressure)	Solvent (Catalyst)	Time (h)	
r.t.	Ether (1 M $LiClO_4$)	24	32
r.t.	Ether (3 M $LiClO_4$)	24	41
r.t.	Ether (5 M $LiClO_4$)	24	49
r.t. (10 kbar)	Toluene	48	17

TABLE V. Hetero Diels–Alder Reaction of Methyl *O*-Acetylisonitrosocyanoacetate with Cyclopentadiene



16 **17a** **17b**

Reaction conditions			Yield (%)	*endo/exo*
Temp. (°C) (Pressure)	Solvent (Catalyst)	Time (h)		
r.t.	None	18	25	6.5
r.t.	Ether	18	12	6.4
r.t.	Ether (5 M $LiClO_4$)	5	51	9.0
r.t. (10 kbar)	Toluene	40	99	7.6

Biehler and his coworkers[23] examined the hetero Diels–Alder reaction of *O*-mesyl- or *O*-tosylisonitrosocyanoacetate with cyclopentadiene and found that these isonitrosomalonates did not react with cyclopentadiene even under heating. We carried out the hetero Diels–Alder reaction of dimethyl *O*-acetylisonitrosomalonate (**14**) with cyclopentadiene in the presence of $LiClO_4$.

The dienophile (**14**) was prepared by nitrosation of dimethyl malonate followed by acetylation. Though the expected reaction did not proceed merely under heating, compound **14** reacted with cyclopentadiene in $LiClO_4$–ether to give the adduct (**15**). The yield was increased with increasing concentration of $LiClO_4$.

High pressure was also found to be effective for the reaction, but the yield was rather low (17%). It should be noted that, if the carbon–nitrogen bond in the adduct (**15**)

can be cleaved with retention of configuration, a novel route to carbocyclic nucleosides and related compounds would be provided.

Methyl *O*-acetylisonitrosocyanoacetate (**16**) was more active than **14**, and was found to react with cyclopentadiene at room temperature even without a catalyst. Though the yield of the adduct (**17**) was low, use of 5 M $LiClO_4$–ether as the solvent improved the yield to 51%. On the other hand, the high-pressure-mediated reaction gave the adduct (**17**) in quantitative yield. The *endo*/*exo* ratio was 9.0 when the reaction was carried out in $LiClO_4$–ether and 7.6 when carried out under high pressure.

In conclusion, it was clarified that $LiClO_4$ remarkably facilitated not only the Diels–Alder reaction of methylenemalonates with cyclopentadiene but also the hetero Diels–Alder reaction using *O*-acetylisonitrosomalonates as the dienophile. The reaction sometimes afforded the [4+2] adduct in a higher yield when compared with the high-pressure condition.

Grieco and his coworkers[7] suggested that the acceleration of Diels–Alder reaction by 5 M $LiClO_4$–ether was due to its internal solvent pressure. From the results of detailed study of the stereochemical aspects of these reactions, it seems reasonable to propose that $LiClO_4$ also behaves as a bidentate Lewis acid catalyst, like titanium tetrachloride. Transformations of **15** and **17** to nucleoside precursors are in progress and the results will be reported soon.

Experimental

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured on a JASCO A-102 spectrometer. Proton-nuclear magnetic resonance (^{1}H-NMR) spectra at 60 and 500 MHz were recorded with JEOL JNM-PMX 60 and JEOL JNM-FX 500 spectrometers using tetramethylsilane (TMS) as an internal standard, respectively. The abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad; br s, broad singlet. All d.e. values of the compounds obtained in the present work were determined from the ^{1}H-NMR spectra in $CDCl_3$ (0.3 ml) in the presence of Eu(fod)$_3$ (25 mg). Low- and high-resolution mass spectra (MS) were obtained on JEOL JMS-DX303 and JEOL JMS-AX500 mass spectrometers, respectively. Wakogel (C-200) and Merck Kiesel-gel 60 F254 were employed for silica gel column and thin layer chromatography (TLC), respectively. The ratios of mixtures of solvents for chromatography are shown as volume/volume. High-pressure reactions were carried out by using a piston–cylinder apparatus equipped with a PK. 15. B pump (Hikari Koatsu Kiki Ltd., Co.).

General Procedure for Diels–Alder Reaction in the Presence of $LiClO_4$ (Method A) A dienophile (1 eq) was dissolved in a solution (2 ml/1 mmol) of $LiClO_4$ and an appropriate solvent (ether, CH_3CN, or MeOH) and then cyclopentadiene (5 eq) was added to the solution with ice cooling. After being shaken or kept at an appropriate temperature, the reaction mixture was poured into ice water, and extracted with ether. The organic layer was washed with water twice and dried over anhydrous Na_2SO_4. The solvent was evaporated off, and the residue was subjected to silica gel column chromatography (50 g/1 g of residue). Elution with an appropriate solvent gave an adduct. The results are shown in Tables I—V.

General Procedure for Diels–Alder Reaction under High Pressure (Method B) A mixture of dienophile (1 eq) and cyclopentadiene (5 eq) in toluene or dichloromethane was placed in a Teflon tube (1.2 ml) with a Teflon stopper, and the tube was filled with dry toluene or dichloromethane. The tube was placed in a high-pressure reactor and pressurized to 10—11 kbar at an appropriate temperature for 40—72 h. The pressure was released and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel (5 g/reaction mixture 1 g) column chromatography using hexane–ethyl acetate.

Dimethyl 3-*endo*- and *exo*-Acetoxybicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (2) 1) A solution of **1** (202 mg, 1 mmol) and cyclopentadiene (330 mg, 5 mmol) in anhydrous ether (5 ml) was kept at room temperature for 20 h. The adduct (**2**) was not detected.

2) According to method A, **1** (202 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in the presence of $LiClO_4$ to give **2**.[11] Hexane–ethyl acetate (2 : 1) was used as an eluent for the silica gel column chromatography. The results are shown in Table I.

Di-*l*-menthyl 3-*endo*- and *exo*-Acetoxybicyclo-[2.2.1]hept-5-ene-2,2-dicarboxylate (4a, b) According to method A, **3** (225 mg, 0.5 mmol) was allowed to react with cyclopentadiene (165 mg, 2.5 mmol) in the presence of $LiClO_4$ to give **4a**, **b**.[16] Hexane–ether (10 : 1) was used as an eluent for the silica gel column chromatography. The results are shown in Table II.

Dimethyl Acetaminomethylenemalonate (10) Ammonia gas was passed over a solution of **11**[12b] (8.7 g, 50 mmol) in absolute MeOH (50 ml) under ice-cooling for 10 min. The mixture was kept at room temperature for 1 h. The solvent and excess ammonia were evaporated off under reduced pressure to give a crystalline residue, which was recrystallized from ether to give 5.9 g (quant.) of dimethyl aminomethylenemalonate as colorless prisms of mp 125—126 °C (ether). *Anal.* Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.28; H, 5.64; N, 8.66. IR ($CHCl_3$): 3540, 1701, 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 3.73, 3.80 (each 3H, s, CO_2Me), 5.8—6.5 (1H, br, NH), 8.10 (1H, dd, J=12, 10 Hz, olefinic H), 8.3—9.0 (1H, br, NH'). A solution of dimethyl aminomethylenemalonate (4.77 g, 30 mmol), acetic anhydride (5 ml), and pyridine (1 ml) was warmed at 60 °C for 48 h. The mixture was concentrated under reduced pressure to give a crystalline residue, which was recrystallized from ether–hexane to give 6.03 g (quant.) of **10** as colorless prisms of mp 56—57 °C (ether–hexane). *Anal.* Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.83; H, 5.28; N, 6.67. IR ($CHCl_3$): 3320, 1720, 1678, 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 2.23 (3H, s, Ac), 3.79, 3.85 (each 3H, s, CO_2Me), 8.53 (1H, d, J=12 Hz, olefinic H), 10.6—11.4 (1H, br, NH).

Dimethyl 3-*endo*-Acetaminobicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (12 *endo*) and Dimethyl 3-*exo*-Acetaminobicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (12 *exo*) 1) According to method A, **10** (201 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in 5 M $LiClO_4$–ether to give **12** *endo* (43 mg, 16%) and **12** *exo* (14 mg, 5%). Hexane–ethyl acetate (1 : 2) was used as an eluent for the silica gel column chromatography. The results are shown in Table III.

12 *endo*: Colorless needles (ether–hexane). mp 104—106 °C. *Anal.* Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.62; H, 6.38; N, 5.08. IR ($CHCl_3$): 3450, 1732, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.8 (2H, m, 7-H), 2.25 (3H, s, Ac), 3.14 (1H, m, 4-H), 3.43 (1H, m, 1-H), 3.67, 3.76, (each 3H, s, CO_2Me), 5.01 (1H, dd, J=8, 5 Hz, 3-H), 6.05 (1H, m, 5-H), 6.27 (1H, m, 6-H), 6.92 (1H, br, NH).

12 *exo*: Colorless needles (ether–hexane). mp 159—161 °C. *Anal.* Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.38; H, 6.46; N, 5.36. IR ($CHCl_3$): 3450, 1736, 1677 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.2 (2H, m, 7-H), 1.96 (3H, s, Ac), 2.71 (1H, m, 4-H), 3.32 (1H, m, 1-H), 3.69, 3.72, (each 3H, s, CO_2Me), 4.85 (1H, dd, J=10, 2 Hz, 3-H), 5.93 (1H, br, NH), 6.09 (1H, m, 5-H), 6.32 (1H, m, 6-H). 2) According to method B, **10** (201 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in toluene under a pressure of 11 kbar at room temperature or 60 °C to give **12** *endo* and *exo* (13 mg, 5%, 45 mg, 17% or 27 mg, 10%, 75 mg, 28%), respectively. 3) According to method B, **10** (201 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in the presence of zinc chloride (5 mg) in dichloromethane under 11 kbar at room temperature to give **12** *endo* and *exo* (38 mg, 14% and 116 mg, 43%).

Dimethyl 3-*endo*- and *exo*-Methoxybicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (13 *endo* and *exo*) According to method A, **11**[22] (174 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in 5 M $LiClO_4$–ether to give **13** (96 mg, 40%) as a colorless oil. Hexane–ethyl acetate (4 : 1) was used as an eluent for the silica gel column chromatography. The ration of *endo* and *exo* was determined to be 3 : 1 from the ^{1}H-NMR spectrum using the signal of the methine proton at the 3-position as a parameter. High-resolution MS *m*/*z* Calcd for $C_{11}H_{13}O_4$ (M^+ – OMe): 209.0814. Found: 209.0805. IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.3—1.5 (2H, m, 7-H), 2.8—3.7 (2H, m, 1-, 4-H), 3.33 (3×2/3H, s, MeO, *endo*), 3.37 (3×1/3H, s, MeO, *exo*), 3.60, 3.73 (each 3H, s, CO_2Me), 4.10 (1/3H, d, J=3 Hz, 3-H, *exo*), 4.80 (2/3H, d, J=7 Hz, 3-H, *endo*), 5.8—6.7 (2H, m, olefinic H).

Dimethyl *O*-Acetylisonitrosomalonate (14) A solution of dimethyl isonitrosomalonate[23c] (3.22 g, 20 mmol), acetic anhydride (15 ml), and pyridine (5 ml) was kept at room temperature for 5 h. The mixture was concentrated under reduced pressure to give an oily substance, which was purified by vacuum distillation to give **14** (3.65 g, 90%) of bp 119—120 °C (3 mmHg) as a colorless oil. High-resolution MS *m*/*z* Calcd for $C_7H_{10}NO_6$ (M^++1): 204.0508. Found: 204.0496. IR ($CHCl_3$): 1801, 1757 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s, Ac), 3.93 (6H, s, 2×CO_2Me).

Dimethyl 2-Acetoxy-2-azabicyclo[2.2.1]hept-5-ene-3,3-dicarboxylate (15) According to method A, **14** (203 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in 5 M $LiClO_4$–ether to give **15** (132 mg, 49%) of mp 119—121 °C as colorless prisms (ether). Hexane–ethyl acetate (2:1) was used as an eluent for the silica gel column chromatography. *Anal.* Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.61; N, 5.20. Found: C, 53.43; H, 5.66; N, 5.21. IR ($CHCl_3$): 1751 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (2H, m, 7-H), 2.04 (3H, s, Ac), 3.60 (1H, m, 4-H), 3.63, 3.69, (each 3H, s, CO_2Me), 4.37 (1H, m, 1-H), 6.23 (1H, dd, $J=7$, 4 Hz, 5-H), 6.46 (1H, dd, $J=7$, 4 Hz, 6-H). 2) According to method B, **14** (203 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in toluene under 10 kbar at room temperature to give **15** (46 mg, 17%).

Methyl *O*-Acetylisonitrosocyanoacetate (16) A solution of methyl isonitrosocyanoacetate[23c] (2.56 g, 20 mmol), acetic anhydride (15 ml), and pyridine (5 ml) was kept at room temperature for 5 h. The mixture was concentrated under reduced pressure to give an oily substance, which was purified by high vacuum distillation to give **16** (3.13 g, 92%) of bp 106—109 °C (0.07 mmHg) as a colorless oil. High-resolution MS *m/z* Calcd for $C_6H_7N_2O_4$ ($M^+ + 1$): 171.0406. Found: 171.0395. IR ($CHCl_3$): 2230, 1820, 1749 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, Ac), 4.02 (3H, s, CO_2Me).

Methyl 2-Acetoxy-3-*exo*-cyano-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate (17a) and Methyl 2-Acetoxy-3-*endo*-cyano-2-azabicyclo-[2.2.1]hept-5-ene-3-*exo*-carboxylate (17b) 1) A solution of **16** (170 mg, 1 mmol) in cyclopentadiene (660 mg, 10 mmol) was kept at room temperature for 18 h. Excess cyclopentadiene was evaporated off to give an oily substance, which was purified by silica gel column chromatography. Elution with hexane–ethyl acetate (2:1) gave **17a** (52 mg, 22%) and **17b** (8 mg, 3%). When this reaction was carried out in ether, **17a**, **b** (*endo*/*exo* = 6.4) was obtained in 12% yield.

17a: Colorless prisms (ether). mp 94—96 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.02; H, 5.10; N, 12.04. IR ($CHCl_3$): 2245, 1753 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.9 (1H, m, 7-H), 2.0—2.4 (1H, m, 7-H), 2.07 (3H, s, Ac), 3.55 (1H, m, 4-H), 3.92, (3H, s, CO_2Me), 4.57 (1H, m, 1-H), 6.53 (1H, dd, $J=7.4$ Hz, 5-H), 6.93 (1H, dd, $J=7$, 4 Hz, 6-H).

17b: Colorless prisms (ether–hexane). mp 52—53 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.09; H, 5.04; N, 11.83. IR ($CHCl_3$): 2250, 1771 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.2 (1H, m, 7-H), 2.13 (3H, s, Ac), 2.2—2.5 (1H, m, 7-H), 3.76 (1H, m, 4-H), 3.80, (3H, s, CO_2Me), 4.37 (1H, m, 1-H), 6.3—6.4 (2H, m, 5-, 6-H). 2) According to method A, **16** (170 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in 5 M $LiClO_4$–ether to give **17a** (108 mg, 46%) and **17b** (12 mg, 5%). 3) According to method B, **16** (170 mg, 1 mmol) was allowed to react with cyclopentadiene (330 mg, 5 mmol) in toluene under 10 kbar at room temperature to give 234 mg (99%) of **17a**, **b** (*endo*/*exo* = 7.6).

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