Diels−Alder Cycloadditions of 3,5-Dibromo-2-pyrone: A New Ambident Diene

Cheon-Gyu Cho,*[1a] Yong-Woo Kim,[1a] Young-Kwan Lim,[1a] Jung-Sang Park,[1a] Haiwon Lee,[1a] and Sangman Koo[1b]

Department of Chemistry and Department of Chemical Engineering, Hanyang University, Seoul 131-791, Korea

ccho@hanyang.ac.kr

Received May 29, 2001

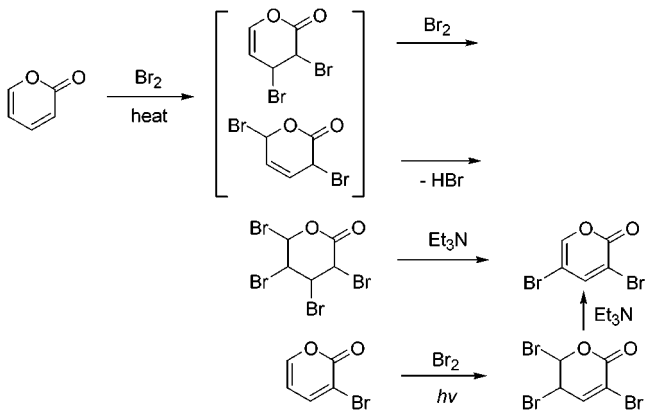
Abstract: D−A cycloadditions of 3,5-dibromo-2-pyrone were investigated with a series of electronically and sterically distinct dienophiles. Our results showed that it is a highly potent ambident diene, being more reactive and stereoselective than monobromo-2-pyrones, and thus capable of generating a variety of bicycloadducts in much higher chemical yields and *endo*/*exo* ratios than monobromo-2-pyrones. Another interesting feature of this study is that the two bromine groups on the cycloadducts could be independently manipulated to produce other synthetically useful bicyclolactones.

Brominated 2-pyrones, for example, 3-bromo- and 5-bromo-2-pyrone, are chameleon-like dienes that can react with both electron-poor and -rich dienophiles via normal- and inverse-electron-demand Diels−Alder cycloadditions with good stereocontrol.[2−5] The resulting functionally rich cycloadducts have been used as key intermediates for various compounds including, especially, a series of physiologically important vitamin D_3 analogues.[6−8] During the course of the study on the Hunsdiecker reaction of 2-pyrone-carboxylic acids, we have discovered a new and convenient synthetic method for 3,5-dibromo-2-pyrone, one step from commercially available coumalic acid.[2,9]

3,5-Dibromo-2-pyrone itself was originally reported by Pirkle in 1969.[10] In the paper,[10a] it was prepared from 2-pyrone, via either a three-step sequence that involved two successive brominations followed by elimination of HBr or a four-step sequence that involved a bromination, HBr elimination, and photochemical bromination, followed by second HBr elimination (Scheme 1).

No synthetic applications have since been reported, evidently owing to its difficult preparation. To evaluate its synthetic utility as a potential ambident diene, we studied its cycloadditions with a series of electronically and sterically distinct dienophiles (Scheme 2).

Scheme 1



Scheme 2

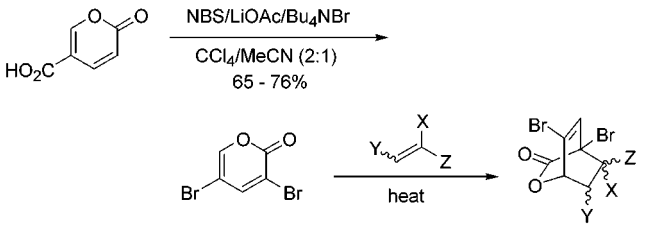
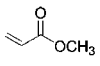
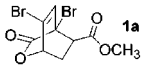
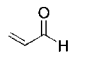
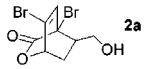
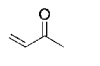
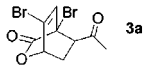
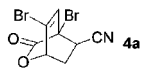
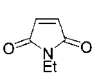
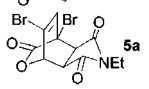
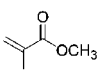
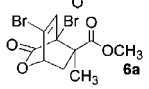
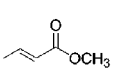
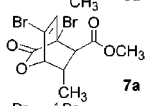
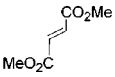
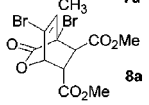
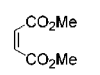


Table 1. D−A Cycloadditions with Electron-Deficient Dienophiles

Entry	Dienophile	Condition	*endo*:*exo*	*endo*-Adduct	Yield(%)[a]
1		toluene 100°C/5h	94:6	 **1a**	84%
2		CH_2Cl_2 50°C/12h	95:5	 **2a**	71%[b]
3		toluene 100°C/5h	94:6	 **3a**	84%
4		toluene 100°C/12h	76:24	 **4a**	90%
5		toluene 100°C/12h	76:24	 **5a**	92%
6		CH_2Cl_2 100°C/24h	86:14	 **6a**	84%
7		toluene 100°C/4d	62:38	 **7a**	82%
8		toluene 100°C/3d	52:48	 **8a**	80%
9		toluene 100°C/3d	64:36	**9a** (same as **8a**)	79%

[a] Total isolated yield (*endo* + *exo*). [b] The cycloadduct was reduced by $NaBH_4$.

Tables 1 and 2 summarize our results on the cycloadditions with various electron-poor and -rich dienophiles, showing that it is indeed a potent ambident diene. In Tables 1 and 2, only the *endo* products were shown for clarity (a, 5-*endo* cycloadduct; b, 5-*exo* cycloadduct). All the cycloadditions were conducted in sealed tubes at elevated temperatures (50−100 °C). Both toluene and

* To whom correspondence should be addressed. Phone: +82+2-2290-0936.

(1) (a) Department of Chemistry. (b) Department of Chemical Engineering.

(2) Afarinkia, K.; Berna-Canovas, J. *Tetrahedron Lett.* **2000**, *41*, 4955.

(3) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.

(4) Afarinkia, K.; Posner, G. H. *Tetrahedron Lett.* **1992**, *33*, 7839.

(5) Posner, G. H.; Afarinkia, K.; Dai, H. *Org. Synth.* **1995**, *73*, 231.

(6) Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Afarinkia, K. *Tetrahedron Lett.* **1991**, *32*, 5295.

(7) Posner G. H.; Lee, J.-K.; White, M. C.; Hutchings, R. H.; Dai, H.; Kachinski, J. L.; Dolan, P.; Kensler, T. W. *J. Org. Chem.* **1997**, *62*, 3299.

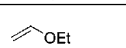
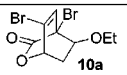
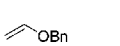
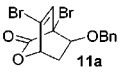
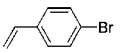
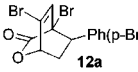
(8) Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. *J. Med. Chem.* **1992**, *35*, 3280.

(9) Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* **2001**, *42*, 1065.

(10) (a) Pirkle, W. H.; Dines, M. *J. Org. Chem.* **1969**, *34*, 2239. (b) Pirkle, W. H.; Dines, M. *J. Heterocycl. Chem.* **1969**, *6*, 1.

10.1021/jo015804r CCC: $22.00
Published on Web 12/08/2001

Table 2. Cycloadditions with Electron-Rich Dienophiles

Entry	Dienophile	Condition	*endo*:*exo*	*endo*-Adduct	Yield(%)[a]
10		CH_2Cl_2 50°C/2d	86:14	 **10a**	75%
11		toluene 100°C/3d	100:0	 **11a**	69%
12		toluene 100°C/12h	87:13	 **12a**	94%

[a] Total (*endo* + *exo*) isolated yield.

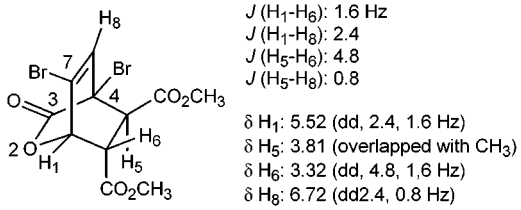


Figure 1.

CH_2Cl_2 were used for each reaction. Except for entries 2, 6, and 9, toluene gave better results than CH_2Cl_2: higher chemical yields and *endo*/*exo* ratios as well as shorter reaction time.

Our study showed that 3,5-dibromo-2-pyrone is more reactive than monobromo-2-pyrones, in both ways; normal- and inverse-electron-demand cycloadditions. For example, 3,5-dibromo-2-pyrone reacted with methyl methacrylate, methyl crotonate and benzyl vinyl ether to provide **6**, **7,** and **11** in yields of 84%, 82%, and 69%, while the same reactions with 3- or 5-bromo-2-pyrone gave the corresponding cycloadducts in the range of 30% yields. It can be thus presumed that the two bromine atoms on 3,5-dibromo-2-pyrone are acting in an additive manner to enhance its reactivity. Since 5-bromo-2-pyrone had been previously shown to be more reactive than 3-bromo-2-pyrone,[3] we can now conclude the reactivity of the bromo-2-pyrone series would be as follows: 3,5-dibromo-2-pyrone > 5-bromo-2-pyrone > 3-bromo-2-pyrone.

Also significant is its higher *endo*/*exo* regioselectivity. For instance, cycloadditions of 3,5-dibromo-2-pyrone with acrylonitrile and benzyl vinyl ether provided the cycloadducts **4** and **10** in *endo*/*exo* ratios of 76:24 and 100:0, respectively, compared to 54:46 and 67:33 for the same reactions with 5-bromo-2-pyrone.

Another interesting feature of this study is that the cycloadditions with both dimethyl fumarate and dimethyl maleate provided a mixture of two diastereomers, in slightly different ratios (entries 8 and 9 in Table 1). Comparison of the coupling patterns of their ^{1}H NMR spectra to other structurally related bicyclolactones as well as decoupling experiments established the relative stereochemistry of **9a** and **9b** being 5-*endo*-6-*exo* and 5-*exo*-6-*endo* isomers (Figure 1).[11] In 5-*exo*-6-*endo* adduct **9a**, the chemical shift for H6 is greater than that of H5, by 0.5

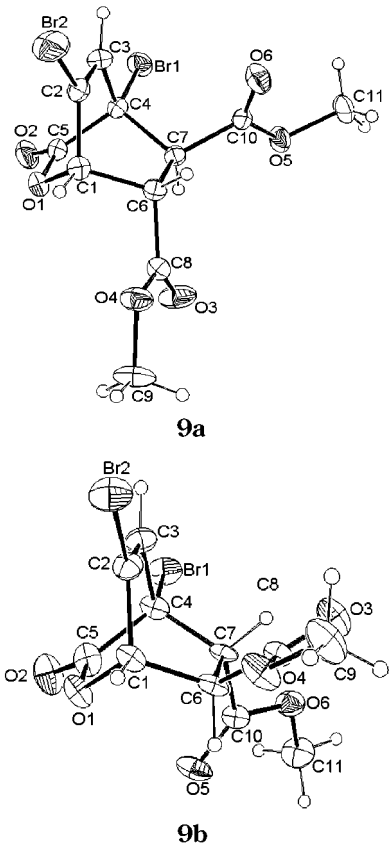
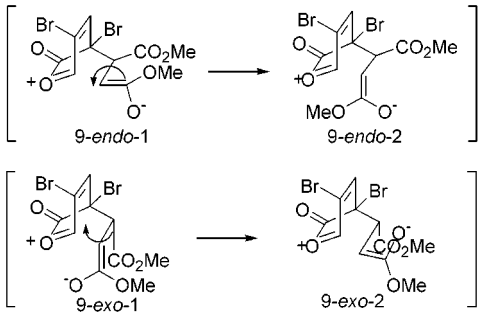


Figure 2. ORTEP representation of the X-ray crystal structure of **9a** and **9b**.

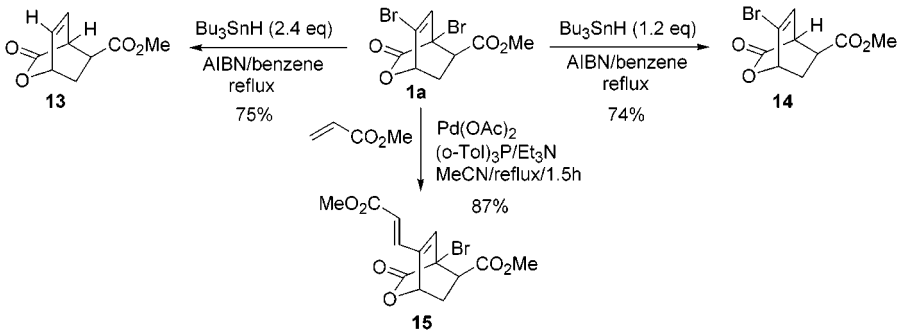
Scheme 3



ppm, which was caused by the magnetic anisotropic effect of the olefin bridge. The same effect should be exerted into the 5-*endo*-6-*exo* adduct **9b**, but the difference in the chemical shifts for H5 and H6 is only 0.08 ppm. This unusually small difference in the chemical shifts suggests that H5 is twisted away from the olefin bridge (thus less shielded) in solution to relieve the vicinal strain between 4-Br and H5 in **9b**. Our structural assignment was ultimately confirmed by X-ray crystallographic analyses of both **9a** and **9b** as shown in Figure 2.

Apparently, stereochemistry in dimethyl maleate was not preserved during the course of the reaction, implying that the cycloaddition proceeds in a stepwise rather than concerted fashion.[12,13] Monitoring of the reaction progress with TLC and GC showed that dimethyl fumarate appeared in the reaction mixture after a few hours. Its concentration increased up to a certain point and slowly decreased as the cycloaddition progressed. Dimethyl maleate alone did not undergo cis−trans isomerization to fumarate in boiling toluene. Although not isolated, ^{1}H

Scheme 4



NMR and GC analysis of the reaction mixture indicated the existence of cis-disubstituted bicyclolactones. We could thus conclude that the cycloaddition with dimethyl maleate is reversible, presumably going through zwitterionic intermediates such as 9-*endo*-1 and 9-*exo*-1, in which C−C bond rotations can take place to give rise to the sterically less crowded 9-*endo*-2 and 9-*exo*-2 (Scheme 3). Further decomposition of 9-*endo*-2 and 9-*exo*-2 furnished the starting pyrone and dimethyl fumarate.

In entry 5, the ^{1}H NMR for **5a** showed CH_2 and CH_3 in $-NCH_2CH_3$ as a doubly splitted quartet and a clean triplet, respectively, while those protons appeared to be a simple quartet and a triplet for **5b** (*exo* cycloadduct). Slow pyramidal inversion of the $-NCH_2CH_3$ group may be attributed to this unusual splitting of CH_2 in **5a**.[14]

Vinyl- and *tert*-alkylbromines on the cycloadducts can be selectively manipulated. As shown in Scheme 4, treatment of the cycloadduct **1a** with 2.4 equiv of Bu_3SnH completely removed both bromine groups to **13**,[15] while use of 1.2 equiv of Bu_3SnH removed only the bromine atom at the bridgehead carbon (C4) to furnish **14**.[16] The Heck coupling reaction with methyl acrylate gave rise to the dienoate **15** in 87% yield.

In summary, we have investigated D−A cycloadditions of 3,5-dibromo-2-pyrone with a series of electronically and sterically distinct dienophiles. Our results have shown that it is a highly potent ambident diene, being more reactive and stereoselective than monobromo-2-pyrones, thus capable of generating a variety of bicycloadducts in much higher chemical yields and *endo*/*exo* ratio than monobromo-2-pyrones. In addition, X-ray crystallographic analyses of **9a** and **9b** have provided a concrete criterion for the ^{1}H NMR spectroscopic structural assignments of *endo* and *exo* cycloadducts, based on chemical shifts and coupling constants. We have also demonstrated that the two bromine groups on the cycloadducts could be independently manipulated to produce other synthetically useful bicyclolactones.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz, with either TMS (δ = 0) or the signal for residual $CHCl_3$ in the $CDCl_3$ solvent (δ 7.24) as internal standards. *J* values are reported in Hz. FT-IR spectra were obtained with KBr pellets. High-resolution mass spectra were measured by using either the chemical ionization or electron impact (70 eV) method. Flash column chromatography was performed with Kieselgel 60 Art 9385 (230−400 mesh). All solvents used were purified according to standard procedures.

3,5-Dibromo-2-pyrone. The original procedure[9] was modified as follows. To a flask charged with 100 mg (0.71 mmol) of coumalic acid in 10 mL of CCl_4 and 5 mL of MeCN were added 500 mg (2.86 mmol, 4 equiv) of NBS, 73 mg (0.71 mmol, 1.0 equiv) of LiOAc, and 46 mg (0.36 mmol, 0.02 equiv) of Bu_4NBr at rt under Ar atmosphere. The resulting mixture was heated at 65 °C for 8−16 h. After disappearance of the starting coumalic acid (monitored by TLC), the reaction mixture was partitioned into 30 mL of CH_2Cl_2 and 30 mL of H_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed with 10% EtOAc in hexanes to give 3,5-dibromo-2-pyrone (R_f: 0.3, 10% EtOAc in hexanes) in 65−76% yield along with small amount of 5-bromo-2-pyrone (R_f: 0.2, 10% EtOAc in hexanes).

Representative Procedure of the D−A Cycloadditions. A mixture of 3,5-dibromo-2-pyrone (51 mg, 0.20 mmol) and methyl acrylate (52 mg, 0.60 mmol) in 2 mL of anhydrous toluene was heated at 100 °C in a sealed tube for 5 h. After the reaction, the reaction mixture was concentrated and chromatographed to give 54 mg (0.16 mmol) of *endo*-**1a** and 3.4 mg (0.01 mmol) of *exo*-**1b**, in yields of 80% and 5%, respectively.

4,7-Dibromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*endo*-carboxylic acid methyl ester (1a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, J = 2.0 Hz, 1H), 5.22 (ddd, J = 4.0, 2.0, 1.2 Hz, 1H), 3.79 (s, 3H), 3.24 (dd, J = 9.6, 4.4 Hz, 1H), 2.73 (ddd, J = 13.2, 9.6, 4.0 Hz, 1H), 2.16 (ddd, J = 13.2, 4.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 165.6, 134.2, 118.9, 80.4, 58.4, 53.2, 41.8, 34.0; FT-IR (KBr, cm^{-1}) 1781, 1731; HRMS (CI) *m*/*z* $(M + 1)^+$ calcd for $C_9H_9Br_2O_4$ 338.8867, found 338.8854.

4,7-Dibromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*exo*-carboxylic acid methyl ester (1b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 2.4 Hz, 1H), 5.22−5.20 (m, 1H), 3.79 (s, 3H), 3.18 (dd, J = 10.8, 5.2 Hz, 1H), 2.49 (ddd, J = 13.6, 5.2, 4.0 Hz, 1H), 2.36 (ddd, J = 13.6, 10.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 164.4, 135.4, 121.3, 79.3, 58.0, 53.1, 48.7, 32.4

4,6-Dibromo-8-*endo*-hydroxymethyl-2-oxabicyclo[2.2.2]-oct-5-en-3-one (2a). Owing to their instability, the initial cycloadducts were reduced with $NaBH_4$ to the corresponding alcohols. We were not able to isolate the minor *exo*-isomeric alcohol. The 71% yield in Table 1 is the isolated yield of the *endo* product only. The *endo*/*exo* ratio was determined at the initial cycloaddition stage from the integrations on the crude ^{1}H NMR spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, J = 2.4 Hz, 1H), 5.18−5.16 (m, 1H), 4.07 (dd, J = 11.2, 4.4 Hz, 1H), 3.66 (dd, J = 11.2, 7.2 Hz, 1H), 2.54 (ddd, J = 13.6, 9.2, 4.0 Hz, 1H), 2.46−2.40 (m, 1H), 2.08 (ddd, J = 13.6, 4.0, 1.6 Hz, 1H), 1.84 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 134.1, 119.4, 80.4, 64.4, 61.8, 42.2, 31.7; FT-IR (KBr, cm^{-1}) 1750; HRMS (CI) *m*/*z* $(M + 1)^+$ calcd for $C_8H_8Br_2O_3$ 309.8839, found 309.8906.

8-*endo*-Acetyl-4,6-dibromo-2-oxabicyclo[2.2.2]oct-5-en-3-one (3a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, J = 2.0 Hz, 1H),

(11) Coupling of bridgehead H (H-1) with 6-*endo*-H is always larger than with 6-*exo*-H in these bicyclolactone systems (4.0 vs 1.6 Hz in this case). Similar trends in the magnitude of coupling constants were reported in ref 1c.

(12) Cho, C.-G.; Posner, G. H. *Bull. Korean Chem. Soc.* **1998**, *19*, 957.

(13) Posner, G. H.; Cho, C.-G.; Anjeh, T. E. N.; Johnson, N.; Horst, R. L.; Kobayashi, T.; Okano, T.; Tsugawa, N. *J. Org. Chem.* **1995**, *60*, 4617.

(14) Slow pyramidal inversion might be responsible for the multiplicity of the *N*-Et group (reported as triplet for $-CH_3$ and multiplet for $-CH_2-$) in the ^{1}H NMR for the cycloadduct made from cyclopentadiene and *N*-ethylmaleimide. Meijer, A.; Otto, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8989.

(15) ^{1}H NMR data for compound **13** is reported in ref 6.

(16) ^{1}H NMR data for compound **14** is reported in ref 4.

5.24−5.22 (m, 1H), 3.44 (dd, J = 9.6, 4.4 Hz, 1H), 2.73−2.66 (m, 1H), 2.34 (s, 3H), 2.03 (ddd, J = 13.2, 4.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 165.4, 133.6, 117.8, 80.0, 57.6, 50.1, 32.9, 31.8; FT-IR (KBr, cm^{-1}) 1766, 1725; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_9H_9Br_2O_3$ 322.8918, found 322.8884.

8-*exo*-Acetyl-4,6-dibromo-2-oxabicyclo[2.2.2]oct-5-en-3-one (3b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 2.4 Hz, 1H), 5.19−5.17 (m, 1H), 3.44 (dd, J = 9.6, 6.0 Hz, 1H), 2.34 (s, 3H), 2.31−2.30 (m, 1H), 2.28−2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 164.5, 135.7, 121.3, 79.3, 57.7, 53.0, 32.4, 32.3

4,7-Dibromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*endo*-carbonitrile (4a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 2.4 Hz, 1H), 5.28−5.26 (m, 1H), 3.46 (dd, J = 9.6, 3.2 Hz, 1H), 2.87−2.80 (m, 1H), 2.40 (ddd, J = 13.6, 3.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 133.6, 121.5, 117.0, 78.9, 56.3, 34.8, 33.4; FT-IR (KBr, cm^{-1}) 2247, 1785; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_8H_6Br_2NO_2$ 305.8765, found 305.8736.

4,7-Dibromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*exo*-carbonitrile (4b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 2.4 Hz, 1H), 5.27 (ddd, J = 4.8, 2.4, 1.6 Hz, 1H), 3.35 (dd, J = 11.2, 4.8 Hz, 1H), 2.74 (ddd, 13.6, 9.6, 4.8, 1H), 2.55 (ddd, J = 13.6, 11.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 134.1, 122.2, 116.5, 79.2, 59.5, 35.2, 33.2, 31.7, 22.8, 14.2

1,11-Dibromo-4-ethyl-8-oxa-4-azatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,9-trion (5a): ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.72 (d, J = 2.0 Hz, 1H), 5.55 (dd, J = 4.4, 2.4 Hz, 1H), 3.89 (dd, J = 8.0, 4.4 Hz, 1H), 3.57 (qd, J = 7.2, 1.2 Hz, 1H), 3.49 (d, J = 8.0 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.1, 163.9, 134.6, 118.2, 78.4, 55.5, 46.8, 45.1, 34.6, 12.7; FT-IR (KBr, cm^{-1}) 1769, 1742; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_{11}H_{10}Br_2NO_4$ 377.8976, found 377.8944.

1,11-Dibromo-4-ethyl-8-oxa-4-azatricyclo[5.2.2.0]undec-10-ene-3,5,9-trion (5b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 2.0 Hz, 1H), 5.54−5.52 (m, 1H), 3.57 (q, J = 7.2 Hz, 2H), 3.47 (bs, 1H), 3.47 (bs, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.6, 162.88, 136.6, 120.9, 79.5, 55.2, 47.8, 47.5, 34.6, 12.6

4,7-Dibromo-5-*exo*-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*endo*-carboxylic acid methyl ester (6a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 2.4 Hz, 1H), 5.18−5.16 (m, 1H), 3.77 (s, 3H), 2.52 (dd, J = 13.6, 1.2 Hz, 1H), 2.35 (dd, J = 13.6, 4.0 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 165.1, 135.4, 117.9, 80.3, 65.7, 52.9, 48.6, 40.6, 23.8; FT-IR (KBr, cm^{-1}) 1784, 1721; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_9H_{11}Br_2O_4$ 352.9023, found 352.9015.

4,7-Dibromo-5-*endo*-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*exo*-carboxylic acid methyl ester (6b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.8 Hz, 1H), 5.15 (ddd, J = 4.0, 2.8, 1.2 Hz, 1H), 3.76 (s, 3H), 2.79 (dd, J = 13.6, 4.0 Hz, 1H), 1.93 (dd, J = 13.6, 1.2 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 165.5, 135.1, 120.1, 78.9, 65.9, 53.2, 51.1, 39.3, 22.6

4,7-Dibromo-6-*exo*-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*endo*-carboxylic acid methyl ester (7a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, J = 2.4, 0.8 Hz, 1H), 4.87 (dd, J = 2.4, 1.2 Hz, 1H), 3.79 (s, 3H), 2.72 (dd, J = 4.8, 0.8 Hz, 1H), 2.47−2.40 (m, 1H), 1.36 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 165.6, 133.7, 119.4, 85.3, 58.3, 54.1, 53.2, 41.9, 18.2; FT-IR (KBr, cm^{-1}) 1774, 1740; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_9H_{11}Br_2O_4$ 352.9023, found 352.9001.

4,7-Dibromo-6-*endo*-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*exo*-carboxylic acid methyl ester (7b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J = 2.8 Hz, 1H), 5.36 (dd, J = 4.0, 2.8 Hz, 1H), 3.79 (s, 3H), 3.10 (dd, J = 4.8, 4.4 Hz, 1H), 2.73 (m, 1H), 1.34 (d, J = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 165.4, 137.5, 118.4, 80.2, 63.3, 52.8, 52.5, 40.8, 19.1

4,7-Dibromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*endo*-6-*exo*-dicarboxylic acid dimethyl ester (8a and 9a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, J = 2.4, 0.8 Hz, 1H), 5.52 (dd, J = 2.4, 1.6 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.81 (1H, overlapped with CH_3 peak), 3.32 (dd, J = 4.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.9, 164.6, 135.2, 118.41, 81.6, 57.6, 54.0, 53.5, 50.7, 48.23; FT-IR (KBr, cm^{-1}) 1786, 1758, 1737; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_{11}H_{11}Br_2O_6$ 396.8921, found 396.8925.

4,7-Dibromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5-*exo*-6-*endo*-dicarboxylic acid dimethyl ester (8b and 9b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (J = 2.0 Hz, 1H), 5.48 (dd, J = 4.0, 2.4 Hz, 1H), 3.81 (s, 6H), 3.72 (dd, J = 5.6, 4.0 Hz, 1H), 3.64 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 167.7, 163.9, 136.7, 120.0, 79.5, 57.4, 53.7, 53.6, 51.5, 50.0; FT-IR (KBr, cm^{-1}) 1800, 1747, 1734; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_{11}H_{11}Br_2O_6$ 396.8921, found 396.8902.

4,6-Dibromo-8-*endo*-ethoxy-2-oxabicyclo[2.2.2]oct-5-en-3-one (10a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J = 2.4 Hz, 1H), 5.15−5.13 (m, 1H), 3.88 (ddd, J = 7.6, 2.0, 1.2 Hz, 1H), 3.76−3.64 (m, 2H), 2.68 (ddd, J = 13.6, 7.6, 3.6 Hz, 1H), 2.00 (ddd, J = 13.6, 2.0, 2.0 Hz, 1H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 133.6, 118.7, 79.8, 76.7, 67.7, 64.4, 37.1, 15.7; FT-IR (KBr, cm^{-1}) 1764; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_{11}H_{11}Br_2O_6$ 396.8921, found 396.8906.

4,6-Dibromo-8-*exo*-ethoxy-2-oxabicyclo[2.2.2]oct-5-en-3-one (10b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 2.4 Hz, 1H), 5.11−5.09 (m, 1H), 3.91(dd, J = 8.8, 2.4 Hz, 1H), 3.66(q, J = 7.2, 2H), 2.39 (ddd, J = 13.6, 8.8, 1.6 Hz, 1H), 2.22 (ddd, J = 13.6, 4.0, 2.4 Hz, 1H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 133.2, 121.9, 80.3, 77.8, 67.3, 63.6, 35.1, 15.2.

***endo*-8-Benzyloxy-4,6-dibromo-2-oxabicyclo[2.2.2]oct-5-en-3-one (11a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.31 (m, 5H), 6.60 (dd, J = 2.4, 0.8 Hz, 1H), 5.11 (ddd, J = 3.6, 2.4, 2.0 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.70 (d, J = 11.6 Hz, 1H), 3.98 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H), 2.57 (ddd, J = 14.0, 8.0, 3.6 Hz, 1H), 2.01 (ddd, J = 14.0, 2.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 136.4, 133.1, 128.3, 128.0, 127.8, 118.4, 79.3, 75.5, 73.3, 63.8, 36.4; FT-IR (KBr, cm^{-1}) 1775; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_{14}H_{13}Br_2O_3$ 386.9231, found 386.9202.

4.6-Dibromo-8-*endo*-(4-bromophenyl)-2-oxabicyclo[2.2.2]-oct-5-en-3-one (12a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 2.4 Hz, 1H), 5.32−5.30 (m, 1H), 3.37 (dd, J = 9.2, 4.4 Hz, 1H), 2.97−2.90 (m, 1H), 2.23 (ddd, J = 14.0, 4.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 137.3, 133.6, 131.3, 130.4, 122.1, 120.2, 80.3, 63.4, 45.3, 36.7; FT-IR (KBr, cm^{-1}) 1781; HRMS (CI) m/z (M + 1)$^+$ calcd for $C_{13}H_{10}Br_3O_2$ 434.8230, found 434.8199.

4.6-Dibromo-8-*exo*-(4-bromophenyl)-2-oxabicyclo[2.2.2]-oct-5-en-3-one (12b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 2.4 Hz, 1H), 5.29−5.26 (m, 1H), 3.39 (dd, J = 10.4, 5.6 Hz, 1H), 2.62 (ddd, J = 14.0, 10.4, 1.6 Hz, 1H), 2.49 (ddd, J = 14.0, 5.6, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 136.7, 136.5, 131.7, 130.2, 122.3, 120.9, 80.4, 63.7, 48.2, 36.0.

4-Bromo-7-*endo*-(2-methoxycarbonylvinyl)-3-oxabicyclo-[2.2.2]oct-7-ene-5-carboxylic Acid Methyl Ester (15). A mixture of 50 mg (0.147 mmol) of **1a**, 0.015 mL (0.162 mmol) of methyl acrylate, 3 mg (0.015 mmol) of $Pd(OAc)_2$, 9 mg (0.030 mmol) of tri(*o*-tolyl)phosphine, and 0.060 mL (0.441 mmol) of Et_3N in 3 mL of anhydrous MeCN was refluxed for 1.5 h with vigorous stirring. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$ and purified by column chromatography (hexane/ethyl acetate: 1/1) to give 44 mg of the product **15** in 87% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 16.0 Hz, 1H), 6.78 (s, 1H), 6.13 (d, J = 16.0 Hz, 1H), 5.58−5.57 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.35 (ddd, J = 10.0, 4.4, 0.8 Hz, 1H), 2.85−2.78 (m, 1H), 1.97 (ddd, J = 13.6, 4.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 166.0, 165.9, 139.0, 137.4, 135.8, 120.1, 72.6, 57.8, 52.7, 51.9, 46.2, 33.3; FT-IR (KBr, cm^{-1}) 1764, 1749, 1724; HRMS (EI) m/z (M^+) calcd for $C_{13}H_{13}BrO_4$ 343.9895, found 343.9895.

Acknowledgment. The financial support of the Ministry of Science and Technology (National Research Laboratory, 99-N-NL-01-C-103) in Korea is acknowledged.

Supporting Information Available: Spectral data of all the new cycloadducts and **13**. X-ray data of **9a** and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015804R