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An Experimental and Computational Investigation of the Diels−Alder Cycloadditions of Halogen-Substituted 2(*H*)-Pyran-2-ones

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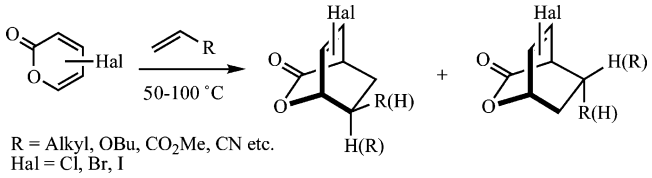

Diels−Alder reactions of 3- and 5-halo-subsituted 2(*H*)-pyran-2-ones with both electron-rich and electron-deficient dienophiles afford stable and readily isolable bridged bicyclic lactone cycloadducts. These cycloadditions proceed with excellent regioselectivity and very good stereoselectivity. In contrast, Diels−Alder reactions of 4-halo-subsituted 2(*H*)-pyran-2-ones afford cycloadducts which are very prone to loss of bridging CO_2 and the subsequent formation of barrelenes ([2.2.2]-cyclooctenes). Furthermore, these cycloadditions proceed with only moderate regio- and stereoselectivity. For both series of the 3- and 5-halo-subsituted 2(*H*)-pyran-2-ones and 4-halo-subsituted 2(*H*)-pyran-2-ones, the reactivity patterns do not significantly change between the halogens. The regio- and stereochemical preferences of the cycloadditions of halo-substituted 2(*H*)-pyran-2-ones are investigated computationally. Calculations were carried out on the transition states leading to the four possible regio- and stereoisomeric cycloadducts by using density functional theory (B3LYP/6-31G*). These studies allow prediction of the regio- and stereoselectivity in these reactions which are broadly in line with experimental observations.

Introduction

The Diels−Alder cycloadditions of 2(*H*)-pyran-2-one, **1**, and its ring-substituted analogues are synthetically important and useful reactions.[1,2] Cycloadditions afford in the first instance bridged bicyclic lactones (Scheme 1). These functionally rich bridged cycloadducts are valuable starting materials for synthesis of highly functionalized six-membered rings found in many natural products.[3−9] Furthermore, under forcing thermal conditions, these cycloadducts undergo loss of CO_2 to afford a cyclohexadiene intermediate that can either undergo further cycloaddition to afford barrelenes[10] or aromatize by loss of hydrogen or by elimination to afford benzenes (Scheme 1). Indeed the formation of benzenes is a very common reaction of 2(*H*)-pyran-2-ones and has been extensively used for the synthesis of many aromatic natural products including lasalocid A,[11] rufesine,[12] imeluteine,[12] chrysophanol,[13] islandicin,[13] emodin,[13] sendaverine,[14] juncusol,[14] and norketoyobirine.[15]

† King's College.
‡ Imperial College.

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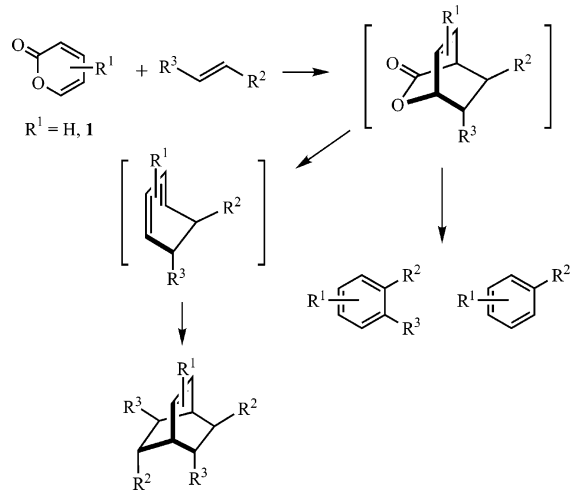
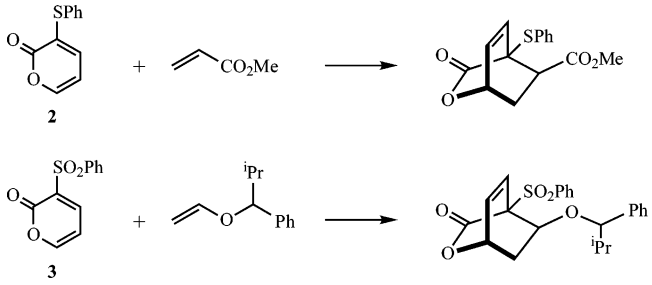
SCHEME 1



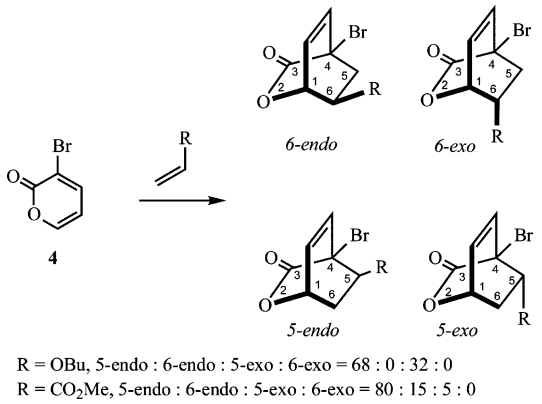
SCHEME 2



Regardless of whether the 2(*H*)-pyran-2-ones are used in the synthesis of functionally rich aromatic or saturated six-membered rings, a requirement for a successful methodology based on their Diels−Alder cycloaddition reaction is that the reactions should proceed efficiently and with regio- and stereoselectivity. This can be best achieved by matching the electronic demand of the dienophile with that of the 2(*H*)-pyran-2-one by means of appropriate ring substitution. For example, Posner has demonstrated that 3-phenylsulfenyl-2(*H*)-pyran-2-one-(**2**)[16,17] and 3-phenylsulfonyl-2(*H*)-pyran-2-one (**3**)[3−6] react with electron-deficient and electron-rich dienophiles respectively and that the reactions proceed to give the isolable cycloadducts with excellent regio- and stereocontrol (Scheme 2). However, there are no examples of thermal cycloadditions of 2(*H*)-pyran-2-one (**1**), itself affording an isolable bridged bicyclic lactone. As a result, the role of substituents on the selectivity of the cycloadditions of 2(*H*)-pyran-2-ones has become an important area of investigation.

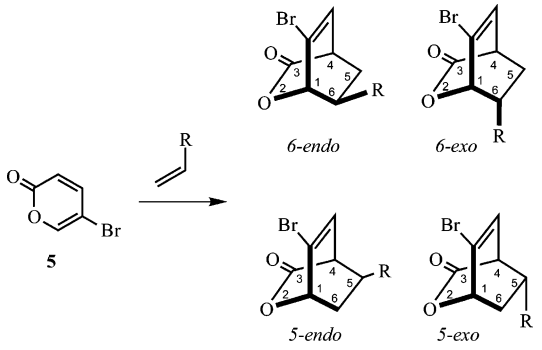
During the investigations on the role of substituents on the cycloaddition chemistry of 2(*H*)-pyran-2-ones, it was found that 3-bromo-2(*H*)-pyran-2-one (**4**) and 5-bromo-2(*H*)-pyran-2-one (**5**) have a most interesting, unique, and useful feature. These two 2(*H*)-pyran-2-ones have no electronic demand and react with electron-rich, electron-poor, and electron-neutral dienophiles with good regio- and stereoselectivity (Schemes 3 and 4).[18−21] Interest-

SCHEME 3



R = OBu, 5-endo : 6-endo : 5-exo : 6-exo = 68 : 0 : 32 : 0
R = CO_2Me, 5-endo : 6-endo : 5-exo : 6-exo = 80 : 15 : 5 : 0

SCHEME 4



R = OBu, 5-endo : 6-endo : 5-exo : 6-exo = 65 : 0 : 35 : 0 (ref 20)
R = COMe, 5-endo : 6-endo : 5-exo : 6-exo = 89 : 11 : 0 : 0 (ref 20)

ingly, it has been shown that 3,5-dibromo-2(*H*)-pyran-2-one is also an ambident diene.[22,23] Cycloadditions of 2(*H*)-pyran-2-one itself are not selective. Therefore, these easily prepared[18,20] bromopyrones represented a significant advantage over 2(*H*)-pyran-2-one with the added bonus that the bromine substituent in cycloadducts could be manipulated[24] and hence expanding the diversity of molecules obtained by this method even further.

That investigation was followed by the discovery that 4-chloro-2(*H*)-pyran-2-one (**6**), in contrast to the bromopyrones but in line with 2(*H*)-pyran-2-one itself, is neither an ambident diene nor undergoes regioselective cycloadditions.[25] Instead, 4-chloro-2(*H*)-pyran-2-one (**6**) undergoes cycloadditions only with electron-deficient dienophiles to afford a mixture of two *endo* cycloadducts which are very prone to loss of CO_2 and formation of barrelenes. Furthermore, we showed that the experimental results of the cycloadditions of both 4-chloro-2(*H*)-pyran-2-one (**6**) and 2(*H*)-pyran-2-one (**1**) favorably compare with those predicted from computational investigation of the Diels−Alder reactions with density functional theory (DFT) calculations.

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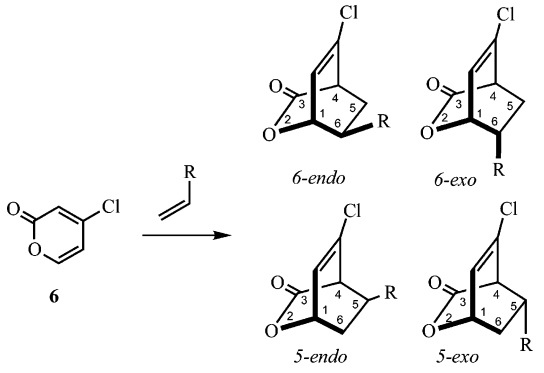
SCHEME 5



R = OBu, No reaction

R = CO_2Me, 5-endo : 6-endo : 5-exo : 6-exo = 41 : 48 : 2 : 9

The significant difference between the outcome of the cycloaddition between 3- and 5-bromo-2(*H*)-pyran-2-ones (**4** and **5**) (Schemes 3 and 4) and 4-chloro-2(*H*)-pyran-2-one (**6**) (Scheme 5) prompted us to investigate further both the role of the halogen substituent and its ring position on the cycloaddition chemistry of 2(*H*)-pyran-2-ones. Specifically, we wanted to know if the observed difference is due to the change in halogen from bromine to chlorine, or due to a change in the position of the substituent. Furthermore, we wanted to explore the generality of the computational model we had developed and were keen to assess its suitability as a general tool for predicting the reactions of substituted 2(*H*)-pyran-2-ones.

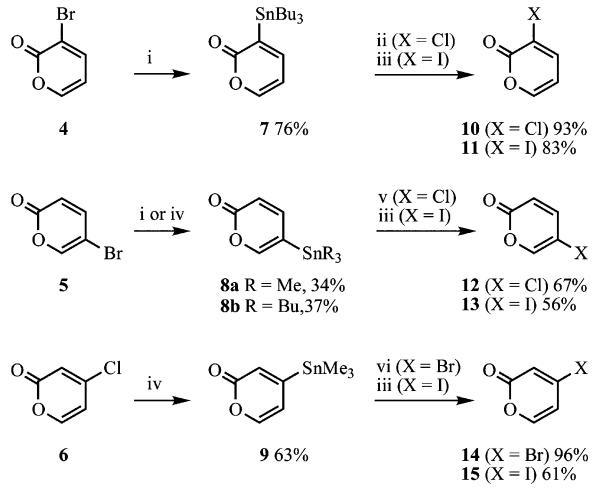
Here, we report the preparation of 3-, 4-, and 5-halogen-substituted 2(*H*)-pyran-2-ones and the results of their cycloaddition to a range of dienophiles. We will also show that the computational model we have tested to predict the reactivity pattern of 2(*H*)-pyran-2-one (**1**) and 4-chloro-2(*H*)-pyran-2-one (**6**) can also successfully rationalize the pattern of reactions of other halo-substituted 2(*H*)-pyran-2-ones.

Results and Discussions

3- and 5-bromo-2(*H*)-pyran-2-ones (**4** and **5**)[18,20] and 4-chloro-2(*H*)-pyran-2-one (**6**)[25] were prepared according to the reported procedures. All three compounds were converted to the corresponding (trialkylstannyl)-2(*H*)-pyran-2-ones **7**, **8**, and **9** by treatment with hexaalkylditin with Pd(0) catalysis.[26] Treatment of these tin derivatives with elemental halogens afforded the corresponding halogen-substituted 2(*H*)-pyran-2-ones **10**−**15** (Scheme 6).[27]

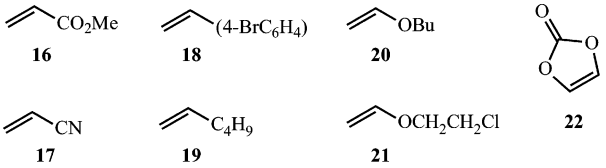
Initial screening of a range of temperatures for the reactions showed that cycloadditions of 3- and 5-halo-substituted 2(*H*)-pyran-2-ones can be carried out at 90−100 °C, whereas to minimize the proportion of barrelene and aromatic byproducts, reactions of 4-halo-substituted 2(*H*)-pyran-2-ones with dienophiles must be maintained at 50−70 °C. We have previously shown that at these temperatures, cycloadduct products are not equilibrating

SCHEME 6[a]



[a] Reagents and conditions: (i) $Pd(PPh_3)_4$, $(Bu_3Sn)_2$, THF, reflux, 44 h; (ii) Cl_2, CCl_4/CH_2Cl_2, rt, 1 h; (iii) I_2, $CHCl_3$, rt, 6 days; (iv) $Pd(PPh_3)_4$, $(Me_3Sn)_2$, THF, reflux, 44 h; (v) Cl_2, CCl_4/CH_2Cl_2, rt, 45 min; (vi) Br_2, $CHCl_3$, −60 °C to rt, 24 h.

and that there is no cycloreversion.[21] The cycloadditions were carried out on a range of electron-deficient dienophiles such as methyl acrylate (**16**) and acrylonitrile (**17**), electron-"neutral" dienophiles such as 4-bromostyrene (**18**) and 1-hexene (**19**), and electron-rich dienophiles such as butyl vinyl ether (**20**), 2-chloroethyl vinyl ether (**21**), and vinylene carbonate (**22**).



The results of the cycloadditions of 4-halopyrones are shown in Table 1. As with 4-chloro-2(*H*)-pyran-2-one (**6**), we found 4-bromo-2(*H*)-pyran-2-one (**14**) and 4-iodo-2(*H*)-pyran-2-one (**15**) to be unreactive toward electron-rich and electron-neutral dienophiles. The only example of an inverse electron demand cycloaddition was with mildly electron-rich vinylene carbonate **22** where traces of a cycloadduct were detected in crude NMR. The cycloadditions of 4-halo-2(*H*)-pyran-2-ones with electron-deficient dienophiles were stereoselective but not regioselective, affording nearly equal ratios of the 5-*endo* and 6-*endo* cycloadducts.

In contrast, cycloadditions of 3-halopyrones (Table 2) and 5-halopyrones (Table 3) proceeded with electron-rich, electron-deficient, and electron-"neutral" dienophiles. Also in contrast to 4-halopyrones, the cycloadditions were regio- as well as stereoselective, affording mostly the 5-*endo* cycloadducts. Interestingly, cycloadditions of 3- and 5-halopyrones with electron-rich and electron-"neutral" dienophiles afforded, in addition to the 5-*endo* cycloadducts, 5-*exo* cycloadducts as the minor products. However, cycloadditions of 3- and 5-halopyrones with electron-deficient dienophiles afforded, in addition to the 5-*endo* cycloadducts, both the 5-*exo* and 6-*endo* cycloadducts as the minor products with the latter more abundant then the former in the cycloaddition with methyl acrylate.

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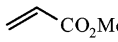
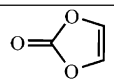
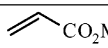
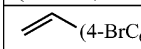
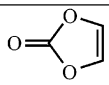
TABLE 1

Dienophile (Condition)	Pyrone Diene	Yield (%)	Cycloadduct (ratio)[a]			
			6-endo	5-endo	6-exo	5-exo
 (50 °C, 14 days)	4-Chloro-2(H)-pyran-2-one **6**	70[b]	48	41	9	2
	4-Bromo-2(H)-pyran-2-one **14**	78	45 (45)	44 (43)	7 (5)	4 (7)
	4-Iodo-2(H)-pyran-2-one **15**	93	47 (47)	39 (37)	8 (9)	6 (7)
 (50 °C, 15 days then 70 °C, 17 days)	4-Chloro-2(H)-pyran-2-one **6**	41[c]	58 (47)	25 (41)	17 (9)	0 (2)
	4-Bromo-2(H)-pyran-2-one **14**	75	50[d] (35)	50[d] (39)	--- (21)	---- (5)
	4-Iodo-2(H)-pyran-2-one **15**	63	64 (46)	20 (28)	16 (26)	0 (0)
 (100 °C, 5 days)	4-Bromo-2(H)-pyran-2-one **14**	7	100		0	

[a] Ratios of cycloadducts are normalized so as to total 100%. Values in parentheses are the ratios from isolated cycloadducts. Assignments of relative configuration of the cycloadducts are based on literature precedence.[1,20,21] [b] Reaction was carried out at 70 °C. [c] Reaction was carried out for 26 days at 70 °C. [d] It was not possible to discern all four isomers in the crude reaction mixture. The ratio refers to the combined 6-substituted to 5-substituted cycloadducts.

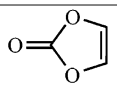
TABLE 2

Dienophile (Condition)	Pyrone Diene	Yield (%)	Cycloadduct (ratio)[a]			
			6-endo	5-endo	6-exo	5-exo
 (100 °C, 3 days)	3-Chloro-2(H)-pyran-2-one **10**	55	15 (21)	80 (79)	0	5(0)
	3-Bromo-2(H)-pyran-2-one **4**	80	15(25)	80(75)	0	5(0)
	3-Iodo-2(H)-pyran-2-one **11**	74[b]	15(23)	85 (77)	0	0
 (100 °C, 3 days)	3-Chloro-2(H)-pyran-2-one **10**	86	14 (7)	54 (66)	7 (6)	25 (21)
	3-Bromo-2(H)-pyran-2-one **4**	78	12 (11)	55 (65)	11 (10)	22 (14)
	3-Iodo-2(H)-pyran-2-one **11**	75	9 (15)	53 (57)	7 (7)	31 (21)
 (100 °C, 3 days)	3-Chloro-2(H)-pyran-2-one **10**	76	0	67 (84)	0	33 (16)
	3-Bromo-2(H)-pyran-2-one **4**	52	0	75 (85)	0	25 (15)
	3-Iodo-2(H)-pyran-2-one **11**	93	0	90 (87)	0	10 (13)
 (100 °C, 3 days)	3-Chloro-2(H)-pyran-2-one **10**	26	100		0	
	3-Bromo-2(H)-pyran-2-one **4**	18	100		0	
	3-Iodo-2(H)-pyran-2-one **11**	24[c]	100		0	
 (100 °C, 3 days)	3-Chloro-2(H)-pyran-2-one **10**	40	0	60	0	40
	3-Bromo-2(H)-pyran-2-one **4**	65[d]	0	68	0	32
	3-Iodo-2(H)-pyran-2-one **11**	78	0	82	0	18

[a] Ratios of cycloadducts are normalized so as to total 100%. Values in parentheses are the ratios from isolated cycloadducts. Assignments of relative configuration of the cycloadducts are based on literature precedence.[1,20,21] [b] Reaction was carried out at 90 °C for 4 days. [c] Reaction was carried out for 12 days. [d] Results for the cycloaddition of (2-chloroethyl)vinyl ether.

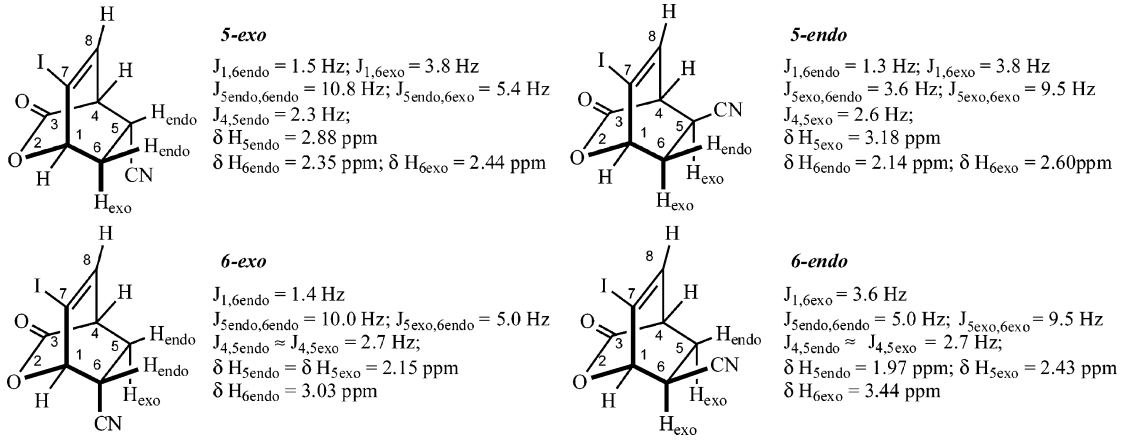
The regio- and stereochemical assignment of the cycloadducts was based on the analysis of the NMR spectra of the cycloadducts according to the earlier empirical rules set out by Posner[1] and us.[20,21] These rules allow us to clearly and unequivocally assign the configuration of the cycloadducts (Scheme 7). This is done by first identifying H-1 or H-4 which always appear at a very narrow range of chemical shift at around 5.5 and 3.5 ppm, respectively. Analysis of the ^3J couplings of these two protons can then determine the regiochemistry of a

TABLE 3

Dienophile (Condition)	Pyrone Diene	Yield (%)	Cycloadduct (ratio)[a]			
			6-endo	5-endo	6-exo	5-exo
CO_2Me (100 °C, 3 days)	5-Chloro-2(H)-pyran-2-one **12**	83 [b]	20 (20)	63 (58)	0	17 (22)
	5-Bromo-2(H)-pyran-2-one **5**	94	20 (20)	70 (65)	0	10 (15)
	5-Iodo-2(H)-pyran-2-one **13**	90	20 (27)	70 (65)	0	10 (8)
CN (100 °C, 3 days)	5-Chloro-2(H)-pyran-2-one **12**	100 [b]	12 (11)	41 (42)	6 (6)	41 (41)
	5-Bromo-2(H)-pyran-2-one **5**	96	10 (11)	42 (40)	6 (7)	42 (42)
	5-Iodo-2(H)-pyran-2-one **13**	55	9 (4)	46 (40)	8 (3)	37 (53)
$n\text{-}C_4H_9$ (100 °C, 3 days)	5-Chloro-2(H)-pyran-2-one **12**	68 [b]	8 (13)	44 (41)	4 (8)	44 (38)
	5-Bromo-2(H)-pyran-2-one **5**	80	10 (17)	42 (39)	7 (6)	41 (38)
	5-Iodo-2(H)-pyran-2-one **13**	85	10 (6)	46 (49)	8 (7)	36 (38)
 (100 °C, 14 days)	5-Chloro-2(H)-pyran-2-one **12**	45	77 (60)		23 (40)	
	5-Bromo-2(H)-pyran-2-one **5**	43	70 (80)		30 (20)	
	5-Iodo-2(H)-pyran-2-one **13**	39	45 (71)		55 (29)	
OCH_2CH_2Cl (100 °C, 3 days)	5-Chloro-2(H)-pyran-2-one **12**	70 [b]	0	65 (73)	0	35 (27)
	5-Bromo-2(H)-pyran-2-one **5**	81	0	70 (72)	0	30 (28)
	5-Iodo-2(H)-pyran-2-one **13**	92	0	70 (72)	0	30 (28)

[a] Ratios of cycloadducts are normalized so as to total 100%. Values in parentheses are the ratios from isolated cycloadducts. Assignment of relative configuration of the cycloadducts are based on literature precedence.[1,20,21] [b] Reaction was carried out for 4 days at 90 °C.

SCHEME 7



cycloadduct. In a 5-substituted cycloadduct, H-4 has one (for the cycloadducts from 4-halo-2(*H*)-pyron-2-one) or two ^3J couplings whereas H-1 has two (for the cycloadducts from 5-halo-2(*H*)-pyron-2-one) or three ^3J couplings. In a 6-substituted cycloadduct, the situation is vice versa. The assignment of the stereochemistry of the cycloadduct is also carried out from the analysis of the NMR spectra. The stereochemistry of H-5 and H-6 protons (and hence the C-5 and C-6 substituents) is determined by analysis of the size of the ^3J couplings of H-1 and H-4. According to the rules,[1,20,21] $^3J_{1,6endo}$ is smaller than $^3J_{1,6exo}$ and $^3J_{4,5endo}$ is smaller than $^3J_{4,5exo}$ (Scheme 7). Furthermore, chemical shift of a proton at an *endo* position is less that that of a proton at an *exo* position in a set of similar cycloadducts (Scheme 7). In addition, the configuration of a selection of cycloadducts was confirmed by X-ray crystallography (see the Supporting Information).

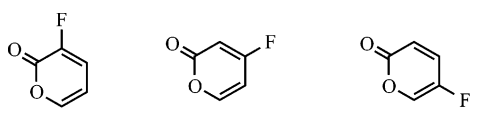
In summary, from the experimental results of the Diels−Alder reactions observed above, it is clear that the nature of the halogen substituent has only a small, sometimes negligible, influence on the cycloaddition of 2(*H*)-pyran-2-ones. Although the isolated yield of reactions differs between chloro-, bromo-, and iodo-substituted 2(*H*)-pyran-2-ones, in both the 3- and 5-substituted series, the distribution of the products does not appear to be significantly different. Therefore, we can conclude that changing the halogen substituent does not significantly change the electronic demand of the 3- and 5-halo-subsituted 2(*H*)-pyran-2-one, although it may influence its reactivity. However, the position of the halogen ring

substituent plays a very important influence on the cycloaddition of 2(*H*)-pyran-2-ones. Broadly speaking, 3- and 5-halo-subsituted 2(*H*)-pyran-2-ones are ambident dienophiles and undergo both normal and inverse electron demand cycloadditions with dienophiles bearing electron-donating and electron-withdrawing polar substituents. These cycloadditions proceed with regio- and stereoselectivity favoring predominantly 5-*endo* cycloadducts. Dienophiles bearing no strongly polar substituents (electron "neutral" dienophiles) or bearing weakly polar substituents also undergo cycloadditions to 3- and 5-halo-subsituted 2(*H*)-pyran-2-ones; however, these cycloadditions are only regioselective favoring the 5-*endo* and 5-*exo* cycloadducts in near equal ratio.

In contrast, 4-halo-subsituted 2(*H*)-pyran-2-ones are normal electron demand dienes and undergo cycloadditions only with electron-deficient dienophiles. These cycloadditions proceed with stereoselectivity but with no regioselectivity favoring predominantly 5-*endo* and 6-*endo* cycloadducts. Dienophiles bearing weakly electron-donating substituents (for example, vinylene carbonate) do undergo inefficient cycloadditions with 4-halo-subsituted 2(*H*)-pyran-2-ones; however, those with no strong polar substituents (electron-"neutral" dienophiles) do not. Again, the isolated yield of reactions differs between 4-chloro-, 4-bromo-, and 4-iodo-substituted 2(*H*)-pyran-2-ones but the distribution of the products does not appear to be significantly different. Therefore, we can conclude that changing the halogen substituent does not significantly change the electronic demand of the 4-halo-subsituted 2(*H*)-pyran-2-one.

Computational Results and Discussions

To understand and predict the regio- and stereoselectivity of the pyrone cycloadditions, we carried out a range of calculations on the four transition states (TS) leading to the four possible stereoisomers, namely the 6-*endo*, the 5-*endo*, the 6-*exo*, and the 5-*exo* cycloadducts, in the cycloadditions of 3-, 4-, and 5-halo-2(*H*)-pyran-2-one **4**−**6** and **10**−**15** with methyl acrylate (MA) and methyl vinyl ether (MVE). Methyl vinyl ether was chosen as a typical electron-rich dienophile for computations. Although this was not one of the dienophiles used in the cycloaddition experiments, we are confident that the results obtained computationally for MVE can be used for comparison with results obtained experimentally for closely related butyl vinyl ether and chloroethyl vinyl ether. Calculations were also carried out on the cycloadditions of 2(*H*)-pyran-2-one (**1**) with methyl acrylate (MA) and methyl vinyl ether (MVE) for comparison, and on the cycloadditions of 3-, 4-, and 5-fluoro-2(*H*)-pyran-2-ones (**23**, **24**, and **25**) with methyl acrylate (MA) and methyl vinyl ether (MVE). Although 3-, 4-, and 5-fluoro-2(*H*)-pyran-2-ones (**23**, **24**, and **25**) were not prepared as part of this study, they were



23 **24** **25**

included as the calculations based on them allow us to better understand trends, differences, and similarlities between halogen substituents. It should be noted that an earlier computational investigation had concluded that 3-fluoro-2(*H*)-pyran-2-one (**23**) should undergo a more efficient cycloaddition with acetylene than 2(*H*)-pyran-2-one (**1**) would do.[28]

Calculations were performed with Gaussian.[29] All transition structures were initially optimized with AM1,[30,31] then reoptimized with B3LYP/6-31G*.[32,33] This DFT method (model chemistry) has been previously shown by Houk to be a reliable method for predicting the regio- and stereoselectivity of the cycloaddition of Danishefski's diene with acrylonitrile,[34] and by us to be a reliable method for predicting the regio- and stereoselectivity of the cycloadditions of 4-chloro-2(*H*)-pyran-2-ones (**6**).[25]

The calculated relative energies of transition states leading to the four possible cycloadducts from the reaction of each of the halopyrones with methyl acrylate (MA) and methyl vinyl ether (MVE) along with the yields of each cycloadduct obtained experimentally (results of cycloaddition with butyl vinyl ether and 2-chloroethylvinyl ether were used for that of methyl vinyl ether) are shown in Tables 4, 5, and 6. The tables also contain information on the distance between the bond-forming atoms in diene and dienophile in each case. This information indicates the degree of asynchronicity in the bond formation during the Diels−Alder cycloaddition and is further evidence in support of the proposed electron demand of the cycloadditions. Figures 1 and 2 show the computed transition structures for transition states leading to the cycloadducts of 5-chloro-2(*H*)-pyran-2-one (**12**) and with MVE and MA respectively, while Figures 3 and 4 show the computed transition structures for transition states leading to the cycloadducts of 5-iodo-2(*H*)-pyran-2-one (**13**) with MVE and MA, respectively. The computational data can be used to proximately predict the ratio of the cycloadducts obtained in these reactions. We can expect

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(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Stratmann, R. E.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Iyengar, S.; Petersson, G. A.; Ehara, M.; Toyota, K.; Nakatsuji, H.; Adamo, C.; Jaramillo, J.; Cammi, R.; Pomelli, C.; Ochterski, J.; Ayala, P. Y.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 01*, Development Version (Revision B.01); Gaussian, Inc.: Pittsburgh, PA, 2001.

(30) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(31) Dewar, M. J. S.; Zoebisch, E. G. *THEOCHEM* (*J. Mol. Struct.*) **1988**, *41*, 1.

(32) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(33) We used the 6-31G* basis for all elements other than iodine. For iodine, we used the 6-311G* all-electron basis defined in: Glukhovtsev, M. N.; Pross, A.; McGrath M. P.; Radom, L. *J. Chem. Phys.* **1995**, *103*, 1878. Taken from the Extensible Computational Chemistry Environment Basis Set Database, Version 12/03/03, as developed and distributed by the Molecular Science Computing Facility, Environmental and Molecular Sciences Laboratory which is part of the Pacific Northwest Laboratory, P.O. Box 999, Richland, WA 99352, and funded by the U.S. Department of Energy.

(34) Ujaque, G.; Norton, J. E.; Houk, K. N. *J. Org. Chem.* **2002**, *67*, 7179.

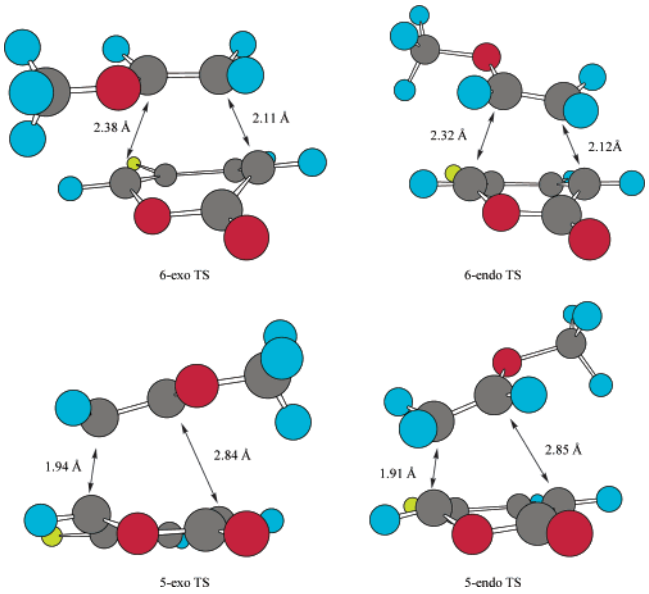


FIGURE 1. Computed transition structures for transition states leading to the cycloadducts of 5-chloro-2(*H*)-pyran-2-one (**12**) with methyl vinyl ether.

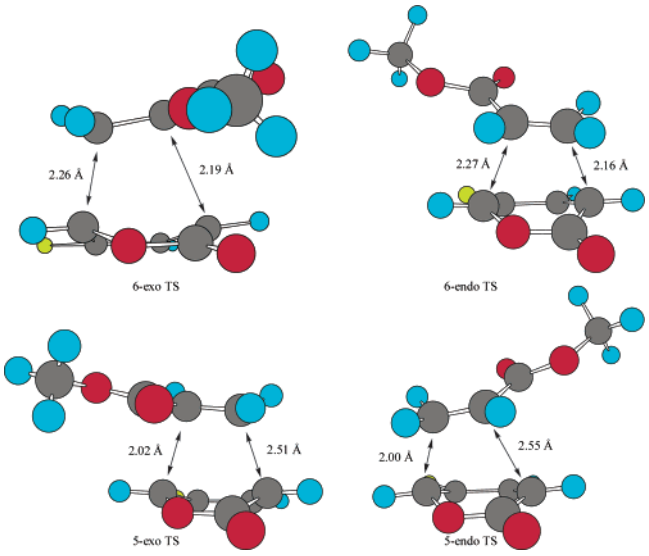


FIGURE 2. Computed transition structures for transition states leading to the cycloadducts of 5-chloro-2(*H*)-pyran-2-one (**12**) with methyl acrylate.

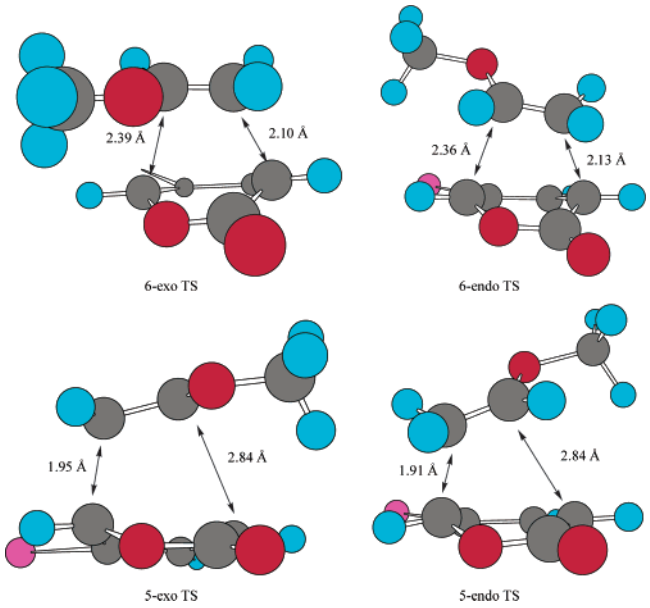


FIGURE 3. Computed transition structures for transition states leading to the cycloadducts of 5-iodo-2(*H*)-pyran-2-one (**13**) with methyl vinyl ether.

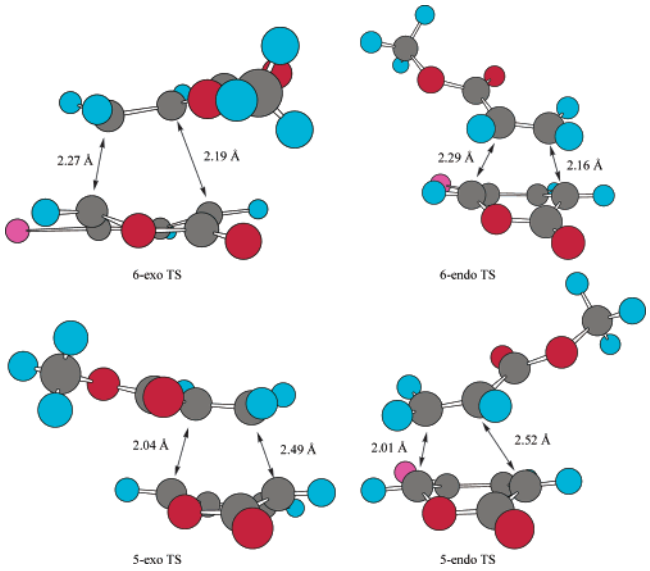


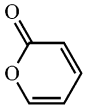
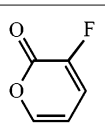
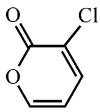
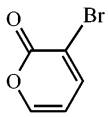
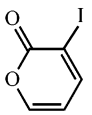
FIGURE 4. Computed transition structures for transition states leading to the cycloadducts of 5-iodo-2(*H*)-pyran-2-one (**13**) with methyl acrylate.

that of the four transition states, the ones with the lower energy are likely to be favored and cycloadducts resulting from them will be observed in larger proportion in the final product mixture. Conversely, transition states which have higher calculated relative energy values are expected to be disfavored and cycloadducts resulting from them will be observed in smaller amounts. Therefore, one expects a correlation between the calculated energy of the four transition states and the yield of the four cycloadducts.

As can be seen from the tables, the theory is very successful in its predictions. For the cycloadditions of 4-halo-2(*H*)-pyran-2-ones with methyl acrylate (MA), an electron-deficient dienophile, the theory correctly predicts that 5-*endo* and 6-*endo* cycloadducts are the major products of the reaction. Interestingly, we can also predict that 5-*endo* and 6-*endo* cycloadducts would have been the major products obtained in the cycloadditions of 4-halo-2(*H*)-pyran-2-ones with methyl vinyl ether (MVE), an electron-rich dienophile. We have been unable to obtain bridged bicyclic lactones in thermal cycloadditions presumably because the activation energy is too great and the cycloadducts are prone to loss of CO_2. The calculations suggest that had it been possible, the products would have been stereoselective but not regioselective.

For the cycloadditions of 3- and 5-halo-2(*H*)-pyran-2-ones with electron-rich dienophile methyl vinyl ether (MVE), the theory correctly predicts that 5-*endo* and 5-*exo* cycloadducts are the expected products of the reaction and that the former is the major product. In contrast, theory predicts that for the cycloadditions of 3- and

TABLE 4. Comparison between the Calculated Energy of Transition States Leading to the Four Possible Cycloadducts and the Experimentally Derived Ratios from the Reactions of 3-Halo-2(*H*)-pyran-2-ones with Methyl Acrylate (MA) and Methyl Vinyl Ether (MVE)

2-pyrone diene	Config.	Cycloaddition with MVE				Cycloaddition with MA			
		ΔH_f (Kcal/mol)[a]	Relative ratio[b]	C1-C6 (Å)	C4-C5 (Å)	ΔH_f (Kcal/mol)[a]	Relative ratio[b]	C1-C6 (Å)	C4-C5 (Å)
	5-endo	0.000	NA	1.91	2.75	0.000	85[c]	1.923	2.6224
	5-exo	0.528	NA	1.935	2.75	2.737	15[c]	1.960	2.589
	6-endo	4.833	NA	2.28	2.15	0.171	35[c]	2.1875	2.1893
	6-exo	7.075	NA	2.37	2.09	2.992	7[c]	2.210	2.200
	5-endo	0.000	NA	1.9336	2.7052	0.000	NA	1.9914	2.5258
	5-exo	0.464	NA	1.9633	2.6998	3.336	NA	2.0243	2.4908
	6-endo	4.133	NA	2.2986	2.1240	0.975	NA	2.2653	2.125
	6-exo	6.110	NA	2.3772	2.0674	3.626	NA	2.288	2.1361
	5-endo	0.000	60	1.8898	2.8255	0.000	80	1.9439	2.5919
	5-exo	0.006	40	1.932	2.8033	3.235	5	1.981	2.554
	6-endo	5.614	0	2.2188	2.1911	1.214	15	2.204	2.1723
	6-exo	7.716	0	2.2784	2.1422	3.785	0	2.225	2.1835
	5-endo	0.000	68	1.891	2.8194	0.000	80	1.954	2.571
	5-exo	0.650	32	1.9319	2.7926	3.461	5	1.995	2.536
	6-endo	6.634	0	2.2341	2.1763	1.711	15	2.2175	2.159
	6-exo	8.688	0	2.2944	2.1288	4.257	0	2.240	2.170
	5-endo	0.000	82	1.8715	2.88	0.000	85	1.923	2.6224
	5-exo	0.545	18	1.9155	2.86	2.980	0	1.960	2.589
	6-endo	5.363	0	2.20	2.21	1.086	15	2.1875	2.1893
	6-exo	6.908	0	2.2545	2.165	3.594	0	2.210	2.200

[a] The difference in the calculated barrier heights, with 5-endo taken as the energy zero. [b] Experimentally obtained (see Tables 1−3). [c] With high pressure.[14]

5-halo-2(*H*)-pyran-2-ones with electron-deficient dienophile methyl acrylate (MA), the 5-*endo* and 6-*endo* cycloadducts are the two expected products of the reaction and that the former is the major product. These predictions agree with experimental observations.

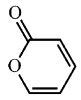
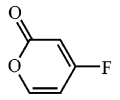
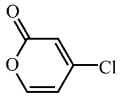
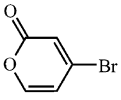
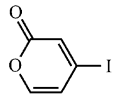
The theory also correctly predicts that the reactions of 3- and 5-halo-2(*H*)-pyran-2-one with methyl acrylate (MA) are less selective than the cycloadditions to methyl vinyl ether (MVE). This is because the energy gaps between the set of four transition states resulting from cycloadditions of 3- and 5-halo-2(*H*)-pyran-2-one with MA are narrower than the ones for the cycloadditions with MVE. This can explain why some 5-*exo* cycloadducts are observed in the cycloadditions of 3- and 5-halo-2(*H*)-pyran-2-one with methyl acrylate. Interestingly, this matches the product distribution previously reported in the cycloadditions of 5-bromo-2(*H*)-pyran-2-one to methyl vinyl ketone,[20] another electron-deficient dienophile.

The combined experimental and computational studies carried out here demonstrate the versatility and usefulness of the cycloadditions of 3- and 5-halo-substituted 2(*H*)-pyran-2-ones and their advantage over 4-halo-substituted 2(*H*)-pyran-2-ones. Furthermore, we can conclude that DFT (B3LYP/6-31G*) calculations are a reliable tool for predicting the regio- and stereochemical preferences in the cycloadditions of halopyrones.

Naturally, generalizations about the role of substituents on any Diels−Alder cycloadditions should be treated cautiously. However, it is interesting to note that cycloadditions of 4-aryl-substituted 2(*H*)-pyran-2-one (**23**) with electron-rich dienophiles are reported to be problematic[35] whereas cycloadditions of 5-aryl-substituted 2(*H*)-pyran-2-one (**24**) with vinylene carbonate proceeds efficiently[36] (Scheme 8). Therefore our study indicates that the lack of reactivity and selectivity in the Diels−Alder reactions of 4-substituted 2(*H*)-pyran-2-ones could be a general feature of the pyrone cycloaddition methodology and a key disadvantage of it. In contrast, reactivity and selectivity of 3- and 5-substituted 2(*H*)-pyran-2-ones as dienes could also be a general feature. Since the efficiency and selectivity of these cycloadditions appear not to be significantly influenced by the nature of the

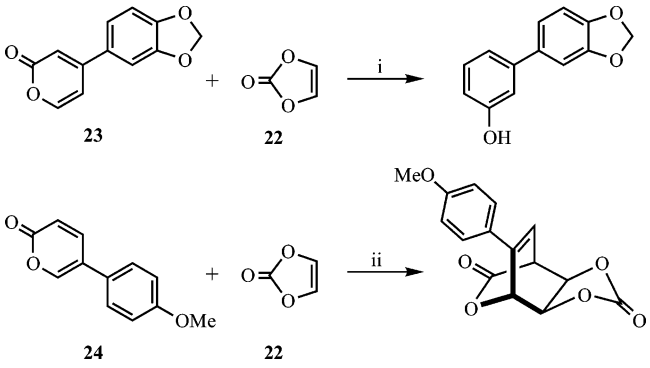
(35) Balazs, L.; Kadas, I.; Toke, L. *Tetrahedron Lett*. **2000**, *41*, 7583.
(36) Afarinkia, K.; Berna-Canovas, J. *Tetrahedron Lett*. **2000**, *41*, 4955.

TABLE 5. Comparison between the Calculated Energy of Transition States Leading to the Four Possible Cycloadducts and the Experimentally Derived Ratios from the Reactions of 4-Halo-2(*H*)-pyran-2-ones with Methyl Acrylate (MA) and Methyl Vinyl Ether (MVE)

2-pyrone diene	Config.	Cycloaddition with MVE				Cycloaddition with MA			
		ΔH_f (Kcal/mol) [a]	Relative ratio [b]	C1-C6 (Å)	C4-C5 (Å)	ΔH_f (Kcal/mol) [a]	Relative ratio [b]	C1-C6 (Å)	C4-C5 (Å)
	5-endo	0.000	NA	1.91	2.75	0.000	85 [c]	1.923	2.6224
	5-exo	0.528	NA	1.935	2.75	2.737	15 [c]	1.960	2.589
	6-endo	4.833	NA	2.28	2.15	0.171	35 [c]	2.1875	2.189
	6-exo	7.075	NA	2.37	2.09	2.992	7 [c]	2.210	2.200
	5-endo	0.000	NA	1.891	2.769	0.000	NA	1.198	2.482
	5-exo	0.973	NA	1.913	2.789	2.809	NA	2.019	2.446
	6-endo	7.328	NA	2.234	2.182	-0.021	NA	2.282	2.109
	6-exo	9.409	NA	2.322	2.112	2.472	NA	2.296	2.122
	5-endo	0.000	NA	1.905	2.795	0.000	41	2.007 [d]	2.476 [d]
	5-exo	0.709	NA	1.933	2.782	1.999	2	2.049 [d]	2.420 [d]
	6-endo	5.980	NA	2.319	2.118	-0.537	48	2.302 [d]	2.110 [d]
	6-exo	7.571	NA	2.419	2.045	1.409	9	2.328 [d]	2.110 [d]
	5-endo	0.000	NA	1.912	2.782	0.000	44	2.006	2.470
	5-exo	1.479	NA	1.935	2.780	2.949	4	2.054	2.410
	6-endo	6.613	NA	2.329	2.109	0.452	45	2.311	2.100
	6-exo	7.950	NA	2.435	2.031	2.343	7	2.335	2.101
	5-endo	0.000	NA	1.914	2.812	0.000	39	2.017	2.480
	5-exo	0.545	NA	1.946	2.783	1.666	6	2.061	2.415
	6-endo	5.363	NA	2.351	2.101	-0.852	47	2.306	2.116
	6-exo	7.409	NA	2.455	2.028	1.086	8	2.334	2.115

[a] The difference in the calculated barrier heights, with 5-endo taken as the energy zero. [b] Experimentally obtained (see Tables 1−3). [c] With high pressure.[14] [d] See ref 25.

SCHEME 8[a]



[a] Reagents and conditions: (i) 115 °C, 10 days, 32% (+60% recovered pyrone); (ii) 100 °C, 5 days, 87% (+10% exo cycloadduct).

halogen, it is very likely that other 3-, 4-, and 5-substituted 2(*H*)-pyran-2-ones will show similar patterns of reactivity.

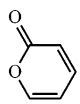
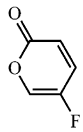
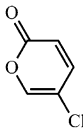
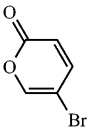
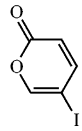
Experimental Section

3-Bromo-2(*H*)-pyran-2-one,[18] 5-bromo-2(*H*)pyran-2-one,[18,22] 4-chloro-2(*H*)-pyran-2-one,[25] 3-(trimethylstannyl)-2(*H*)-pyran-2-one,[26] and 5-(trimethylstannyl)-2(*H*)-pyran-2-one[26] were prepared according to literature procedure.

3-(Tributylstannyl)-2(*H*)-pyran-2-one, 7. In a dry round-bottom flask, hexa(*n*-butyl)ditin (8.5 g, 7.4 mL, 14.64 mmol), 3-bromo-2(*H*)-pyran-2-one (**4**) (2.11 g, 12.0 mmol), and Pd(PPh$_3$)$_4$ (423 mg, 0.363 mmol) were added to tetrahydrofuran (20 mL). The mixture was refluxed under an argon atmosphere for 43 h, then cooled to room temperature. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography, eluting with 20% v/v ether in petroleum ether (60−80 °C) to give 3.48 g (76%) of a yellow oil. ^{1}H NMR δ 7.43 (dd, 1 H, J = 2.2 Hz, 5.1 Hz, H-6), 7.37 (dd, 1H, J = 2.2 Hz, 6.0 Hz, H-4), 6.13 (dd, 1H, J = 5.2 Hz, 6.0 Hz, H-5), 1.52 (m, 6H, 3 × SnCH_2Pr), 1.33 (m, 6H, CH_2-Et), 1.08 (m, 6H, 3 × CH_2Me), 0.89 (t, 9H, J = 7.3 Hz, 3 × CH_3); ^{13}C NMR δ 165.3 (C-2), 152.0 (C-6), 151.5 (C-4), 133.4 (C-3), 107.1 (C-5), 29.3 (3 × SnCH_2), 27.7 (3 × SnCH$_2$$CH_2$), 14.0 (3 × CH_3), 10.1 (J_{Sn} = 356.8 Hz, 340.9 Hz, 3 × SnCH_2); IR 3092, 2957, 2925, 2871, 2853, 1706, 1621, 1526, 1464, 1376, 1331, 1237, 1129, 1083, 958, 875, 779, 693, 670, 600 cm^{-1}; *m/z* 329 [100, (M$^+$ − ^{n}Bu)], 328 (36), 327 (75), 326 (29), 325 (43), 315 (54), 313 (81), 311 (55), 259 (13), 257 (20), 255 (14), 215 [25, (MH$^+$ − 3 × ^{n}Bu)], 213 (21), 201 (12), 199 (17), 197 (12), 177 (18), 175 (13), 121 (9), 117 (5), 57 (15); HRMS calcd for $C_{13}H_{21}O_2Sn$ (M$^+$ − ^{n}Bu) 329.05634, found 329.05718.

5-(Tributylstannyl)-2(*H*)-pyran-2-one, 8b. In a dry round-bottom flask, hexa(*n*-butyl)ditin (0.80 mL, 1.58 mmol), 5-bromo-2(*H*)-pyran-2-one (**5**) (199 mg, 1.14 mmol), and Pd(PPh$_3$)$_4$ (41 mg, 35 μmol) were added to toluene (5 mL). The mixture was refluxed under an argon atmosphere for 69 h, then cooled to room temperature. The solvent was removed under reduced

TABLE 6. Comparison between the Calculated Energy of Transition States Leading to the Four Possible Cycloadducts and the Experimentally Derived Ratios from the Reactions of 5-Halo-2(*H*)-pyran-2-ones with Methyl Acrylate (MA) and Methyl Vinyl Ether (MVE)

2-pyrone diene	Config.	Cycloaddition with MVE				Cycloaddition with MA			
		ΔH_f (Kcal/mol) [a]	Relative ratio [b]	C1-C6 (Å)	C4-C5 (Å)	ΔH_f (Kcal/mol) [a]	Relative ratio [b]	C1-C6 (Å)	C4-C5 (Å)
	5-endo	0.000	NA	1.91	2.75	0.000	85 [c]	1.923	2.6224
	5-exo	2.737	NA	1.935	2.75	2.737	15 [c]	1.960	2.589
	6-endo	0.171	NA	2.28	2.15	0.171	35 [c]	2.1875	2.1893
	6-exo	2.992	NA	2.37	2.09	2.992	7 [c]	2.210	2.200
	5-endo	0.000	NA	1.913	2.822	0.000	NA	1.991	2.576
	5-exo	0.249	NA	1.944	2.812	2.750	NA	2.026	2.518
	6-endo	3.328	NA	2.306	2.156	1.051	NA	2.262	2.160
	6-exo	6.562	NA	2.408	2.087	4.270	NA	2.280	2.179
	5-endo	0.000	70	1.9072	2.8473	0.000	63	2.000	2.548
	5-exo	0.142	30	1.9387	2.8386	2.125	17	2.025	2.513
	6-endo	5.634	0	2.3186	2.1182	1.435	20	2.165	2.269
	6-exo	7.570	0	2.3764	2.1062	3.436	0	2.192	2.264
	5-endo	0.040	70	1.897	2.858	0.000	70	1.986	2.556
	5-exo	0.000	30	1.9292	2.843	2.070	10	2.016	2.514
	6-endo	5.118	0	2.3307	2.1397	0.399	20	2.265	2.159
	6-exo	7.811	0	2.356	2.1167	3.398	0	2.253	2.194
	5-endo	0.000	70	1.912	2.841	0.000	70	2.011	2.524
	5-exo	0.120	30	1.945	2.836	2.044	10	2.037	2.494
	6-endo	6.230	0	2.359	2.129	1.539	20	2.286	2.159
	6-exo	7.509	0	2.389	2.098	3.038	0	2.273	2.186

[a] The difference in the calculated barrier heights, with 5-endo taken as the energy zero. [b] Experimentally obtained (see Tables 1−3). [c] With high pressure.[14]

pressure and the crude material was purified by flash chromatography, eluting with 20% v/v ethyl acetate in petroleum ether (60−80 °C) to give 163 mg (37%) of a yellow oil. ^{1}H NMR δ 7.25 (dd, 1 H, J = 2.0 Hz, 9.1 Hz, H-4), 7.19 (dd, 1H, J = 1.3 Hz, 2.0 Hz, H-6), 6.33 (dd, 1H, J = 1.3 Hz, 9.1 Hz, H-3), 1.21−1.75 (m, 18H, 9 × CH_2), 0.92 (t, 9H, J = 7.5 Hz, 3 × CH_3); ^{13}C NMR δ 162.6 (C-2), 154.7 (C-4), 149.2 (C-6), 117.6 (C-3), 113.1 (C-5), 29.3 (3 × CH_2), 27.6 (3 × CH_2), 14.0 (3 × CH_3), 10.1 (J_{Sn} = 354.1 Hz, 338.4 Hz, CH_2); IR 2958, 2913, 2857, 1740, 1712, 1606, 1580, 1521, 1460, 1410, 1373, 1337, 1217, 1129, 1071, 1021, 959, 873, 826 cm^{-1}; *m/z* 387 (2, M^+), 385 (2, M^+), 329 [37, ($MH^+ - {}^n$Bu)], 328 (14), 327 (29), 326 (12), 325 (17), 319 (11), 317 (19), 315 (65), 314 (25), 313 (100), 312 (35), 311 (69), 310 (17), 309 (27), 295 (10), 291 (56), 290 (20), 289 (42), 288 (17), 287 (24), 259 (17), 257 (27), 255 (20), 215 [6, ($MH^+ - 3 \times {}^n$Bu)], 177 (15), 175 (11); HRMS (ESI) calcd for $C_{17}H_{30}O_2Sn$ 409.11720, found 409.11610.

4-(Trimethylstannyl)-2(*H*)-pyran-2-one, 9. In a dry round-bottom flask, hexamethylditin (1.19 g, 3.63 mmol), 4-chloro-2(*H*)-pyran-2-one (**6**) (0.39 g, 3.0 mmol), and $Pd(PPh_3)_4$ (0.12 g, 0.09 mmol) were added to tetrahydrofuran (6 mL). The mixture was refluxed under an argon atmosphere for 44 h, then cooled to room temperature. The solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography, eluting with 30% v/v ether in petroleum ether (60−80 °C) to give 490 mg (63%) of a white solid. Mp 40 °C; ^{1}H NMR δ 7.39 (dd, 1H, J = 1.3 Hz, 5.0 Hz, H-5), 6.46 (dd, 1H, J = 0.9 Hz, 1.3 Hz, H-3), 6.24 (dd, 1H, J = 0.9 Hz, 5.0 Hz, H-6), 0.33 [s, 9H, J_{Sn} = 27.3 Hz, 28.3 Hz, Sn-(CH_3)$_3$]; ^{13}C NMR 164.3 (C-2), 160.1 (C-4), 149.3 (C-5), 125.0 (C-3), 111.8 (C-6), −9.4 [J_{Sn} = 408 Hz, Sn(CH_3)$_3$]; IR 3064, 2915, 1700, 1645, 1598, 1251, 1192, 1175, 1096, 999, 862, 807, 782, 573, 531 cm^{-1}; *m/z* 260 (39, M^+), 258 (29), 256 (19), 245 (82, M^+ − Me), 244 (26), 243 (61), 242 (24), 241 (39), 232 (95, $M^+ - 2 \times$ Me), 231 (31), 230 (69, $M^+ - 2 \times$ Me), 229(29), 228 (42), 217 (74, $M^+ - 3 \times$ Me), 216 (27), 215 (57, $M^+ - 3 \times$ Me), 214 (22), 213 (38), 187 (22), 185 (20), 183 (14), 169 (20), 167 (18), 165 (100, ^{120}SnMe$_3$), 164 (31, ^{119}SnMe$_3$), 163 (78, ^{118}SnMe$_3$), 162 (28, ^{117}SnMe$_3$), 161 (55, ^{116}SnMe$_3$), 150 (37), 149 (23), 148 (34), 135 (41), 133 (32), 131 (21), 120 (18), 119(12), 118 (14), 95 (16, M^+ − SnMe$_3$), 81 (6), 69 (9); HRMS calcd for $C_8H_{12}O_2SnNa$ 282.97570, found 282.97523.

3-Chloro-2(*H*)-pyran-2-one, 10. To a solution of 3-(tibutylstannyl)-2(*H*)-pyran-2-one (**7**) (1.0 g, 2.6 mmol) in dry dichloromethane (50 mL, 0.05 mmol/mL) was added a solution of chlorine gas (227 mg, 3.2 mmol, 1.2 equiv) in carbon tetrachloride (43 mL, 0.075 mmol/mL) during 10 min via syringe. The resulting solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, eluting with 30% v/v ethyl acetate in petroleum ether (60−80 °C) to afford 316 mg (93%) of a white solid. Mp 82 °C; ^{1}H NMR δ 7.48 (dd, 1 H, J = 1.9 Hz, 7.0 Hz, H-6), 7.47 (dd, 1H, J = 1.9 Hz, 5.2 Hz, H-4), 6.23 (dd, 1H, J = 5.2 Hz, 7.0 Hz, H-5); ^{13}C NMR δ 158.9 (C-2), 150.6 (C-6), 140.3 (C-4), 123.8 (C-3), 106.1 (C-5); IR 3104, 3066, 3028, 1722, 1627, 1528, 1335, 1226, 1094, 1014, 986, 962, 863, 778, 745 cm^{-1}; *m/z* 132 (33, M^+ for ^{37}Cl), 130 (100, M^+ for ^{35}Cl), 104 (18), 102 (56), 74 (9), 73 (8), 39 (17); HRMS calcd for $C_{10}H_6Cl_2O_4Na$ (2M + Na) 282.95356, found 282.95360.

3-Iodo-2(*H*)-pyran-2-one, 11. A solution of 3-(tributylstannyl)-2(*H*)-pyran-2-one (**7**) (793 mg, 2.06 mmol) in chloroform (40 mL) was placed in a dry round-bottom flask wrapped with aluminum foil. Then a solution of iodine (523 mg, 2.06 mmol) in chloroform (100 mL) was added, via pressure equalizing addition funnel, during 20 min. The resulting mixture was stirred at room temperature for 6 days. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, eluting with 30% v/v ether in petroleum ether (60−80 °C) to give 380 mg (83%) of a yellowish solid. Mp 66 °C; ^{1}H NMR δ 7.95 (dd, 1 H, J = 1.9 Hz, 6.8 Hz, H-6), 6.52 (dd, 1H, J = 1.9 Hz, 5.0 Hz, H-4), 6.01 (dd, 1H, J = 5.0 Hz, 6.8 Hz, H-5); ^{13}C NMR δ 158.6 (C-2), 152.0 (C-6), 151.6 (C-4), 107.3 (C-5), 86.8 (C-3); IR 3098, 2967, 2923, 2852, 1713, 1622, 1522, 1464, 1378, 1329, 1235, 1091, 959, 837, 752, 640 cm^{-1}; *m/z* 222 (100, M$^+$), 194 (28), 165 (5), 95 [8, (M$^+$ − I)]; HRMS calcd for $C_5H_3IO_2Na$ 244.90699, found 244.90705.

5-Chloro-2(*H*)-pyran-2-one, 12. Method A: To a solution of 5-(tibutylstannyl)-2(*H*)-pyran-2-one (**8b**) (585 mg, 1.52 mmol) in dry dichloromethane (30 mL, 0.05 mmol/mL) was added via syringe a solution of chlorine gas (142 mg, 2 mmol, 1.3 equiv) in carbon tetrachloride (27 mL, 0.075 mmol/mL) during 10 min. The resulting solution was stirred at room temperature for 45 min. The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 20% v/v ethyl acetate in petroleum ether (60−80 °C) to afford 129 mg (67%) of a white solid.

Method B: To a solution of coumalic acid (2.67 g, 19 mmol) in acetonitrile and water (5:1, 120 mL) were added *N*-chlorosuccinimide (5.09 g, 38 mmol) and lithium acetate (2.52 g, 38 mmol), respectively. The resulting mixture was stirred at room temperature for 6 days after which it was diluted with water (100 mL) and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduce pressure. The residue was purified by flash chromatography, eluting with 20% v/v ethyl acetate in petroleum ether (60−80 °C) to give 200 mg (8%) of the desired product as a yellow solid together with ca. 4% of 3,5-dichloropyrone. Mp 54−58 °C dec; ^{1}H NMR δ 7.59 (dd, 1 H, J = 0.9 Hz, 2.6 Hz, H-6), 7.34 (dd, 1H, J = 2.6 Hz, 9.9 Hz, H-4), 6.30 (dd, 1H, J = 0.9 Hz, 9.9 Hz, H-3); ^{13}C NMR δ 159.9 (C-2), 150.1 (C-6), 146.4 (C-4), 118.0 (C-3), 101.2 (C-5); IR 3076, 2925, 2855, 1749, 1621, 1536, 1227, 1170, 1127, 1071, 945, 834, 785, 730, 664 cm^{-1}; *m/z* 132 (33, M$^+$ for ^{37}Cl), 130 (100, M$^+$ for ^{35}Cl), 104 (20), 102 (60), 74 (19), 73 (25). Anal. Calcd for $C_5H_3ClO_2$: C, 46.01, H, 2.32. Found: C, 45.91, H, 2.43.

5-Iodo-2(*H*)-pyran-2-one, 13. A solution of 5-(trimethylstannyl)-2(*H*)-pyran-2-one (**8a**) (340 mg,1.3 mmol) in chloroform (25 mL) was placed in a dry round-bottom flask wrapped with aluminum foil. Then a solution of iodine (340 mg, 1.34 mmol) in chloroform (50 mL) was added, via pressure equalizing addition funnel, during 20 min. The resulting mixture was stirred at room temperature for 6 days. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, eluting with 20% v/v ethyl acetate in petroleum ether (60−80 °C) to give 160 mg (56%) of a yellowish solid. Mp 100 °C; ^{1}H NMR δ 7.62 (dd, 1H, J = 1.0 Hz, 2.5 Hz, H-6), 7.38 (dd, 1H, J = 2.5 Hz, 9.7 Hz, H-4), 6.22 (dd, 1H, J = 1.0 Hz, 9.7 Hz, H-3); ^{13}C NMR δ 159.3 (C-2), 153.9 (C-6), 149.7 (C-4), 118.3 (C-3), 67.6 (C-5); IR 3056, 2978, 2923, 2852, 1734, 1711, 1594, 1523, 1464, 1378, 1323, 1215, 1147, 11221025, 941, 857, 829, 791, 625, 602 cm^{-1}; *m/z* 222 (100, M$^+$), 194 (54), 166 (9), 127 (5, I$^+$), 95 [16, (M$^+$ − I)], 67 (5), 39(34); HRMS calcd for $C_5H_3IO_2Na$ 244.90699, found 244.90685.

4-Bromo-2(*H*)-pyran-2-one, 14. A solution of 4-(trimethylstannyl)-2(*H*)-pyran-2-one (**9**) (260 mg, 1 mmol) in chloroform (20 mL) was cooled to −60 °C and 1 equiv of a solution of bromine (160 mg, 2 mmol) in chloroform (40 mL) was added via a syringe over 15 min. After addition the cold bath was removed and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography, eluting with 30% v/v ethyl acetate in petroleum ether (60−80 °C) to give 169 mg (96%) of a yellow solid. Mp 49 °C; ^{1}H NMR δ 7.37 (dd, 1 H, J = 0.8 Hz, 5.6 Hz, H-6), 6.65 (dd, 1H, J = 0.8 Hz, 1.8 Hz, H-3), 6.40 (dd, 1H, J = 1.8 Hz, 5.6 Hz, H-5); ^{13}C NMR δ 159.7 (C-2), 150.7 (C-6), 140.0 (C-4), 118.6 (C-3), 111.1 (C-5); IR 3031, 1730, 1648, 1609, 1535, 1406, 1293, 1237, 1167, 1083, 1013, 968, 957, 864, 811, 783, 722, 661, 612, 575 cm^{-1}; *m/z* 176 (68, M$^+$ for ^{81}Br), 174 (69, M$^+$ for ^{79}Br), 147 [99, (M$^+$ − 29)], 145 [100, (M$^+$ − 29)], 132 (5), 130 (9), 119 (18), 117 (17), 95 [13, (M$^+$ − Br)], 80 (5, Br$^+$), 67 (48), 50 (12), and 39 (86), 38 (38), 37 (22); HRMS calcd for $C_5H_3{}^{81}BrO_2$ 175.92905, found 175.92919.

4-Iodo-2(*H*)-pyran-2-one, 15. A solution of 4-(trimethylstannyl)-2(*H*)-pyran-2-one (**9**) (610 mg, 2.35 mmol) in chloroform (40 mL) was placed in a dry round-bottom flask wrapped with aluminum foil. Then a solution of iodine (600 mg, 2.36 mmol) in chloroform (80 mL) was added, via pressure equalizing addition funnel, during 20 min. The resulting mixture was stirred at room temperature for 6 days. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 35% v/v ether in petroleum ether (60−80 °C) to give 320 mg (61%) of a yellow solid. Mp 50 °C; ^{1}H NMR δ 7.21 (dd, 1 H, J = 0.9 Hz, 5.5 Hz, H-6), 6.95 (dd, 1H, J = 0.9 Hz, 1.6 Hz, H-3), 6.53 (dd, 1H, J = 1.6 Hz, 5.5 Hz, H-5); ^{13}C NMR δ 158.9 (C-2), 149.9 (C-6), 125.9 (C-3), 115.5 (C-5), 113.7 (C-4); IR 2923, 2852, 1724, 1646, 1601, 1563, 1519, 1403, 1288, 1241, 1169, 1088, 1004, 960, 846, 813, 795, 721, 651, 599, 574 cm^{-1}; *m/z* 222 (96, M$^+$), 194 (100, M$^+$ − 28); HRMS calcd for $C_5H_3IO_2Na$ 244.90699, found 244.90802.

Typical Cycloaddition: Reaction of 3-Chloro-2(H)-pyran-2-one and Methyl Acrylate. A sealed pressure tube (purchased from Aldrich Chemical Co. Cat. No. Z18, 109-9) was charged with 3-chloro-2(*H*)-pyran-2-one (**10**) (94 mg, 0.72 mmol), methyl acrylate (0.5 mL, 5.6 mmol, 8 equiv), a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (acting as an antipolymerization agent), and a small magnetic stir bar. The pressure tube was sealed and immersed in an oil bath maintained at 100 °C. After 3 days, the tube was cooled to room temperature and the contents were stripped of volatile materials. Proton nuclear magnetic resonance of the crude residue indicated the presence of two isomers of cycloadducts. Pure samples of the 5-endo and 6-endo cycloadducts were obtained by silica gel chromatography, using 20% v/v ethyl acetate in petroleum ether. The combined isolated yield of cycloadducts was 85 mg, 55%.

Methyl 4-chloro-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5$_{endo}$-carboxylate: mp 116 °C; ^{1}H NMR δ 6.57 (dd, 1H, $J_{1,7}$ = 5.2 Hz, $J_{7,8}$ = 8.0 Hz, H-7), 6.48 (dm, 1H, $J_{7,8}$ = 8.0 Hz, H-8), 5.31 (m, 1H, H-1), 3.54 (s, 3H, CO_2CH_3), 3.17 (ddd, 1H, $J_{1,5}$ = 0.8 Hz, $J_{5,6endo}$ = 4.2 Hz, $J_{5,6exo}$ = 10.0 Hz, H-5), 2.73 (ddd, 1H, $J_{1,6exo}$ = 4.1 Hz, $J_{5,6exo}$ = 10.0 Hz, $J_{6exo,6endo}$ = 13.4 Hz, H-6$_{exo}$), 1.98 (ddd, 1H, $J_{1,6endo}$ = 1.2 Hz, $J_{5,6endo}$ = 4.2 Hz, $J_{6endo,6exo}$= 13.4 Hz, H-6$_{endo}$); ^{13}C NMR δ 171.0 (*C*O$_2$CH$_3$), 168.3 (C-3), 135.6 (C-7), 131.1 (C-8), 73.7 (C-1), 67.0 (C-4), 53.1 (CO$_2$*C*H$_3$), 44.4 (C-5), 33.8 (C-6); IR 3087, 3055, 2961, 2926, 2854, 1768, 1737, 1455, 1437, 1362, 1264, 1214, 1181, 1168, 1063, 1042, 997, 950, 939, 870, 844, 805, 741, 705, 651, 618, 585 cm^{-1}; *m/z* 219 (6), 218 (4), 217 (14, MH$^+$), 185 [2, (M$^+$ − OMe)], 172 [28, (M$^+$ − CO$_2$)], 157 [8, (M$^+$ − CO$_2$Me)], 137 [32, (M$^+$ − CO$_2$ − Cl)], 115 (30), 114 (20), 113 [100, (M$^+$ − CO$_2$ − CO$_2$Me)], 112 (46), 105 (30), 102 (9), 93 (15), 78 (24), 77 (96), 65 (8), 59 (12), 55 (5), 51 (17), 50 (9); HRMS (ESI) calcd for $C_9H_9{}^{35}ClO_4Na$ 239.00816, found 239.00941.

Methyl 4-chloro-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-6$_{endo}$-carboxylate: mp 60 °C; ^{1}H NMR δ 6.49 (dd, 1H, $J_{1,8}$ = 1.7 Hz, $J_{7,8}$ = 8.0 Hz, H-8), 6.41 (dd, 1H, $J_{1,7}$ = 4.9 Hz, $J_{7,8}$ = 8.0 Hz, H-7), 5.42 (ddd, 1H, $J_{1,8}$ = 1.7 Hz, $J_{1,6}$ = 3.9 Hz, $J_{1,7}$ = 4.9 Hz, H-1), 3.67 (s, 3H, CO_2CH_3), 3.42 (ddd, 1H, $J_{1,6}$ = 3.9 Hz, $J_{6,5endo}$ = 5.9 Hz, $J_{6,5exo}$ = 9.2 Hz, H-6), 2.43 (dd, 1H, $J_{5exo,6}$ = 9.2 Hz, $J_{5exo,5endo}$ = 12.7 Hz, H-5$_{exo}$), 2.37 (dd, 1H, $J_{5endo,6}$ = 5.9 Hz, $J_{5endo,5exo}$= 12.7 Hz, H-5$_{endo}$); ^{13}C NMR δ 170.4 (*C*O$_2$-

CH_3), 169.1 (C-3), 138.78 (C-8), 130.0 (C-7), 73.8 (C-1), 64.8 (C-4), 53.2 (CO_2CH_3), 44.8 (C-6), 34.6 (C-5); IR 3081, 2952, 2922, 2852, 1780, 1738, 1436, 1364, 1306, 1259, 1205, 1116, 1057, 1025, 969, 927, 799, 714 cm^{-1}; *m/z* 219 (7), 218 (6), 217 (10, MH^+), 185 [10, ($M^+ - OMe$)], 172 [25, ($M^+ - CO_2$)], 157 [6, ($M^+ - CO_2Me$)], 137 [15, ($M^+ - CO_2 - Cl$)], 115 (32), 114 (20), 113 [100, ($M^+ - CO_2$,CO_2Me)], 112 (43), 102 (9), 78 (12), 77 (73), 65 (7), 55 (12), 51 (11); HRMS (ESI) calcd for $C_9H_9{}^{35}ClO_4Na$ 239.00816, found 239.00752.

Typical Cycloaddition: Reaction of 5-Bromo-2(H)-pyran-2-one and Methyl Acrylate. A sealed pressure tube (purchased from Aldrich Chemical Co. Cat. No. Z18, 109-9) was charged with 5-bromo-2(*H*)-pyran-2-one (**5**) (66 mg, 0.38 mmol), methyl acrylate (0.6 mL, 6.7 mmol, 18 equiv), a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (acting as an antipolymerization agent) and a small magnetic stirrer bar. The pressure tube was sealed and immersed in an oil bath maintained at 100 °C. After 3 days, the tube was cooled to room temperature and the contents were stripped of volatile materials. Proton nuclear magnetic resonance of the crude residue indicated the presence of 3 isomers of cycloadducts. Silica gel chromatography with 30% v/v ethyl acetate in petroleum ether afforded pure samples of the 5-endo and 5-exo cycloadducts as well as a sample of the 6-endo product contaminated with traces of the 5-endo and 5-exo cycloadducts. The combined isolated yield of cycloadducts was 93 mg, 94%.

Methyl 7-bromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5_{endo}-carboxylate: ^1H NMR δ 6.53 (dd, 1H, $J_{1,8} = 2.4$ Hz, $J_{4,8} = 6.5$ Hz, H-8), 5.16 (m, 1H, H-1), 3.91 (dd, 1H, $J_{4,5} = 2.7$ Hz, $J_{4,8} = 6.5$ Hz, H-4), 3.72 (s, 3H, CO_2CH_3), 3.05 (dm, 1H, $J_{5,6exo} = 9.4$ Hz, H-5), 2.50 (ddd, 1H, $J_{1,6exo} = 3.9$ Hz, $J_{5,6exo} = 9.8$ Hz, $J_{6exo,6endo} = 14.0$ Hz, H-6_{exo}), 2.26 (ddd, 1H, $J_{1,6endo} = 1.4$ Hz, $J_{5,6endo} = 4.0$ Hz, $J_{6exo,6endo} = 14.0$ Hz, H-6_{endo}); ^{13}C NMR δ 171.7 (C-3), 170.8 (CO_2CH_3), 129.3 (C-8), 122.0 (C-7), 80.9 (C-1), 53.2 (CO_2CH_3), 45.5 (C-4), 37.2 (C-5), 30.1 (C-6); IR 3005, 2954, 2850, 1766, 1734, 1615, 1436, 1359, 1275, 1235, 1214, 1158, 1073, 1042, 1014, 995, 951, 902, 808, 783, 767, 736, 642, 521 cm^{-1}; *m/z* 262 (14, M^+ for ^{81}Br), 260 (14, M^+ for ^{79}Br), 231 [17, (M^+ for $^{81}Br-OMe$), 229 [18, (M^+ for $^{79}Br-OMe$)], 218 [16, (M^+ for $^{81}Br-CO_2$)], 216 [16, (M^+ for $^{79}Br-CO_2$)], 187 (6), 185 (6), 176 [14, (M^+ for ^{81}Br − 86, retro-Diels−Alder)], 174 [14, (M^+ for ^{79}Br − 86, retro-Diels−Alder)], 159 [90, (M^+ for $^{81}Br-CO_2-CO_2Me$)], 158 (40), 157 [93, (M^+ for $^{79}Br-CO_2-CO_2Me$)], 156 (34), 147 (11), 145 (11), 93 (37), 78 (95), 77 (100), 65 (11), 60 (10), 59 (19), 55 (60); HRMS calcd for $C_9H_9{}^{79}BrO_4Na$ 282.95825, found 282.95796. Anal. Calcd for $C_9H_9BrO_4$: C, 41.41, H, 3.47. Found: C, 41.61, H, 3.34.

Methyl 7-bromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-6_{endo}-carboxylate: ^1H NMR δ 6.68 (dd, 1H, $J_{1,8} = 2.6$ Hz, $J_{4,8} = 6.8$ Hz, H-8), 5.42 (dd, 1H, $J_{1,8} = 2.6$ Hz, $J_{1,6} = 3.9$ Hz, H-1), 3.74 (s, 3H, CO_2CH_3), 3.56 (dm, 1H, $J_{4,8} = 6.8$ Hz, H-4), 3.42 (ddd, 1H, $J_{1,6} = 3.9$ Hz, $J_{5endo,6} = 5.9$ Hz, $J_{5exo,6} = 9.0$ Hz, H-6), 2.11−2.20 (m, 2H, H-5); ^{13}C NMR δ 171.4 (C-3), 170.4 (CO_2CH_3), 132.7 (C-8), 119.1 (C-7), 80.8 (C-1), 53.0 (CO_2CH_3), 43.6 (C-4), 42.8 (C-6), 23.8 (C-5).

Methyl 7-bromo-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-5_{exo}-carboxylate: ^1H NMR δ 6.66 (dd, 1H, $J_{1,8} = 2.5$ Hz, $J_{4,8} = 6.9$ Hz, H-8), 5.20 (m, 1H, H-1), 3.81 (dd, $J_{4,5} = 2.3$ Hz, $J_{4,8} = 6.9$ Hz, H-4), 3.76 (s, 3H, CO_2CH_3), 2.83 (ddd, 1H, $J_{4,5} = 2.3$ Hz, $J_{5,6exo} = 5.3$ Hz, $J_{5,6endo} = 10.8$ Hz, H-5), 2.52 (ddd, 1H, $J_{1,6exo} = 3.9$ Hz, $J_{5,6exo} = 5.3$ Hz, $J_{6endo,6exo} = 14.0$ Hz, H-6_{exo}), 2.19 (ddd, 1H, $J_{1,6endo} = 1.7$ Hz, $J_{5,6endo} = 10.8$ Hz, $J_{6endo,6exo} = 14.0$ Hz, H-6_{endo}); ^{13}C NMR δ 170.4 (CO_2CH_3), 168.9 (C-3), 130.5 (C-8), 123.5 (C-7), 80.8 (C-1), 53.4 (CO_2CH_3), 45.8 (C-4), 39.3 (C-5), 29.7 (C-6); IR 2978, 2924, 2846, 1773, 1734, 1437, 1353, 1265, 1207, 1132, 1009, 801, 737 cm^{-1}; *m/z* 263 (49, MH^+ for ^{81}Br), 261 (49, MH^+ for ^{79}Br), 231 [11, (M^+ for $^{81}Br-OMe$)], 229 [11, (M^+ for $^{79}Br-OMe$)], 218 [16, (M^+ for $^{81}Br-CO_2$)], 217 (24), 216 [16, (M^+ for $^{79}Br-CO_2$)], 215 (21), 203 (10), 201 (12), 187 (9), 185 (11), 176 [8, (M^+ for ^{81}Br − 86, retro-Diels−Alder)], 174 [9, (M^+ for ^{79}Br − 86, retro-Diels−Alder)], 160 (11), 159 [99, (M^+ for $^{81}Br-CO_2-CO_2Me$)], 158 (50), 157 [100, (M^+ for $^{79}Br-CO_2-CO_2Me$)], 156 (45), 147 (11), 145 (11), 137 (45), 93 (32), 78 (44), 77 (64), 65 (5), 60 (8), 59 (11), 55 (11); HRMS calcd for $C_9H_9{}^{79}BrO_4Na$ 282.95764, found 282.95723.

Typical Cycloaddition: Reaction of 5-Iodo-2(H)-pyran-2-one and (2-Chloroethyl) Vinyl Ether. A sealed pressure tube (purchased from Aldrich Chemical Co. Cat. No. Z18,109-9) was charged with 5-iodo-2(*H*)-pyran-2-one (**13**) (48 mg, 0.216 mmol), (2-chloroethyl) vinyl ether (0.5 mL, 6.1 mmol, 28 equiv), a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (acting as an antipolymerization agent), and a small magnetic stirrer bar. The pressure tube was sealed and then immersed in an oil bath maintained at 100 °C. After 3 days, the tube was cooled to room temperature and the contents were stripped of volatile materials. Proton nuclear magnetic resonance of the crude residue indicated the presence of two cycloadducts. A pure sample of the mixed isomers was obtained by silica gel chromatography, using 20% v/v ethyl acetate in petroleum ether. The combined isolated yield of cycloadducts was 65 mg, 92%.

7-Iodo-5_{endo}-(2-chloroethoxy)-3-oxo-2-oxabicyclo[2.2.2]-oct-7-ene and 7-iodo-5_{exo}-(2-chloroethoxy)-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene: ^1H NMR 5-*endo* cycloadduct δ 6.76 (dd, 1H, $J_{1,8} = 1.7$ Hz, $J_{4,8} = 6.5$ Hz, H-8), 5.17 (dt, 1H, $J_{1,6endo} \approx J_{1,8} = 1.7$ Hz, $J_{1,6exo} = 3.8$ Hz, H-1), 4.01 (dm, 1H, $J_{5,6exo} = 7.8$ Hz, H-5), 3.84 (dd, 1H, $J_{4,5} = 3.2$ Hz, $J_{4,8} = 6.5$ Hz, H-4), 3.69 (m, 2H, OCH_2CH_2Cl), 3.57 (dd, 2H, $J = 5.6$ Hz, 11.1 Hz, OCH_2CH_2Cl), 2.51 (ddd, 1H, $J_{1,6exo} = 3.8$ Hz, $J_{5,6exo} = 7.8$ Hz, $J_{6exo,6endo} = 14.3$ Hz, H-6_{exo}), 1.76 (dm, 1H, $J_{6exo,6endo} = 14.3$ Hz, H-6_{endo}), and 5-*exo* cycloadduct δ 6.76 (dd, 1H, $J_{1,8} = 1.9$ Hz, $J_{4,8} = 6.7$ Hz, H-8), 5.14 (m, 1H, H-1), 3.89 (dt, 1H, $J_{4,5} \approx J_{5,6exo} = 3.3$ Hz, 3.3 Hz, $J_{5,6endo} = 8.8$ Hz, H-5), 3.75 (dd, 1H, $J_{4,5} = 3.3$ Hz, $J_{4,8} = 6.7$ Hz, H-4), 3.68−3.60 (m, 4H, OCH_2CH_2Cl), 2.30 (ddd, 1H, $J_{1,6endo} = 1.5$ Hz, $J_{5,6endo} = 8.8$ Hz, $J_{6exo,6endo} = 14.1$ Hz, H-6_{endo}), 1.96 (dt, 1H, $J_{1,6exo} \approx J_{5,6exo} = 3.4$ Hz, $J_{6exo,6endo} = 14.1$ Hz, H-6_{exo}); ^{13}C NMR 5-*endo* cycloadduct δ 170.1 (C-3), 136.5 (C-8), 90.6 (C-7), 83.7 (C-1), 71.9 (C-5), 69.8 (OCH_2CH_2Cl), 50.1 (C-4), 43.0 (OCH_2CH_2Cl), 34.9 (C-6), and 5-*exo* cycloadduct δ 170.1 (C-3), 136.4 (C-8), 94.4 (C-7), 83.8 (C-1), 73.5 (C-5), 69.8 (OCH_2CH_2Cl), 49.9 (C-4), 42.8 (OCH_2CH_2Cl), 33.7 (C-6); IR 3076, 2956, 2924, 2863, 1761, 1684, 1601, 1460, 1430, 1355, 1301, 1260, 1169, 1113, 1025, 1008, 990, 917, 874, 800, 762, 738, 666, 638, 623 cm^{-1}; *m/z* 330 (10), 328 (27, M^+), 223 (13), 222 [100, (M^+ − 106, retro Diels−Alder)], 194 (33), 109(12), 108 (36), 107 (31), 106 [87, (M^+ − 222, retro-Diels−Alder)], 95 (10), 78 (17), 77 (8), 66 (7), 65 (11), 63 (29), 62 (6), 57 (6); HRMS calcd for $C_9H_{10}{}^{35}ClIO_3Na$ 350.925536, found 350.92643.

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Supporting Information Available: Experimental procedures and characterization of all previously unreported compounds; drawings, crystal data, and coordinates of all crystal structures in pdb format; and coordinates of all transition states in pdb format and absolute energies of all transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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